CHAPTER 81

Antiepileptic Drugs

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Epilepsy may be defined as a paroxysmal, self-sustaining, and self-limiting cerebral dysrhythmia characterized by an abnormal and excessive EEG discharge and a loss of consciousness. It may or may not be associated with body movements or hyperactivity of the autonomic nervous system. The epileptic attack is initiated by an abnormal focus of electric discharge, originating either in the grey matter or in the other part of the brain. The discharge spreads to other parts of the CNS and results in convulsions and other manifestations of the disorder.

There are many conditions that result in seizures. These include the entire range of neurological diseases from infection to neoplasm to head injuries. Contrary to popular opinion, hereditary factors are involved in only a few subtypes of seizures. The antiepileptic drugs described in this chapter also are used in patients who have febrile seizures or who have seizures as a result of an acute illness such as meningitis, even though the term epilepsy is not applied to such patients unless they later develop chronic seizures. Seizures also may result from an acute toxic or metabolic disorder; in such cases appropriate therapy is directed to the specific abnormality, such as hypocalcemia. In most cases of epilepsy, the choice of medication is dictated by the seizure classification.

Based on a modification of the International Classification (*Epilepsia* 1981; 22:489), epileptic seizures may be divided into two groups:

I. *Partial Seizures* (Focal Seizures).
   A. Partial seizures with elementary symptomatology (cortical focal). Generally without impairment of consciousness. Includes seizures confined to a single limb or muscle group (Jacksonian motor epilepsy), those who have sensory or somatosensory symptoms (Jacksonian sensory epilepsy) and those who have other limited symptoms, depending on the particular cortical area involved.
   B. Partial seizures with complex symptomatology (temporal lobe, psychomotor seizures). Generally with impairment of consciousness. Attacks of confused behavior with a wide variety of clinical manifestations, associated with bizarre generalized EEG activity during the seizure and temporal lobe abnormalities during the interictal period.
   C. Partial seizures secondarily generalized.

II. *Generalized Seizures* (bilaterally, symmetrical seizures). Includes absences (*petit mal*), characterized by brief, abrupt loss of consciousness associated with synchronous, 3-per-second spike-and-wave pattern in the EEG, usually with symmetrical clonic motor activity (eyelid blinking or jerking of entire body). *Bilateral massive epileptic myclonus,* isolated clonic jerks with brief burst of multiple spikes in EEG; *infantile spasms,* motor spasms with bizarre diffuse changes in the interseizure EEG, ie, hypsarrhythmia and progressive mental retardation; *clonic seizures,* rhythmic clonic contraction of all muscles, loss of consciousness and autonomic manifestations; *tonic seizures,* opisthotonos, loss of consciousness, and autonomic manifestations; *tonic-clonic seizures* (grand mal), characterized by a sequence of maximal tonic spasms of all body musculature followed by synchronous clonic jerking and profound depression of all central functions; *atonic seizures,* loss of postural tone with sagging of the head or falling; *akinetic seizures,* impaired consciousness and complete muscle relaxation, secondary to excessive inhibitory discharge.

The limitation of this type of description is that it is confined to describing individual seizure types and does not take into account a description of the numerous epileptic syndromes which continue to be described. To satisfy the need for a more accurate description of a seizure disorder, the International Classification of Epilepsies and Epileptic Syndromes was proposed to supplement the above classification. An epileptic syndrome is characterized by a variety of signs and symptoms. A particular syndrome will attempt to incorporate a number of items, including type of seizure, etiology, anatomy, precipitating factors, age of onset, severity, chronicity, diurnal and circadian cycling and often prognosis (*Epilepsia* 1989; 30(4):389).

A number of specific childhood epileptic syndromes have been recognized and classified by age. The notable examples include Early Myoclonic Encephalopathy; Lennox-Gastaut Syndrome; Absence Epilepsy Syndromes such as typical absence, juvenile absence and juvenile myoclonic epilepsy; and Progressive Myoclonic Epilepsy. One major advantage of this classification is that it recognizes that a simple partial seizure can progress to a complex partial seizure, and then to a secondary generalized seizure. In so doing, this classification does not require that a seizure be classified into one specific seizure category (*Univ Rep Epilepsy* 1992; 1(1):1).

One approach to the treatment of seizure disorders employs the use of antiepileptic drugs. The many medical therapies of antiquity have been replaced by a rational therapeutic approach which had its origin in the beginning of the 19th century. It has progressed from the use of bromides in 1857 and phenobarbital in 1912 to the modern era marked by introduction of diphenylhydantoin (phenytoin) in 1938. The clinical efficacy of the latter established the fact that chemicals effective in epilepsy need not be hypnotics and stimulated the laboratory search for other effective anticonvulsant agents. As a result, a number of anticonvulsant barbiturates, benzodiazepines, deoxybarbiturates, dipropylacetic acid derivatives, hydantoins, oxazolidinediones, and succinimides have been introduced in the last 50 years. Since 1993, five new drugs have been approved for the adjunctive treatment of partial seizures (ie, felbamate, gabapentin, lamotrigine, topiramate, and tiagabine). Of these five, serious idiosyncratic adverse effects have been identified for felbamate which include aplastic anemia and hepatic failure. As a result of these advances in drug therapy, it generally is stated that 50% of all individuals who have epileptic disorders can be satisfactorily controlled with available drugs and that the incidence of seizures can be reduced in another 25% of epileptic persons.

Knowledge of the underlying causes of various types of seizure disorders is still incomplete. Nevertheless, most experimental models of epilepsy are designed to simulate, either in isolated animal brain tissues (*in vitro*) or in the intact laboratory animal (*in vivo*), various chemical, electrical or overt manifestations of the disorder.

The mechanisms of action of currently marketed anticonvulsant drugs are not understood fully. Although numerous molecular targets exist wherein anticonvulsants may exert an effect, the final common pathway appears to be through modulation of voltage-gated and/or neurotransmitter-gated ion channels. Most of the prototype anticonvulsants presently are thought to exert their primary action by

- Reducing sustained, high-frequency, repetitive firing of action potentials by modulating voltage-dependent sodium channels (phenytoin, carbamazepine, and valproate).
- Enhancing GABA-mediated inhibitory neurotransmission via a receptor-gated chloride channel (benzodiazepines).
- Modulating neurotransmitter release and neuronal bursting through an effect on voltage-gated and receptor-gated calcium channels (ethosuximide, dimethadione, and valproate (*Epilepsia* 1989; 30 (4):389).

In addition, newer anticonvulsant substances still under preclinical development have been found to open potassium channels (*Brain Res* 1989; 495:189; *Eur J Pharmacol* 1989;167:181). Another promising area currently being pursued involves identifying novel therapies that are aimed at either reducing excitation by blocking specific excitatory amino-acid receptors and those aimed at enhancing inhibition by blocking high-affinity uptake of neuronally released GABA. It is anticipated that the increased appreciation of the processes underlying the initiation, propagation, and amelioration of seizure activity will lead to the introduction of mechanistically novel drugs in the not-too-distant future.

No one anticonvulsant drug is effective equally in all types of epilepsy. Hence, antiepileptic therapy must be individualized and drug therapy selected on the basis of seizure type, epileptic syndrome, and patient response. In generalized tonic-clonic seizures (*grand mal*) and simple and complex partial (focal, psychomotor), the drugs of choice are phenytoin, carbamazepine, or valproate; in generalized absence seizures (*petit mal*), ethosuximide and valproate with clonazepam as an alternate; for myoclonic epilepsy, valproate. It should be noted that valproate is effective in all of the above.

Status epilepticus, a succession of tonic-clonic seizures without intervening return of consciousness, requires prompt intravenous medication. The objective of treatment is suppression of the seizures, but all of the drugs used to treat this medical emergency can be lethal if they are given too rapidly or in overdosage. Intravenous diazepam is preferred by many clinicians, but since it is short-acting, maintenance must be started promptly. Some clinicians prefer intravenous phenytoin, especially in patients already on this drug. Phenobarbital is an effective alternative for the management of this disorder. If these drugs do not suppress the continuous seizure activity, general anesthesia may be used as an emergency treatment.

Until the 1970s, antiepileptic polytherapy was the most widely accepted practice in the treatment of epilepsy. Now, monotherapy is considered the superior therapeutic practice in the management of this disorder. This change was encouraged by refinements in diagnosis and the availability of broad-spectrum antiepileptics such as valproic acid. Successful monotherapy involves three basic principles.

- Careful diagnosis of the specific type of seizures
- Accurate selection of the most suitable antiepileptic drug for the patient's seizures
- Appropriate drug use and monitoring

Monotherapy has been shown to improve seizure control and reduce the risk of idiosyncratic reactions, dose-related adverse effects, and complex drug interactions. Monotherapy also encourages better patient compliance and is cost effective.

When should plasma antiepileptic drug levels be measured? Ideally, plasma levels should be measured in the steady state at fixed times in relation to the drug dosage interval. For most drugs that are eliminated according to processes that follow monoexponential kinetics, virtually steady-state plasma levels are achieved after approximately five drug-elimination half-lives. In the case of antiepileptics, the elimination half-lives are so long, in relation to dosage regimens, that the change in plasma level over a dosage interval is likely to be within the experimental error in an individual drug concentration measurement. Therefore, unless the dosage is changed or other drug therapy added, the time of measurement of antiepileptic drug levels does not present too much of a problem.

From a clinical standpoint antiepileptic drug levels should be monitored at the outset of therapy, to see if a satisfactory plasma level has been obtained initially and during the course of therapy. The latter is especially important if the seizures are not controlled, intercurrent illness develops, antiepileptic drug dosage is changed, dosage of any other drug is changed or symptoms occur that appear to be caused by the drug. It also is important to monitor the epileptic patient during pregnancy, since antiepileptic drug levels tend to fall during pregnancy and rise again during puerperium. Such monitoring increases the changes of controlling epilepsy in patients and decreases the risk of their being overdosed in the process.

Behavioral disturbances and cognitive effects have been observed in patients on antiepileptic drug therapy (*Pediatrics* 1985; 76:644). Phenobarbital is associated with hyperactivity, fussiness, lethargy, disobedience, and stubbornness; phenytoin with unsteadiness, involuntary movements, tiredness, and alterations of emotional state; carbamazepine with sleep disorders, agitation, irritability, and emotional liability; clonazepam with irritability, aggression, hyperactivity, disobedience, and antisocial activities; and valproic acid with drowsiness. In addition, some have been shown to induce deficits in neuropsychological tests and impair attention and short-term memory. Physicians and parents should be alert for such behavioral and cognitive changes. Of the newer antiepileptic drugs, topiramate has the greatest liability for inducing cognitive impairment. However, this effect can be markedly reduced or even eliminated by initiating therapy at low doses and after a slow-titration rate.

Antiepileptic drugs may add to or potentiate the action of other CNS depressants, including other anticonvulsants and alcohol. A number of drugs, when concurrently administered with various antiepileptic agents, have been reported to alter the patient's response either to the antiepileptics or the other drugs.

Whether or not the effects are clinically significant cannot be stated categorically; they must be evaluated by careful observation of the individual patients, with monitoring of blood plasma levels of the concurrently administered drugs after which dosage adjustments of the interacting drugs may be necessary. For these reasons patients on antiepileptic medication should not take other drugs, either OTC or prescription, without the knowledge and approval of the physician responsible for their seizure therapy.

As tricyclic antidepressants may precipitate seizures, patients being treated with anticonvulsants should be observed closely for decreased seizure control if tricyclic antidepressant therapy is commenced; if necessary, the dosage of the anticonvulsant should be adjusted.

Children of epileptic mothers who receive anticonvulsant medication during the early months of pregnancy have an increased incidence of birth defects. The risk is approximately 7% as compared with 2% or 3% in the general population. Data are more extensive with respect to phenytoin, phenobarbital, and trimethadione. More recent observations indicate that valproate may be associated with spinal defects in the fetus.

Although systematic or anecdotal reports suggest a possible similar association with the use of all known anticonvulsant drugs, therapeutic abortion should be considered when trimethadione has been used during pregnancy. The great majority of mothers on anticonvulsant medication, however,

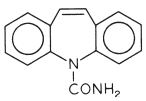
deliver normal infants. It also is important to note that anticonvulsant drugs should not be discontinued in patients in whom the drug is administered to prevent generalized tonic-clonic seizures because of the strong possibility of precipitating status epilepticus with an attendant hypoxia and threat to life. In individual cases where the severity and frequency of the seizure disorder are such that the removal of medication does not pose a serious threat to the patient, discontinuation of the drug may be considered prior to and during pregnancy, although it cannot be said with any confidence that even seizures do not pose some hazard to the developing embryo or fetus. The prescribing physician will wish to weigh the risk/benefit of these considerations in treating or counseling epileptic women of childbearing age.

Antiepileptic agents have several uses in the nonepileptic patient. They have been used to soften the seizures in patients undergoing electroshock therapy, control convulsions occurring in dementia paralytica and tetanus, and lessen muscular rigidity in certain cases of cerebral palsy. Phenytoin administered intravenously has been reported to be effective in suppressing recurrent cardiac arrhythmias. In addition, phenytoin, trimethadione, and phenacemide have been employed for the treatment of disturbed nonepileptic psychotic patients, particularly in catatonic excitement states, and in the management of children who have behavioral disorders. The latter use is especially intriguing and warrants careful clinical study. In addition, a number of the established as well as the newer generation antiepileptic drugs are sometimes employed in the management of bipolar disorder, aggression, and certain forms of chronic pain.

ACETAZOLAMIDE—page 1425.

CARBAMAZEPINE

5*H*-Dibenz[*b, f*]azepine-5-carboxamide; Tegretol



[298-46-4]$C_{15}H_{12}N_2O$ (236.27).

Preparation—5*H*-Dibenz[*b*, *f*]azepine, which may be prepared by thermal deammoniation of 2-(*o*-aminostyryl) aniline hydrochloride, is condensed with carbamoyl chloride by refluxing in an inert solvent in the presence of sodamide. US Pat 2,948,718.

Description—White to off-white powder; melts within a range of 3° between 187 and 193°.

Solubility—Practically insoluble in water; soluble in alcohol or in acetone.

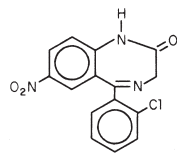
Comments—Considered the drug of choice for complex partial seizures (temporal lobe, psychotomotor). It is preferred by many physicians for generalized tonic-clonic seizures (grand mal) and simple partial (focal, Jacksonian) seizures, particularly in patients who have not responded to other less-toxic anticonvulsants. It sometimes is effective in patients who have mixed seizure patterns which include the above, or other partial or generalized seizures. It is also useful in treatment of pain associated with true trigeminal neuralgia. Beneficial results also have been reported in glossopharyngeal neuralgia. Carbamazepine also has been used with some benefit for the management of acute mania, maintenance therapy of bipolar affective disorder and for the management of aggression and alcohol withdrawal syndrome (*Am Pharm* 1993; NS33(2): 47). The drug has a neutral pK_a; from 60% to 73% of the drug is bound to plasma protein, volume distribution usually is between 0.8 to 1.4L/kg; and half-life varies from 10 to 25 hr in adults and 8.5 to 19 hr in children. Therapeutic plasma levels range from 4 to 12 μg/mL. It should not be used in combination with other drugs; for example, troleandomycin, erythromycin, cimetidine, isoniazid, and propoxyphene inhibit the metabolism of carbamazepine and elevate the plasma concentration of this agent. The steady-state plasma concentration of carbamazepine is reduced by the concomitant administration of felbamate (see brainstem). In contrast, felbamate increases the concentration of carbamazepines-active metabolites. On the other hand, carbamazepine decreases the plasma levels of clonazepam, diazepam, ethosuximide, phenytoin, phenobarbital, primidone, and valproic acid.

To minimize adverse effects, initial dosage and daily increments should be limited to 200 mg. Adverse are encountered in approximately 50% of patients who have serum levels from 8.5 to 10 μg/mL, but few occur with concentrations less than 5 μg/mL. Diplopia, dizziness, drowsiness, and ataxia occur with concentrations greater than 6 μg/mL; nystagmus may occur at serum levels below the therapeutic range. Other reactions include anorexia and nausea, rash (including the Stevens-Johnson syndrome), and edema. More-serious adverse effects include aplastic anemia, agranulocytosis, thrombocytopenia, and transient leukopenia. Therefore, all patients should be subjected to a complete blood test before being placed on the drug; additional blood tests should be done at weekly intervals during the first month of therapy, every 2 weeks during the 2nd and 3rd month, and at monthly intervals as long as the patient is on the drug. Patients should be made aware of the early toxic signs and symptoms of hematological problems such as fever, sore throat, ulcers in the mouth, easy bruising, and petechial or purpuric hemorrhage. If any blood abnormality is observed, the drug should either not be used or stopped if the patient is already on the drug. If adverse effects are of such severity that the drug must be withdrawn, the physician must be aware that abrupt discontinuation of any anticonvulsant drug in a responsive patient may lead to increased seizure incidence or even status epileptics.

The safe use of the drug in pregnancy, lactation and in women of childbearing age has not been established. See the introductory statement.

CLONAZEPAM

2*H*-1,4-Benzodiazepin-2-one, 5-(2-chlorophenyl)-1,3-dihydro-7-nitro-, Klonopin



[1622-61-3] $C_{15}H_{10}ClN_3O_3$ (315.72).

Preparation—*o*-Chlorobenzoyl chloride is reacted with *p*-nitroaniline to form 2-amino-5-nitro-2′-chlorozophenone, and this is condensed with bromacetyl to form 2-bromoacetamido-5-nitro-2′-chlorobenzophenone, then with ammonia to form the corresponding acetamido compound. The acetamido compound is converted to its hydrochloride with anhydrous HCl in methanol, dissolved in boiling methanol, and cyclized to clonazepam with pyridine as the catalyst.

Description—Light-yellow, crystalline powder; faint odor; melts at approximately 238°; pK_a 1.5 (deprotonation of nitrogen in 4 position), 10.5 (deprotonation of nitrogen in 1 position).

Solubility—Practically insoluble in water; slightly soluble in alcohol; sparingly soluble in chloroform; slightly soluble in ether.

Comments—One of the drugs of choice for the management of myoclonic epilepsy. It also is useful alone or as an adjunct in the management of several types of generalized seizures such as absence (petit mal) attacks not responsible to either valproate or ethosuximide, the Lennox–Gestaut syndrome (petit mal variant) and akinetic seizures. Approximately 87% of the drug is bound to plasma protein; volume distribution is 3.2 L/kg and its half-life varies from 19 to 46 hr in adults and from 13 to 33 hr in children. Therapeutic plasma levels range from 20 to 80 ng/mL.

As with diazepam, which it resembles, tolerance develops in approximately 30% of patients as shown by a loss of anticonvulsant activity; adjustment of dosage may reestablish efficacy. Consequently, the drug should be withdrawn gradually during simultaneous substitution of another anticonvulsant. When used in patients who have mixed seizure types, it may increase the incidence or precipitate the onset of generalized tonic-clonic seizures (grand mal). This may require the use of either increased dosage or addition of other antiepileptic medication. Like other benzodiazepines, it is characterized in laboratory animals by its remarkable ability to antagonize pentylenetetrazole-induced seizures; it also has a taming effect in aggressive primates and induces muscle weakness and hypnosis.

Its depressant effects may be potentiated by alcohol, narcotics, barbiturates, nonbarbiturate hypnotics, antianxiety agents, the phenothiazines, thioxanthene, and butyrophenone classes of antipsychotic agents, monoamine oxidase inhibitors and the tricyclic antidepressants, as well as by other anticonvulsant drugs. Phenobarbital or phenytoin may decrease steady-state plasma levels of this drug by enzyme induction. Its concomitant use with valproate may produce absence status.

The most frequently occurring side effects are referable to CNS depression; drowsiness occurs in approximately 50% of patients and ataxia in approximately 30%. Other adverse reactions, listed by systems are

- *Neurological:* abnormal eye movements, aphonia, choreiform movements, coma, diplopia, dysarthria, dysdiadochokinesis, *glassy-eyed*

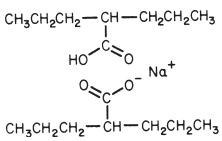
appearance, headache, hemiparesis, hypotonia, nystagmus, respiratory depression, slurred speech, tremor and vertigo.
- *Psychiatric:* confusion, depression, forgetfulness, hallucinations, hysteria, increased libido, insomnia, psychosis, and suicidal tendencies.
- *Respiratory:* chest congestion, rhinorrhea, shortness of breath, and hypersecretion in upper respiratory passages.
- *Cardiovascular:* palpitations.
- *Dermatological:* hair loss, hirsutism, skin rash, and ankle and facial edema.
- *Gastrointestinal:* anorexia, coated tongue, constipation, diarrhea, dry mouth, encopresis, gastritis, hepatomegaly, increased appetite, nausea and sore gums.
- *Genitourinary:* dysuria, enuresis, nocturia, and urinary retention.
- *Musculoskeletal:* muscle weakness and pains.
- *Miscellaneous:* dehydration, general deterioration, fever, lymphadenopathy, and weight loss or gain.
- *Hematopoietic:* anemia, leukopenia, thrombocytopenia, and eosinophilia.

Its safe use in pregnancy, in lactation, and in women of childbearing age has not been established. See the introductory statement.

DIAZEPAM—page 1489.

DIVALPROEX SODIUM

Pentanoic acid, 2-propyl-, sodium salt (2:1); Depakote



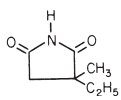
Sodium hydrogen bis(2-propylvalerate)[76584-70-8] $C_{16}H_{31}NaO_4$ (310.41).

Preparation—Neutralization of a solution of valproic acid (page ??) with 1/2 equivalent of sodium hydroxide and the solvent removed yields the product.

Comments—An antiepileptic agent that dissociates in the GI tract into two molecules of valproate. Hence, it has the same indications, adverse reactions, and contraindications as valproate. It differs from valproate, however, in that it is available in tablet form. See *Valproate Sodium,* page 1508.

ETHOSUXIMIDE

2,5-Pyrrolidinedione, 3-ethyl-3-methyl-, Zarontin



2-Ethyl-2-methylsuccinimide [77-67-8]$C_7H_{11}NO_2$ (141.17).

Preparation—Methyl ethyl ketone is condensed with ethyl cyanoacetate to yield ethyl 2-cyano-3-methyl-2-pentenoate, which, in ethanolic solution, adds hydrogen cyanide to form ethyl 2,3-dicyano-3-methylpentanoate. Proton-catalyzed saponification of the latter ester is accompanied by decarboxylation to produce 2-methyl-2-ethylsuccinonitrile. This, on heating with aqueous ammonia, cyclizes to ethosuximide. US Pat 2,993,835.

Description—White to off-white crystalline powder or waxy solid; characteristic odor; stable in light, air and heat at 37°; melts at approximately 50°; pK_a 9.5.

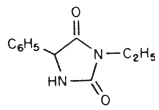
Solubility—Soluble in alcohol or ether; freely soluble in water or chloroform; very slightly soluble in solvent hexane.

Comments—The drug of choice for control of uncomplicated absence seizures (*petit mal*). It suppresses the paroxysmal 3 cycles/s spike and the wave activity associated with lapses of consciousness characteristic of this disorder. It should not be used alone in mixed seizure types since it may increase the incidence of generalized tonic-clonic seizures in such patients. It is absorbed completely after oral administration. The drug is not bound to plasma protein; volume distribution is 0.7 L/kg; its half-life is approximately 60 hr in adults and 30 hr in children. It is excreted slowly in the urine; approximately 20% is excreted unchanged and as much as 50% as the hydroxylated metabolite or its glucuronide or as both. Therapeutic plasma levels range from 40 to 100 μg/mL. Maximal serum concentrations are usually achieved within 5 days after oral surgery is begun.

Adverse effects involve the GI, hemopoietic, nervous, and integumentary systems. GI symptoms occur frequently and include anorexia, nausea, vomiting, cramps, epigastric distress, and abdominal pain; blood disturbances such as leukopenia, agranulocytosis, pancytopenia, aplastic anemia, and eosinophilia have occurred; neurologic and sensory reactions observed include drowsiness, headache, dizziness, euphoria, hyperactivity, and ataxia; skin manifestations include urticaria, Stevens–Johnson syndrome, lupus erythematosus, and pruritic erythematous rashes; other reactions reported include myopia, vaginal bleeding, gum hypertrophy, and hirsutism. Periodic blood and urine tests should be made on patients who are taking the drug. It should be with extreme caution in patients known to have liver or renal disease. Its safe use in pregnancy, lactation, and women of childbearing age has not been established. See the introductory statement.

ETHOTOIN

Imidazolidin-2,4-dione, 3-ethyl-5-phenyl-, Peganone



[86-35-1]$C_{11}H_{12}N_2O_2$ (204.23).

Preparation—From mandelonitrile and urea to form *N*-(α-cyanobenzyl) urea that cyclizes with HCl to yield the imino derivative of hydantoin. Hydrolysis of the imine followed by ethylation with C_2H_5I forms ethotoin. See *Ber,* 1888; 21:2320.

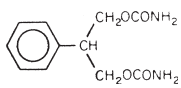
Descriptions—White, crystalline powder; melts about 94°.

Solubility—Sparingly soluble in water; freely soluble in alcohol.

Comments—Used for the management of generalized tonic-clonic and complex partial seizures. With plasma levels less than 8 μg/mL, the half-life ranges from 3 to 9 hr. Therapeutic plasma levels range from 15 to 50 μg/mL. It is contraindicated in patients who have hepatic and hematological disorders. Untoward effects include nausea, vomiting, fatigue, dizziness, headache, diplopia, nystagmus, skin rash, numbness, fever, diarrhea, and chest pain. Ataxia and gum hyperplasia have occurred rarely; lymphadenopathy has been reported in some patients. See the introductory statement on the use of antiepileptics during pregnancy.

FELBAMATE

1, 3-Propanediol, 2-phenyl-, bis(carbamate) ester; Felbatol



[25451-15-4] $C_{11}H_{14}N_2O_4$ (238.24).

Comments—The first new drug approved for the management of epilepsy since 1978. It represents the first new chemical entity to emerge from the National Institute for Neurological Disorders and Stroke's comprehensive Anticonvulsant Drug Development Program. Felbamate is approved for the add-on treatment of partial seizures in patients 14 years of age and older. It also has been approved for the adjunctive therapy of partial and generalized seizures associated with Lennox–Gastaut syndrome, which is characterized by a mixture of several seizure types and usually is uncontrolled with other available anticonvulsants.

In laboratory animal models of epilepsy, it is effective against seizures induced by maximal electroshock, pentylenetetrazol, or picrotoxin. This unique profile is broader than that of phenytoin, carbamazepine, or ethosuximide, and slightly narrower than that of valproate; this suggests that felbamate has the ability to limit the spread of seizure activity and to raise seizure threshold. Its mechanism of action has yet to be clearly established. However, felbamate has been shown to inhibit high-frequency repetitive firing of spinal cord neurons and to modulate the strychnine-insensitive glycine recognition site of the NMDA receptor-ionophore complex. Felbamate is a weak inhibitor at the benzodiazepine recognition site of the $GABA_A$ receptor and the $GABA_A$-receptor. It is devoid of any activity at the MK-801 binding site of the NMDA-preferring receptor.

Felbamate is well absorbed after oral administration. Absorption of the tablet formulation does not appear to be affected by food. Approximately 40% to 50% of the absorbed dose is excreted in the urine unchanged. An additional 40% appears as unidentified metabolites and conjugates. It is approximately 22% to 25% bound to protein and displays a terminal half-life of 20 to 23 hrs. The C_{max} and AUC are proportional to dose after single and multiple doses over a range of 100 to 800 mg and single doses of 1200 to 3600 mg.

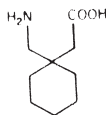
Felbamate is reported to produce only mild dose-related side effects. The most common adverse reactions seen in adults receiving felbamate monotherapy include anorexia, vomiting, insomnia, nausea, and headache. The most commonly reported side effects in pediatric patients during adjunctive therapy are anorexia, vomiting, headache, and somnolence.

Unfortunately, felbamate use has been associated with an increased risk of aplastic anemia and acute hepatic failure. Recognition of this liability has clearly curtailed felbamate use since 1994. Now, both physicians and patients are required to sign an informed consent form prior to felbamate's being dispensed.

The addition of felbamate to other anticonvulsant drugs affects the steady-state plasma concentrations of the coadministered drug. It has been shown in clinical trials to increase the plasma concentration of phenytoin or valproate, decrease the plasma concentration of carbamazepine, and increase the concentration of the active metabolite of carbamazepine. Phenytoin and carbamazepine have been shown to increase the clearance of felbamate and to reduce its steady-state concentration. The available data suggest that there is no significant effect of valproate on the clearance of felbamate. These interactions necessitate careful titration of felbamate and scheduled dosage reduction of concomitant anticonvulsants when it is administered concurrently with other antiseizure drugs. The safety and efficacy of felbamate during pregnancy has not been established and the drug should only be used during pregnancy if clearly needed.

GABAPENTIN

Cyclohexaneacetic acid, 1-(aminomethyl)-, Neurontin



[60142-96-3] $C_9H_{17}NO_2$ (171.24).

Preparation—Cyclohesane-1,1-diacetic acid is monoesterified with methanol and the ester reacted with ethyl chloroformate in the presence of triethylamine followed by reaction with sodium azide to yield the 1-isocyanatomethyl derivative of the monoester. This latter compound is converted to the 1-(aminomethyl) product and the lactam, through the cyclization of the ester and the free amine. The mixture is refluxed with dilute HCl to give the product. US Pat 4,024,175 (1977).

Description—White crystals melting about 164°–167°; HCl melts about 70° · pK_{A1} 3.68; pK_{A2} 10.7.

Solubility—Greater than 100 mg/mL in water at pH 7.4.

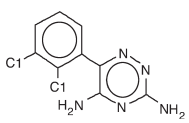
Comments—Approved as adjunctive therapy for the management of partial seizures in adults. Although the precise mechanism of action of gabapentin remains unknown, several molecular mechanisms have been proposed. These include an ability to limit sustained repetitive firing of action potentials with prolonged exposure. This effect suggests an action at the voltage-sensitive sodium channel. Furthermore, gabapentin has been found to increase brain GABA levels in epilepsy patients. Last, gabapentin may modify neurotransmitter release through an interaction with the a2d auxiliary subunit of the voltage-sensitive calcium channel.

Side effects are fairly mild but may include dizziness and aggressiveness at higher therapeutic doses. In some patients, gabapentin may produce significant weight gain. Gabapentin is not significantly metabolized in humans; nor does it induce liver enzymes. Gabapentin, which is excreted unchanged by the kidneys, is the only new antiepileptic drug to be introduced into the US market since 1993. As such, it displays minimal potential for drug–drug interactions. One major disadvantage of gabapentin is its short half-life (approximately 4–6 hrs), which necessitates multiple daily dosing (3–4 times a day).

Gabapentin has been endorsed as an effective drug for the management of neuropathic pain. However, its use for this indication is currently relegated as off-label.

LAMOTRIGINE

1,2,4-Triazine-3,5-diamine, 6-(2,3-dichlorophenyl)-, Lamictal



[84057-84-1] $C_9H_7Cl_2N_5$ (256.09).

Preparation—Reaction of 2,3-dichlorobenzoyl chloride with cyanide ion forms the benzoylcyanide derivative that is then treated with aminoguanidine to form a Schiff base through loss of water between the carbonyl group and the one primary amine function of the guanidine. Ring closure by addition of the lone free primary amino group remaining on the guanidine moiety to the nitrile function is accomplished by base catalysis and yields the product. US Pat 4,602,017 (1986).

Description—White crystals melting about 217°.

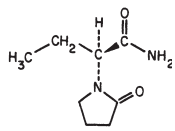
Comments—Approved for the adjunctive management of partial seizures in adults. In addition, anecdotal evidence suggests that lamotrigine is effective against a broad spectrum of seizure disorders, including generalized absence seizures. In addition to its anticonvulsant effects, lamotrigine appears to be effective in the management of bipolar disorder; however, this use is currently unapproved by the FDA. Lamotrigine, like phenytoin and carbamazepine, appears to exert its anticonvulsant effect through its ability to inhibit voltage-sensitive sodium channels in a voltage- and use-dependent manner.

Lamotrigine use does not affect the metabolism of other antiepileptic drugs; however, the metabolism of lamotrigine can be modified by the addition of other drugs. This latter effect is particularly problematic when lamotrigine is administered in conjunction with valproic acid.

Lamotrigine is generally well tolerated in both normal and epilepsy patients. However, the incidence of a severe life-threatening rash with lamotrigine use had led the FDA to issue a *black box* warning in 1997. There appears to be a greater risk in children (1:100) as opposed to adults (1:1000). The risk of rash is lower with slower titration rates. Patients should be counseled to contact their physician at the first sign of rash. The incidence of rash appears to be greater with concomitant use of valproic acid. This is most likely related to the ability of valproic acid to increase lamotrigine plasma levels by modification of the metabolism of lamotrigine. For example, the half-life of lamotrigine is increased from 24 to 59 hrs by concomitant administration of valproic acid.

LEVETIRACETAM

1- Pyrrolidineacetamide, (*S*)-α-ethyl-2-oxo-, Keppra



[102767-28-2] $C_8H_{14}N_2O_2$ (170.21).

Preparation—Butyrolactam and 2-oxobutyric acid are condensed by dehydration using refluxing toluene with a Dean-Stark trap to form 2- (2-oxopyrrolidino)-2-butenoic acid (*Z* to *E* ratio - 80:1). Recrystallization from acetone improves the *Z* to *E* ratio to 149:1. The unsaturated acid is converted to the acyl chloride with PCl_5 then to the amide with dry NH_3. Asymmetric hydrogenation of the unsaturation using Rh-(Et,Et)DUPHOS catalyst is 97% stereoselective and yields primarily the *S*- product. US Pat 4,997,955(1991) and US Pat 6,713,635(2004).

Description—White to off white powder from acetone, with a bitter taste; melts about 119°.

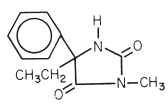
Solubility—In (g/100 mL) of solvent: water(104), $CHCl_3$ (65.3), methanol(53.6), ethanol(16.5), acetonitrile(5.7); practically insoluble in hexane.

Comments—The precise mechanism(s) by which levetiracetam exerts its antiepileptic effect is unknown and does not appear to derive from any interaction with known mechanisms involved in inhibitory and excitatory neurotransmission. The antiepileptic activity of levetiracetam was assessed in a number of animal models of epileptic seizures. Levetiracetam did not inhibit single seizures induced by maximal stimulation with electrical current of different chemoconvulsants and showed only minimal activity in submaximal stimulation and in threshold tests. Protection was observed, however, against secondarily generalized activity from focal seizures induced by pilocarpine and kainic acid, two chemoconvulsants that induce seizures that mimic some features of human complex partial seizures with secondary generalization.

MEPHENYTOIN—see RPS-20, page 1425.

METHSUXIMIDE

2,5-Pyrrolidinedione, 1,3-dimethyl-3-phenyl-, Celontin



N,2-Dimethyl-2-phenylsuccinimide [77-41-8]$C_{12}H_{12}NO_2$ (203.24).

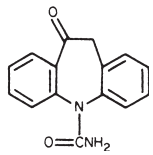
Preparation—2-Methyl-2-phenylsuccinic acid is dissolved in excess 40% methylamine. The water and excess urine are distilled off, and the residue of the di(methylamine) salt of the acid is pyrolyzed at 250° until no more distillate is formed. The residue of crude methsuximide may be purified by vacuum ditilation. US Pat 2,643,257.

Description—White to grayish white, crystalline powder; odorless or not more than a slight odor; melts about 53°.

Comments—Similar in spectrum to *Ethosuximide* (ie, absence seizures). It does not worsen or increase generalized tonic-clonic seizures.

OXCARBAZEPINE

5*H*-Dibenz[*b,f*]azepine-5-carboxamide, 10,11-dihydro-10-oxo-, Trileptal



[28721-07-5] $C_{15}H_{12}N_2O_2$ (252.27).

Preparation—10-Methoxy-5*H*-dibenz[*b,f*]azepine is treated with phosgene to form the 5-carbonyl chloride which is converted to the amide with ammonia, then refluxed with 2*N* HCl to yield the 10-oxo-10,11-dihydro derivative which is oxcarbazepine. US Pat 3,642,775(1972).

Description—White to faint orange crystals from ethanol, melting about 215°.

Solubility—Slightly soluble in chloroform, methylene chloride, acetone or methanol; practically insoluble in ethanol, ether or water.

Comments—The pharmacological activity of oxcarbazepine is primarily exerted through the 10-monohydroxy metabolite (MHD) of oxcarbazepine. The precise mechanism by which oxcarbazepine and MHD exert their antiseizure effect is unknown; however, in vitro electrophysiological studies indicate that they produce blockade of voltage-sensitive sodium channels, resulting in stabilization of hyperexcited neural membranes, inhibition of repetitive neuronal firing, and diminution of propagation of synaptic impulses. These actions are thought to be important in the prevention of seizure spread in the intact brain. In addition, increased potassium conductance and modulation of high-voltage activated calcium channels may contribute to the anticonvulsant effects of the drug. No significant interactions of oxcarbazepine or MHD with brain neurotransmitter or modulator receptor sites have been demonstrated.

PARAMETHADIONE—see RPS-20, page 1426.
PHENACEMIDE—see RPS-20, page 1426.
PHENSUXIMIDE—see RPS-20, page 1426.

PHENYTOIN

2,4-Imidazolidinedione, 5,5-diphenyl-, Diphenylhydantoin; Dilantin

5,5-Diphenylhydantoin [57-41-0] $C_{15}H_{12}N_20_2$ (252.27). See *Phenytoin Sodium* for the formula.

Preparation—Phenytoin sodium, prepared as described below yields the base on acidification of its aqueous solution.

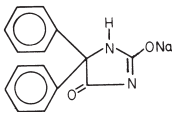
Description—White powder, odorless; melts about 295°.

Solubility—Practically insoluble in water; slightly soluble in cold alcohol, chloroform, or ether.

Comments—See *Phenytoin Sodium.*

PHENYTOIN SODIUM

2,4-Imidazolidinedione, 5,5-diphenyl-, monosodium salt; Diphenylhydantoin Sodium Salt; Diphenylhydantoin Sodium; Soluble Phenytoin; Dilantin Sodium



5,5-Diphenylhydantoin sodium salt [630-93-3] $C_{15}H_{11}N_2NaO_2$ (274.25).

Preparation—By treating benzaldehyde with a solution of sodium cyanide, 2 mol of benzaldehyde are condensed (benzoin condensation) into 1 mol of benzoin, which is oxidized to benzil with nitric acid or cupric sulfate. The benzil is then heated with urea and in the presence of sodium ethoxide or isopropoxide, forming phenytoin sodium.

Description—White, odorless powder; somewhat hygroscopic and on exposure to air, gradually absorbs carbon dioxide with the liberation of the base. pK_a 8.32.

Comments—One of the drugs of choice for the management of generalized tonic-clonic (grand mal) seizures, complex partial (temporal lobe; psychomotor) seizures, and simple partial (focal, Jacksonian) seizures. It is not recommended for the management of pure absence (petit mal) epilepsy. Parenterally, it is used for the control of status epilepticus of the generalized tonic-clonic (grand mal) type and in the management of seizures occurring during neurosurgery. Intravenous phenytoin sodium may be useful in the treatment of paroxysmal atrial tachycardia, ventricular tachycardia, and digitalis-induced cardiac arrhythmias. Oral phenytoin sodium also may afford benefit in the treatment of behavioral disorders and, in large doses, the management of trigeminal neuralgia. It is much less effective in the latter than carbamazepine. Approximately 87% to 93% of the drug is bound to plasma protein, volume distribution ranges from 0.5 to 0.8 L/kg, and half-life is approximately 22 hrs in adults and 18 to 22 hrs in children. Therapeutic plasma levels range from 10 to 20 μg/mL in adults and 5 to 20 μg/mL in children. Toxic levels range from 30 to 50 μg/mL, and lethal levels are approximately 100 μg/mL.

It acts on the motor cortex where it stabilizes the neuronal membrane and inhibits the spread of the seizure discharge. Present evidence suggests that it limits sustained high-frequency repetitive firing by blocking Na^+-channels in a use- and frequency-dependent manner. It also enhances calcium binding to phospholipids in neuronal membranes. These effects result in a more stable membrane configuration.

These observations are in harmony with the fact that its most easily demonstrated properties are its ability to limit the development of maximal seizure activity and to reduce the spread of the seizure process from the active focus. Both features are undoubtedly related to its clinical usefulness.

There are two distinct forms of Phenytoin Sodium Capsules: the rapid-release type (Prompt Phenytoin Sodium Capsules) and the slow-dissolution type (Extended Phenytoin Sodium Capsules). The former have a dissolution rate of not less than 85% in 30 min and are used for 3- or 4-times/day dosing, whereas the latter has a slow dissolution rate of 15% to 35% in 30 min, 45% to 65% in 1 hr, and not less than 85% in 2 hr and may be used for once/day dosing. Studies comparing doses of 100 mg three times a day of Prompt Phenytoin Sodium Capsules with a single, daily dose of 300 mg of Extended Phenytoin Sodium Capsules (Dilantin Kapseals, *Parke-Davis*) indicate that absorption, peak plasma levels, biological half-life, difference between peak and minimum values, and urinary recovery are equivalent. *Because of the differences in dissolution rates among various brands, physicians should be cautioned to keep patients on one manufacturer's product.*

Its metabolism may be altered significantly by concomitant use of other drugs. Drugs that increase the serum levels include chloramphenicol, dicumarol, tolbutamide, isoniazid, phenylbutazone, acute alcohol intake, salicylates, chlordiazepoxide, phenothiazines, felbamate, diazepam, estrogens, ethosuximide, halothane, methylphenidate, sulfonamides, cimetidine, and trazodone. Drugs that *decrease* the serum levels include carbamazepine, chronic alcohol abuse, reserpine, and preparations containing calcium. Drugs that *either increase or decrease* the serum levels include phenobarbital, valproic acid, and valproate sodium.

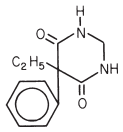
This is a fairly safe anticonvulsant, although many adverse effects have been observed. Nystagmus may appear with serum concentrations of 8 to 20 μg/mL and is nearly always present at higher levels. At concentrations greater than 30 μg/mL, ataxia and dysarthria commonly occur. Gingival hyperplasia and hirsutism are often intolerable, particularly in the young. A morbilliform rash may occur, usually in the first 10 days of treatment, and it rarely progresses to exfoliate dermatitis or the Stevens-Johnson syndrome; the drug should be stopped if a rash appears. There also are reports of peripheral neuropathy, a lupus erythematous syndrome, hepatitis, lymphadenopathy, megaloblastic anemia and rickets, and osteomalacia because of interference with vitamin D metabolism. Serum folic acid and vitamin K levels also may be depressed, and bleeding disorders have been reported in infants born to mothers taking the drug. Overdosage causes an acute cerebellar syndrome, delirium, and rarely, coma.

It is contraindicated in patients who have a history of sensitivity to hydantoins. Abrupt withdrawal of this medication may precipitate status epilepticus; when the dosage needs to be reduced or when substitution of another antiepileptic appears desirable, such alteration in therapy should be done gradually. Recent reports suggest an association between the use of anticonvulsant drugs by women who have epilepsy and an increased incidence of birth defects in children born to these

women. The prescribing physician should weigh the benefit and risk potential of antiepileptic agents when treating or counseling epileptic women of childbearing age. See the introductory statement.

PRIMIDONE

4,6-(1*H*,5*H*)-Pyrimidinedione, 5-ethyldihydro-5-phenyl-, Mysoline



[125-33-7] $C_{12}H_{14}N_2O_2$ (218.25).

Preparation—A solution of ethylphenylmalonamide (I) in a large molecular excess of formamide (II) is refluxed for 2 hr. The cyclization may be viewed as being brought about by a Cannizzaro type of disproportionation of II followed by a deammoniation and a dehydration between I and the highly reactive methanolamine resulting from the disproportionation.

Description—White, odorless; crystalline powder; slightly bitter taste; melts about 281°.

Solubility—1 g in 2000 mL water or 200 mL alcohol; slightly soluble in most organic solvents.

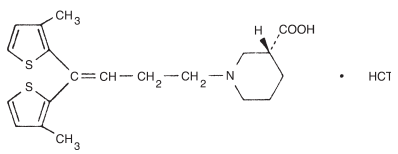
Comments—Either alone or in combination with other antiepileptics, used as alternate therapy in the control of generalized tonic-clonic seizures (grand mal), complex partial seizures (temporal lobe; psychomotor), and focal epileptic seizures. It is metabolized to phenylethylmalonamide (PEMA) and phenobarbital. Phenobarbital formation ranges from 15% to 25%. The plasma half-life of PEMA is 24 to 48 hr, whereas that of phenobarbital is 48 to 120 hr. Both substances tend to accumulate during chronic medication.

PEMA is an active antiepileptic but is less potent and less toxic than phenobarbital. From 0% to 30% of this drug is bound to plasma protein, volume distribution averages 0.6 L/kg and plasma half-life in adults range from 9 hr in combination therapy to 15 hr in monotherapy; in children, half-life varies from 6 to 8 hr. Therapeutic plasma concentrations range from 6 to 12 μg/mL for this drug and from 15 to 45 μg/mL for pheobarbital. Few interactions with other drugs have been reported, but those for phenobarbital also apply. The ratio of phenobarbital to this unmetabolized drug in serum is significantly higher in epileptic patients treated with a combination of this drug and phenytoin than in patients on this drug alone. It decreases the prothrombin response to dicumarol and warfarin. Also, concurrent treatment with valproate increases the plasma level of phenobarbital in patients on this drug.

The most frequent side effects include ataxia and vertigo; these tend to disappear with continued or reduced therapy. Occasionally, nausea, anorexia, vomiting, fatigue, irritability, emotional disturbances, diplopia, nystagmus, drowsiness, and morbilliform rashes occur. Megaloblastic anemia may occur as a rare idiosyncrasy; this anemia responds to folic acid, 15 mg a day, without the medicine's being discontinued.

TIAGABINE HYDROCHLORIDE

3-Piperidinecarboxylic acid, 1-[4,4-(bis-(3-methyl-2-thienyl)-3-butenyl]-, hydrochloride; Gabitril



[145821-59-6] $C_{20}H_{25}NO_2S_2.HCl$ (412.02).

Preparation—Cyclopropyl magnesium bromide and 2,2′-dithienyl ketone yield an oil that is treated with aqueous HBr to yield 4,4′-bis(2-thienyl)-1-bromobutene-3, which is refluxed with ethyl nipecotate and potassium carbonate in acetone and purified by column chromatography to form tiagabine methyl ester. The ester is saponified with alcoholic base to yield the acid which is converted to the hydrochloride. US Pat 5,010,090 (1991); *J Med Chem* 1993; 36:1776.

Description—Off-white crystals melting about 192° (decompn); base melts about 64°. pK_{a1} 3.3; pK_{a2} 9.4.

Solubility—Approximatley 30 mg/mL in water; insol in hydrocarbon solvents.

Comments—Approved for the adjunctive treatment of partial seizures in adults. Tiagabine was introduced into the US market in 1997 and was derived from a mechanistic-based drug discovery program that targeted the GABA-uptake carrier in the CNS. By selectively blocking GABA reuptake into both neurons and glial, tiagabine enhances GABA-mediated neurotransmission within the CNS. It is through this effect that tiagabine is thought to exert its anticonvulsant action.

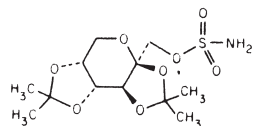
Tiagabine is highly protein bound and extensively metabolized by the hepatic P-450 drug-metabolizing enzyme system. Both of these properties of tiagabine are likely to contribute to numerous drug–drug interaction and should be considered when tiagabine is added to the therapeutic regimen of patients who have epilepsy. The short half-life (7–9 hr) of tiagabine may necessitate multiple daily dosing (three to four times a day). Tiagabine does not appear to induce the metabolism of other antiepileptic drugs. For example, in patients being concomitantly treated with an enzyme-inducing antiepileptic drug (eg, phenytoin, carbamazepine, and phenobarbital), the half-life of tiagabine can be reduced from 7–9 to 4–7 hr.

Because an increase in seizure frequency has been reported after the discontinuation of therapy, the dosage should be reduced slowly.

The most commonly reported side effects associated with tiagabine use include somnolence, dizziness, and cognitive effects.

TOPIRAMATE

β-D-Fructopyranose, 2,3:4,5-bis-*O*-(1-methylethylidene)-, sulfamate; Topamax



[97240-79-4] $C_{12}H_{21}NO_8S$ (339.37).

Preparation—Fructose and acetone form the diacetonide (acetal) with the hydroxyl group in the C-1 position remaining free. The hydroxyl hydrogen is treated with NaH to form the alkoxide and then with sulfamoyl chloride to yield the product. US Pat 4,513,006 (1985); *J Med Chem,* 1987; 30: 880.

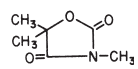
Description—White crystals that melt about 126°.

Comments—Topiramate was approved for the adjunctive treatment of partial seizures in 1996. Anecdotal reports suggest that the anticonvulsant profile of topiramate also includes efficacy against generalized seizures, including absence and myoclonic seizures. Topiramate has been reported to possess multiple mechanisms of action. For example, it appears to inhibit voltage-sensitive sodium channels, block non–NMDA-evoked glutamate currents, enhance GABA-evoked chloride currents, and inhibit carbonic anhydrase.

In clinical trials, the most troublesome adverse effects associated with topiramate use were CNS related. These included somnolence, fatigue, and certain troublesome cognitive side effects such as psychomotor slowing and word-finding difficulties. The cognitive effects associated with topiramate use were later shown to be lessened when the titration rate was decreased. There appears to be greater incidence of renal stones associated with topiramate use; however, this effect is reduced by maintenance of adequate hydration and probably is related to the carbonic inhibitory properties of topiramate. Last, a significant percentage of patients experienced weight loss.

TRIMETHADIONE

2,4-Oxazolidinedione, 3,5,5,-trimethyl-,Tridione



[127-48-0] $C_6H_9N0_3$ (143.14).

Preparation—By a series of reaction beginning with acetone and involving the following steps: conversion with HCN to acetone cyanhydrin, hydrolysis, and esterification with alcohol to ethyl dimethylglycolae, condensation with urea to 5,5-dimethyloxazolidine-2,4-dione and methylation with dimethyl sulfate to trimethadione.

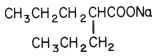
Description—White, crystalline granules; slight, camphor-like odor; melts about 46°.

Solubility—Soluble in water; freely soluble in alcohol, ether, or chloroform.

Comments—An alternate for the treatment of refractory generalized absence seizures. A frequent and troublesome adverse effect is hemeralopia.

VALPROATE SODIUM

Pentanoic acid, 2-propyl-, sodium salt; Depakene



Sodium 2-propylpentanoate; sodium 2-propylvalerate [1069-66-5] $C_8H_{15}NaO_2$ (166.20).

Preparation—Valproic acid may be synthesized from 4-heptanol by successive conversions to 4-bromoheptane with HBr, to 4-cyanoheptane with HCN and to 2-proplpentanoic (valproic) acid by alkaline hydrolysis of the 4-cyanoheptane.

Description—White, crystalline powder; odorless; saline taste; pK_a 4.95.

Solubility—Soluble in water or in alcohol.

Comments—It is unique both in its experimental and clinical profile of anticonvulsant action. It is effective in nontoxic doses against tonic seizures induced by either electroshock or strychnine, as well as against minimal-threshold seizures induced by either pentylenetetrazol, bicuculline, or picrotoxin. Clinical efficacy confirms this broad spectrum of antiepileptic activity. It is one of the drugs of choice in the management of simple absence seizures. Similarly, atypical absence seizures and myoclonic epilepsies respond well and, since there has never been an entirely satisfactory drug for these types of childhood epilepsy, this is an important advance. It also is effective in generalized tonic-clonic. In some refractory patients it has been used effectively in the management of partial seizures with complex symptomatology (psychomotor or temporal lobe seizures) or myoclonic and akinetic seizures. Like carbamazepine, valproate has been used with some success in the management of bipolar disorder and in the treatment of aggression or violence (*Am Pharm* 1993; NS33 (2): 47).

Approximately 90% to 95% is bound to plasma protein, volume distribution ranges from 0.1 to 0.5 L/kg (mean 0.2 L/kg), and half-life varies from 6 to 17 hr in adults and 4 to 14 hr in children. Therapeutic plasma levels range from 50 to 100 μg/mL; levels greater than 100 μg/mL are potentially toxic. More than ten metabolites have been identified in human blood and urine. Only 0.5% to 20% is excreted unchanged in the urine. Of the several metabolites, only 2-propyl-2-pentenoic acid (2–2-en-VPA) has been shown to accumulate in the brain. The 2–VPA metabolite is approximately 1.3 times more potent than the parent drug and may contribute significantly to the anticonvulsant effect of chronically administered valproate.

The precise mechanism of its anticonvulsant action is still unknown. It has been postulated that its administration inhibits GABA-transaminase and thus increases the concentration of cerebral GABA. However, other saturated straight-chain fatty acids (propionic, butyric, and pentanoic) that lack anticonvulsant properties are more potent inhibitors of GABA-transaminase than is valproic acid. It has been also reported that there is a strong correlation between the anticonvulsant potency of valproate and other branched-chain fatty acids and their ability to reduce the concentration of cerebral aspartate.

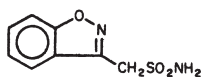
It may decrease binding to serum proteins or block hepatic metabolism of phenobarbital. Administration of the drug to patients in a steady state while on phenobarbital (or primidone, which is metabolized to phenobarbital) can increase the plasma levels of phenobarbital from 35% to 200%, causing excessive somnolence. Present evidence indicates this is caused by an immediate decrease in the rate of elimination of phenobarbital. This drug interacts unpredictably with phenytoin; it has been associated not only with lowered serum phenytoin levels and increased seizure frequency, but also with increased free phenytoin levels and phenytoin toxicity. Valproate also has been found to increase the clearness of felbamate significantly and to reduce its plasma concentration correspondingly. Conversely, phenobarbital, primidone, phenytoin, and other drugs may induce enzymes that metabolize this drug and reduce its half-life. In contrast, felbamate has been shown to increase the plasma concentration of valproate when the two drugs are administered concurrently.

More than 40 cases of fatal hepatic failure have been reported in patients on this therapy. The risk of hepatic failure is drastically less in patients on monotherapy (*ca* 1/37,000) compared with those on polytherapy (*ca* 1/6500). Moreover, the incidence is much greater in children younger than 2 yr and who are on polytherapy (monotherapy, 1.42/10,000; polytherapy, *ca* 1/500).

The most commonly observed side effects in patients on monotherapy (valproate) are weight gain (11%), sedation (10%), nausea (6%), headache (3%), tremor (3%), hair loss (1%), and dizziness (1%). Other rarely observed untoward effects include skin rashes, enuresis, insomnia, anxiety, fatigue, and paresthesias. Teratogenic effects have been reported in animals. Moreover, its use by women who have epilepsy during the first trimester (3 months) of pregnancy has been reported by the Centers for Disease Control, United States Public Health Service (USPHS), to be associated with increased risk (1.2%) of spina bifida in their infants (*MMWR* 1982; 31). Although the majority of women who have epilepsy and who are taking this drug will give birth to nonaffected babies, it is recommended that they consider prenatal testing for neural tube defects.

ZONISAMIDE

2-Benzisoxazole-3-methanesulfonamide; Zonegran



[68291-97-4] $C_8H_8O_3S$ (212.23).

Preparation—A mixture of 3-bromoethyl-1,2-benzisoxazole with sodium sulfite in methanol/water is stirred at 50° for 4 hrs, vacuum distilled and crystallized to yield

3-(1,2-benzisoxazolyl)methanesulfonic acid, converted to the acid chloride with $POCl_3$ and then treated with ammonia to form the amide which is zonisamide. *J Med Chem* 1974; 22:180.

Description—White needles from ethyl acetate melting about 163°; pK_a 12.2.

Solubility—Sparingly soluble in water (0.8 mg/mL), chloroform or hexane; soluble in methanol, ethanol, ethyl acetate or acetic acid.

Comments—The precise mechanism through which zonisamide exerts its antiseizure activity is unknown. It demonstrated anticonvulsive activity in several experimental models. The effects may be produced through action at sodium and calcium channels. In vitro pharmacological studies suggest that zonisamide blocks sodium channels and reduces voltage-dependent, transient inward currents (T-type Ca^{2+} currents, consequently stabilizing neuronal membranes and suppressing neuronal hypersynchronization. In vitro binding studies have demonstrated that zonisamide binds to the GABA/benzodiazepine receptor ionophore complex in an allosteric fashion which does not produce changes in chloride flux. Other in vitro studies have demonstrated that zonisamide suppresses synaptically driven electrical activity without affecting postsynaptic GABA or glutamate responses or neuronal or glial uptake of $[^3H]$-GABA. Thus, zonisamide does not appear to potentiate the synaptic activity of GABA. In vivo microdialysis studies demonstrated that zonisamide facilitates both dopaminergic and serotonergic neurotransmission. Zonisamide also has weak carbonic anhydrase inhibiting activity, but this pharmacologic effect is not thought to be a major contributing factor in the antiseizure activity of zonisamide.

OTHER ANTIEPILEPTIC DRUGS

Several other established antiepileptic drugs are available for management of seizure disorders; however, these have been relegated to late-stage treatment primarily because of the development of less toxic and more efficacious agents.

CHAPTER 82

Psychopharmacologic Agents

Joel Shuster, PharmD, BCPP

Many conditions that afflict people are related to mental function. Some of these are transient with symptoms that are moderately uncomfortable but that are not incapacitating. Often, these symptoms are responses to events in our lives, but in some cases there is not an identified precipitating cause. On the other end of the spectrum are severe mental disorders that prevent an individual from functioning appropriately in society. It is estimated that approximately 20% of people will suffer sometime during their life from a mental condition that affects their ability to function with normal efficiency. Although some of the conditions related to mental function can be resolved through counseling and nondrug therapy, management of others requires pharmacological intervention. Although pharmacotherapy does not cure mental disorders in the same sense that antibiotics cure infectious diseases, the available drugs do control most symptomatic manifestations and behavioral problems, facilitate the patient's tendency toward remission, and improve his or her capacity for social, occupational, and familial adjustment.

Drugs that alter the mind and behavior have attracted the attention of man since the beginning of recorded history. Without the benefits of science and medicine, mankind has sought emotional comfort or novelty through the use of drugs for a venerable period of time. To cite two examples, alcohol and opium have been used for this purpose since antiquity. However, it was the inadvertent discovery of the unusual psychotomimetic properties of lysergic acid diethylamide in 1943 and the subsequent demonstration that these effects were similar to those induced by mescaline that marked the beginning of psychopharmacology. Additional interest in this new science was created with the introduction of chlorpromazine for the empiric treatment of mental disorders. The successful clinical use of this agent not only led to the realization that behavior can be studied objectively in laboratory animals but also resulted in the discovery of a host of new drugs that stimulate, sedate, or otherwise change behavior.

More than 1500 compounds classified as psychoactive or psychotropic drugs have been described, and approximately 20% of all prescriptions written in the US are for medications intended to alter mental processes and behavior. Those agents employed in the treatment of psychotic illnesses and depressant disorders are the focus of this chapter. Antianxiety drugs are not discussed here because the spectrum of effects of these agents includes sedative-hypnotic actions. These drugs are covered in Chapter 80 with the conventional sedative and hypnotic agents.

ANTIPSYCHOTIC AGENTS

One of the major uses of the antipsychotic drugs is treatment of schizophrenia. Manifestations of the disease include two types of symptoms: positive and negative. Positive symptoms tend to be exaggerations of normal functioning. For example, a distortion of perceptions may be manifest as an auditory hallucination, and a distortion of thought process may be manifest as delusions. Negative symptoms involve loss of normal functioning and include blunted affect, asociality, reduced ability to relate to others, lack of motivation and drive, narrowing of ideation, and poverty of speech. The spectrum of symptoms varies widely between afflicted persons. To aid in diagnosis and treatment, psychiatrists have classified schizophrenia into various types: disorganized (hebephrenic), paranoid, catatonic, undifferentiated, and residual. Symptoms usually manifest during the early years of adulthood, and approximately 1% of people are affected across all cultures and ethnic groups. Oftentimes, the symptoms are debilitating relative to the ability to function in society. The illness is chronic, and less than 20% of patients recover fully from a single episode of psychosis. Rates of employment among people who have schizophrenia rarely exceed 20%, and schizophrenia accounts for approximately 10% of all suicides.

The cause of schizophrenia is unknown, although it is almost certainly the result of flawed neurochemistry. The fact that major symptoms do not manifest until young adulthood suggests that abnormalities in brain development might be involved. Imaging techniques show alterations in patterns of activity in a variety of brain regions, with the prefrontal cortex and the thalamic areas being particularly affected. Because an underlying morphological or structural deficit likely is the cause of schizophrenia, pharmacotherapy cannot cure but can only hope to normalize the balance between various brain circuits.

The first successful pharmacological treatment of schizophrenia was introduced in 1952 with the advent of the use of chlorpromazine (which was originally marketed as a new antihistamine) to treat psychotic illness. Over the years, other antipsychotic drugs with similar efficacy have become available. These drugs are now grouped together under the title "typical" antipsychotics or neuroleptics. They are mainly effective against the positive symptoms of schizophrenia and often cause both short- and long-term movement disorders. Thus, in schizophrenic patients, the typical antipsychotics reduce or eliminate the positive symptoms of hallucinations, delusions, and thought disorganization in a majority of patients. The widespread use of these moderately safe compounds has greatly reduced the number of chronic patients residing in public mental hospitals, shortened the duration of hospitalization for acute episodes, and shifted the focus of treatment of mental disorders from institutional care to community-based ambulatory treatment programs. This clinical efficacy is accompanied by significant adverse effects. Depending on the agent used, adverse effects include sedation, dry mouth, sexual dysfunction, akathisia, bradykinesia, rigidity, and sometimes tardive dyskinesia. Although these drugs are a major advance in the treatment of

schizophrenia, as many as 33% of those treated do not respond to therapy, and as many as 40% of those whose symptoms are alleviated by drug therapy discontinue their medication because of adverse effects. In addition to their use to treat schizophrenia, several of these drugs are also effective antiemetic and antinausea agents.

A new type of antipsychotic medication became available with the introduction of clozapine in 1990. After its success, other medications with similar clinical profiles have been developed. These *atypical* or *novel* antipsychotic agents are effective against both the positive and the negative symptoms of schizophrenia and seldom cause movement disorders. Although the atypical agents are more expensive than the typical drugs, recent evaluations of the total costs of treatment show that the atypical drugs are economically superior. This is because the increased efficacy and higher rate of compliance result in fewer hospital admissions and other emergency interventions.

Although pharmacotherapy normalizes many aspects of thinking and emotion, the antipsychotic drugs alone do not allow most patients to function fully in society. Intensive training in social and job-related skills is often required.

The mechanism of action of the antipsychotic agents is complex, and many details remain to be established. However, evaluation of properties shared by effective antipsychotic agents provides clues to their mechanism of action. All of the typical antipsychotic agents block postsynaptic dopaminergic receptors (in the basal ganglia, hypothalamus, limbic system, brainstem, and medulla) and act as competitive antagonists of dopamine centrally and peripherally. The clinically observed potency of the drugs in this class is directly correlated with the affinity for binding to the D2 family of dopaminergic receptors. This observation coupled with the fact that drugs increase dopaminergic activity (levodopa, amphetamine, cocaine, apomorphine) aggravate schizophrenia or produce it in some nonpsychotic individuals led to the hypothesis that excessive activity of dopaminergic systems may be a cause of schizophrenia. However, the dopamine hypothesis of schizophrenia does not account for all of the pathology of the disease. For example, many patients do not respond to treatment with drugs that block dopaminergic receptors, the degree of dopaminergic receptor block shown in positron emission tomography (PET) scans does not correlate with clinical responses, and the atypical agents show little dopaminergic receptor antagonism. Some of the atypical antipsychotic drugs have a high affinity for the serotonin 5-HT2 receptor, making it likely that a combination of interference with some subset of dopaminergic and serotonergic neurotransmission is required for clinical effectiveness. However, the situation may be even more complex, as some studies suggest a correlation of clinical efficacy with α-adrenoceptor blocking potency.

Relating to mechanism of action of antipsychotic drugs, schizophrenic patients often require weeks of treatment to attain therapeutic benefit, and many patients experience an increase in clinical efficacy with long duration of treatment. These and other observations suggest that it is the response of brain systems to long-term effects of the antipsychotic drugs that accounts for their therapeutic effectiveness. One experimental model supporting this concept shows that chronic treatment of animals with any active antipsychotic drug results eventually in the loss of ability (called depolarization block) of these drugs to increase ventral-tegmental area dopaminergic cell firing.

The effective antipsychotic drugs vary significantly in selectivity and potency for the three known subtypes of receptor within the dopaminergic D2 family, and all, to some degree, are competitive antagonists of other neurotransmitters. This variation in activity at a variety of receptors accounts for differences in adverse effects of the drugs. The extrapyramidal toxicity appears to be related to antagonism of the dopaminergic D2 family of receptors in the caudate-putamen brain areas. The extrapyramidal toxicity also is related inversely to the central anticholinergic properties of the drugs. Many of the various peripheral effects, including the cardiovascular effects of some of these agents, are attributable to anticholinergic properties and peripheral α-adrenergic blockade.

A drug with significantly different action is lithium carbonate. Its major use is in the treatment of bipolar (manic depressant) affective disorder. In addition, it is sometimes used as an adjunct with other antipsychotic drugs in the treatment of a variety of psychotic disorders.

Typical Antipsychotics

Several different typical antipsychotics are available. Structurally, they can be divided into five groups: phenothiazines, thioxanthenes, butyrophenones, dihydroindolone derivatives, and dibenzoxazepines. The numerous phenothiazines and related congeners have qualitatively similar clinical efficacy, but their potency and side effects are influenced significantly by their chemical structure. For example, congeners with an aliphatic side chain, such as chlorpromazine, are fairly low in potency and high in sedative effects. Conversely, congeners with a piperazine constituent are more potent and have less sedative effects but more prominent extrapyramidal toxicity. A thioxanthene is a phenothiazine in which the nitrogen at the 10 position is replaced by a carbon atom with a double bond to the side chain. Thus phenothiazines and thioxanthenes are closely related chemically and have many biological effects in common.

Experimentally, the phenothiazines suppress or abolish conditioned avoidance responses in trained rats, prevent morphine-induced mania in cats, and reduce the toxicity of amphetamine in aggregated mice. Many of these compounds also suppress vomiting from apomorphine, irradiation, and motion sickness but, in laboratory animals, do not affect the emesis from morphine, veratrum alkaloids, digitalis, and copper sulfate. In addition, they decrease spontaneous motor activity, lower electroshock seizure threshold, and cause skeletal muscle relaxation. The phenothiazines also exhibit weak adrenolytic, hypotensive, antispasmodic, hypothermic, and antihistaminic effects.

In general, the typical antipsychotic drugs are highly lipid soluble and protein bound (92–99%). Consequently, they tend to have large volumes of distribution (usually more than 7 L/kg); bioavailability after oral administration is variable and low (25–35%). Plasma half-life tends to be short, ranging from 10 to 20 hr, but the duration of the antipsychotic action is much longer. Metabolites may be found in the urine weeks after the last dose of drug. This suggests that large amounts of the drug are sequestered in the tissues.

The phenothiazines are indicated for the management of psychotic disorders, control of nausea and vomiting, control of manic depression, relief of intractable hiccups and acute intermittent porphyria, and as an adjunct in the treatment of tetanus. The thioxanthenes (chlorprothixene and thiothixene) are used for the management of the symptoms of psychotic disorders. Butyrophenone (haloperidol) also is employed for the management of symptoms of psychoses, including schizophrenia, the manic phase of manic depressive illness or psychotic reactions associated with organic brain syndrome or mental retardation. Dibenzoxazepine (loxapine succinate) is indicated for the management of schizophrenia.

Many of the contraindications to the use of these drugs are similar. For example, they are contraindicated in comatose patients who have received large amounts of central nervous system (CNS)-depressant drugs (alcohol, barbiturates, narcotics, etc.), in patients who have Parkinson's disease and in patients who have a known history of hypersensitivity to these agents. It is not known whether there is cross sensitivity between the phenothiazines and the thioxanthenes, but this possibility should be kept in mind.

The safe use of many of these agents during pregnancy has not been established with respect to possible adverse effects on fetal development. The safe use of thioxanthenes in children

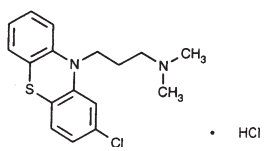
has not been established. It is recommended that these agents not be used in children younger than 12 years of age. Geriatric or debilitated patients usually require a lower initial dose of these agents; the dose then is increased as needed and tolerated. Both phenothiazines and thioxanthenes have an anticholinergic effect; hence, they should be used with extreme caution in patients who have a history of glaucoma or prostatic hypertrophy. All agents in these groups tend to impair the mental and the physical ability required for operating a motor vehicle or complex hazardous machinery. Patients should be warned accordingly.

Phenothiazines and thioxanthenes may significantly affect the actions of other drugs (see Chapter 102 for additional information concerning specific drug interactions). They may increase, prolong, or intensify the action of CNS depressants (anesthetics, alcohol, barbiturates, narcotics, etc); therefore, appropriate adjustments in dosage of narcotics and barbiturates should be made when such agents are to be administered concomitantly. These agents also lower convulsive threshold; hence, they should be used with extreme caution in patients who have a history of epilepsy. They also should be cautiously used in patients receiving atropine and related drugs because of the possible additive anticholinergic effect. Because these agents have antiemetic properties, they may mask signs of drug overdosage and obscure symptoms of brain tumor or intestinal obstruction. These agents also should be used with extreme caution in patients who have cardiovascular disease, chronic respiratory disorders, impaired liver function, or a history of gastric ulcer; the aggravation of a preexisting ulcer has been reported.

Although not all the adverse reactions listed herein have occurred after administration of either phenothiazines or thioxanthenes, the chemical and the pharmacological similarities of the two groups suggest that all of the known side effects and toxicities associated with these agents should be kept in mind. CNS effects include drowsiness, particularly during the first or the second week of therapy; and extrapyramidal reactions (EPS or EPRs) may be fairly common. Extrapyramidal effects are usually of three types: (1) Parkinsonian-like syndrome, (2) dystonia and dyskinesia, including torticollis, tics, and other involuntary muscle movements, and (3) akathisia, shown by restlessness and an urge to move about. Hyperreflexia has been reported in the newborn when phenothiazines are used during pregnancy. *Grand mal* seizures, catatonic-like states, psychotic symptoms, and cerebral edema also have been reported. Cardiovascular effects include postural hypotension, tachycardia, bradycardia, faintness, dizziness, and cardiac arrest. Hematological effects, including agranulocytosis, eosinophilia, leukopenia, hemolytic anemia, thrombocytopenic purpura, and pancytopenia have been reported. Liver jaundice has been observed but is usually reversible. Allergic reactions of urticaria or dermatitis also occur in approximately 5% of patients. Photosensitivity, resulting in an increased propensity to sunburn, occurs in some patients. Antipsychotic drugs exert endocrine effects: these agents block ovulation, suppress the menstrual cycle, and cause infertility and pseudopregnancy, lactation, and breast engorgement in females. They reduce urinary levels of gonadotropins, estrogens, and progestins. In males, gynecomastia or changes in libido have been observed. Cholesterol levels also are increased significantly. Other reported reactions include dry mouth, nasal congestion, constipation, myosis, mydriasis, urinary retention, increased appetite, weight gain, peripheral edema, fever, and suppression of cough reflex. The last may enhance the potential of aspiration or asphyxia. Prolonged therapy with antipsychotic drugs at high doses may cause pigmentation of exposed skin areas; ocular changes consisting of lenticular and corneal opacities, epithelial keratopathies, and pigmentary retinopathy; impaired vision (Table 82-1). See also Chapter 61.

CHLORPROMAZINE HYDROCHLORIDE

10*H*-Phenothiazine-10-propanamine, 2-chloro-*N*,*N*-dimethyl-, monohydrochloride; Thorazine Hydrochloride



2-Chloro-10-[3-(dimethylamino)propyl]phenothiazine monohydrochloride [69-09-0] $C_{17}H_{19}ClN_2S \cdot HCl$ (355.32)

Table 82-1. Table of Typical Antipsychotic Drugs

GENERIC NAME	TRADE NAME	COMMENTS
Chlorpromazine	Thorazine	A phenothiazine with low clinical potency, medium extrapyramidal toxicity, high sedative effect, and high hypotensive action
Droperidol	Inapsine	A butyrophenone with low clinical potency, medium extrapyramidal toxicity, and high sedative effect—only approved for sedation and treatment of nausea and vomiting; high hypotensive action
Fluphenazine	Permitil, Prolixin	A phenothiazine with high clinical potency, high extrapyramidal toxicity, low sedative effect, and low hypotensive action
Haloperidol	Haldol	A butyrophenone with high clinical potency, high extrapyramidal toxicity, low low sedative effect, and low hypotensive action
Loxapine	Loxitane	A dibenzoxazepine with medium clinical potency, medium extrapyramidal toxicity, low sedative effect, and low hypotensive action
Mesoridazine	Serentil	A phenothiazine with medium clinical potency, low extrapyramidal toxicity, high sedative effect, and medium hypotensive action
Molindone	Moban	A dihydroindolone with medium clinical potency, low extrapyramidal toxicity, medium sedative effect, and no hypotensive action
Perphenazine	Trilafon	A phenothiazine with high clinical potency, medium extrapyramidal toxicity, medium sedative effect, and low hypotensive action
Pimozide	Orap	High clinical potency, high extrapyramidal toxicity, low sedative effect, and low hypotensive action
Prochlorperazine	Compazine	A phenothiazine used for treatment of nausea and vomiting
Promazine	Sparine	A phenothiazine with low clinical potency, medium extrapyramidal toxicity, high sedative effect, and high hypotensive action
Thioridazine	Mellaril	A phenothiazine with low clinical potency, low extrapyramidal toxicity, high sedative effect medium, and hypotensive action
Thiothixene	Navane	A thioxanthene with high clinical potency, medium extrapyramidal toxicity, medium sedative effect, and medium hypotensive action
Trifluoperazine	Stelazine	A phenothiazine with high clinical potency, high extrapyramidal toxicity, low sedative effect, and low hypotensive action

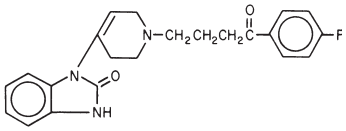
Description—White or slightly creamy white, odorless, crystalline powder; darkens on prolonged exposure to light; melts about 196°.

Solubility—1 g in 1 mL of water, 1.5 mL of alcohol, or 1.5 mL of chloroform; insoluble in ether or in benzene.

Comments—A *phenothiazine* with low clinical potency, medium extrapyramidal toxicity, high sedative effect, and high hypotensive action.

DROPERIDOL

2*H*-Benzimidazol-2-one, 1-[1-[4-(4-fluorophenyl)-4-oxobutyl]-1,2,3,6-tetrahydro-4-pyridinyl-1,3-dihydro-, Inapsine



1-[1-[3-(*p*-Flurorbenzoyl)propyl]-1,2,3,6-tetrahydro-4-pyridyl]]-2- benzimidazolinone [548-73-2] $C_{22}H_{22}FN_3O_2$ (379.43).

Preparation—4-Chloro-4′-flurobutyrophenone is prepared from γ-butyrolactone and reacted with 1-(1,2,3,6-tetrahydro-4-pyridyl)-2-benzimidazolinone in the presence of a suitable condensing agent. US Pat 3,161,645.

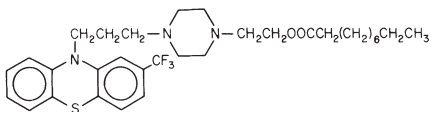
Description—White to light tan, amorphous or microcrystalline powder; odorless and tasteless (*Note:* Because this compound is extremely potent, no taste test is recommended.); sensitive to light, air, and heat; hygroscopic; melts at approximately 146° after being dried in a vacuum at 70° for 4 hr, pK_a 7.6.

Solubility—1 g in 10,000 mL of water, 140 mL of alcohol, 4 mL of chloroform, or 500 mL of ether.

Comments—A *butyrophenone* with low clinical potency, medium extrapyramidal toxicity, high sedative effect, and high hypotensive action. It is approved only for sedation and treatment of nausea and vomiting.

FLUPHENAZINE DECANOATE

1-Piperazineethanol, 4-[3-[2-(trifluoromethyl)-10*H*-phenothizin-10-yl]-propyl]-, decanoate (ester); Prolixin Decanoate



[30909-31-4] $C_{32}H_{44}F_3N_3O_2S$ (591.77).

Preparation—Fluphenazine (see *Fluphenazine Hydrochloride*) is esterified with decanoyl chloride in the presence of pyridine. US Pats 3,194,733 and 3,394,131.

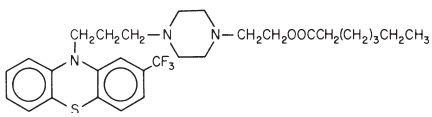
Description—Pale yellow to yellowish orange viscous liquid with a characteristic odor; light sensitive; melts about 31°.

Solubility—Insoluble in water; soluble in alcohol, acetone, benzene, or ether.

Comments—See *Fluphenazine Hydrochloride*.

FLUPHENAZINE ENANTHATE

Prolixin Enanthate



[2746-81-8] $C_{29}H_{38}F_3N_3O_2S$ (549.69).

Preparation—Fluphenazine is esterified through reaction with enanthoyl chloride in the presence of pyridine. For the preparation of fluphenazine, see *Fluphenazine Hydrochloride*. US Pat 3,058,979.

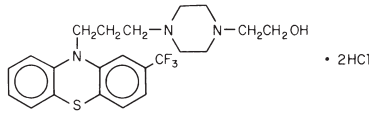
Description—Pale yellow to yellow-orange, clear to slightly turbid, viscous liquid with a characteristic odor; *not recommended to be tasted*; unstable in strong light, but stable in air at room temperature.

Solubility—1 g in <1 mL of alcohol, <1 mL of chloroform, or 2 mL of ether; insoluble in water.

Comments—See *Fluphenazine Hydrochloride*.

FLUPHENAZINE HYDROCHLORIDE

Permitil; Prolixin



[146-56-5] $C_{22}H_{26}F_3N_3OS.2HCl$ (510.44).

Preparation—Fluphenazine may be prepared by condensing 2-(trifluoromethyl)-10-(3-chloropropyl)phenothiazine with 1-piperazineethanol in toluene with the aid of sodamide. Reaction of the purified base with a double molar quantity of hydrogen chloride yields the official salt. The starting phenothiazine compound may be prepared by heating 3-(trifluoromethyl)diphenylamine with sulfur and condensing the resulting 2-(trifluoromethyl)phenothiazine with 1-bromo-3-chloropropane. US Pat 3,058,979.

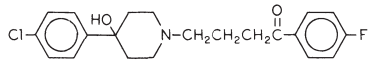
Description—White or nearly white, odorless, crystalline powder; melts within a 5° range above 225°.

Solubility—1 g in 1.4 mL of water or 6.7 mL of alcohol; slightly soluble in chloroform; practically insoluble in ether.

Comments—A *phenothiazine* with high clinical potency and extrapyramidal toxicity, low sedative effect, and low hypotensive action.

HALOPERIDOL

1-Butanone, 4-[2-(chlorophenyl)-4-hydroxy-1-piperidinyl]-1-(4-fluorophenyl)-, Haldol



4-[4-(p-Chlorophenyl)-4-hydroxypiperidino-4′-fluorobutyrophenone [52-86-8]

$C_{21}H_{23}ClFNO2$ (375.87).

Preparation—4-(*p*-Chlorophenyl)-4-piperidinol is condensed with 4-chloro-4′-fluorobutyrophenone in a toluene solution. The haloperidol thus formed is isolated and recrystallized from a solvent such as diisopropyl ether. The starting substituted piperidinol may be prepared from *p*-chloro-α-methylstyrene by the method described by Schmidle and Mansfield (*J Am Chem Soc* 1956; 78:1702).

Description—White to faintly yellowish, odorless, amorphous, or microcrystalline powder; light sensitive and nonhygroscopic; saturated solution is neutral to litmus; melts about 150°; pK_a 8.2 to 8.3.

Solubility—1 g in >10,000 mL of water, 60 mL of alcohol, 15 mL of chloroform, or 200 mL of ether.

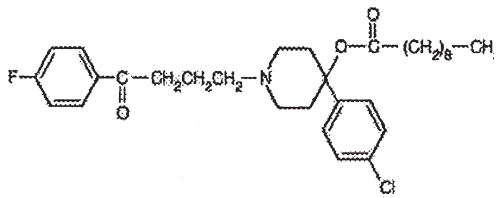
Comments—A butyrophenone that is indicated for the management of symptoms of psychotic disorders and the control of tics and vocal utterances of Tourette's Disorder. Haloperidol is effective for the treatment of severe behavior problems in children who have combative, explosive hyperexcitability. Haloperidol is effective in the short-term treatment of hyperactive children who show excessive motor activity with accompanying conduct disorders consisting of some or all of the following symptoms: impulsivity, difficulty sustaining attention, aggressiveness, mood lability, and poor frustration tolerance. Haloperidol should be reserved for use in managing behavioral problems of children who fail to respond to psychotherapy or other medications.

The bioavailability of haloperidol has been reported to be approximately 60% via the oral route. The half-life of elimination ranges from 12 to 38 hr after oral administration of the drug but is reduced to 10 to 19 hr after intravenous administration. Therapeutic plasma levels usually range from 3 to 10 ng/mL, but some patients require significantly higher levels before adequate antipsychotic effects are observed.

Haloperidol is contraindicated in severe toxic CNS depression or comatose states from any cause and in individuals who are hypersensitive to this drug or who have Parkinson's disease. Potential adverse effects from the use of haloperidol include tardive dyskinesia (potentially irreversible, involuntary, dyskinetic movements—rhythmical involuntary movements of tongue, face, mouth or jaw), neuroleptic malignant syndrome (hyperpyrexia, muscle rigidity, altered mental status, autonomic instability), extrapyramidal symptoms (Parkinson-like symptoms, akathisia, dystonia). Care should be exercised when antihypertensive agents, general anesthetics, hypnotics, alcohol, analgesics, and other CNS depressants are used concomitantly with this drug, because it may potentiate their actions. There is considerable variation from patient to patient in the amount of medication required for treatment.

HALOPERIDOL DECANOATE

Decanoic acid, 4-(4-chlorophenyl)-1-[4-(4-fluorophenyl)-4-oxo-butyl]-4-piperidinyl ester; Haldol Decanoate



[74050-97-8] $C_{31}H_{41}ClFNO_3$ (530.13).

Preparation—The alcohol moiety of the ester is obtained by the condensation of 4-(*p*-chloro-4′-fluorobutyrophenone and 4-(*p*-chlorophenyl)-4-piperidinol in toluene solution which is esterified with decanoyl chloride. *JACS* 1956; 78:1702 and Eur Pat Appl 260,070.

Description—Log P 3.98.

Solubility—Almost insoluble in water (0.01 mg/mL), but is soluble in most organic solvents. The IM injection is in sesame oil.

LITHIUM CARBONATE

Carbonic acid, dilithium salt; Eskalith

Dilithium carbonate [554-13-2] Li_2CO_3 (73.89).

Preparation—Lithium chloride is metathesized with sodium carbonate in aqueous solution.

Description—White, light, granular powder; melts about 62°.

Solubility—1 g in 78 mL of cold water or 140 mL of boiling water; slightly soluble in alcohol; dissolved by dilute acids.

Comments—Indicated for the treatment of *bipolar disorder*, both for treatment of acute mania and for prophylaxis against recurrences. Other psychiatric conditions that may be benefited include recurrent severe depressions without manic episodes, schizoaffective psychosis, episodic alcoholism, periodic antisocial behavior, and periodic schizophrenic illness. Bipolar affective (manic depressive) is a very serious psychiatric disorder characterized by wide fluctuations in mood. Patients who have cyclic attacks of mania have many symptoms that resemble paranoid schizophrenia (grandiosity, bellicosity, paranoid thoughts, and over activity). These are interspersed with periods of fairly normal mood and behavior and periods of depression. Maintenance therapy with lithium prevents or diminishes the intensity of subsequent episodes of mania in those manic-depressive patients. The overall success rate for achieving remission from the manic phase of bipolar disorder is reported to be 60% to 80%.

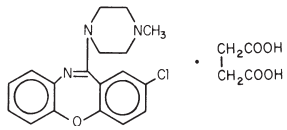
Neither the cause of bipolar disorder nor the mechanism of action of lithium is known. The best-defined pharmacological effect of lithium is alteration of second messenger pathways involving inositol phosphate compounds. Lithium blocks several enzymes involved in recycling of inositol compounds, eventually leading to a depletion of phosphatidylinositol-4,5-bisphosphate, the membrane precursor of inositol-based second messengers and diacylglycerol. Lithium also inhibits second messenger systems involving adenylyl cyclase, alters sodium transport in nerve and muscle cells, and affects a shift toward interneuronal metabolism of catecholamines and serotonin.

Lithium carbonate is completely absorbed 6 to 8 hours after oral administration. Its plasma half-life is approximately 24 hr. It is excreted by the kidneys, and approximately 80% of filtered lithium is reabsorbed by a carrier in the renal tubules. Lithium competes for this carrier with sodium, and therefore sodium depletion decreases renal excretion of lithium, resulting in lithium accumulation. The lithium ion is distributed in total body water but is concentrated in various tissues to different degrees. After a steady state has been reached, approximately 40% is contained in cerebrospinal fluid, and renal clearance is somewhat constant. Serum levels should be maintained between 0.7 and 1.3 mEq/L. Adverse effects are noted at levels higher than 1.5 mEq/L, and serious toxicity is common when concentrations exceed 2.0 mEq/L. Because toxicity develops at serum levels little higher than effective therapeutic levels, frequent monitoring and dosage adjustments are mandatory for successful therapy.

Nausea, vomiting, and diarrhea are presumptive evidence of toxicity and indicate the dose should be reduced. The most common untoward effects are slight tremor and polyuria; these ordinarily do not require a reduction in dosages. CNS effects, such as slurred speech, blurred vision, confusion, and lethargy, require immediate withdrawal of the drug and the administration of sodium chloride (at least 4 g extra a day) to facilitate the excretion of lithium. Adverse cardiovascular effects include arrhythmias and hypotension. Goiter, hypothyroidism, and diabetes insipidus also have been observed. Lithium should not be used in patients who have cardiovascular or renal disease. Lithium must be used with caution during pregnancy as it can cause cardiac and other birth defects. The drug should not be used in children younger than 12 yr.

LOXAPINE SUCCINATE

Dibenz[*b,f*][1,4]oxapine, 2-chloro-11-(4-methyl-1-piperazinyl)-, butanedioate (salt); Loxitane



[27833-64-3] $C_{18}H_{18}ClN_3).C_4H_6O_4$ (445.90).

Preparation—A method of synthesis of loxapine starting with anthone oxime is described in US Pat 3,412,193. Other procedures are summarized in *CA* 1965; 63:11592h.

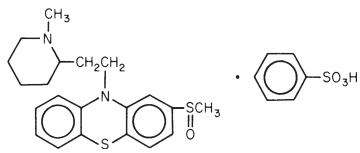
Description—White to off-white, crystalline powder; pK_a 6.6 (loxapine).

Solubility—Slightly soluble in water or alcohol.

Comments—A *dibenzoxazepine* with medium clinical potency and extrapyramidal toxicity, low sedative effect, and low hypotensive action.

MESORIDAZINE BESYLATE

10*H*-Phenothiazine, 10-[2-(1-methyl-2-piperidinyl)ethyl]-2-(methylsulfinyl)-, monobenzenesulfonate; Serentil



[32672-69-8] $C_{21}H_{26}N_2OS_2.C_6H_6O_3S$ (544.74).

Preparation—Nitrophenide [bis(3-nitrophenyl)disulfide)] is converted by a series of reactions into 2-(methylthio)phenothiazine. Oxidation with H_2O_2 yields the corresponding sulfinyl compound that is reacted with 1-methyl-2-(2-chloroethyl)piperidine in the presence of a suitable condensing agent and the mesoridazine thus formed is converted, with benzenesulfonic acid, to the besylate salt. US Pat 3,084,161.

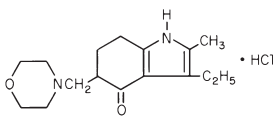
Description—White to pale yellow, crystalline powder with a faint odor; melts about 178°.

Solubility—1 g in 1 mL of water, 11 mL of alcohol, 3 mL of chloroform, or 6300 mL of ether.

Comments—A *phenothiazine* with medium clinical potency, low extrapyramidal toxicity, high sedative effect, and medium hypotensive action.

MOLINDONE HYDROCHLORIDE

4*H*-Indol-4-one, 3-ethyl-1,4,6,7-tetrahydro-2-methyl-5-(4-morpholinylmethyl)-, monohydrochloride; Moban



[15622-68-8] $C_{16}H_{24}N_2O_2.HCl$ (312.84).

Preparation—From 4-(morpholinyl)-1,3-cyclohexanedione and 2-oximino-3-pentanone in acetic acid by refluxing with powdered zinc yields the base that may be converted to the hydrochloride by usual procedures. See Belg Pat 670,798; *CA* 1966; 65,7148f.

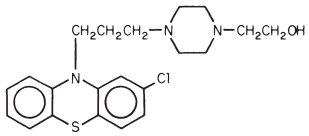
Description—White crystals; melts about 180°.

Solubility—Freely soluble in water or alcohol.

Comments—A *dihydroindolone* with medium clinical potency, low extrapyramidal toxicity, medium sedative effect, and no hypotensive action.

PERPHENAZINE

1-Piperazineethanol, 4-[3-(2-chloro-10*H*-phenothiazin-10-yl)propyl]-, Trilafon



[58-39-9] $C_{21}H_{26}ClN_3OS$ (403.97).

Preparation—A toluene solution of 2-chloro-10-(3-chloropropyl) phenothiazine and 1-piperpazineethanol is refluxed with sodamide and the resulting perphenazine purified by means of vacuum distillation. US Pat 2,766,235.

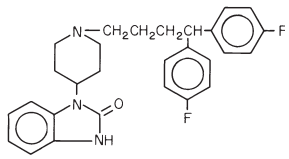
Description—White to creamy white, light-sensitive powder; almost odorless and has a bitter taste; melts about 97°.

Solubility—1 g in 7 mL of alcohol or 13 mL of acetone; practically insoluble in water; freely soluble in chloroform.

Comments—A *phenothiazine* with high clinical potency, medium extrapyramidal toxicity, medium sedative effect, and low hypotensive action.

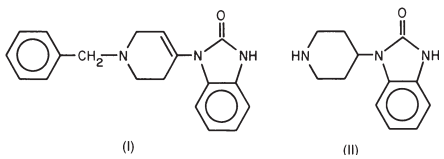
PIMOZIDE

2*H*-Benzimidazol-2-one, 1-[1-[4,4-bis(fluorophenyl)butyl]-4-piperindinyl]-1,3-dihydro-, Orap



[2062-78-4] $C_{28}H_{29}F_2N_3O$ (461.55).

Preparation—The ethyl ester of 1-benzyl-4-oxo-3-piperidinecarboxylic acid and *o*-phenylenediamine are condensed, with the loss of the elements of water and ethanol, to yield I. With hydrogen and Pd catalyst, the benzyl group is removed from I, and the unsaturation is reduced to give II, 1(2*H*)-(4-piperindinyl)benzimidazol-2-one. The other necessary intermediate is formed from a Grignard reaction between *p*-fluoro-phenylmagnesium bromide and ethyl cyclohexylpropanecarboxylate to give 4,4′-difluorophenyl)-4-chloro-1-butene. Catalytic reduction of the 1,1-bis(4-fluorophenyl)-4-chloro-1-butene. Catalytic reduction of the double bond followed by condensation with II in the presence of Na_2CO_3 yields pimozide.



(I) (II)

Description—Crystals; melts about 216°; pK_a, 7.32.

Solubility—Practically soluble in water; 1 g in 140 mL of alcohol, 5 mL of chloroform, or 500 mL of ether; slightly soluble in dilute aqueous acid solution.

Comments—Has high clinical potency, high extrapyramidal toxicity, low sedative effect, and low hypotensive action.

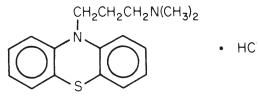
PROCHLORPERAZINE

For the full monograph, see page 1312.

Comments—A *phenothiazine* used for treating nausea and vomiting.

PROMAZINE HYDROCLORIDE

10*H*-Phenothiazine-10-propanamine, *N*,*N*-dimethyl-, monohydrochloride; Sparine; Prozine



10-[3-Dimethylamino)propyl]phenothiazine monohydrochloride [53- 60-1] $C_{17}H_{20}N_2S.HCl$ (320.88).

Preparation—Phenothiazine is dissolved in an inert solvent and condensed with 3-chloro-*N*,*N*-dimethylproplyamine in the presence of sodium hydride to yield promazine. After purification, it is dissolved in an organic solvent and reacted with an equimolar quantity of HCl.

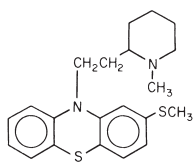
Description—White to slightly yellow, practically odorless, crystalline powder; oxidizes upon prolonged exposure to air and acquires a blue or pink color; melts within a 3° range between 172° and 182°

Solubility—1 g in 3 mL of water; free soluble in chloroform.

Comments—A *phenothiazine* with low clinical potency, medium extrapyramidal toxicity, high sedative effect, and high hypotensive action.

THIORIDAZINE

10*H*-Phenothiazine, 10-[2-(1-methyl-2-piperdinyl)ethyl]-2-(methylthio)-, Mellaril-S



[50-52-2] $C_{21}H_{26}N_2S_2$ (370.57).

Preparation—2-(Methlythio)phenothiazine, which may be prepared by reacting 2-chlorophenothiazine with (methylthio)sodium, is condensed with 2-(1-methyl-1-piperidyl)ethyl chloride with the aid of a dehydrochlorinating agent such as sodamide. US Pat 3,239,514.

Description—Crystals; melts about 73°; pK_a 9.5 (methylamino group).

Solubility—1 g in 6 mL of alcohol; practically insoluble in water.

Comments—See *Thioridazine Hydrochloride.*

THIORIDAZINE HYDROCHLORIDE

10*H*-Phenothiazine, 10-[2-(1-methyl-2-piperdinyl)ethyl]-2-(methylthio)-, Mellaril

[130-61-0] $C_{21}H_{26}N_2S_2 \cdot HCl$ (407.03).

For the structure and preparation of the base, see *Thioridazine*.

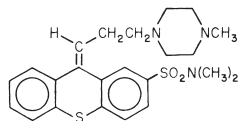
Description—White to slightly yellow, granular powder with a faint odor and a very bitter taste; stable in moderate heat, nonhygroscopic and darkens on exposure to light; melts within a range of 3° between 157° and 163°; pH (1 in 100 solution) between 4.2 and 5.2.

Solubility—1 g in 9 mL of alcohol or in 10 mL of water; freely soluble in chloroform or methanol; slightly soluble in benzene; insoluble in ether.

Comments—A *phenothiazine* with low clinical potency, low extrapyramidal toxicity, high sedative effect, and medium hypotensive action.

THIOTHIXENE

(*Z*)-9*H*-Thioxanthene-2-sulfonamide, *N*,*N*-dimethyl-9-[3-(4-methyl-1-piperazinyl)propylidene]-, Navane



[5591-45-7 and 3313-26-6(*Z*)] $C_{23}H_{29}N_3O_2S_2$ (443.62).

Preparation—2-Chlorobenzoic acid is converted into its 5-dimethylsulfamoyl derivative by successive reaction with chlorosulfonic acid and dimethylamine. The chlorine is then replaced with the

phenylthio group by treatment with benezenethiol in the presence of alkali, and the resulting 2-phenylthio derivative is cyclized with polyphosphoric acid to form *N*, *N*-dimethyl-9-oxothioxanthene-2-sulfonamide. Reaction of this compound with [3-(4-methyl-1-piperidyl)-propylidene]triphenylphosphorane replaces the oxo oxygen with the appropriately substituted propylidene group to yield thiothixene. US Pat number 3,310,553.

Description—White to tan, crystalline powder; practically odorless; very bitter taste; unstable in light; melts about 150° (*cis* or *Z* isomer).

Solubility—Practically insoluble in water; 1 g in 110 mL of anydrous alcohol, 2 mL of chloroform, or 120 mL of ether; slightly soluble in methanol or acetone.

Comments—A *thioxanthene* with high clinical potency, medium extrapyramidal toxicity, medium sedative effect, and medium hypotensive action.

THIOTHIXENE HYDROCHLORIDE

(*Z*)-9*H*-Thioxanthene-2-sulfonamide, *N*,*N*-dimethyl-9-[3[3-(4-methyl-1-piperazinyl)propylidene]-, dihydrochloride, dihydrate, Navane Hydrochloride

[22189-31-7 and 49746-09-0(*Z*)] $C_{23}H_{29}N_3O_2S_2.2HCl.2H_2O$ (552.57); *anhydrous* [49746-04-5] (516.54). For the structure of the base, see *Thiothixene*.

Preparation—*Thiothixene* is reacted with aqueous HCl, and the hydrochloride is crystallized there from.

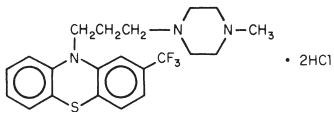
Description—White, or nearly white, crystalline powder; slight odor; affected by light.

Solubility—1 g in 8 mL of water, 270 mL of anhydrous alcohol, or 280 mL of chloroform; practically insoluble in benzene, acetone, or ether.

Comments—See *Thiothixene*.

TRIFLUOPERAZINE HYDROCHLORIDE

10*H*-Phenothiazine, 10-[3-(4-methyl-1-piperazinyl)propyl]-2-(trifluoromethyl)-, dihydrochloride; Stelazine



[440-17-5] $C_{21}H_{24}F_3N_3S.2HCl$ (480.42).

Preparation—By the process described for *Trifluprom azine Hydrochloride*, except that 1-(3-chloropropyl)-4-methylpiperazine is used as the condensing amine in place of (3-chloropropyl)dimethylamine. US Pat 2,921,069.

Description—White to pale yellow, crystalline powder; practically odorless; bitter taste; melts about 242° with decomposition. pK_a 8.1 (piperazine).

Solubility—1 g in 3.5 mL of water, 11 mL of alcohol, or 100 mL of chloroform; insoluble in ether; protect aqueous solutions from light.

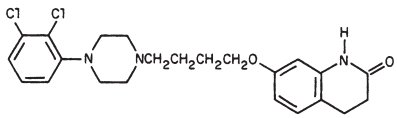
Comments—A *phenothiazine* with high clinical potency, high extrapyramidal toxicity, low sedative effect, and low hypotensive action.

Atypical or Novel Antipsychotics

Antipsychotics are classified as atypical based on three important clinical observations. Atypical antipsychotic agents are effective against the negative symptoms of schizophrenia (as well as the positive symptoms), often effective in patients refractory to treatment with typical antipsychotics, and seldom induce motor-related adverse effects. These agents have significant activity on central serotonergic tracts, especially $5HT_2$ receptors. Other serotonin receptors may be affected. Clozapine, the first of these agents to appear, was approved for use in the US in 1989. The major limitation to use of clozapine has been that it induces agranulocytosis in approximately 1% of those receiving it. Thus, patients being treated with clozapine need to have routine blood analyses performed. Other agents have become available that do not induce agranulocytosis and that appear to have an efficacy similar to that of clozapine. They also have a reduced adverse effect spectrum compared with typical antipsychotics. Treatment with all of these atypical or novel antipsychotic agents is associated with improved efficacy and better rates of compliance than is treatment with the typical antipsychotics. The absence of motor-related adverse effects appears to correlate with lower affinity for the D2-specific receptor within the family of dopaminergic D2 receptors. Risperidone, and to a lesser degree olanzapine, do elicit motor disorders at higher doses; hence these do not fit into the class of atypical antipsychotics as completely as the other agents. The newest agents, quetiapine, ziprasidone, and aripiprazole have very low EPS potential. Many of these agents have a propensity to cause lipid abnormalities and/or glucose intolerance (or the development of diabetes mellitus) (Table 82-2).

ARIPIPRAZOLE

2(1*H*)-Quinolinone, 7-[4-[4-(2,3-dichlorophenyl)-1-piperazinyl]butoxy]-3,4-dihydro-, Abilify



[129722-12-9] $C_{23}H_{27}Cl_2N_3O_2$ (448.39).

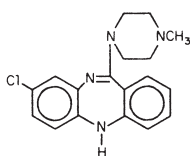
Preparation—7-Hydroxy-3,4-dihydro-2(1*H*)-quinolinone is refluxed with 1,4-dibromobutane plus K_2CO_3 in DMF to form the 7-(4-bromobutoxy) derivative which iscondensed with 1-(3,4-dichlorophenyl)piperazine to yield the product. *J Med Chem* 1998; 41:658. Also US Pat 5,006,528 (1991).

Description—White, crystalline powder from ethanol melting about 139°.

Comments—Classed as an *atypical antipsychotic*, this agent may have a unique mechanism of action in that it may modulate dopamine activity in a different manner than other atypical antipsychotic agents. Adverse effects include gastrointestinal effects and hypotension early in therapy, but the drug is very well tolerated. Weight gain is less than with most other agents.

CLOZAPINE

5*H*-Dibenzo[*b*,*e*][1,4]diazepine, 8-chloro-11-(4-methyl-1-piperazinyl)-, Clozaril



[5786-21-0] $C_{18}H_{19}ClN_4$ (326.83).

Table 82-2. Atypical Antipsychotic Drugs

GENERIC NAME	TRADE NAME	COMMENTS
Aripiprazole	Abilify	Adverse effects are moderate and include sedation and orthostatic hypotension.
Clozapine	Clozaril	Adverse effects include sedation, orthostatic hypotension, weight gain. Must monitor WBC count for possible agranulocytosis. Monitor blood sugar.
Olanzapine	Zyprexa	Adverse effects include orthostatic hypotension, sedation, weight gain and mild antimuscarinic effects. Higher doses may produce extrapyramidal effects. Monitor blood sugar.
Quetiapine	Seroquel	Adverse effects include dizziness, somnolence, agitation, and weight gain
Risperidone	Risperdal	Adverse effects include nasal congestion, orthostatic hypotension, insomnia, and possible extrapyramidal symptoms. Monitor blood sugar.
Ziprasidone	Geodon	Adverse effects are moderate and include sedation and hypotension.

Preparation—Clozapine may be prepared by means of intramolecular condensation of 2-amino-4-chlorodiphenylamine-2′-carboxylic acid 4-methylpiperazide in the presence of phosphorous oxychloride and *N*, *N*-dimethylformamide. The desired product is extracted with benzene, extracted from the organic solution with dilute acetic acid, and then precipitated by addition of concentrated ammonia water. Neth Pat 293,201.

Description—Yellow, tasteless crystals; melts between 183° and 184°.

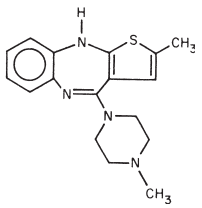
Solubility—Slightly soluble in water; soluble in ether.

Comments—A *dibenzodiazepine-derived atypical antipsychotic* indicated for the management of symptoms of schizophrenia. In several trials, clozapine has been effective in patients refractory to treatment with typical antipsychotic drugs. In addition to its antipsychotic actions, clozapine may also help reduce aggressive and hostile behavior and the risk of suicide. It has also been used in the treatment of L-dopa–induced psychotic symptoms in patients who have Parkinson's disease.

Although clozapine does not produce the extrapyramidal symptoms and other motor irregularities associated with typical antipsychotic drugs, it does have significant adverse effects. These include drowsiness, headaches, disturbed sleep, dizziness, fever (5%), changes in blood pressure (less than 10%), tachycardia (25%), cardiac arrhythmias, dry mouth or hypersalivation (50–80%), nasal congestion, pallor, bowel irregularities, nausea or vomiting, respiratory irregularities and rash (2%), and seizures (3-5%). The most serious problem is agranulocytosis, which occurs in 0.5% to 1.5% of patients taking the drug. More than 95% of incidents of agranulocytosis occur within the first 6 months of therapy. Patients taking clozapine should be monitored closely with weekly white blood cell (WBC) assessments for the first 6 months. After 6 months of therapy the WBC must be measured every 2 weeks. Another adverse effect is a rebound psychosis from discontinuance of drug therapy. May cause weight gain and an increased tendency for glucose intolerance (de novo diabetes mellitus).

OLANZAPINE

10*H*-Thieno[2,3-*b*][1,5]benzodiazepine, 2-methyl-4-(4-methyl-1-piperazinyl)-, Zyprexa



[132539-06-1] $C_{17}H_{20}N_4S$ (312.43).

Preparation—A mixture of sulfur, propanol, DMF, and trimethylamine are heated during the addition of malononitrile to produce 2-amino-5-methylthiophene-3-carbonitrile. Reaction of this compound with 2-fluoronitrobenzene and sodium hydride forms 2-(2-nitroanilino)-5-methylthiophene-3-carbonitrile, which is subsequently treated with anhydrous stannous chloride to close the diazepine ring. The diazepine with 1-methylpiperazine in DMSO yields the product (base).

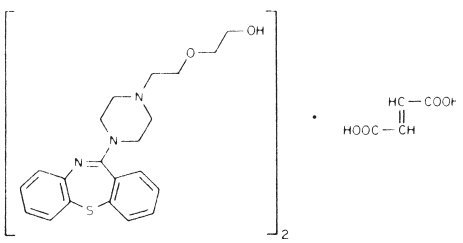
Description—Yellow crystals.

Solubility—Practically insoluble in water.

Comments—An atypical antipsychotic. Its adverse effects include orthostatic hypotension, sedation, and mild antimuscarinic activity. Higher doses may produce extrapyramidal effects. May cause weight gain and an increased tendency for glucose intolerance (de novo diabetes mellitus).

QUETIAPINE FUMARATE

Ethanol, 2-[2-(4-dibenzo[*b*,*f*][1,4[-thizaepin-11-yl-1-piperazinyl)ethoxy]-, (*E*)-2-butanedioate (2:1) salt; Seroquel



[111974-72-2] $(C_{21}H_{25}N_3O_2S_2)_2.C_4H_4O_4$ (833.11).

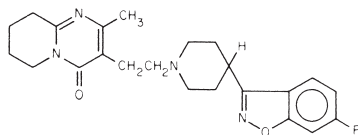
Preparation—The cyclic amide, dibenzo[*b*,*f*][1,4]thiazepin-11-one is converted to the 11-chloro derivative with phosphorus oxychloride. Nucleophilic displacement of the halogen by 2-[2-(piperazin-1yl)ethoxy]ethanol yields the product (base). The salt is prepared by mixing saturated solutions of the base and fumaric acid in ethanol. *Drugs of the Future* 1986; 21:483–489.

Description—White crystals that melt about 129°; base, 172°; HCl, 218°

Comments—An *atypical antipsychotic*. Its adverse effects include dizziness, somnolence, and weight gain.

RISPERIDONE

4*H*-Pyrido[1,2-*a*]pyrimidin-4-one, 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-2-methyl-, Risperdal



[106266-06-2] $C_{23}H_{27}FN_4O_2$ (410.49).

Preparation—A Friedel-Crafs condensation of 1-acetylpiperidone-4-carbonyl chloride and 2,4-difluorobenzene, followed by hydrolysis of the *N*-acetyl group yields 4-(2,4-difluorobenzoyl)piperidone and the benzoyl carbonyl is converted to the oxime. With alkali, the fluorine atom in the 2-position is displaced through ring closure to form the isoxazole moiety. The secondary amine of the piperidine ring is alkylated with 3-(2-chloroethyl)pyrido[1,2-*a*]pyrimidin-4-one to yield the product.

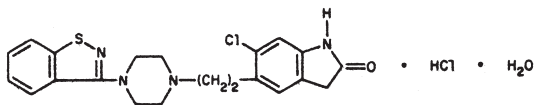
Description—Off-white crystals that melt about 170°.

Solubility—Practically insoluble in water; freely soluble in methylene chloride; soluble in methanol and 0.1 *M* HCl.

Comments—An *atypical antipsychotic* and *neuroleptic*. Its adverse effects include nasal congestion, orthostatic hypotension, insomnia, and possible extrapyramidal symptoms (EPS). Causes more EPS (at higher doses) than other atypical agents. May cause weight gain and an increased tendency for glucose intolerance (de novo diabetes mellitus).

ZIPRASIDONE HYDROCHLORIDE

2*H*-Indol-2-one, 5-[2-[4-(1,2-benzisothiazol-3-yl)-1-piperazin-yl]ethyl]-6-chloro-1,3-dihydro-, monohydrochloride, monohydrate; Geodon, Zeldox



[13898-67-9] $C_{21}H_{21}ClN_4OS.HCl.H_2O$ (467.42).

Preparation—By refluxing 5-(2-chloroethyl)oxindole and *N*-(1, 2-benzisothiazol-3-yl)piperazine with sodium carbonate and sodium iodide in methyl isobutyl ketone, followed by evaporation of the solvent and chromatography on silica gel with 4% methanol in methylene chloride. The salt is formed from the amine by addition of ether saturated with HCl gas. US Pat 4,831,031 (1989).

Description—White to faint pink powder. Hemihydrate melts above 300°.

Comments—An *atypical antipsychotic*, this agent must be given with food twice daily for maximum effect. Adverse effects include somnolence and minor QT_c prolongation. Currently, this is the only atypical antipsychotic available in a parenteral (IM) formulation.

Antidepressants

Antidepressants relieve the symptoms of depressive disorders. Depression is a common ailment, which afflicts approximately 5% to 6% of the population. It estimated that 10% to 15% of people experience depression sometime during their lifetime. The diagnosis of depression excludes behaviors resulting from normal bereavement, physical conditions, and drug use. Depression varies significantly in intensity and in the clinical symptoms manifested. Patients who have depression experience symptoms of depressed mood or loss of interest or pleasure in normal activities. They commonly complain of fatigue, decreased productivity, changes in appetite or weight, insomnia

or somnolence, difficulty concentrating, and anhedonia. For such patients, nearly 75% experience clinically significant improvement with antidepressant drug treatment, and approximately 50% experience complete recovery. Treatment is characterized by a long interval (weeks to months) from the time that the patient begins taking medication to the time that improvement in symptoms occurs.

Many antidepressants are also indicated or used effectively for a variety of psychiatric disorders including generalized anxiety disorder (GAD), post-traumatic stress disorder (PTSD), obsessive-compulsive disorder (OCD), social anxiety disorder, and eating disorders.

Several effective antidepressants are currently available. These drugs vary significantly in chemical and pharmacological properties. One convenient way of characterizing the drugs is to combine the chemical and the pharmacological criteria and group the drugs into four major categories: tricyclic (based on three rings in the chemical structure), selective serotonin reuptake inhibitors (SSRIs) (based on pharmacological action), monoamine oxidase inhibitors (MAOIs) (based on pharmacological effect), and heterocyclics (whatever does not fit into the other three categories).

Generally, when tested in a broad population of patients, all of the antidepressants have equal efficacy. However, the drugs have significantly different spectra of adverse effects. Thus, the choice of drug is often made on the basis of least potential adverse effects. The SSRIs and some of the agents from the heterocyclic group show significantly less incidence of adverse effects than the tricyclic agents or the MAOIs. Clinical trials indicate equal efficacy of antidepressants when tested across a wide population. Recent research indicates that some patients who are refractory to treatment with most antidepressant drugs may still respond to one of the other antidepressant drugs. Because standard criteria are not available for determining what agent is effective in the nonresponding group, several agents may need to be tried.

The SSRIs (citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline) are currently the most commonly used antidepressant drugs. Generally, these have a low incidence of adverse effects, especially when compared with the tricyclic antidepressants and the MAOIs. Some adverse effects associated with the SSRIs are related to their ability to increase synaptic levels of serotonin. Because the GI tract utilizes more serotonin than any other body organ, the most common adverse effects are GI disturbances. Other adverse effects include headache, incoordination, sleep disturbance, sexual dysfunction, and tremor. Sexual dysfunction is becoming increasingly recognized with this class of agents. Anorgasmia is the most common effect, but loss of libido and erectile dysfunction are also seen. Some of these effects are transient and disappear with continued use of the drug. In some patients, a potentially fatal "serotonin syndrome" can occur. Symptoms of the serotonin syndrome include agitation, diaphoresis, diarrhea, fever, hyperreflexia, incoordination, mental status changes, myoclonus, shivering, and tremor. The syndrome is usually associated with a defect in serotonin metabolism accompanied by the stimulation of release of serotonin from its storage sites. MAO inhibitors have caused many of these reactions and are contraindicated in combination with SSRIs. Meperidine has also been implicated. The syndrome has been precipitated by the concomitant use of St. John's Wort. Nonprescription cold remedies and diet pills contain agents that release serotonin (dextromethorphan, sympathomimetics) may precipitate the syndrome in patients taking SSRIs. Other prescription drugs that affect serotonin levels such as the newer migraine agents and antiemetics may also precipitate such a reaction. The syndrome is reversible when the stimulus for serotonin release is removed, and it can be treated acutely with serotonin antagonists such as cyproheptadine or propranolol. Dantrolene may be used for hyperthermia.

The heterocyclic group (amoxapine, bupropion, maprotiline, mirtazapine, nefazodone, trazodone, and venlafaxine) of antidepressants (sometimes termed miscellaneous antidepressants) have little in common other than clinical efficacy. These drugs have a different spectrum of adverse effects from the SSRI group and can often be taken by patients who do not tolerate the SSRIs. The drugs in the heterocyclic group have a much lower incidence of adverse effects than the tricyclic or the MAOI antidepressants.

The tricyclic antidepressant compounds (amitriptyline, clomipramine, desipramine, doxepin, imipramine, nortriptyline, protriptyline, and trimipramine) generally have antianxiety and sedative properties. Some tricyclic antidepressants (imipramine and, to a lesser extent, amitriptyline and nortriptyline) are also helpful in alleviating enuresis in children and adolescents. The tricyclic antidepressant drugs induce a wide variety of adverse effects. Because all of these drugs have antagonist activity at muscarinic receptors, many adverse effects are related to this action. The most common include dryness of the mouth, constipation, blurred vision, and drowsiness. Other adverse effects associated with tricyclic antidepressants are excessive perspiration and weight gain. Occasionally, manic episodes, tremors, heart block, tachycardia and other arrhythmias, rashes, and facial sweating are observed. Cholestatic jaundice, bone-marrow depression, epileptiform seizures, peripheral neuropathy, and photosensitization occur rarely. Urinary retention, especially in men, also has been reported. Doses must be increased very slowly to allow patient to accommodate to adverse effects.

The MAOIs (isocarboxazid, phenelzine, and tranylcypromine) are used for symptomatic relief of severe reactive or endogenous depression in hospitalized or closely supervised patients who have not responded to other antidepressant therapy. They must be used with caution because they are more toxic than the other antidepressant drugs. The untoward reactions produced by MAOIs include postural hypotension. In addition, certain foods and drugs when combined with a MAOI can produce a hypertensive crisis characterized by headache, palpitation, nausea and vomiting, and, occasionally, subarachnoid or intracranial hemorrhage. This reaction may be induced by the ingestion of certain kinds of sharp cheese, yeast extracts, broad beans, chicken livers, pickled herring, and chocolate. Other adverse reactions include restlessness, insomnia, dry mouth, nausea, dizziness, constipation, and anorexia; occasionally, patients may experience flushing, urinary retention, tremors, impotence, and paresthesias; and rarely, patients might develop skin rash, hepatitis, tinnitus, muscle spasms, and mania.

The mechanism by which antidepressant drugs exert their effects is complex. Certain conclusions emerge from a comparison of pharmacology of active agents. All antidepressant drugs affect norepinephrine and serotonin synapses in the brain. However, the nature of the acute effects on synaptic transmission and the selectivity for one of these two neurotransmitter systems varies significantly. The MAOIs increase amount of monoamine neurotransmitters available by interfering with their metabolism. Several of the tricyclic drugs and the SSRI class block uptake of neurotransmitters from the synapse into the presynaptic terminal. Drugs that selectively block uptake of either serotonin or norepinephrine are effective antidepressants. Further, there seems little evidence to distinguish between effectiveness of these two types of antidepressants. Drugs that block the uptake of norepinephrine or serotonin selectively are equally effective as drugs that block the uptake of both neurotransmitters. Several antidepressant drugs are antagonists at the serotonin 5-HT2A receptor, and this antagonism has been postulated to reduce anxiety. As all of the antidepressant drugs necessitate 3 to 4 weeks or more of therapy before clinical benefit is observed, it would appear that neuronal adaptations to the presence of the drugs correlate with efficacy. All of the compounds that enhance norepinephrine neurotransmission induce a delayed down regulation of β-adrenergic receptors and a decreased ability to increase levels of cyclic adenosine monophosphate (cAMP) by activation of β-adrenergic receptors. Such observations suggest that clinical effectiveness may be produced through adaptations in second-messenger systems stimulated by norepinephrine. All of the compounds that enhance serotonergic neurotransmission

appear to alter the balance between effects mediated by presynaptic and postsynaptic serotonin receptors, such that an increase in serotonergic transmission is observed.

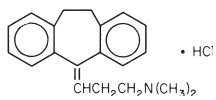
Patients taking antidepressants should avoid all other medications, including over-the-counter (OTC) preparations, unless specifically approved by their physician. They should be advised not to use alcoholic beverages and to limit the amount of caffeine-containing beverages while on these medications. Special precautions should be taken when antidepressants are used with other medications. The tricyclic compounds may decrease the effect of anticonvulsant medication, necessitating dosage adjustment. Many tricyclic agents potentiate the effects of antihistaminics, antimuscarinics, and other CNS depressants; block the antihypertensive effects of clonidine and guanethidine; alter blood glucose levels; and decrease the effectiveness of hypoglycemic medication. Their effectiveness is reduced by concurrent use of estrogens. Their concurrent use with MAOIs should be avoided as a hyperpyretic crisis, severe convulsions, and death may occur. A minimum of 14 days should elapse between the discontinuance of MAOIs and the initiation of tricyclic antidepressant therapy and vice versa. Likewise, concurrent use of tricyclic antidepressants with sympathomimetics may result in severe hypertension or hyperpyrexia; these agents may enhance the possibility of cardiac arrhythmias in patients on thyroid medication. The tricyclic compounds are contraindicated in patients who have congestive heart failure, angina pectoris, and paroxysmal tachycardia. Also, they should be used with caution in patients who have urinary retention, glaucoma, diabetes, impaired liver function, asthma, and a history of convulsive seizures.

MAOIs potentiate the effects of many other drugs (barbiturates, insulin, procaine, adrenergic agents, methyldopa, thiazide diuretics, anti-Parkinson agents, phenothiazines, and morphine analgesics); thus, a reduced dosage of each agent is necessary if the drugs are used concomitantly. The MAOIs should not be administered with or immediately after other MAOIs or other antidepressants. Such combinations can produce a hypertensive crisis, fever, significant sweating, excitation, delirium, tremor, twitching, convulsions, chorea, and circulatory collapse. At least 14 days should elapse between discontinuing an MAOI and the institution of another antidepressant or MAOI. A similar period should elapse before patients on MAOIs undergo elective surgery. The MAOIs should not be used in patients who have cerebrovascular defects or in patients who have cardiovascular disease, hypertension, or pheochromocytoma.

The safe use of tricyclic compounds or MAOIs during pregnancy or lactation has not been established. These agents should not be used in children younger than 12 years for the same reason. Also, geriatric, adolescent, and black patients on tricyclic compounds usually require reduced dosage; this is thought to be related to slower drug metabolism. Antidepressant drugs are toxic agents and should be employed only with a full knowledge of their precautions and potential adverse effects (Table 82-3).

AMITRIPTYLINE HYDROCHLORIDE

1-Propanamine, 3-(10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5-ylidene)-*N*,*N*-di-methyl-, hydrochloride; Elavil



[549-18-8] $C_{20}H_{23}N.HCl$ (313.87).

Table 82-3. Antidepressant Drugs

GENERIC NAME	TRADE NAME	COMMENTS
Amitriptyline	Elavil	A tricyclic with high sedation, intense antimuscarinic effects, high hypotension, and weight gain
Amoxapine	Asendin	A heterocyclic with moderate sedation and moderate antimuscarinic effects
Bupropion	Wellbutrin	A heterocyclic with no sedation, no antimuscarinic effects
Citalopram	Celexa	An SSRI with low sedation, no antimuscarinic effects
Clomipramine	Anafranil	A tricyclic with high sedation, intense antimuscarinic effects, high hypotension, and weight gain
Desipramine	Norpramin, Pertofrane	A tricyclic with low sedation, low antimuscarinic effects
Doxepin	Sinequan	A tricyclic with high sedation, intense antimuscarinic effects, moderate hypotension, and weight gain
Duloxetine Hydrochloride	Cymbalta	An SSRI with low sedation, no antimuscarinic effects
Escitalopram	Lexapro	An SSRI with low sedation, no antimuscarinic effects. Active s-enantiomer of citalopram
Fluoxetine	Prozac	An SSRI with no sedation, no antimuscarinic effects
Fluvoxamine	Luvox	An SSRI: only approved in US for obsessive-compulsive disorder
Imipramine	Tofranil	A tricyclic with moderate sedation, moderate antimuscarinic effects, high hypotension, and weight gain
Isocarboxazid	Marplan	An MAOI with low sedation, low antimuscarinic effects, and weight gain
Maprotiline	Ludiomil	A heterocyclic with moderate sedation and moderate antimuscarinic effects
Mirtazapine	Remeron	A heterocyclic with high sedation, no antimuscarinic effects
Nefazodone	Serzone	A heterocyclic with low sedation, low antimuscarinic effects; black box warning for possible hepatotoxicity
Nortriptyline Hydrochloride	Aventyl, Pamelor	A tricyclic with moderate sedation and moderate antimuscarinic effects
Paroxetine	Paxil	A SSRI with low sedation, no antimuscarinic effects
Phenelzine Sulfate	Nardil	An MAOI with low sedation, low antimuscarinic effects, and weight gain
Protriptyline Hydrochloride	Vivactil	A tricyclic with no sedation, moderate antimuscarinic effects
Sertraline	Zoloft	A SSRI with low sedation, no antimuscarinic effects
Tranylcypromine	Parnate	A MAOI with low sedation, low antimuscarinic effects
Trazodone Hydrochloride	Desyrel	A heterocyclic with high sedation, no antimuscarinic effects
Trimipramine	Surmontil	A tricyclic with high sedation, high antimuscarinic effects, high hypotension, and weight gain
Venlafaxine	Effexor	A heterocyclic with no sedation and no antimuscarinic effects

Preparation—Phthalic anhydride is reacted with phenylacetic acid to form 3-benzylidenephthalide, which is hydrogenated to 2-phenethylbenzoic acid. Conversion to the acid chloride followed by intramolecular dehydrochlorination yields the ketone (5*H*-dibenzo[*a*,*d*]cyclohepten-5-one), which is grignardized with 3-(dimethylamino)propyl chloride. Dehydration of the resulting tertiary carbinol gives amitriptyline, which is dissolved in a suitable solvent and converted to the hydrochloride by a stream of HCl. US Pat 3,205,264.

Description—White or practically white, odorless or practically odorless, crystalline powder or small crystals; melts about 197°; pH (1 in 100 solution) 5 to 6; pK_a 9.4.

Solubility—1 g in in 1 mL water, 1.5 mL alcohol, 1.2 mL chloroform, or 1 mL methanol; insoluble in ether.

Comments—A *tricyclic* used for the relief of symptoms of depression. Endogenous depression is more amenable to amitriptyline therapy than are other depressive states. It is useful in the management of depression accompanied by anxiety. It is also useful in temporarily alleviating enuresis in children and adolescents.

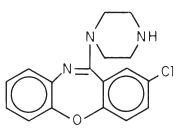
Amitriptyline is contraindicated in patients who have shown previous hypersensitivity to it. It should not be given concomitantly with MAOIs. Hyperpyretic crises, severe convulsions, and deaths have occurred in patients receiving tricyclic antidepressant and MAO-inhibiting drugs simultaneously. When a MAOI is replaced with amitriptyline, a minimum of 14 days withdrawal should be allowed before initiation of the new therapy. Amitriptyline is not recommended for use during the acute recovery phase after myocardial infarction.

Amitriptyline is absorbed rapidly after either oral or parenteral administration; (31–61% is bioavailable); peak plasma levels occur within 2 to 12 hr; 96% is bound to plasma proteins. The plasma half-life ranges from 31 to 46 hr; volume of distribution is 5 to 10 L/kg; therapeutic plasma levels range from 80 to 200 ng/mL. It is metabolized in the liver by P-450 2D6. At least one active metabolite, nortriptyline, has been identified. Approximately 25% to 50% is excreted in the urine as inactive metabolites within 24 hr; small amounts are excreted in the feces via the bile.

Adverse effects associated with amitriptyline include drowsiness, xerostomia, tremor, fatigue, weakness, blurring of vision, constipation, urinary retention, edema, tachycardia, and orthostatic hypotension. Most untoward effects can be controlled by a reduction in dosage. Patients taking large doses over an extended period should be watched closely for possible changes in liver and hematopoietic functions.

AMOXAPINE

Dibenz[*b*,*f*][1,4]oxazepine, 2-chloro-11-(1-piperazinyl)-, Asendin



[14028-44-5] $C_{17}H_{16}ClN_3O$ (313.79).

Preparation—See *Helv Chim Acta* 1967; 50:245.

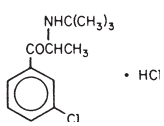
Description—White crystals; melting about 175°.

Solubility—Practically insoluble in water; freely soluble in chloroform; sparingly soluble in acetone or methanol.

Comments—A *heterocyclic* with moderate sedative and antimuscarinic effects.

BUPROPION HYDROCHLORIDE

1-Propanone, 1-(3-chlorophenyl)-2-[(1-dimethylethyl)amino)-, hydrochloride; Wellbutrin, Zyban



[31677-93-7] $C_{13}H_{18}ClNO.HCl$

Preparation—*m*-Chlorobenzonitirile is reacted with ethyl Grignard reagent in ether to produce *m*-chlorobenzyl ethyl ketone, which is brominated in dichloromethane. The product is reacted with tertiary butyl amine in acetronitrile to yield bupropion base. Treatment of an ethereal solution of the base with dry HCl yields the salt. Ger Offen 2,059,618.

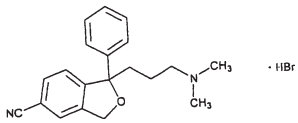
Description—White solid; melting about 233° to 234°.

Solubility—1 g in 3.5 mL water or 5 mL ethanol.

Comments—A *heterocyclic* with no sedative or antimuscarinic effects. Also used as an aid in smoking cessation

CITALOPRAM HYDROBROMIDE

5-Isobenzofurancarbonitrile, 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-, monohydrobromide; Celexa



1-[3-(Dimethyamino)propyl]-1-(*p*-fluorophenyl)-5-phthalan- carbonitrile monohydrobromide [59729-33-8] $C_{20}H_{21}FN_2O.HBr$ (405.30).

Preparation—A multi-step synthesis involving the interaction of the Grignard reagent from *p*-bromochlorobenzene and 5-bromophthalide to form 4′-chloro-4-bromo-2-(hydroxymethyl)benzophenone (I). I, with another Grignard, 3-dimethylaminopropyl-magnesium chloride, yields α-(3-dimethylaminopropyl)-α-(*p*-chlorophenyl-α-4-bromo-2-hydroxymethyl)benzyl alcohol, which is cyclized with hot phosphoric acid to give the 5-bromophthalan. Conversion of the bromine atom to 5-cyano with copper cyanide affords the product. US Pat 6,455,710(2002); *Eur J Med Chem Ther* 1977;12:289.

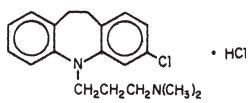
Description—Crystals from 2-propanol melting about 182°.

Solubility—Sparingly soluble in water; soluble in ethanol.

Comments—An *SSRI*, indicated for treatment of depression.

CLOMIPRAMINE HYDROCHLORIDE

5*H*-Dibenz[*b*,*f*]azepine-5-propanamine, 3-chloro-10,11-dihydro-*N*,*N*-dimethyl-, monohydrochloride; Anafranil



[17321-77-6] $C_{19}H_{21}ClN_2.HCl$ (351.32).

Preparation—3,9-Dichloroacridine is refluxed with P_2O_5 in dry xylene to form 3-chloro-5*H*-dibenz[*b*,*f*]azepine, which is catalytically reduced using PtO_2 in ethanol at room temperature giving 3-chloro-10,11-dihydro-5*H*-dibenz[*b*,*f*]azepine. Treatment of the latter compound with sodamide in toluene followed by reaction of the sodio salt with 3-chloro-*N*,*N*-dimethylpropylamine gives the free amine which is converted to the hydrochloride. *J Org Chem* 1961; 26:135.

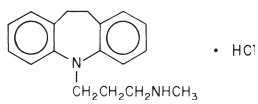
Description—Crystals from methanol/ether melting about 190°. Log P, 3.3; pK_a 3.6–4.6.

Solubility—Ethanol, 1 in 5; water, 1 in 8. Freely soluble in methanol or methylene chloride. Insoluble in ether or benzene.

Comments—A *tricyclic*, with high sedative and intense antimuscarinic effects, causing hypotension and weight gain. Initially indicated only for obsessive-compulsive disorder.

DESIPRAMINE HYDROCHLORIDE

5*H*-Dibenz[*b*,*f*]azepine-5-propanamine, 10,11-dihydro-*N*-methyl-, monohydrochloride; Norpramin; Pertofrane



[58-28-6] $C_{18}H_{22}N_2.HCl$ (302.85).

Preparation—Pyrolysis of the methanesulfonate of 4,4′-diaminobibenzyl results in cyclization with formation of 10,11-dihydro-5*H*-dibenz[*b*,*f*]azepine. This is condensed with *N*-(3-chloropropyl)-*N*-methylbenzylamine in the presence of alkali to form *N*-benzylated desipramine, which, after debenzylation through reductive cleavage, is reacted with an equimolar quantity of HCl. Brit Pat 908,788; US Pat 3,454,698.

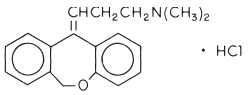
Description—White to off-white, crystalline powder; odorless; bitter taste; unstable after long exposure to light, heat, and air; melts within a 5° range between 208° and 218°; pK_a 10.2 (methylamino).

Solubility—1 g in 12 mL of water, 14 mL of alcohol, 3.5 mL of chloroform, or >10,000 mL of ether.

Comments—A *tricyclic* with low sedative and antimuscarinic effects. Active metabolite of imipramine.

DOXEPIN HYDROCHLORIDE

1-Propanamine, 3-(dibenz[*b,e*]oxepin-11(6*H*)-ylidene)-*N,N*-dimethyl-, hydrochloride; Adapin; Sinequan



[1229-29-4; 4698-39(*E*); 251127-31-5(*Z*)] $C_{19}H_{21}NO.HCl$ (315.84). Doxepin hydrochloride, an (*E*) and (*Z*) geometric isomer mixture, contains the equivalent of not less than 85.0% and not more than 92.0% of $C_{19}H_{21}NO$ (doxepin), calculated on the dried basis. It contains not less than 12.0% and not more than 16.0% of the (*Z*)-isomer and not less than 72.0% and not more than 78.0% of the (*E*)-isomer.

Preparation—6,11-Dihydrodibenz[*b,e*]oxepin-11-one is prepared from ethyl 2-(bromomethyl)benzoate and phenol to produce 2-(phenoxymethyl)benzoic acid, which is converted to 6,11-dihydrobenzo[*b,e*]oxepin-11-one by cyclization with polyphosphoric acid. This latter compound is transformed to 11-[3-(dimethylamino)propyl]-6*H*-dibenz[*b,e*]oxepin-11-ol through Grignard reaction with 3-(dimethylamino)propyl chloride. Dehydration of the alcohol with mineral acid yields the base that is reacted with HCl.

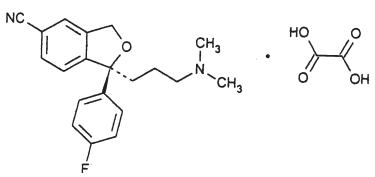
Description—White, odorless, bitter, crystalline substance; decomposes slowly in light, nonhygroscopic up to 75% RH, and relatively stable in heat; melts about 188°; pK_a 8.

Solubility—1 g in 1 mL water, 2 mL alcohol, or 10 mL chloroform.

Comments—A *tricyclic* with high sedative and intense antimuscarinic effects, causing moderate hypotension and weight gain.

ESCITALOPRAM OXALATE

***S*-(+)-5-Isobenzofurancarbonitrile, 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-, oxalate (salt; 1:1); Lexapro**



[219861-08-2] $C_{20}H_{21}FN_2O.C_2H_2O_4$ (414.43).

Preparation—Escitalopram is the (*S*)-isomer of the racemic citalopram. The isomer is produced by resolution of the enantiomer and conversion to the oxalate salt. US Pat 6,455,710.

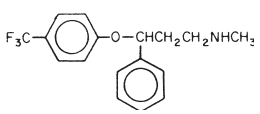
Description—White to off-white powder.

Solubility—Freely soluble in methanol or DMSO. Soluble in normal saline, sparingly soluble in water or ethanol, slightly soluble in ethyl acetate.

Comments—An *SSRI*, it is the active S-enantiomer of citalopram (see above). Dosage is half that of citalopram. No advantage over citalopram.

FLUOXETINE HYDROCHLORIDE

Propylamine, (±)-3-(*p*-trifluoromethylphenoxy)-*N*-methyl-3-phenyl-, Prozac, Serafem



[56296-78-7] $C_{17}H_{18}F_3NO.HCl$ (345.79, hydrochloride salt).

Preparation—β-(Dimethylamino)propiophenone is reduced by diborane to the corresponding secondary alcohol. The hydroxyl group is substituted by chlorine using hydrochloric acid in chloroform. The product is reacted with sodium 4-trifluoromethylphenoxide in a Williamson synthesis to produce the dimethyl analog of the desired compound. Mono-demethylation is accomplished by successive reaction with BrCN and KOH. German Pat 2,500,110.

Description—Off-white crystalline solid.

Solubility—1 g in 70 mL of water.

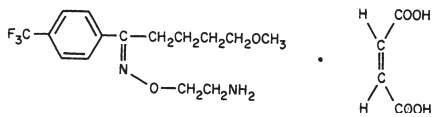
Comments—An *SSRI* indicated for treatment of depression, obsessive-compulsive disorder, and bulimia nervosa. Besides its use in the treatment of major depression, fluoxetine also has been used in patients who have bipolar disorder, obesity, and panic attacks.

Although fluoxetine has a wide margin of safety, it can have undesirable actions on nervous and GI systems that cause discontinuance in 15% of patients. These effects include anxiety, nervousness, insomnia, dizziness, headaches, and nausea. Significant weight loss may occur. Fluoxetine is contraindicated in patients known to be allergic to it. Fluoxetine should not be used in combinations with an MAOI or within 14 days of discontinuing therapy with an MAOI. Fluoxetine forms an active metabolite norfluoxetine, which has a half-life of approximately 7 to 9 days. Therefore, after stopping fluoxetine, allow at least a 5-week interval before starting an MAOI.

Fluoxetine is well absorbed from the GI tract (60–80%), and peak plasma levels occur 4 to 8 hr after administration. The elimination half-life of fluoxetine is approximately 2 to 3 days (range of 1–9 days), and the half-life of its active metabolite, norfluoxetine, is 7 to 9 days (range of 3–15 days); thus, adverse effects may disappear slowly after discontinuing the drug. Fluoxetine is metabolized principally in the liver, and blood levels are increased in patients who have liver dysfunction.

FLUVOXAMINE MALEATE

1-Pentanone, *E*-5-methoxy-1-[4-(trifluoromethyl)phenyl]-, *O*-(2-aminoethyl) oxime; Luvox



[54739-18-3] $C_{15}H_{21}F_3N_2O_2.C_4H_4O_4$ (434.41).

Preparation—A Friedel Crafts reaction of α,α,α-trifluorotoluene and 5-methoxyvaleryl chloride forms 1-(4-trifluormethylphenyl)-5-methoxyvalerophenone, which with 2-aminoxyethyl amine hydrochloride yields the oxime product. US Pat 4,058,225 (1978).

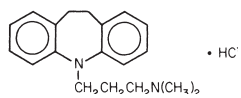
Description—White to off-white, odorless crystals that melt about 121°.

Solubility—Sparingly soluble in water; freely soluble in ethanol or chloroform; practically insoluble in ether.

Comments—An *SSRI* approved in the US only for obsessive-compulsive disorder.

IMIPRAMINE HYDROCHLORIDE

5*H*-Dibenzo(*b,f*]azepine-5-propanamine, 10,11-dihydro-*N,N*-dimethyl-, mono-hydrochloride; Tofranil, Janamine



[113-52-0] $C_{19}H_{24}N_2.HCl$ (316.87).

Preparation—Dimerization of *o*-nitrotoluene is affected with sodium ethoxide and an oxidizing agent to produce 1,2-bis(*o*-nitrophenyl)ethane. This compound is reduced to the corresponding diamine, 2-(*o*-aminophenethyl)aniline hydrochloride, which is condensed with 3-chloro-*N,N*-dimethylpropylamine by refluxing in benzene solution with the aid of sodamide. The basic constituents are then extracted with aqueous HCl and the extract is rendered alkaline and extracted with ether. After drying, the solvent is evaporated and the residue is vacuum distilled to yield the base. Treatment with alcoholic HCl produces the hydrochloride. US Pat 2,553,736.

Description—White to off-white, odorless crystalline powder; melts about 172°; pK_a 9.4.

Solubility—1 g in approximately 5 mL of water, approximately 10 mL of alcohol, or approximately 15 mL of acetone; insoluble in ether or benzene.

Comments—A *tricyclic* with moderate sedative and antimuscarinic effects, causing hypotension and weight gain.

IMIPRAMINE PAMOATE

5-[3-(Dimethylamino)propyl]-10,11,-dihydro-d*H*-dibenz[*b,f*]-azepine compound (2:1) with 4,4-methylene-bis][3-hydroxy-2-naphthoic acid]; Tofranil-PM

For the structure and preparation of the base, see *Imipramine Hydrochloride*.

[10075-24-8] $C_{19}H_{24}N_2)_2.C_{23}H_{16}O_6$ (949.20).

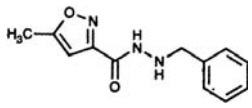
Description—Yellow powder; tasteless; odorless.

Solubility—Insoluble in water; soluble in alcohol, ether, or chloroform.

Comments—See *Imipramine Hydrochloride*.

ISOCARBOXAZID

3-Isoxazolecarboxylic acid, 5-methyl-, 2-(phenylmethyl)hydrazide; Marplan



[59-63-2] $C_{12}H_{13}N_3O_2$ (231.26).

Preparation—Acetonylacetone is reacted with nitric acid to form 5-methyl-3-is-oxazolecarboxylic acid, which is converted to the ethyl ester. The ester, with hydrazine hydrate, forms the acid hydrazide, which is condensed with benzaldehyde to yield the 2-benzylidenehydrazide. This latter compound is reduced with $LiAlH_4$ to the product. *J Med Pharm Chem* 1960; 2:133. *Anal Profiles of Drug Subst* v 2, p 295-314.

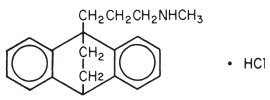
Description—White to off-white crystalline powder from methanol; slight characteristic odor; stable in dry air; melts about 106°; pK_a 10.4. Octanol/water partition coefficient, 30.

Solubility—Sparingly soluble in hot water; very soluble in ethanol, glycerol or propylene glycol.

Comments—An *MAOI* with low sedative effects. Was off the market for a few years and was then reintroduced in 1998. No advantages over phenelzine or tranylcypromine.

MAPROTILINE HYDROCHLORIDE

9,10-Ethananthracene-9(10*H*)-propanamine, *N*-methyl-, hydrochloride; Ludiomil



[10347-8] $C_{20}H_{23}N.HCl$ (313.87).

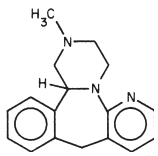
Preparation—Refer to *Helv Chim Acta* 1969; 52:1385.

Description—White crystals; melting about 230°; pK_a 10.5.

Comments—A *heterocyclic* with moderate sedative and antimuscarinic effects.

MIRTAZAPINE

Pyrazino[2,1-*a*]pyrido[2,3-*c*][2]benzazepine, (±)1,2,3,4,10, 14*b*-hexahydro-2-methyl-, Remeron



[61337-67-5] $C_{17}H_{19}N_3$ (265.36).

Preparation—The reaction of 2-chloropyridine-3-carbonitrile and 3-phenyl-1-methylpiperazine forms 2-(4-methyl-2-phenylpieridin-1-yl)nicotrinonitrile. Hydrolysis of the nitrile to the acid followed by reduction with diborane converts the carboxyl to a carbinol. Concentrated sulfuric acid closes the azepine ring and yields the product.

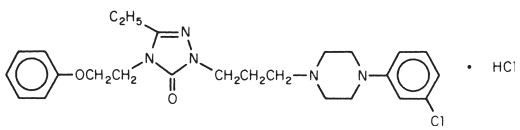
Description—White to off-white crystals that melting about 116°.

Solubility—Slightly soluble in water.

Comments—A *heterocyclic* with high sedative and no antimuscarinic effect.

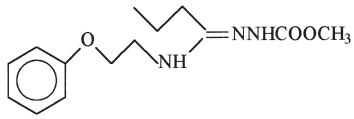
NEFAZODONE HYDROCHLORIDE

3*H*-1,2,4-Triazol-3-one, 2-[3-[4-(3-chlorophenyl)-1-piperazinyl)]-propyl]-5-ethyl-2,4-dihydro-4-(2-phenoxyethyl)-, monohydrochloride; Serzone



[82752-99-6]$C_{25}H_{32}ClN_5O_2.HCl$ (506.48).

Preparation—Heating phenol and 2-ethyloxazoline yields *N*-(2-phenoxyethyl)propionamide, which with phosgene forms the imidoyl chloride derivative. This latter compound with ethyl hydrazinocarboxylate, yields I. *J Hetero Chem* 1985; 22:11211. US Pat 4,338,317 (1982).



(I)

Compound I undergoes base-catalyzed intramolecular rearrangement to form the triazole moiety of the drug. The secondary amine fragment of the triazole is alkylated with 1-(3-chlorophenyl)-4-(3-chloropropyl)piperazine to form the product (base).

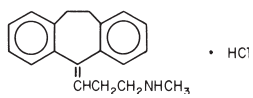
Description—White, nonhygroscopic crystals that melt about 187° (slow cooling); polymorph, which melts about 182° (rapid cooling) from 2-propanol; m 177° from ethanol. See US Pat 4,338,317 (1982).

Solubility—Freely soluble in chloroform; soluble in propylene glycol; slightly soluble in water or polyethylene glycols.

Comments—A *heterocyclic* with low sedative and antimuscarinic effects. Has black box warning for possible hepatotoxicity.

NORTRIPTYLINE HYDROCHLORIDE

1-Propanimine, 3-(10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5-ylidene)-*N*-methyl-, hydrochloride; Aventyl; Pamelor



[894-71-3] $C_{19}H_{21}N.HCl$ (299.84).

Preparation—10,11-Dihydro-5*H*-dibenzo[*a*,*d*] cyclohepten-5-one, which may be prepared as described under *Cyproheptadine Hydrochloride*, is reacted with an alkali metal derivative of *N*-methyl-2-propynylamine and the product hydrolyzed to form the carbinol. The acetylenic bond is then saturated by hydrogenation and the resulting carbinol dehydrated to yield nortriptyline (base). Reaction of the base with hydrogen chloride produces the hydrochloride.

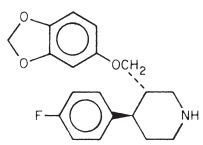
Description—White to off-white powder; slight, characteristic odor; melts within a range of 3° between 215° and 220°. pK_a is 9.73.

Solubility—1 g in 90 mL water, 30 mL alcohol, 20 mL chloroform, or 10 mL methanol.

Comments—A *tricyclic* with moderate sedative and antimuscarinic effects. Active metabolite of amitriptyline.

PAROXETINE

Piperidine, (3*S*-*trans*)-3-[(1,3-benzodioxol-5-yloxy)methyl]-4-(4-fluorophenyl)-, Paxil (as the hydrochloride)



[61869-08-7] $C_{19}H_{20}FNO_3.HCl$ (365.87).

Preparation—A Grignard reaction between 4-fluorophenylmagnesium bromide and methyl 1,2,5,6-tetrahydronicotinate produces methyl 4-(4-fluorophenyl)nipecotate. This ester is reduced with $LiAlH_4$ and the resulting carbinol condensed with 3,4-methylenedioxybenzyl alcohol in the presence of cyclohexylcarbodiimide to yield the product, an ether (base). US Pat 4,721,723 (1988) and US Pat 4,007,196 (1977).

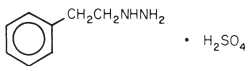
Description—Off-white powder that melts about 120° to 134°; HCl. $\frac{1}{2}H_2O$, 131°; maleate, 138°; $[\alpha]_D$ - 87° (c = 5, ethanol).

Solubility—Soluble 5.4 mg/mL in water.

Comments—An *SSRI* with low sedative and no antimuscarinic effects. More drug interactions than most SSRIs. Also indicated for social anxiety disorder, GAD, OCD, PTSD, and panic disorder.

PHENELZINE SULFATE

Hydrazine, (2-phenylethyl)-, sulfate (1:1); Nardil



Phenethylhydrazine sulfate (1:1) [156-51-4] $C_8H_{12}N_2.H_2SO_4$ (234.27).

Preparation—Phenethyl alcohol is reacted with thionyl chloride to give phenethyl chloride, which is then added to hydrazine hydrate to yield phenethylhydrazine hydrochloride. Reaction with sodium hydroxide liberates the base, which is then reacted sulfuric acid to form the sulfate. US Pat 3,314,855.

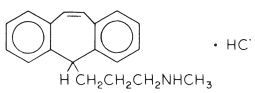
Description—White to yellowish-white powder; characteristic odor; subject to oxidation and must be protected from heat and light; melts about 166°; pH (1 in 100 solution) 1.4 to 1.9.

Solubility—1 g in about 7 mL water; practically insoluble in alcohol, chloroform, or ether.

Comments—An MAOI with low sedative and antimuscarinic effects, causing weight gain.

PROTRIPTYLINE HYDROCHLORIDE

5*H*-Dibenzo[*a*,*d*]cycloheptene-5-propanamine, *N*-methyl-, hydrochloride; Vivactil



[1225-55-4] $C_{19}H_{21}N.HCl$ (299.84).

Preparation—5*H*-Dibenzo[*a*,*d*]cyclohepten-5-one, prepared as described under *Cyproheptadine Hydrochloride* (page 1547), is reduced to the corresponding carbinol that is then converted to the 5-chloromethyl compound (I). Reaction with HCl gives the hydrochloride.

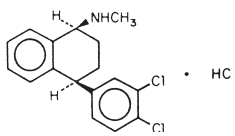
Description—White to yellowish powder; odorless or has not more than a slight odor; a bitter taste; reasonably stable in light, air, and heat under the usual prevailing temperature conditions; melts about 168°; pH (1 in 100 solution) 5 to 6.5.

Solubility—1 g in 2 mL water, 4 mL alcohol, 2.3 mL chloroform, or 2 mL methanol; practically insoluble in ether.

Comments—A *tricyclic* with no sedative and moderate antimuscarinic effects.

SERTRALINE HYDROCHLORIDE

Naphthalenamine, (1*S*-*cis*)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-*N*-methyl-, hydrochloride, Zoloft



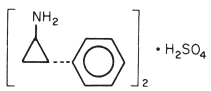
[79559-97-0] $C_{17}H_{17}Cl_2N.HCl$ (342.70).

Preparation—4-(3,4-Dichlorophenyl)-3,4-dihydro-1(2*H*)-naphthalenone, methylamine, and titanium tetrachloride are reacted to form a Schiff base, which then is reduced with sodium borohydride to produce a mixture of geometric isomers. The *cis* and *trans* isomers are separated by use of chromatography on silica gel. The purified base is dissolved in ether and converted to the salt with HCl gas in ether. *J Med Chem* 1984; 27:1508.

Comments—An *SSRI* with low sedative and antimuscarinic effects. Also indicated for OCD, PTSD, panic disorder, and pre-menstrual dysphoric disorder.

TRANYLCYPROMINE SULFATE

Cyclopropanamine, *trans*-(±)-2-phenyl-, sulfate (2:1); Parnate



[13492-01-8] $(C_9H_{11}N)_2.H_2SO_4$ (364.46).

Preparation—Styrene is reacted with ethyl diazoacetate to form ethyl 2-phenylcyclopropanecarboxylate. Saponification of this ester with sodium hydroxide and subsequent acidification yields a mixture of the *cis* and the *trans* forms of the corresponding acid, and the *trans* form is isolated by fractional crystallization from water. The *trans* acid is then subjected to the Curtius reaction, whereby carboxyl is transformed successively through the acyl chloride, acyl azide, and isocyanate states to yield finally the base. Reaction with a 1/2 equimolar quantity of H_2SO_4 gives the sulfate. US Pat 2,997,422.

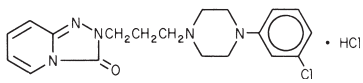
Description—White, crystalline powder; odorless or a faint, cinnamaldehyde-like odor; slightly acid taste; stable in light, heat, and air; melts with decomposition at 218°; pK_a 8.2.

Solubility—1 g in 25 mL of water; slightly soluble in alcohol or ether; practically insoluble in chloroform.

Comments—An *MAOI* with low sedative and antimuscarinic effects.

TRAZODONE HYDROCHLORIDE

1,2,4-Triazolo[4,3-*a*]pyridin-3(2*H*)-one, 2-[3-[4-(3-chlorophenyl)-1-piperazinyl]propyl]-, monohydrochloride; Desyrel



[25332-39-2] $C_{19}H_{22}ClN_5O.HCl$ (408.33).

Preparation—Semicarbazide and 2-chloropyridine are condensed with loss of water and ammonia to form 1,2,4-triazolo[4,3-*a*]pyridin-3(2*H*)-one, which on treatment with 1-(3-chlorophenyl)4,3-chlorophenyl)piperazine (I) and sodamide, yields trazodone. I is prepared form 1-(3-chlorophenyl)piperazine with 1-bromo–3-chloropropane. See US Pat 3,381,009.

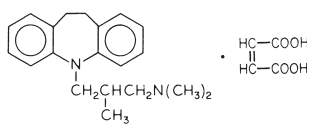
Description—White crystals; melts about 90°; pK_a (in 50% ethanol) 6.14.

Solubility—Sparingly soluble in water or alcohol; soluble in chloroform.

Comments—A *heterocyclic* with high sedative and no antimuscarinic effects.

TRIMIPRAMINE MALEATE

5*H*-Dibenz[*b*,*f*]azepine-5-propanamine, 10,11-dihydro-*N*,*N*, β-trimethyl-, (*Z*)-2-butenedioate (1:1); Surmontil



[521-78-8] $C_{20}H_{26}N_2.C_4H_4O_6$ (410.51).

Preparation—As per imipramine, page 1520, except that the side chain is attached with 3-(dimethylamino)-2-methylpropylchloride. See *Compt Rend* 1961; 252:2117.

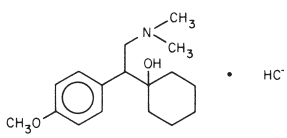
Description—White crystals; bitter taste; slight numbing characteristic; melts about 143°; pK_a 7.72 (dimethylamino).

Solubility—Slightly soluble in water or in alcohol; freely soluble in chloroform.

Comments—A *tricyclic* with high sedative, antimuscarinic, and hypotensive effects, causing weight gain.

VENLAFAXINE HYDROCHLORIDE

Cyclohexanol, (±)-1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl-, hydrochloride; Effexor



[99300-78-4] $C_{17}H_{27}NO_2.HCl$ (313.87).

Preparation—Under basic conditions an aldol-type condensation of the anion nucleophile of 4-methoxyphenylacetonitrile and cyclohexanone yield 2-(2-hydroxycyclohexyl)-2-(4-methyoxyphenyl)acetonitrile. Reduction of the nitrile to the primary amine followed by *N*-methylation gives the product (base). *J Med Chem* 1990; 33:2899. US Pat 4,535,186 (1985).

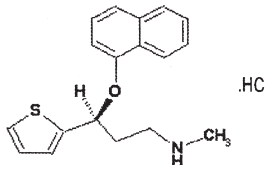
Description—Off-white crystals that melt about 217°; (+)-form, 102° to 104° from ethanol; (−) form, 241° from methanol or ether. Octanol-0.2 *M* NaCl partition coefficient, 0.543.

Solubility—Soluble at 572 mg/mL in 0.2 *M* NaCl.

Comments—A *heterocyclic* with no antimuscarinic effects. May cause increase in blood pressure of 5-7 mm Hg. Also indicated for GAD.

DULOXETINE HYDROCHLORIDE

2-Thiophenepropaneamine, (*S*)-*N*-methyl-γ-(1-naphthyloxy)-, hydrochloride; Cymbalta



136434-34-9] $C_{18}H_{19}NOS.HCl$ (333.88).

Preparation—*Tetr Lett* 1990; 31:1990 and US Pat 5,023,269 (1991).

Description—White solid, pK_a (66% DMF/water)9.6.

Solubility—Slightly soluble in water.

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CHAPTER 83

Analgesic, Antipyretic, and Anti-Inflammatory Drugs

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Analgesics are agents that relieve pain without significantly disturbing consciousness or altering other afferent input (sensory modalities). Hence, many drugs that are used to relieve pain are not truly analgesics. For example, general anesthetics reduce pain, but interfere with consciousness; local anesthetics reduce pain by blocking peripheral nerve fibers that carry other sensory input; antispasmodics indirectly relieve certain kinds of pain by relaxing smooth muscle; and adrenal corticoids relieve pain associated with rheumatoid arthritis by their anti-inflammatory action. These drugs are considered elsewhere in this text. Antipyretics are drugs that reduce elevated body temperature (fever) to normal levels. Certain analgesics and antipyretics also possess anti-inflammatory properties; such substances are used in the treatment of arthritis and other inflammatory conditions. The drugs considered in this chapter have demonstrated analgesic action (or antagonism), with or without antipyretic or anti-inflammatory action. The drugs include opioid (morphine-like) agonists and antagonists, mixed-action agents, traditional NSAIDs (non-steroidal anti-inflammatory drugs), COX-2 inhibitors, and acetaminophen.

Pain serves several useful purposes. It warns of present or potential tissue damage and activates reflex or conscious withdrawal of the affected tissue from the source of injury, and it elicits a natural tendency to protect the injured site in order to prevent further injury. However, persistent pain adversely affects a patient's quality of life, can lead to pain hypersensitivity due to an increase in excitability of spinal cord neurons ('central sensitization'), and can delay recovery. Analgesics can inhibit the sensation of pain or alter the perception of pain. Modulation of the affective component of pain can improve a patient's quality of life even in the presence of a continuing sensation of pain. Since pain often originates from multiple sources, it involves multiple types of pain and multiple pain transmission pathways. Because of the multifaceted nature of some pain, treatment can often benefit from, or require, a combination of pharmacologic and non-pharmacologic approaches. The optimal pharmacologic treatment of pain requires classification of the type of pain and not merely of the severity of pain. Hence, an understanding of the differences in the mechanisms of action of the commonly available analgesics is helpful for the judicious selection of the optimal agent. A particularly important aspect of the treatment of pain is that a variety of chemical signals can be involved. Inflammatory pain may be an additional component of the overall pain profile. For example, pain caused by an inflammatory condition might best be treated with a 'weaker' anti-inflammatory drug, such as a cyclooxygenase inhibitor, rather than with a 'stronger'–but not anti-inflammatory–opioid analgesic.

At the site of an injury, tissues are damaged and cells release chemical mediators that trigger a pain signal. The released substances, such as histamine, bradykinin, and postaglandins, are either inherently painful or amplify the pain signal transmitted by other chemical mediators. The pain signal is transmitted from the site of injury to the central nervous system (CNS) via primary afferent sensory neurons. The anatomy of neurons influences the characteristics of the pain signal. For example, primary afferents of the Aδ type are highly myelinated and transmit their action potential rapidly–giving rise to a 'sharp' and localized type of pain. In contrast, C-fiber afferents are less heavily myelinated, slower conducting, and give rise to a more 'dull', diffuse, or vague type of pain. The cell bodies of afferent neurons, which comprise the DRG (dorsal root ganglion), can be damaged, giving rise to aberrant or false pain signaling (perhaps one explanation of 'phantom' pain). The signal enters the CNS through the dorsal horn of the spinal cord; many of the primary afferent fibers synapse in the *substantia gelatinosa* and adjacent layers, where neurotransmitters and neuromodulators are located within synapses between primary and secondary neurons. Substance P and glutamate are considered to be important mediators of the pain signal at this level. The secondary fibers decussate within the spinal cord and travel to the brain in ascending pathways such as the lateral spinothalamic tract. Within thalamic and associated nuclei, an affective component is superimposed upon the pain sensation. For example, an awareness of the magnitude of the discomfort and an emotional overlay is added to the pain sensation and memory of previously experienced pain is recruited. Higher CNS centers, including the cerebral cortex, contribute an additional affective component to the pain signal. Individual, cultural, and religious differences in pain response or interpretation are partly explained by this level of processing of the pain signal. In addition to these ascending pathways that carry the signal to higher CNS centers for processing, evaluation, and response, descending pathways modulate transmission of the incoming pain signal. Several neurotransmitter systems are involved in this descending modulation, including the endogenous opioid system (endorphins, enkephalins), norepinephrine from the *locus cœruleus*, and 5-hydroxytryptamine (serotonin) from the *raphe* nuclei. These pathways can be activated subconsciously or consciously, possibly accounting for the large placebo effect observed in clinical trials.

From the above considerations, it is clear that the mechanism(s) of action of a particular analgesic will determine the types of pain that the drug can be expected to treat. Although there are many analgesics available either by prescription or over-the-counter (OTC), there are relatively few categories from which to choose based upon the pharmacologic mechanism of action. The major categories of current analgesic pharmacotherapy are: (1) opioids; (2) mixed-action analgesics; (3) traditional NSAIDs and the newer selective cyclooxygenase-2 (COX-2) inhibitors; (4) acetaminophen, which is not an NSAID; (5) adjuvants (drugs not thought of as primarily analgesic, but are helpful in certain situations); and (6) combinations of these.

Table 83-1. Profile of the Analgesic Categories Most Commonly Used to Treat Pain

Opioids
- Maximum single-agent analgesic efficacy.
- Not anti-inflammatory
- MOA: 7-TM GPCR receptors (μ, δ, and κ)
- PK: good absorption; moderate onset; hepatic metabolism; renal excretion
- AEs: constipation; respiratory depression; abuse potential

NSAIDs
- Good analgesic efficacy (less than opioids)
- Anti-inflammatory
- MOA: inhibition of COX-1 and COX-2
- PK: good absorption; rapid onset; hepatic metabolism; renal excretion
- AEs: GI bleeding (potentially fatal); retention of Na^+/H_20

COX-2 inhibitors
- Analgesic efficacy equivalent to traditional NSAIDs
- Ant-iinflammatory
- MOA: selective inhibition of COX-2
- PK: good absorption; rapid onset; hepatic metabolism; renal excretion
- AEs: to be established (possible cardiovascular, renal)

Acetaminophen
- Efficacy equivalent to traditional NSAIDs and COX-2 inhibitors
- Not anti-inflammatory
- MOA: not known (central)
- PK: good absorption; rapid onset; hepatic metabolism; renal excretion
- AEs: hepatotoxicity in overdose or compromised liver

MOA = mechanism of action; PK = pharmacokinetics; AE = adverse effects; 7-TM GPCR = 7-transmembrane spanning G protein-coupled receptors.

The characteristics of the major classes of currently available analgesics can be summarized as shown in Table 83-1.

OPIOID ANALGESICS

The analgesic properties of opium ('juice' of *Papaver somniferum*) and derivatives has been known for centuries. Morphine (after Morpheus, the Greek god of dreams) was isolated by Sertürner in 1806. Opioid receptors were discovered in the early 1970s by three groups: Pert & Snyder (*Science* 179:1011, 1973); Simon et al. (*PNAS* 70:1947, 1973); and Terenius (*Acta Pharmacol Toxicol* 32:317, 1973). Based on the assumption that the body would not have receptors for opioid drugs unless it produces an endogenous opioid-like substance, Hughes and Kosterlitz at the University of Aberdeen in Scotland isolated and identified such material, which they called *enkephalins*, from pig brain (*Nature* 258:577, 1975). Two of the identified brain peptides have the structure tyrosine-glycine-glycine-phenylalanine-X, differing only in the *N*-terminal amino acid (Met-enkephalin when X = methionine and Leu-enkephalin when X = leucine). The enkephalins are now known to be members of a family of endogenous opioids, which also includes endorphins (contracted from endogenous and morphine) and dynorphins. *Opiates* are drugs derived from opium and include, for example, morphine and codeine. *Opioids* is a general term referring to natural, synthetic, or endogenous morphine-related substances. *Narcotics* ('stupor') are drugs of certain legal status, the term has lost any pharmacologic specificity. Opioid analgesics fundamentally minic the action of endogenous opioids.

It is now known that opioid analgesics produce their effects by binding to (affinity) and activation of (intrinsic activity; efficacy) the opioid receptors. There are three major types of opioid receptors, which are termed μ, δ, and κ. Each has been cloned and each is a 7-TM GPCR (7-transmembrane G protein-coupled receptor). Most of the currently used opioid analgesics act primarily at μ receptors; some have an admixture of activity at the other types. Opioid receptors are located pre- and post-synaptically along the pain transmission pathways. High densities of receptors are found in the dorsal horn of the spinal cord and higher CNS centers. Opioid receptors in the brainstem are responsible for the respiratory depressant effects produced by opioid analgesics. Constipation results from activation of opioid receptors in the CNS and in the GI tract. Opioid receptors in higher CNS centers probably account for the effect of opioids on the affect component of pain. The cellular actions of opioid agonist analgesics involve enhancement of neuronal K^+ efflux and inhibition of Ca^{2+} influx. Enhanced K^+ efflux increases the transmembrane potential, which hyperpolarizes neurons and makes them less likely to respond to a pain stimulus. Because Ca^{2+} entry is necessary for vesicle merging with neuronal membranes and the subsequent release of neurotransmitters into the synapse, inhibition of Ca^{2+} entry by opioid analgesics decreases neurotransmitter release from neurons located along the pain transmission pathway.

The available opioid analgesics are derivatives of a relatively small number of chemical groups (eg, phenanthrenes, phenylheptylamines, phenylpiperidines, morphinans, and benzomorphans). Pharmacologically, opioids differ in their affinity for opioid receptors and in their intrinsic activity; some have high efficacy (eg, morphine); others moderate efficacy (eg, codeine); whereas others have zero efficacy, ie, are antagonists (eg, naloxone). Some opioid derivatives exhibit mixed agonist-antagonist activity (eg, nalbuphine).

Morphine is the prototype of the opioid analgesics, all of which have similar actions and overlapping clinical usefulness. They are used in the management of almost all types of moderate to severe pain, to inhibit cough and treat gastrointestinal (GI) and urinary tract disorders. They depress respiration at high doses, increase nonpropulsive intestinal spasms, decrease the propulsive motility of the small and the large intestines, and diminish biliary, pancreatic, and intestinal secretions. The consequences of these actions are periods of slight atony, causing a delay in the passage of bowel contents and an increase in stool viscosity. Constipation at analgesic doses is not uncommon. Also, they cause nausea and vomiting in some individuals and may induce cutaneous pruritus. These and other actions of morphine and related compounds tend to limit their usefulness. If these agents are given for long periods, tolerance to the analgesic effect develops so that the dose must be periodically increased to obtain equivalent pain relief.

The opioid analgesics generally are *contraindicated* in patients who have myxedema, Addison's disease, and hepatic cirrhosis. Such patients are especially sensitive to these agents. Consequently, respiratory depression, stupor, and even coma may result from relatively small doses of the opioids. Because opioids decrease ventilation, which causes hypercapnia and progresses to cerebrovascular dilatation and increased intracranial pressure, they should be used with caution in head injuries, cerebral edema, and delirium tremens. These agents also should be used with caution in patients who have cardiac arrhythmias, chronic ulcerative colitis, and impaired kidney function. Moreover, opioid analgesics cross the placental barrier; hence, newborn infants whose mothers have been administered such analgesics during labor should be observed closely for signs of respiratory depression and be treated for opioid overdosage if necessary. Individuals sensitive to a particular opioid agent, or group of agents, should avoid these drugs.

The analgesic and depressant effects of these agents provide the basis for many interactions with other drugs. Alcohol, antihistamines, muscle relaxants, antipsychotics, tricyclic antidepressants, or sedative-hypnotics may interact with opioids to intensify their overlapping actions, such as respiratory depression and anticholinergic effects. Particular caution is necessary if monoamine oxidase inhibitors (MAOIs) are administered concurrently with opioid analgesics because of intensification of action (use of meperidine in patients treated with MAOIs has pro-

duced severe and occasionally fatal reactions). Doses of the opioid analgesics should be adjusted to avoid these enhanced reactions.

Tolerance and physical dependence develop, which, combined with euphoria, can contribute to excess use or abuse by susceptible/predisposed individuals. For these reasons, it is important that morphine and its derivatives be taken only as directed by the physician (never in a greater dose, more often, or longer than prescribed) and never be used for pain when some other type of analgesic is satisfactory. Because drowsiness and decreased alertness are not uncommon, the patient taking any opioid analgesics usually should avoid tasks that require intact reflexes, coordination, and mental alertness. Many of the drugs described in this section come under the control of the *Comprehensive Drug Abuse Prevention and Control Act of 1970*. This law, commonly referred to as the *Controlled Substances Act*, is designed to regulate the distribution of all drugs with abuse potential as designated by the Drug Enforcement Administration, Department of Justice. The actual abuse by pain patients has been documented to be quite low and many patients unnecessarily go undertreated for their pain.

OPIUM

Gum Opium; Crude Opium; Raw Opium; Thebaicum; Meconium

The air-dried milky exudate obtained by incision of unripe capsules of *Papaver somniferum* Linné or its variety *album* De Candolie (Fam *Papveraceae*). It yields not less than 9.5% of anyhydrous morphine.

History—As a medicinal drug, it has been known and cultivated for many centuries, but it was not until the investigations of Sertüner, published in the early 1800s, that it was known that the drug contained certain definite principles now called *alkaloids.*

Dioscorides, in the 2nd century, was the first writer to discuss opium and its uses at length. He gave the recipe for a preparation called *diacodion,* which is the prototype of the formerly official syrup of poppies. Paracelsus used opium extensively in the 15th century and referred to it as the "stone of immortality." Van Helmont, early in the 17th century, used opium so freely that he was referred to as Doctor Opiatus. Sydenham, a little later in the same century, praised opium as the most valuable gift of God to man.

The principal opium exporting countries have been Turkey, Iran, Yugoslavia, and India. The Turkish and Yugoslavian products are nearly alike in their physical properties: color, odor, and consistency. Iranian and Indian opiums, although closely resembling each other, differ from the former in physical properties—they are darker and have a somewhat different odor and consistency. There also is a significant difference between the two groups in the amounts of the principal opium alkaloids.

Constituents—It owes its activity to the opioid alkaloids; 25 have been found in the various kinds of opiums, and several more have been suspected, but their existence has not been confirmed. Three acids occur combined with the alkaloids—*viz,* meconic, lactic, and sulfuric acids. Also present are *meconin* [$C_{10}H_{10}O_4$], pectin, glucose, mucilage, caoutchoue, wax and odorous, fatty, and coloring matters.

Description—More or less rounded, oval, brick-shaped or elongated, somewhat flattened masses, usually approximately 8 to 15 cm in diameter and weighing approximately 300 g to 2 kg each. Externally, it is pale olive-brown or olive-gray, having a coarse surface and covered with a thin coating consisting of fragments of poppy leaves and, at times, with fruits of a species of *Rumex* adhering from the packing. It is more or less plastic when fresh, becoming hard or tough on storage. Internally, it is reddish brown and coarsely granular. It has a very characteristic odor and a bitter taste.

Comments—It owes its chief pharmacological effects to its morphine content, other alkaloids not being present in sufficient amount to modify significantly the morphine type of action. Thus, it has many of the same uses as morphine, but the latter drug nearly always is preferred, inasmuch as it can be administered in a variety of ways. The average adult dose of opium is 60 mg, taken orally. This is the equivalent of 6 mg of morphine. Like morphine, this drug has *analgetic* and other *opioid* effects. It acts as an *antiperistaltic* agent by causing spasm of the bowel musculature and preventing propulsive movements. Traditionally, it is used for *diarrheas* and *dysenteries* rather than morphine. It produces *sedation* and *sleep.* It also controls *cough* and *dyspnea.* Thus, it has a variety of therapeutic uses in medicine and surgery.

Caution—Opium, and all opium derivatives and related synthetic compounds, are listed in Schedule II of the *Controlled Substances Act* (Chapter 111). It should not be dispensed except upon the presentation of a physician's prescription. See *Morphine.*

Powdered Opium is opium dried at a temperature not exceeding 70° and reduced to a fine powder and yields 10.0–10.5% of anhydrous morphine. It may contain any of the diluents, with the exception of starch, permitted for powdered extracts under *Extracts.*.

Description—Light brown to moderate yellowish brown, consisting chiefly of yellowish-brown to yellow, more or less irregular and granular fragments of latex, varying from 15 to 150 μm in diameter; a few fragments of strongly lignified, thick-walled, 4- to 5-sided or narrowly elongated, epidermal cells of the poppy capsule; few fragments of tissues of poppy leaves, poppy capsules, and, occasionally, *Rumex* fruits. In addition, there are the microscopic characteristics of the diluent if any has been used in the preparation of the powder.

Comments—A pharmaceutical necessity for *Paregoric.* See *Opium* and *Morphine.*

Paregoric [Camphorated Opium Tincture USP XVI; Paregoric Elixir; Tinctura Opii Benzoica; Tinctura Thebaica Benzoica] yields, from each 100 mL, 35 to 45 mg of anhydrous morphine.

Preparation—Macerate powdered opium (4.3 g), anise oil (3.8 mL), benzoic acid (3.8 g), and camphor (3.8 g) for 5 days, with occasional agitation, in a mixture of diluted alcohol (900 mL) and glycerin (38 mL). Then filter, and pass enough diluted alcohol through the filter to obtain 950 mL of total filtrate. Assay a portion of this filtrate as directed in the USP, and dilute the remainder with a sufficient quantity of diluted alcohol containing, in each 100 mL, 0.4 mL of anise oil, 400 mg of benzoic acid, 400 mg of camphor, and 4 mL of glycerin, to produce a solution containing, in each 100 mL, 40 mg of anhydrous morphine.

History—This preparation was originated about 1715 by Professor LeMort of the University of Leyden. It was official in the 1721 edition of the London Pharmacopaeia as *Elixir Asthmaticum,* which was changed to *Elixir Paregoricum,* meaning soothing elixir, in 1746. It also has been known as *Tinctura Camphorae Composita* and *Tinctura Opii Benzoica,* and the formula has changed in minor details many times since its introduction into medicine. *Alcohol Content:* 44–46%.

Comments—An *antidiarrheal agent* and mild *anodyne* in *cough, nausea,* and *abdominal pains.* It should never be used to quiet restless infants, as a habit may be induced. It contains 0.4% opium. Paregoric is listed in *Schedule III* of the *Controlled Substances Act*; hence, it only can be obtained on a prescription order (either oral or written) of a licensed practitioner.

MORPHINE

History—Morphine was the first alkaloid discovered. In the 17th and 18th centuries, many attempts were made to separate from opium the active ingredient. Preparations thought to represent these active principles but were really extracts, were employed in medicine under the name of *Magisterium Opii.* Bucholz was the first to endeavor to obtain a crystalline product from opium. About 1800 learned apothecaries of the time devoted their attention to the separation of the suspected active drug. One of these apothecaries, Derosne, succeeded in isolating narcotine in 1803, and the following year Seguin read a paper to the Institute of France describing the isolation of a substance that is now recognized as morphine. He did not publish his paper, however, until 1814 and in 1806, Frierich William Adam Sertüner, an apothecary of Einbeck, Germany, announced the separation of a basic crystalline substance that existed in opium in combination with a special acid. He later published, in 1817, the results of further investigation in which he named the substance *morphium* and described it as a *vegetable alkali.* Liebig, in 1831, assigned to it the formula $C_{34}H_{36}N_2O_6$, which was later modified by Laurent to the present formula, $C_{17}H_{19}NO_3$ (285.33).

It was only after almost 100 years of intensive research that the correct structural formula, which adequately explains the chemical transformations of morphine, could be proposed. Final confirmation of this structure came with the successful total synthesis of morphine in 1952.

Preparation—Several processes are in use. In all or nearly all of them the morphine and most of the other opium alkaloids are extracted from the opium with water alone or with slightly acidulated water. In one of the processes, the extract, after concentration, is neutralized, a solution of calcium chloride added, and the mixture filtered and further concentrated. Crude morphine hydrochloride crystallizes and is purified by precipitation with ammonia and recrystallized as the sulfate or hydrochloride. In another process the concentrated water extract is mixed with alcohol and made alkaline with ammonia. The morphine, being but slightly soluble in dilute alcohol, separates, whereas the greater part of the other alkaloids remain in solution. The crude morphine so obtained is purified by repeated crystallization as the sulfate or hydrochloride and reprecipitation if necessary in the presence of alcohol.

Description—*Monohydrate:* colorless or white, shining, rhombic prisms, fine needles or a crystalline powder; darkens on exposure to air; a saturated aqueous solution is alkaline to litmus; melts with decomposition at approximately 255°.

Solubility—*Monohydrate:* 1 g in approximately 5000 mL water (1100 mL boiling water), 210 mL alcohol (98 mL boiling alcohol), 1220 mL chloroform, 6500 mL ether, or 100 mL lime water; insoluble in benzene; readily soluble in solutions of fixed alkali or alkaline earth hydroxides from which it is reprecipitated by ammonium chloride or sulfate.

Comments—An *analgesic, adjunct to anesthesia, antitussive, and nonspecific antidiarrheal agent*. It is a strong analgesic, altering the psychological response to pain and suppressing anxiety and apprehension. It is the drug of choice for the treatment of pain associated with myocardial infarction and for dyspnea associated with acute left ventricular failure and pulmonary edema. It is used in small to moderate doses to relieve constant dull pain and in moderate to large doses to alleviate intermittent, sharp pain of traumatic or visceral origin. Although effects may begin earlier, maximal analgesic effect occurs approximately 20 min after intravenous injection, 50 to 90 min after subcutaneous injection, and 30 to 60 min after intramuscular injection. Analgesia persists for approximately 4 hr, but, in some patients, it may be as short as 2.5 hr or as long as 7 hr.

Although its role as a *preanesthetic* medication is still being elucidated, it generally is agreed that it is of particular value when pain is present preoperatively, in selected types of cardiac surgery, and in poor-risk patients in general. It is an effective *antitussive* agent, but because of its erratic absorption after oral administration and its dependence liability, it should be used as an antitussive agent only when cough is associated with severe pain and cannot be controlled by antitussives having less potential for abuse. This drug and other opioids, such as paregoric, are the most effective and prompt-acting *nonspecific antidiarrheal* agents. They act by enhancing tone in long segments of the longitudinal muscle and inhibiting propulsive contraction of both circular and longitudinal muscle. They are used to treat acute, self-limited diarrhea.

When administered orally, it is absorbed rapidly but incompletely and metabolized equally rapidly to the glucuronide. Thus, the plasma levels after this route are usually only 1/5 to 1/3 those obtained after parenteral injection. The half-life of morphine in plasma or serum during the first 6 hr is between 2 and 3 hr; the serum half-life, between 6 and 48 hr after intravenous administration, ranges from 10 to 44 hr. Approximately 35% of the drug is bound, primarily to the albumin fraction. After parenteral administration 70–80% is excreted during the first 48 hr with 60% as conjugated morphine. After oral administration, approximately only 60% of a given dose is excreted; this probably reflects the incomplete absorption from the GI tract.

Overt symptoms of *overdosage* include coma, pinpoint pupils, and depressed respiration. Shock, decreased body temperature, and pulmonary edema may occur. Treatment includes establishing a patent airway and ventilating the patient. If significant respiratory depression occurs, a suitable opioid antagonist, such as naloxone, should be administered. Other supportive measures should be applied as indicated. Morphine is a *Schedule II* drug under the *Controlled Substances Act*.

MORPHINE SULFATE

Morphinan-3,6-diol, (5α,6α)-7,8-didehydro-4,5-epoxy-17-methyl-, sulfate (2:1) (salt), pentahydrate

[6211-15-0] $(C_{17}H_{19}NO_3)_2.H_2SO_4.5H_2O$ (758.83); *anhydrous* [64-31-3] (668.76).

Description—White, feathery, silky crystals, as cubical masses of crystals, or as a white crystalline powder; odorless and when exposed to air gradually loses water of hydration; darkens on prolonged exposure to light.

Solubility—1 g in 16 mL water, 570 mL alcohol, 1 mL water at 80° or approximately 240 mL alcohol at 60°; insoluble in chloroform or ether.

Comments—See *Morphine* and *Morphine Sulfate Injection.*

MORPHINE SULFATE INJECTION

A sterile solution of morphine sulfate in water for injection. It may contain suitable antimicrobial agents.

Preparation—Solutions of morphine sulfate at a pH above 7 decompose quickly even at room temperature. At a pH of less than 5.5, no change is reported in a 1% solution heated for 1 hr. The pH should be between 2.5 and 6.0. Sterilization should be conducted with a minimum of heat.

Comments—Indicated for the relief of severe pain. It is effective in the control of postoperative pain as well as for relieving preoperative apprehension. Its most important actions are on the brain, especially its higher functions. An initial transitory stimulation is followed by depression of the brain, its higher functions, and its medullary centers. The reflexes and spinal functions usually are stimulated. It affects perception in such a way that the patient is more tolerant to discomfort and pain. In addition it appears to interfere with pain conduction. It depresses the respiratory center, stimulates the vomiting center, depresses the cough reflex, constricts the pupils, increases the tone of the GI and genitourinary tracts, and produces mild vasodilation.

It is contraindicated in bronchial asthma, respiratory depression, or idiosyncrasy to the drug. Overdoses may cause respiratory depression, coma, and death. The drug should be used with caution in extreme ages (infants and elderly) as well as in the debilitated patient, or in patients who have increased intracranial pressure, toxic psychoses, myxedema, or prostatic hypertrophy. Untoward reactions may include allergic reactions, nausea, vomiting, constipation, urinary retention, depression, delirium, and convulsions. Morphine Sulfate Injection is a *Schedule II* drug under the *Controlled Substances Act.*

CODEINE

Morphinan-6-ol, (5α,6α)-7,8-didehydro-4,5-epoxy-3-methoxy-17-methyl-, monohydrate; Methylmorphine

[6059-47-8] $C_{18}H_{21}NO_3.H_2O$ (317.38); *anhydrous* [76-57-3] (299.37).

History—Isolated from opium by the French chemist Robiquet in 1832, who gave it a name derived from the Greek word meaning poppy 'capsules'.

Preparation—Although some codeine is obtained from opium directly, the quantity is not sufficient to meet the extensive use of this alkaloid as a valuable medicinal agent. Much more codeine is used than morphine. This need is met by making it by partial synthesis from morphine. The process involves methylating the phenolic OH of the latter with phenyltrimethylammonium hydroxide. Dry morphine is dissolved in a solution of potassium hydroxide in absolute alcohol, the methylating agent added, and the solution heated. After cooling, water is added, the solution acidified with sulfuric acid, the dimethylaniline product separated, and the alcohol removed by distillation. Treatment with caustic soda solution precipitates the codeine, while any unreacted morphine is held in solution by the sodium hydroxide. The crude codeine is purified by crystallization as the sulfate.

Description—Colorless or white crystals, or a white, crystalline powder; effloresces slowly in dry air and is affected by light; when rendered anhydrous by drying at 80°, it melts within a 2° range between 154° and 158°; sublimes (anhydrous) under reduced pressure; pH (saturated aqueous solution) approximately 9.8.

Solubility—1 g in 120 mL water, 2 mL alcohol, about 0.5 mL chloroform, 50 mL ether, or about 20 mL benzene. When heated in an amount of water insufficient for complete solution, it melts to oily drops that crystallize on cooling.

Incompatibilities—Precipitated from its aqueous solution by most *alkaloidal precipitants* but not by sodium, potassium or ammonium carbonate, or sodium bicarbonate. Aqueous solutions are sufficiently alkaline to precipitate other less soluble alkaloids from solutions of their salts. Ammonia may be liberated from *ammonium salts.*

Comments—May be viewed as morphine with less ceiling efficacy, which fails to produce proportionately greater analgesia as the dose is increased. Indeed, large amounts of codeine may cause excitement. Average doses are *sedative*, *analgetic*, and *antitussive*. When administered by the oral route 30 to 60 mg is equivalent in analgesic effectiveness to approximately 650 mg of aspirin; subcutaneously, 60 mg is somewhat less effective than 10 mg of morphine. Because of different mechanisms of action, codeine plus salicylates or acetaminophen produces enhanced analgesic action.

Codeine is useful for inducing sleep in the presence of mild pain. It is absorbed rapidly after either oral or parenteral administration; onset of action occurs in 15 to 30 min, and analgesia is maintained for 4 to 6 hr. Codeine is metabolized mainly in the liver where it undergoes *O*-demethylation, *N*-demethylation and partial conjugation with glucuronic acid. The drug is excreted largely in the urine as narcodeine and free and conjugated morphine. Like morphine, this drug also produces cortical and respiratory depression, but serious degrees of either are practically unknown. It is less apt than morphine to cause nausea, vomiting, constipation, and miosis. Both tolerance and addiction occur, however, and the same precautions should be observed in its use as for morphine. *Naloxone* is a specific antagonist in cases of acute intoxication.

This drug, like morphine, is employed as an *analgetic*, *sedative*, *hypnotic*, *antiperistaltic*, and *antitussive* agent. It commonly is given in combination with aspirin, acetaminophen, or other agents. Administered alone, codeine is a *Schedule II* drug under the *Controlled Substances Act*. *In combination with aspirin-like drugs, it is classified as Schedule III.*

CODEINE PHOSPHATE

Morphinan-6-ol, (5α,6α)-7,8-didehydro-4,5-epoxy-3-methoxy-17-methyl-, phosphate (1:1) (salt), hemihydrate

[41444-62-6] $C_{18}H_{21}NO_3.H_3PO_4.1/2H_2O$ (406.37); *anhydrous* [52-28-8] (397.36).

Preparation—By dissolving codeine in an equimolecular quantity of aqueous phosphoric acid, adding alcohol, and allowing the salt to crystallize from solution.

Description—Fine, white, needle-shaped crystals or a white, crystalline powder; odorless; readily loses water of hydration on exposure to air and is affected by light; solutions are acid to litmus and levorotatory.

Solubility—1 g in 2.5 mL water, 325 mL alcohol, 0.5 mL water at 80°, or 125 mL boiling alcohol.

Comments—See *Codeine, Morphine,* and *general statement.* Being more soluble then codeine sulfate, the phosphate is preferred to the sulfate.

CODEINE SULFATE

Morphinan-6-ol, (5α,6α)-7,8-didehydro-4,5-epoxy-3-methoxy-17-methyl-, sulfate (2:1) (salt), trihydrate

[6854-40-6] $(C_{18}H_{21}NO_3)_2.H_2SO_4.3H_2O$ (750.86); *anhydrous* [1420-53-7] (698.81).

Preparation—By crystallization from a solution of codeine in diluted H_2SO_4.

Description—White crystals, usually needle-like or a white, crystalline powder; effloresces in dry air and is affected by light; aqueous solution is practically neutral or only slightly acid to litmus.

Solubility—1 g in 30 mL water, 1300 mL alcohol, or approximately 6.5 mL water at 80°; insoluble in chloroform or ether.

Incompatibilities—See the *Alkaloids*. It reacts with *phenobarbital sodium* to produce free alkaloid and phenobarbital, both of which may precipitate unless the vehicle contains a moderate proportion of alcohol.

Comments—See *Codeine, Morphine,* and the introductory statement.

Semisynthetic Opioid Analgesics

In the effort to obtain an agent with the advantages of morphine or codeine without their disadvantages, chemists have modified the structure of these natural alkaloids of opium. Some of these modifications, eg, hydrocodone, hydromorphone, or nalorphine result from making minor chemical alterations in the natural alkaloids, the characteristic nucleus remaining intact. For pharmacological convenience, all of these agents are classified here as semisynthetic opioids. In general, the pharmacological properties exhibited by these agents differ quantitatively from those of the parent substance, but qualitatively they are similar. The several semisynthetic agents employed clinically are described below.

HYDROCODONE BITARTRATE

Morphinan-6-one, (5α)-4,5-epoxy-3-methoxy-17-methyl-, [*R*-(*R*,R**)]-2,3-dihydroxybutanedioate (1:1), hydrate (2:5); Dihydrocodeinone Bitartrate**

[34195-34-1] [6190-38-1] $C_{18}H_{21}NO_3.C_4H_6O_6.2\ 1/2H_2O$ (494.50); *anhydrous* [143-71-5] (449.46).

Preparation—This synthetic alkaloid, 7,8-dihydrocodeinone, is prepared either by catalytic rearrangement of codeine or by controlled hydrolysis and oxidation of dihydrothebaine.

Description—Fine white crystals or a fine white crystalline powder; affected by light; pH (1 in 50 solution) 3.2 to 3.8.

Solubility—1 g in 16 mL water; slightly soluble in alcohol; insoluble in ether or chloroform.

Comments—For the relief of moderate to severe pain and for the symptomatic relief of cough. It is an opioid that is somewhat more sedating and addictive than codeine, and is a *Schedule III* drug under the *Controlled Substances Act*. *It frequently is combined with other drugs such as aspirin-like analgesics, antihistamines, expectorants, and sympathomimetics.*

HYDROMORPHONE HYDROCHLORIDE

Morphinan-6-one-, (5α)-4,5-epoxy-3-hydroxy-17-methyl-, hydrochloride, Dihydromorphinone Hydrochloride; Dilaudid Hydrochloride

[71-68-1] $C_{17}H_{19}NO_3.HCl$ (321.80).

Hydromorphone hydrochloride is 7,8-dihydromorphinone hydrochloride.

Preparation—By electrolytic reduction of morphine or by oxidation of dihydromorphine and then reacting with HCl. US patent 2,649,454.

Description—Fine, white, odorless, crystalline powder, affected by light; aqueous solution is practically neutral or only slightly acid to litmus.

Solubility—1 g in about 3 mL water; sparingly soluble in alcohol; practically soluble in ether.

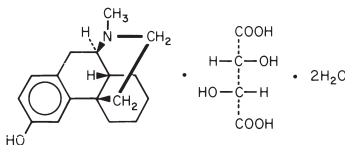
Incompatibilities—Reactions characteristic of alkaloids are generally applicable to this substance.

Comments—A semisynthetic *analgetic*, chemically and pharmacologically similar to morphine, indicated for the relief of moderate to severe pain of myocardial infarction, cancer, trauma (soft tissue and bone), biliary and renal colic, burns, and postoperative pain. It also is used occasionally for its antitussive effects. It is one-fifth as potent orally as intramuscularly; the peak effect occurs later, and the duration of analgesia is longer after oral administration. After parenteral administration, analgesic action is apparent within 15 to 30 min and lasts for 4 to 5 hr. After oral administration, onset of analgesia is approximately 30 min. Slower absorption and hence longer relief from pain can be obtained from its use in suppository form. It has less tendency to cause sleep than morphine when given in equivalent analgetic doses, and thus relief from pain can be obtained without sleep or stupefaction. It is contraindicated in bronchial asthma, respiratory depression, or idiosyncrasy to the drug. It is claimed that the drug causes less constipation and vomiting than morphine; also, it produces less euphoria. However, tolerance and addiction do occur with the drug, and it must be used with the same precautions as for morphine. It can be given by mouth, by rectum in suppository form, or injected subcutaneously or intravenously (in emergency). The high-dose injection (10 mg/mL) should be used only in patients who are tolerant to the opioids and require large doses of these drugs for relief.

Caution—This drug, being a morphine derivative, is a *Schedule II* drug under the *Controlled Substances Act*. *Naloxone* is a specific antagonist in cases of acute intoxication.

LEVORPHANOL TARTRATE

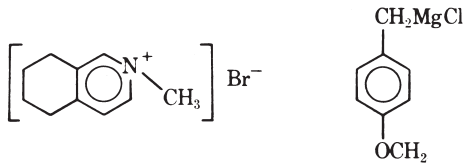
Morphinan-3-ol, 17-methyl-, [*R*-(*R,*R**)]-2,3-dihydroxybutanedioate (1:1) (salt), dihydrate; Levo-Dromoran**



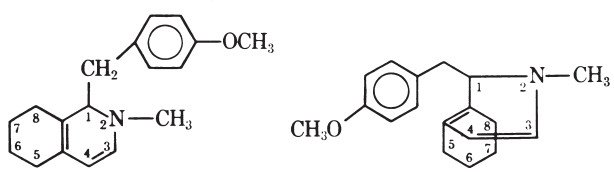
17-Methylmorphinan-3-ol tartrate (1:1) (salt) dihydrate [5985-38-6] $C_{17}H_{23}NO.C_4H_6O_6.2H_2O$ (443.49); *anhydrous* [125-72-4] (407.46).

Preparation—5,6,7,8-Tetrahydro-2-methylisoquinolinium bromide (I) is metathesized with *p*-methoxybenzyl magnesium bromide (II), and the product rearranges at the expense of the 1,2-double bond to form 1-(*p*-methoxybenzyl)-2-methyl-1,2,5,6,7,8-hexahydroisoquinoline (III). III may be redrawn as shown below to display the ensuing reactions more clearly. A solution of the hydrochloride of III is then hydrogenated at the 3,4-positions with the aid of platinized charcoal, and subsequent treatment with ammonia liberates the *dl*-1,2,3,4,5,6,7,8-octahydro compound (IV), which may be resolved into its (+)- and (−)-enantiomers by the usual procedures. The final step in the preparation of the base involves heating the (−)-enantiomer with phosphoric acid at 150° whereby cyclization between the isoquinoline residue and the benzene ring occurs at the expense of the remaining double bond of the isoquinoline. During the treatment with phosphoric acid, the methoxy group simultaneously is converted to hydroxy, thus producing levorphanol (V).

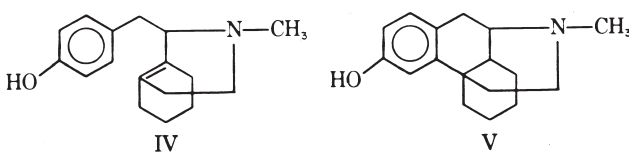
The tartrate may be produced by dissolution of the base in aqueous tartaric acid solution and crystallizing.



I II



III III (Redrawn)



IV V

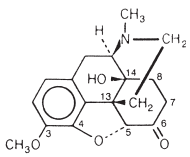
Description—Practically white, odorless, crystalline powder; melts about 115° (anhydrous, about 207°).

Solubility—1 g in 50 mL water or 120 mL alcohol; insoluble in chloroform and ether.

Comments—A potent synthetic analgesic related chemically and pharmacologically to morphine. It produces analgesia at least equal to that of morphine and greater than that of meperidine with much smaller doses than either. It also is longer acting than either of the above; from 6 to 8 hr of pain relief can be achieved after either oral or parenteral administration. Its margin of safety is essentially the same as that of morphine, but it is less likely to produce nausea, vomiting, and constipation. It is indicated whenever an opioid analgesic is required; it is effective for moderate to severe pain and is used parenterally for preoperative sedation as well as an adjunct to nitrous oxide-oxygen anesthesia. The drug is contraindicated in acute alcoholism, bronchial asthma, increased intracranial pressure, respiratory depression, and anoxia. Other precautions and adverse reactions are similar to those induced by other opioid analgesics. It is an opioid with addiction liability similar to that of morphine; therefore, the same precautions should be observed when prescribing this drug as for morphine. The drug is a *Schedule II* drug under the *Controlled Substances Act*.

OXYCODONE HYDROCHLORIDE

4,5-Epoxy-14-hydroxy-3-methoxy-17-methylmorphinan-6-one Hydrochloride; Dihydrodihydroxycodeinone Hydrochloride; OxyContin



[124-90-3] $C_{18}H_{21}NO_4$.HCl (351.83).

Preparation—From thebaine, also obtained from opium. Thebaine is the 3,6-dimethoxy-$\Delta^{6,8}$-diene that on oxidation with H_2O_2 inserts an OH at position 14 and a hemiacetal at 6. Hydrolysis of the hemiacetal forms the ketone at position 6; see Manske, *Chemistry of the Morphine Alkaloids,* Oxford Press, 1954. The hydrochloride is prepared from the base by the usual means.

Description—Odorless, white, crystalline powder; saline, bitter taste; melts with decomposition between 274° and 278°.

Solubility—1 g in 10 mL water or 60 mL alcohol.

Comments—For the relief of moderate to moderately severe pain. Like codeine and methadone, it retains one half of its analgesic activity after oral administration. It often is used to relieve postoperative, postextractional, and postpartum pain. Although oxycodone has less analgesic capability than morphine, it possesses comparable addiction potential and is a *Schedule II* drug under the *Controlled Substances Act*. *It frequently is used in combination with aspirin or acetaminophen*.

OXYMORPHONE HYDROCHLORIDE

(5α)-Morphinan-6-one, 4,5-epoxy-3,14-dihydroxy-17-methyl-, hydrochloride; Numorphan

[357-07-3] $C_{17}H_{19}NO_4$.HCl (337.80).

Preparation—Thebaine is dissolved in aqueous formic acid and treated with 30% hydrogen peroxide, after which neutralization with aqueous ammonia yields 14-hydroxycodeinone. This then is dissolved in acetic acid and hydrogenated with the aid of palladium-charcoal catalyst to form 14-hydroxy-7,8-dihydrocodeinone (oxycodone). In the form of its hydrochloride, this compound is demethylated by means of heating with pyridine hydrochloride to yield crude oxymorphone hydrochloride, which then is purified. US Pat 2,806,033.

Description—White, acicular crystals or as a white or slightly off-white powder; odorless; darkens on prolonged exposure to light; pH (aqueous solutions) approximately 5.

Solubility—1 g in 4 mL water, 100 mL alcohol, >1000 mL chloroform or >1000 mL ether.

Comments—A semisynthetic opioid analgesic with actions, uses, and side effects similar to those of hydromorphone and morphine, except it possesses no significant antitussive activity. After parenteral administration, 1 mg of this drug is approximately equivalent in analgesic activity to 10 mg of morphine. Onset of action is rapid; initial effects usually are seen within 5 to 10 min, duration of action is approximately 3 to 6 hr. It satisfactorily controls postoperative pain, the more severe pain of advanced neoplastic diseases, and other types of pain that ordinarily can be controlled by morphine. It also is used parenterally for preoperative medication as well as a supplement to anesthesia. Except that it is somewhat less constipating, the overall incidence and severity of side effects are similar to those of morphine. Its addiction liability is approximately the same as morphine. It is a *Schedule II* drug under the *Controlled Substances Act*.

Opioid Antagonists

Although *N*-allylnorcodeine was observed in 1915 to prevent or abolish morphine- and heroin-induced respiratory depression, more than 25 yr elapsed before it was demonstrated that *N*-allylnormorphine (nalorphine; no longer available in the US) had even more pronounced morphine-antagonizing properties. Even then the clinical significance of this antagonizing effect was not explored until 1951. Two years later it was shown that nalorphine would precipitate acute abstinence syndromes in postaddicts who had been given morphine, methadone, or heroin for brief periods. It also was shown that nonaddicted subjects given large doses of nalorphine exhibited dysphoria and anxiety rather than euphoria. Subsequently, it was noted that, although nalorphine antagonized the analgesic effects of morphine, it was a potent analgesic when given to patients who have postoperative pain.

Except for meperidine, the substitution of an allyl group for the *N*-methyl group in most of the opioids (eg, morphine, levorphanol, methadone, oxymorphone, and phenazocine) results in drugs with varying levels of opioid antagonistic effect. It should be emphasized that this is not restricted to allyl substitution, because the substitution of other groups (methallyl, propyl, isobutyl, propargyl, or cyclopropargylmethyl) for the *N*-methyl group of opioid analgesics also produces substances that are antagonists.

The term *antagonist*, as used in this section, includes naloxone and naltrexone, which are antagonists with little or no agonist actions. These competitive opioid antagonists are effective in the management of *severe respiratory depression* induced by opioid drugs and of *asphyxia neonatorum* caused by administration of these drugs to the expectant mother and for the *diagnosis or treatment of opioid addiction*.

NALOXONE HYDROCHLORIDE

(5α)-Morphinan-6-one, 4,5-epoxy-3,14-dihydroxy-17-(2-propenyl)-, hydrochloride, Narcan

[357-08-4] $C_{19}H_{21}NO_4$.HCl (363.84); *dihydrate* [51481-60-8] (399.87).

Preparation—*Oxymorphone* is demethylated and the resulting 4,5α-epoxy-3,14-dihydroxymorphinan-6-one is *N*-allylated by reaction in ethanol with allyl bromide in the presence of $NaHCO_3$. The resulting naloxone is reacted with ethanolic HCl. US Pat 3,254,088.

Description—White to slightly off-white powder; aqueous solutions are acidic; melts about 203°.

Solubility—Soluble in water; slightly soluble in alcohol; practically insoluble in chloroform or ether.

Incompatibilities—Long-chain or high-molecular-weight anions (forms relatively insoluble salts) and with alkaline solutions (base precipitates if concentration is high enough); however, the injection is compatible with bulk IV solutions that are slightly alkaline. Also, oxygen, oxidizing agents, bisulfites, or metabisulfites.

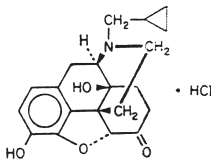
Comments—A synthetic opioid antagonist essentially devoid of opioid agonist properties. Hence, it does not possess morphine-like properties, such as respiratory depression, psychotomimetic effects, and pupillary constriction, characteristic of other opioid antagonists. Available evidence suggests that it antagonizes these opioid effects by competing for the same receptor sites. It is the drug of choice for management of respiratory depression induced by natural and synthetic opioid analgesics, including depression induced by the partial agonist pentazocine. It also is indicated for diagnosis of acute opioid overdosage. It is not effective against nonopioid respiratory depression. Naloxone has been used to detect opioid abuse and can precipitate severe opioid withdrawal symptoms in physically dependent patients. The use of this drug may diminish opioid-dependent euphoria and help reduce the desire for these drugs.

The drug rapidly disappears from serum in man. After an intravenous dose, naloxone is distributed rapidly in the body. The onset of activity generally is apparent within 2 to 5 min; the onset of action is only slightly less rapid when administered by the subcutaneous or intramuscular routes. The mean half-life in adults ranges from 30 to 81 min

(means of 64 and12 min); the mean half-life in neonates is 3.1 and 0.5 hr. It is metabolized in the liver, primarily by glucuronide conjugation, and excreted in the urine. This short duration of action necessitates multiple dosing. Hence, considerable research effort has been directed toward the development of antagonists with a much longer duration of action (see Naltrexone following). Safe and effective use in children younger than 12 yr and in pregnant women has not been established. Adverse effects are said to be rare and usually consist of nausea and vomiting. It is *unscheduled* under the *Controlled Substances Act*.

NALTREXONE HYDROCHLORIDE

Morphinan-6-one, (5α)-17-(cyclopropylmethyl)-4,5-epoxy-3,14-dihydroxy-, Trexan



[16676-29-2] $C_{19}H_{21}NO_4.HCl$ (377.87).

Preparation—From normophine by oxidation at the allylic positions C6 and C14; hydrogenation of the C7-8 double bond and *N*-alkylation with cyclopropylmethyl halide. US Pat 3,332,950.

Description—White crystals; melts about 275°.

Solubility—1 g in approximately 1 mL water.

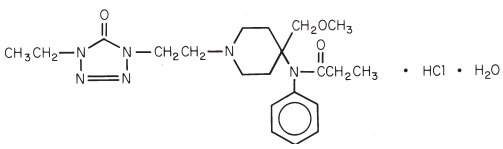
Comments—Naltrexone generally has little or no agonist activity. Its opioid antagonist activity is reported to be 2 to 9 times that of naloxone and 17 times that of nalorphan. Consequently, it is used as an adjunct to the maintenance of the opioid-free state in detoxified, formerly opioid-dependent, individuals. It also has been used in the treatment of postconcussional syndrome unresponsive to other treatments. It is absorbed rapidly and almost completely after oral administration, but undergoes extensive first-pass metabolism in the liver. Only 5–20% of an orally administered dose reaches systemic circulation unchanged. The major metabolite is 6β-naltrexol; this also is a pure antagonist and may contribute to the opioid receptor blockade. Mean elimination half-lives for naltrexone and 6β-naltrexol are 3.9 and 12.9 hr, respectively; pharmacological effects are apparent for 24 and 72 hr and appear to be independent of dose. The drug does not accumulate after chronic administration but is excreted primarily in the urine. Adverse effects most frequently observed (10%) include anxiety, nervousness, headache, low energy, abdominal cramps, nausea, vomiting, and joint and muscle pain. Liver test abnormalities and lymphocytosis have been reported. Patients should wear some identification indicating they are taking this drug.

SYNTHETIC OPIOID AGONIST/ANTAGONIST

The undesirable side effects of morphine and addiction potential stimulated the search for synthetic drugs that would be as analgesic as morphine but have fewer undesirable effects and less addiction potential. Although the ideal analgesic agent has yet to be developed, currently available synthetic agents have valuable analgesic and pharmacological properties that are described in this section.

ALFENTANIL HYDROCHLORIDE

Propanamide, *N*-[1-[2-(4-ethyl-4,5-dihydro-5-oxo-1*H*-tetrazol-1-yl)ethyl]-4-(methoxymethyl)-4-piperidinyl]-*N*-phenyl-, monohydrochloride, monohydrate; Alfenta



[70879-28-6] $C_{21}H_{32}N_6O_3.HCl$ (471.00).

Preparation—See *J Med Chem* 1986; 29:2290.

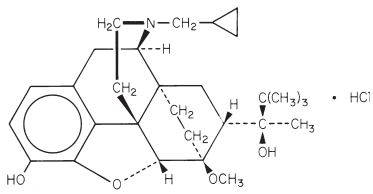
Description—White crystals; melts at 138°.

Comments—A potent synthetic opioid analgesic related to fentanyl but with a more rapid onset of action and a shorter duration of opioid effects. The brief duration (30–60 min after 50 mg/kg intravenous) is advantageous for short surgical procedures but requires frequent injection or continuous infusion for longer operations. Because it is less lipid-soluble than fentanyl, it is less likely to accumulate with prolonged or repeated administration.

Adverse effects include muscular rigidity (chest wall, trunk, and extremities), hypotension and bradycardia, respiratory depression, nausea, vomiting, and dizziness. Large doses over a long period also may prolong postoperative awakening and respiratory depression. It is a *Schedule II* drug under the *Controlled Substances Act*.

BUPRENORPHINE HYDROCHLORIDE

6,14-Ethenomorphinan-7-methanol, 17-(cyclopropylmethy)-α-(1,1-dimethylethyl)-4,5-epoxy-18,19-dihydro-3-hydroxy-6-methoxy-α-methyl-, hydrochloride; Buprenex



Preparation—From thebaine; US Pat 3,433,791.

Description—White crystalline powder; aqueous solutions are weakly acidic.

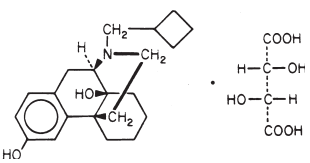
Solubility—Slightly soluble in water.

Comments—A semisynthetic centrally acting opioid analgesic derived from thebaine, it is used for the relief of moderate to severe pain particularly associated with postoperative discomfort. It is approximately 30 times as potent as morphine and exerts its analgesic effect by binding to CNS opioid receptors. It is classified as a partial agonist and exhibits antagonist effects in higher doses. Onset of analgesia occurs within 15 min after intramuscular injection, peaks at 1 hr and persists for up to 6 hr. Approximately 96% is bound to plasma protein and metabolized by the liver. Terminal half-life is 2 to 3 hr. The drug is excreted in the feces as free buprenorphine. Chronic use may produce psychological dependence and may infrequently produce limited physical dependence. Adverse effects related to the *CNS* include sedation (66%), dizziness (5–10%), headache (1–5%), confusion, slurred speech, depression, and hallucinations; *cardiovascular* adverse effects are hypotension or hypertension, tachycardia or bradycardia; *GI* adverse effects are nausea and vomiting, dry mouth, dyspepsia, or flatulence; *respiratory* adverse effects are hypoventilation, dyspnea, or cyanosis; *ophthalmological* adverse effects are miosis, blurred vision, diplopia, or conjunctivitis; *other adverse effects* include pruritus, urinary retention, flushing, chills or coldness, and tinnitus. Safety and efficacy in children has not been established.

Buprenorphine has recently been approved for use in the treatment of opioid abuse.

BUTORPHANOL TARTRATE

(−)-Morphinan-3,14-diol, 17-(cyclobutylmethyl)-, [*R*(*R,*R**)]-2,3-dihydroxybutanedioate (1:1) salt; Stadol**



(−)-17-(Cyclobutylmethyl)morphinan-3,14-diol tartrate (1:1) salt [58786-99-5] $C_{21}H_{29}NO_2.C_4H_6O_6$ (477.55).

Preparation—Total synthesis of *N*-substituted 3,14-dihydroxymorphinans, including butorphanol, from 7-methoxy-1-tetralone, has been reported by Monkovic *et al* (*J Am Chem Soc* 1973; 95:7910).

Description—White, crystalline powder; melts about 219°.

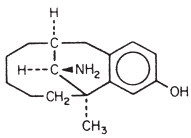
Solubility—Soluble in water.

Comments—A potent analgesic with both opioid agonist and antagonist effects. Analgesic potency is 3. 5 to 7 times that of morphine, 30 to 40 times that of meperidine, 15 to 20 times that of pentazocine, and 1/40 the antagonist potency of naloxone. It is indicated for moderate to severe postsurgical pain to supplement balanced anesthesia and to relieve postpartum pain. After intramuscular injection, analgesia begins within 10 min, reaches peak activity in 30 to 60 min and

persists for 3 to 4 hr. After intravenous administration, peak activity is reached within a few minutes. A 2-mg intramuscular dose is equivalent in analgesic effect to 10 mg of morphine. Although completely absorbed from the GI tract after oral administration, it undergoes approximately 80% first-pass metabolism. Adverse effects observed are similar to those observed after morphine, including dizziness, lightheadedness, and nausea. Transient but disturbing psychotomimetic reactions have been reported after doses of 2 to 4 mg. Two mg depresses the respiration to the same extent as 10 mg of morphine; slow, shallow respiration has been reported in patients taking recommended doses of the drug. The respiratory depression and other effects can be reversed by naloxone. Like pentazocine, the drug increases arterial resistance and the work of the heart; consequently, it is contraindicated in patients who have acute myocardial infarction. It is known to cause euphoria, and tolerance to the analgesic effect has been reported in animals. It also can precipitate withdrawal in opioid-dependent patients. It is a *Schedule IV* drug under the *Controlled Substances Act*.

DEZOCINE

(−)(5α,11α,13*S*)-5,11-Methanobenzocyclodecen-3-ol, 13-amino-5,6,7,8,9,10,11,12-octahydro-5-methyl-, Dalgan**



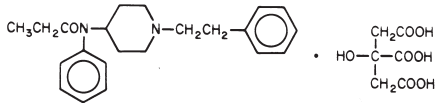
[53648-55-8] $C_{16}H_{23}NO$ (245.37).

Preparation—1-Methyl-7-methoxy-2-tetralone is treated with $Br(CH_2)_5Br$ and NaH to insert a pentamethylene bridge between positions 1 and 3 of the tetralone molecule. Reductive amination of the carbonyl group with NH_2OH and Ni/H_2 followed by demethylation of the 7-methoxy group with HBr affords the product; *J Med Chem* 1973; 16:595.

Comments—A synthetic opioid agonist-antagonist structurally similar to pentazocine. Its analgesic and pharmacokinetic properties are similar to morphine. Its adverse effects are like those of other opioid analgesics and include nausea, vomiting, sedation, and respiratory depression. Dizziness, anxiety, disorientation, hallucinations, and sweating also have been reported. Dezocine is not recommended for use in patients physically dependent on opioids. Extreme caution should be exercised if dezocine is used in combination with other CNS-depressant drugs due to an increased risk to the patient. Although it is likely that because of its opioid agonist-antagonist properties, dezocine has less abuse potential than some of the other opioid analgesics, it probably does have some potential for dependence, particularly in patients who have a history of opioid drug abuse. Dezocine is metabolized extensively in the liver by glucuronide conjugation and excreted in the urine.

FENTANYL CITRATE

Propanamide, *N*-phenyl-*N*-[1-(2-phenylethyl)-4-piperidinyl]-, 2-hydroxy-1,2,3-propanetricarboxylate (1:1); Sublimaze; ing of Innovar



N-(1-Phenethyl-4-piperidyl)propionanilide citrate (1:1) [990-73-8] $C_{22}H_{28}N_2O.C_6H_8O_7$ (528.60).

Preparation—One method consists of condensing propionyl chloride with *N*-(4-piperidyl)aniline, then treating the resulting *N*-(4-piperidyl)propionanilide with phenethyl chloride, aiding each condensation by the presence of a suitable dehydrochlorinating agent. Reaction of the base with an equimolar portion of citric acid yields the (1:1) citrate. US Pat 3,164,600.

Description—White, crystalline powder or glistening crystals; odorless and tasteless (*Note:* because this compound is extremely potent, no taste test is recommended); stable in air; melts at 147° to 152°; pK_a 8.3.

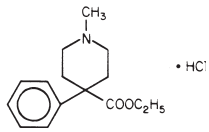
Solubility—1 g in approximately 40 mL of water, 140 mL of alcohol or 350 mL of chloroform.

Comments—A potent opioid analgesic with rapid onset and short duration of action when administered parenterally. Administration of the base via a transdermal patch has a much slower onset (8–12 hr) and a longer duration of action (>72 hr) and often is used to manage chronic pain that necessitates an opioid analgesic. It has a profile of pharmacological action similar to morphine, except that it does not cause emesis or release histamine. Equianalgesia can be obtained with a dose 1/150 that of morphine. After intravenous injection, peak analgesia appears within 3 to 5 min and lasts 30 to 60 min. Fentanyl produces signs and symptoms typical of opioid analgesics, such as miosis, euphoria, and respiratory depression. It is used primarily as an analgesic for the control of pain associated with all types of surgery. It also can be used as a supplement to all agents commonly employed for general and regional anesthesia. It also is an ingredient in *Fentanyl Citrate and Droperidol Injection*, see RPS-18, page 1045.

It is contraindicated in children 2 yr and younger, in asthmatic patients, and in patients who have a history of myasthenia gravis. Other depressant drugs, such as barbiturates, major tranquilizers, tricyclic antidepressants, opioids, and general anesthetics have an additive or potentiating effect on the drug. Its safe use in pregnancy has not been established. It crosses the placental barrier; use during labor may lead to respiratory depression in the newborn infant. It should be used with caution in patients who have liver and kidney disease. Adverse reactions include respiratory depression, apnea, muscular rigidity, and hypotension. Less frequently, nausea and vomiting may occur. Infrequently, dizziness, visual disturbance, itching, euphoria, and spasms of the sphincter of Oddi have been observed. It is a *Schedule II* drug under the *Controlled Substances Act*.

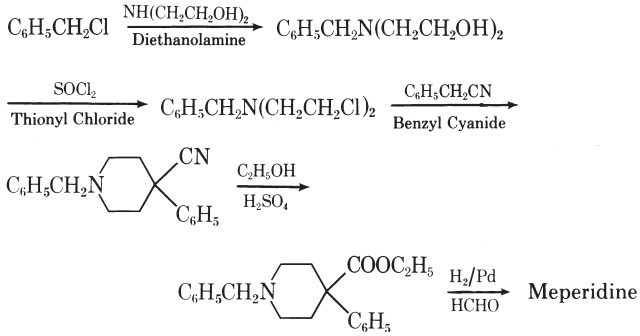
MEPERIDINE HYDROCHLORIDE

4-Piperidinecarboxylic acid, 1-methyl-4-phenyl-, ethyl ester, hydrochloride; Pethidine Hydrochloride; Dolantin, Dolantol, Eudolat, Isonipecaine; Demerol Hydrochloride



Ethyl 1-methyl-4-phenylisonipecotate hydrochloride [50-13-5] $C_{15}H_{21}NO_2.HCl$ (283.80).

Preparation—One of several methods in which benzyl chloride, diethanolamine, and benzyl cyanide are used in the following principal steps:



Removal of the *N*-benzyl group is accomplished by catalytic hydrogenation in acetic acid solution in which a palladium catalyst is used. The addition of formaldehyde to the reduction mixture followed by further catalytic hydrogenation leads to meperidine. The free base is converted to the hydrochloride by neutralization with HCl.

Description—Fine, white, crystalline, odorless powder; stable in air at ordinary temperatures; pH (1 in 20 solution) approximately 5; melts between 186° and 189°; pK_a 7.7 to 8.15.

Solubility—Very soluble in water; soluble in alcohol; sparingly soluble in ether.

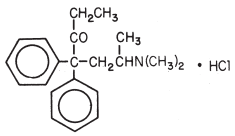
Comments—A synthetic opioid analgesic with multiple actions qualitatively similar to those of morphine; the most prominent of these actions are on the CNS and on organs composed of smooth muscle. It acts principally to induce analgesia and sedation. It is indicated for preoperative use, relief of moderate to severe pain, support anesthesia, and obstetrical analgesia. It crosses the placental barrier; use during labor may lead to respiratory depression in the newborn infant. Available evidence suggests it produces less smooth muscle spasm, constipation, and depression of cough reflex than equianalgesic doses of morphine. In a 60- to 80-mg parenteral dose, it essentially is equal in analgesic effec-

tiveness to 10 mg of morphine; the onset of action is slightly more rapid, and the duration of action is somewhat shorter than morphine.

It is significantly less effective by the oral than by the parenteral route. After intravenous administration of meperidine in healthy adults, the volume distribution at steady state was 269 L; plasma clearance was 1.06 L/min; and elimination half-life was 3.6 hr. Evidence exists that the disposition of meperidine varies between day and night, with elimination half-life shorter and plasma clearance greater at night. It is contraindicated in patients on MAO inhibitors; it inconsistently has precipitated severe, and occasionally fatal, reactions within 14 days in patients who have received such medication. The drug should be used with caution and in reduced dosage in patients on other opioid analgesics, general anesthetics, phenothiazines, sedatives, tricyclic antidepressants, and other CNS depressants. Major adverse reactions include respiratory depression, circulatory depression, respiratory arrest, shock, and cardiac arrest. The most frequent untoward effects include dizziness, sedation, nausea, vomiting, and sweating. Other adverse reactions include euphoria, weakness, headache, agitation, tremor, seizures, transient hallucinations, and disorientation. Some of the CNS toxicity may be due to the neurotoxic metabolite, normeperidine. Because of concern about the incidence and severity of the CNS adverse effects, many clinicians recommend its short-term use only in otherwise healthy adults who are unable to receive other agents. Other effects involving the GI tract, cardiovascular system, and genitourinary tract are similar to morphine. Analgesia is possible with doses that do not cause stupefaction, a decided advantage over morphine. Pain usually is relieved within 20 min to 1 hr, analgesia lasting from 2 to 5 hr. Naloxone is a specific antagonist in cases of acute intoxication It is a *Schedule II* drug under the *Controlled Substances Act*.

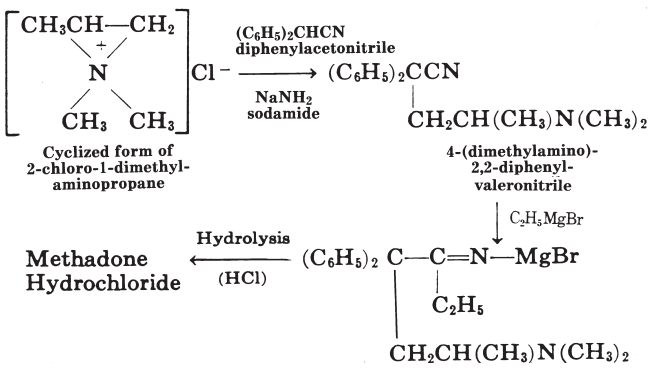
METHADONE HYDROCHLORIDE

3-Heptanone, 6-(dimethylamino)-4,4-diphenyl-, hydrochloride; Dolophine Hydrochloride



Amidone Hydrochloride; [1095-90-5] $C_{21}H_{27}NO.HCl$ (345.91).

Preparation—Diphenylacetonitrile is condensed with 2-chloro-1-dimethylaminopropane in the presence of sodamide, yielding 4-(dimethylamino)-2,2-diphenylvaleronitrile and an unwanted isomeric nitrile in approximately equal amounts. The isomers are separated and the former is subjected to Grignard addition with ethyl magnesium bromide. Subsequent hydrolysis in the presence of hydrochloric acid yields methadone hydrochloride.



Description—Colorless crystals or a white, crystalline, odorless powder; pH (1 in 100 solution) 4.5 to 6.5; optically inactive (the official salt is a racemic mixture of which only the levo form has analgetic activity).

Solubility—1 g in 13 mL water, 8 mL alcohol, or 3 mL chloroform; practically insoluble in ether or glycerin.

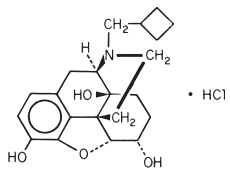
Comments—A synthetic *opioid analgesic* with multiple actions quantitatively similar to morphine, the most prominent of which involve the CNS and organs composed of smooth muscle. The principal actions of therapeutic value are those of *analgesia*, *sedation*, and *detoxification* or *temporary maintenance* in opioid addiction. It also has significant *antitussive* properties but is no longer approved for this use in the US. It is rapidly but probably incompletely absorbed after oral administration, because only 52% of a given dose appears in the urine. Mean plasma levels of 182 and 420 ng/mL have been reported in patients maintained on a daily oral dose of 40 and 80 mg, respectively, 71–87% of which is in bound form. The half-life is approximately 25 hr, with a range of 13 to 47 hr. A parenteral dose of 8 to10 mg is approximately equivalent in analgesic effectiveness to 10 mg of morphine; onset and duration of action of the two drugs are similar.

It is approximately half as potent orally as parenterally. It is indicated for the relief of moderate to severe pain, for detoxification treatment of opioid addiction, and for temporary, or sometimes long-term, maintenance treatment of opioid addiction. If it is administered for heroin treatment for longer than 3 wk, the procedure passes from treatment of the acute withdrawal syndrome (detoxification) to maintenance therapy; the latter use can be undertaken *only* in approved programs, unless the addict is hospitalized for conditions other than addiction. Its abstinence syndrome qualitatively is similar to that of morphine; however, the onset is slower, the course more prolonged, and the symptoms less severe. It can produce drug dependence of the morphine type; therefore, it should be prescribed and administered with the same degree of caution as morphine.

It is contraindicated in patients known to be sensitive to it. The drug should be used with caution and in reduced dosage in patients on other opioid analgesics, general anesthetics, phenothiazine, and other tranquilizers, sedative-hypnotics, tricyclic antidepressants, MAOIs, and CNS depressants as respiratory depression; hypotension, profound sedation, or coma may result. Patients on a maintenance program are given methadone only as an oral liquid form and should not be given pentazocine or rifampin because these drugs may induce withdrawal symptoms. The safe use of the drug in pregnancy has not been established. It is not recommended for obstetrical analgesia, because its long duration may induce respiratory depression in the newborn. Adverse reactions are similar to those for other opioid analgesics (see especially *Meperidine*). It is widely employed in the withdrawal management of patients addicted to morphine, heroin, and related opioid drugs. *Naloxone* is an effective antagonist in cases of acute intoxication. It is a *Schedule II* drug under the *Controlled Substances Act*.

NALBUPHINE HYDROCHLORIDE

(5α,6α)-Morphinan-3,6,14-triol, 17-(cyclobutylmethyl)-4,5-epoxy-, hydrochloride, Nubain



[23277-43-2] $C_{21}H_{27}NO_4.HCl$ (393.91)

Preparation—Refer to US Pat 3,393,197.

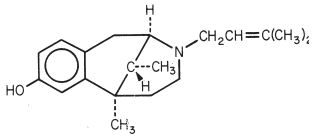
Description—*Base:* white crystals; melts about 230°.

Comments—For the relief of moderate to severe pain. It also may be used for preoperative analgesia, as a supplement to surgical anesthesia and for obstetrical analgesia during labor. It is related chemically to oxymorphone and to the opioid antagonist naloxone. It possesses both agonist and antagonist properties. Thus, it resembles pentazocine pharmacologically. Its analgesic potency when administered parenterally, on a milligram basis, is approximately the same as that of morphine and approximately three to four times greater than that of pentazocine; its antagonistic potency is approximately 10 times greater than that of pentazocine. The onset of action occurs within 2 to 3 min after intravenous administration and within 15 min after intramuscular or subcutaneous administration; it is metabolized in the liver; its plasma half-life is 5 hr and the duration of effect is 3 to 6 hr. Adverse reactions are the same as those for morphine and other potent analgesics. Those most frequently observed include sedation (36%), sweaty or clammy skin (9%), nausea and vomiting (6%), dizziness and vertigo (5%), dry mouth (4%), and headache (3%). Respiratory depression may occur with usual doses of nalbuphine, but it is not dose related; however, it plateaus with a cumulative intravenous dose of approximately 30 mg. The abrupt withdrawal after prolonged administration causes opioid-like abstinence symptoms that are milder than those of morphine but more intense than those of pentazocine. Although it possesses opioid antagonist activity, evidence exists that in nondependent patients it does not antagonize an opioid analgesic administered just before, concurrently, or just after an injection of the drug. Therefore, patients receiving opioid

analgesics, general anesthetics, phenothiazines, other sedatives, hypnotics, or CNS depressants concomitantly may exhibit additive effects. Thus, the dose of one or both agents should be reduced. Clinical experience to support use in children younger than 18 yr is presently unavailable.

PENTAZOCINE

2,6-Methano-3-benzazocin-8-ol, (2α,6α,11*R)-1,2,3,4,5,6-hexahydro-6,11-dimethyl-3-(3-methyl-2-butenyl)-, Talwin**



[359-83-1] $C_{19}H_{27}NO$ (285.43).

Preparation—1,2,3,4,5,6-Hexahydro-6,11-dimethyl-2,6-methano-3-benzazocin-8-ol (I) is condensed with 1-bromo-3-methyl-2-butene by refluxing in *N,N*-dimethylformamide in the presence of sodium bicarbonate. The reaction mixture is filtered, and the crude pentazocine is isolated by means of a suitable solvent extraction process and finally crystallized from aqueous methanol. US patent 3,250,678.

Compound I may be prepared by the following sequence of reactions: 3,4-dimethylpyridine methiodide is converted to 1,3,4-trimethyl-2-(*p*-methoxybenzyl)-1,2-dihydropyridine with *p*-methoxybenzylmagnesium chloride, reduced to 1,3,4-trimethyl-2-(*p*-methoxybenzyl)-1,2,5,6-tetrahydropyridine with sodium borohydride, cyclized (with H_3PO_4 or HBr) to 1,2,3,4,5,6-hexahydro-3,6,11-trimethyl-2,6-methano-3-benzazocin-8-ol, esterified with acetic anhydride and reacted with cyanogen bromide to form 3-cyano-1,2,3,4,5,6-hexahydro-6,11-dimethyl-2,6-methano-3-benzazocin-8-ol acetate, and hydrolyzed with dilute HCl to compound I.

Description—White to pale tan, crystalline powder; odorless; slightly bitter taste; stable in light, heat (ambient room temperature), and air; melts between 147° and 158°; pK_a approximately 8.95.

Solubility—1 g in >1000 mL of water, 11 mL of alcohol, 2 mL of chloroform or 42 mL of ether.

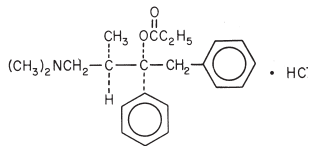
Comments—A synthetic analgesic agent. When administered orally in a 50-mg dose, it appears to be equivalent in analgesic effectiveness to 60 mg of codeine. When given in usual parenteral doses, it is as effective in relieving moderate to severe pain as usual parenteral doses of morphine, meperidine, butorphanol, or nalbuphine. Significant analgesia occurs within 15 to 30 min after oral administration, 15 to 20 min after intramuscular injection, and 2 to 3 min after intravenous administration. Duration of action is usually 3 hr or longer. Half-life after intramuscular administration is 2.1 hr. Onset, duration of action, and degree of pain relief are related both to dose and to the severity of pain. It weakly (approximately 1/50 that of nalorphine) antagonizes the analgesic effect of morphine and meperidine. It also produces incomplete reversal of the cardiovascular, respiratory, and behavioral depression induced by morphine and meperidine. It also has some sedative properties. It is indicated for the control of moderate to severe pain. It is contraindicated in patients hypersensitive to it. It should be used with caution in patients who have head injuries and increased intracranial pressure. Except during labor, its use during pregnancy has not been established. Because of limited experience in children younger than 12 yr, its use in this age group is not recommended. Patients on the drug should be warned not to drive an automobile, operate machinery, or expose themselves to hazards. Although some patients on therapeutic doses exhibit acute CNS manifestations (hallucinations, disorientation, and confusion), such instances are rare and usually clear spontaneously.

GI (nausea, vomiting, diarrhea, infrequent constipation, and abdominal distress), CNS (dizziness, lightheadedness, sedation, euphoria, headache, disturbed dreams, insomnia, syncope, visual blurring, and hallucinations), autonomic (sweating, flushing, and chills), allergic (rash, urticaria, and edema of the face), and cardiovascular (hypotension and tachycardia) adverse effects have been reported. Respiratory depression has also been included among these adverse effects.

Pentazocine has been reported to cause psychological and physical dependence after both oral and parenteral use. This is more common in patients who have a history of drug abuse. It has been abused in combination with the antihistamine, tripelennamine, by parenteral injection. This combination is reported to cause effects similar to those of heroin. It is a *Schedule IV* drug under the *Controlled Substances Act*.

PROPOXYPHENE HYDROCHLORIDE

Benzeneethanol, [*S*-(*R,*S**)]-α-[2-(dimethylamino)-1-methylethyl]-α-phenyl-, propanoate (ester), hydrochloride; Darvon**



[1639-60-7] $C_{22}H_{29}NO_2.HCl$ (375.94).

Preparation—The Mannich base formed by condensation of propiophenone and dimethylamine with formaldehyde is grignardized with benzyl magnesium chloride to produce a mixture of the racemates of the two diastereoisomers (designated commercially as α and β) of the alcohol. The desired α-*dl* form is isolated by fractional crystallization and resolved by means of *d*-camphorsulfonic acid. The desired α-*d* enantiomorph is propionylated with propionic acid in the presence of trimethylamine to form propoxyphene, which adds an equivalent of HCl in forming the hydrochloride.

Description—White, crystalline powder; odorless; bitter taste; melts within a 3° range between 163.5° and 168.5°.

Solubility—Freely soluble in water; soluble in alcohol, chloroform, or acetone; practically insoluble in benzene or ether.

Comments—A mild analgesic structurally related to the opioid analgesic methadone. Although its pharmacological properties resemble those of the opioids as a group, it does not compare with them in analgesic potency. Well-controlled studies indicate that the milligram potency of propoxyphene is approximately one-third to two-thirds that of codeine. It appears that its effectiveness in a dose of 32 mg is questionable, and in a dose of 65 mg it is not more, and usually less, effective than the same dose of codeine or 650 mg of aspirin. It has no anti-inflammatory or antipyretic action and little antitussive activity, despite the fact its levo isomer is used for this purpose. It is indicated for the control of *mild-to-moderate* pain. It is absorbed completely after oral administration; however, first-pass elimination of 30% to 70% significantly reduces its bioavailability. The apparent volume of distribution is 700 to 800 L; oral clearance is 1.3 to 3.6 L/min; and half-life is 6 to 12 hr. The major metabolite, norpropoxyphene, has a half-life of 30 to 36 hr. It is contraindicated in patients hypersensitive to it and to aspirin, phenacetin, or caffeine. The drug should not be used during pregnancy unless in the physician's judgment the potential benefits exceed the potential hazards. The most frequent adverse effects are dizziness, sedation, nausea, and vomiting. Other adverse reactions include constipation, abdominal pain, skin rashes, lightheadedness, headache, weakness, euphoria, dysphoria, and minor visual disturbances. The chronic ingestion of 800 mg/day has caused toxic psychoses and convulsions. The depressant effects of propoxyphene may be experienced with those of other depressant drugs, such as alcohol, tranquilizers and sedative-hypnotics. Moreover, deaths have been reported in patients on excessive doses, either alone or in combination with other CNS depressant drugs. Because both psychological and physical dependence have been induced with this agent, it should be prescribed with the same degree of caution as codeine. Drowsiness or dizziness may occur, which may impair ability to drive or perform other tasks requiring alertness. It is not recommended for children.

PROPOXYPHENE NAPSYLATE

Benzeneethanol, [*S*-(*R,*S**)]-α-[2-(dimethylamino)-1-methylethyl]-α-phenyl-, propanoate (ester), compound with 2-naphthalenesulfonic acid (1:1) monohydrate; Darvon-N**

[26570-10-5] $C_{22}H_{29}NO_2.C_{10}H_8O_3S \cdot H_2O$ (565.72); *anhydrous* [17140-78-2] (547.71).

For the structure of the base, see *Propoxyphene Hydrochloride.*

Preparation—*Propoxyphene* is reacted with an equimolar quantity of aqueous 2-naphthalenesulfonic acid and the salt is crystallized therefrom.

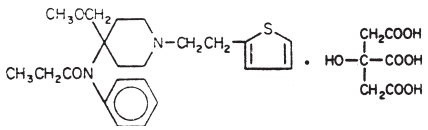
Description—White, bitter, crystalline powder; essentially no odor; melts in a 4° range between 158° and 165°.

Solubility—1 g in 10,000 mL water, 15 mL alcohol, or 10 mL chloroform; soluble in ether.

Comments—Actions, uses, and precautions are the same as *Propoxyphene Hydrochloride,* except that, because of its larger molecular weight, a dose of 100 mg is needed instead of the 65-mg dose of the hydrochloride. This compound permits more stable liquid and tablet dosage forms because of its very slight solubility in water.

SUFENTANIL

Propanamide, *N*-[4-(methoxymethyl)-1-[2-(thienyl)ethyl]-4-piperidinyl]-*N*-phenyl-, 2-hydroxy-1,2,3-propanetricarboxylate (1:1); Sufenta



[60561-17-3] $C_{22}H_{30}N_2S.C_6H_8O_7$ (578.68).

Preparation—*Arzneimittel-Forsch* 26:1521, 1976.

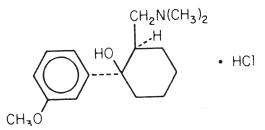
Description—White crystals; melts about 97°.

Comments—A strong opioid analgesic. Its analgesic potency is 5 to 12 times that of fentanyl on a weight basis. High doses can cause amnesia and a loss of consciousness. It is used for balanced anesthesia in general surgery as an adjunct to nitrous oxide and oxygen. It also may be used for induction of surgical anesthesia and as the sole anesthetic agent with a muscle relaxant and oxygen for cardiovascular and neurosurgical procedures. Given intravenously it is metabolized rapidly (elimination half-life, 2.4 hr). The volume of distribution is 2.5 L/kg; 92.5% is bound to plasma protein; plasma clearance is 0.8 L/min. The most common adverse effects include respiratory depression and skeletal muscle rigidity. The rapid intravenous administration of sufentanil may induce a general increase in muscle tone, including chest-wall spasm. Other adverse effects include bradycardia, hypotension, and hypertension. After low doses recovery time is approximately the same as that for fentanyl. Sufentanil is a *Schedule II* drug under the Federal *Controlled Substances Act*.

Mixed-Action

TRAMADOL HYDROCHLORIDE

Cyclohexanol, (±)-*cis*-2-[dimethylaminomethyl]-1-(3-methoxyphenyl)-, hydrochloride; Ultram; Zydol



[22204-88-2]$C_{16}H_{25}NO_2$.HCl (299.84).

Preparation—See US Pat 3,652,589 (1965).

Description—White crystals that melt at approximately 180°

Solubility—Soluble in water.

Comments—It exerts analgesic effect partly by activating the μ opioid receptor, but it is neither an opium derivative nor a semisynthetic derivative. It also inhibits the neuronal reuptake of norepinephrine and serotonin, which is thought to contribute to its analgesic effects. The pain-relieving action of tramadol is only partially blocked by naloxone. It is effective against moderate to moderately severe postoperative, gynecologica, obstetric, cancer, and other pain. Tramadol's principal metabolite is 6 times more potent as an analgesic and has 200 greater affinity for the μ receptor. Although tramadol shares pharmacological and adverse effects of other opioid agonists, such as drowsiness, dry mouth, nausea, and pruritus, the abuse potential appears to be low. Consequently, tramadol is not subject to regulation by the Federal *Controlled Substances Act* of 1970 and is not a scheduled substance. Tramadol causes minor tolerance and withdrawal. In addition, respiratory depression is significantly less than with morphine. The onset of analgesia with this drug occurs within 1 hr and peaks at 2 to 4 hr. Usually the duration of the pain relief is 3 to 6 hr. Seizures have occurred in patients using tramadol.

ANALGESICS, ANTIPYRETICS, AND ANTI-INFLAMMATORIES

Drugs of the analgesic, antipyretic, and anti-inflammatory class include a heterogeneous group of compounds that, unlike those presented in the preceding section, are without significant addiction liability and, therefore, are not subject to regulation under the *Controlled Substances Act*. Many of these agents affect pain, fever, and inflammation and are referred to as the nonsteroidal anti-inflammatory drugs (NSAIDs). Consequently, they are used widely for minor aches and pains, headaches, the general feeling of malaise that accompanies febrile illnesses, and to alleviate symptoms of rheumatic fever, arthritis, gout, and other musculoskeletal disturbances. Acetaminophen is not an NSAID, because it lacks significant anti-inflammatory action, but it has uses similar to the NSAIDs. Several agents (eg, allopurinol, colchicine, probenecid) have pain-relieving properties in various conditions (eg, gout, arthritis); however, because they are of no value in other types of pain, they cannot be classed as true analgesic drugs and are not discussed in this section.

Nonsteroidal Anti-inflammatory Drugs

The principal mechanism of action for all NSAIDs appears to be inhibition of prostaglandin synthesis by blocking the activity of the precursor enzyme, cyclooxygenase (COX). Their actions on prostaglandins likely account for many of the side effects of the NSAIDs. Although, in general, there is little difference between the efficacy of different NSAIDs, some patients may respond to one agent better than another. This is difficult to predict and often necessitates trial and error to find the most suitable drug.

The discovery that NSAIDs inhibit prostaglandin biosynthesis was made by John Vane and coworkers in the early 1970s. Tissue injury activates an enhanced conversion of arachidonic acid to prostaglandins *via* the COX pathway, which is so-named because COX enzymes catalyze the conversion. Because some prostaglandins amplify pain signals, inhibition of COX results in analgesia. NSAIDs have good analgesic efficacy, but less than that of opioids; a relatively rapid onset; well-known adverse effects, including potentially fatal gastrointestinal bleeding and disturbance of salt and water balance. They also have a relatively well-defined mechanism of action. All of the effects of NSAIDs–analgesic, antiinflammatory, antipyretic, and antiplatelet–are believed to be due, directly or indirectly, to inhibition of the biosynthesis of prostanoids, such as PGE_2, which induce inflammation and sensitize nociceptors. Inhibition of other routes of arachidonic acid metabolism, such as the lipoxygenase pathway, does not produce a strong analgesic effect. From x-ray crystallographic studies, it appears that most traditional NSAIDs bind to the polar amino acid arginine at position 120 (Arg^{120}) of cyclooxygenase enzymes. There are at least 2 COX isozymes (COX-1 and COX-2). Because COX-1 and COX-2 isozymes both have an arginine in position 120, the traditional NSAIDs inhibit the catalytic activity of both COX isoforms (ie, they are nonselective COX inhibitors).

The clinical usefulness of NSAIDs is restricted by several adverse effects. Phenylbutazone has been implicated in hepatic necrosis and granulomatous hepatitis; and sulindac, indomethacin, ibuprofen, and naproxen has been implicated in hepatitis and cholestatic hepatitis. Transient increases in serum aminotransferases, especially alanine aminotransferase, have been reported. All of these drugs, including aspirin, because of their inhibition of prostaglandins, can interfere with regulation of glomerular filtration and renal sodium and water excretion. Thus, the NSAIDs can cause fluid retention and decrease sodium excretion, followed by hyperkalemia, oliguria and anuria. Moreover, all of these drugs can adversely affect the stomach and may even cause peptic ulceration. Other side effects include diarrhea with meclofenamate; tinnitis with aspirin; headache with indomethacin, and upper abdominal pain with ketoprofen, meclofenamate, and tolmetin. The ranking of NSAIDs according to toxicity shows indomethacin, tolmetin, and melofenamate to be the most toxic with coated or buffered aspirin and ibuprofen the least. Blood dyscrasias associated with NSAIDs are rare, but death has been attributed to the use of these drugs (estimates range to over 10,000 per year in the United States). All of them can interfere with platelet

function and may cause bleeding in patients taking anticoagulants. In addition, agranulocytosis or aplastic anemia have been reported in patients on indomethacin, ibuprofen, fenoprofen, naproxen, tolmetin, and piroxicam. Phenylbutazone has caused agranulocytosis and aplastic anemia, especially in the elderly,and may cause leukemia.

Other adverse effects attributed to these drugs include dermatitis and allergic reactions as well as CNS effects, such as sedation, agitation, headaches, and tinnitis. Patients taking these drugs for long periods should have periodic white cell counts and determinations of serum creatinine levels and hepatic enzyme activities.

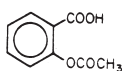
Salicylate-like Nonsteroidal Anti-inflammatory Drugs

The salicylate group of analgesics and antipyretics are commonly employed. Indeed, these are consumed at a rate in excess of 10,000 tons annually. In general, salicylates are contraindicated in hypersensitive individuals and in those who have GI disturbances, particularly hemorrhaging ulcers. They also should be used with caution in patients on anticoagulant therapy and avoided in patients on uricosurics. The salicylates interact with a wide variety of agents, some of which are important clinically, whereas others are largely of theoretical interest. Nevertheless, the well-informed pharmacist should be knowledgeable of the potential interactions between salicylate drugs:

Antidiabetic agents (increased hypoglycemia)
Oral anticoagulants (displacement of anticoagulants from protein binding sites, increased anticoagulant effect)
Uricosuric agents (relative effect of large and small doses of salicylates)
Antiarthritic drugs (may lower plasma concentrations of these agents)
Alcohol (which enhances GI bleeding)
Tetracycline (may complex with buffering agent in some aspirin products)

ASPIRIN

Benzoic acid, 2-(acetyloxy)-,



Acetylsalicylic acid [50-78-2] $C_9H_8O_4$ (180.16).

Preparation—Salicylic acid is acetylated directly with acetic anhydride and the crude material purified by recrystallization from benzene or various other nonaqueous solvents. A granulated form of aspirin, either white or colored, also is available commercially for compression into tablets.

Description—White crystals, commonly tabular or needle-like, or a white, crystalline powder; odorless or a faint odor; stable in dry air (in moist air it gradually hydrolyzes into salicylic and acetic acids, the odor of the latter becoming noticeable); melts about 135°, but the exact melting temperature varies with the conditions of the test; an alcoholic solution is not colored violet by ferric chloride (distinction from salicylic acid).

Solubility—1 g in approximately 300 mL water, 5 mL alcohol, 17 mL chloroform, or approximately 10 to 15 mL of ether; less soluble in absolute ether; dissolves with decomposition in aqueous solutions of alkali hydroxides or carbonates.

Incompatibilities—Can form a damp to pasty mass when triturated with *acetanilid, acetophenetidin, antipyrine, aminopyrine, methenamine, phenol,* or *salol.* Powders containing aspirin with an alkali salt such as *sodium bicarbonate* may become gummy on contact with atmospheric moisture owing to a partial solution and subsequent hydrolysis of the aspirin. Hydrolysis likewise occurs in admixture with salts containing water of crystallization. Solutions of alkali acetates and citrates, as well as alkalies themselves, dissolve this drug, but the resulting solutions hydrolyze rapidly to form salts of acetic and salicylic acids. Sugar and glycerin have been shown to hinder the decomposition. It very slowly liberates hydroidic acid from *potassium* or *sodium iodide.* Subsequent oxidation by the air produces free iodine.

Comments—Of the salicylate drugs, aspirin (acetylsalicylic acid) is the most frequently used. All commercially available salicylates have similar pharmacological properties, so aspirin is discussed as the prototype for this group. Aspirin is employed as an antipyretic and analgetic in a variety of conditions. It is indicated for the relief of pain from simple headache, discomfort, and fever associated with the common cold and minor muscular aches and pains. When drug therapy is indicated for the reduction of a fever, it is one of the most effective and safest drugs.

Epidemiological evidence has suggested the possibility of an association between the use of aspirin in the treatment of fever in children who have varicella (chickenpox), a common cold, or influenza virus infections and the subsequent development of Reyes syndrome. The current opinion is that aspirin should not be prescribed under usual circumstances for children who have upper respiratory, viral infections. If control of fever, aches, and pains are necessary, alternative measures should be employed.

In gout and in acute rheumatic fever, the salicylates, including aspirin, have a fairly specific action. In gout, large doses must be given often, and the results are somewhat less drastic than with phenylbutazone or allopurinol. In acute rheumatic fever, full doses are given every hour until salicylism occurs (ringing in ears, dizziness); thereafter, it is given every 4 hr for days or weeks. In neither of the above-mentioned conditions are the salicylates a cure, and other forms of treatment are employed simultaneously. After oral administration, peak plasma levels are reached within 1 to 2 hr, and fairly constant levels are maintained for 4 to 6 hr.

Plasma half-life after oral administration of 1 g of aspirin ranges from 4.7 to 9 hr, with an average of 6 hr. With toxic doses (10–20 g) the half-life may be increased to 22 hr. A direct correlation between plasma levels and clinical effectiveness has not been established, but analgesia usually is achieved at plasma levels of 15 to 30 mg/100 mL, anti-inflammatory activity at 20 to 40 mg/100 mL, and some symptoms of salicylism at 35 mg/100 mL. It is bound poorly to plasma protein; nevertheless, with therapeutic doses, from 50% to 80% is bound to plasma proteins.

Adverse effects from usual doses of the drug are infrequent; most common are GI disturbances (dyspepsia, nausea, vomiting, and occult bleeding). Prolonged administration of large doses (3.6 g/day) results in occult bleeding and may result in anemia. Massive GI hemorrhage can occur and, although its relation to peptic ulcer is uncertain, a nonsalicylate analgesic may be preferred in high-risk patients.

As evidenced by substantial fecal blood loss, alcohol increases the gastric bleeding caused by aspirin in many patients. Concomitant use of the drug and corticosteroids or pyrazolone derivatives (phenylbutazone) may increase the risk of GI ulceration. Its use with fenoprofen, ibuprofen, indomethacin, or naproxen may cause a lowering of plasma concentrations and thus reduce the effectiveness of the latter drugs. It displaces highly bound coumarin-type anticoagulants from protein-binding sites and thus increases the concentrations and effects of the anticoagulants.

The hypoglycemic action of oral sulfonylureas may be increased by concurrent administration of the drug. The uricosuric activity of probenecid and sulfinpyrazone are inhibited when either drug is administered simultaneously with aspirin. Buffered aspirin formulations that contain calcium, magnesium, or aluminum may form complexes with tetracycline from which absorption of the antibiotic is impaired.

Salicylates account for many accidental poisonings that may result from promiscuous use of large doses of these agents by the laity. To avoid accidental poisoning of children, this drug and other salicylate drugs should be kept out of their reach; also, caution in use of these drugs in children who have fever and dehydration is necessary because they are particularly prone to intoxication from relatively small doses of the drugs. In addition, some few people manifest idiosyncrasy in the form of an allergic sensitivity to salicylates, especially this drug, and may suffer from serious, if not fatal, asthma after ingestion of a single 300-mg dose. Consequently, it should be used with great care in patients who have asthma, nasal polyps, or allergies.

It crosses the placental barrier and is excreted into breast milk. As use of aspirin before delivery may have inhibited platelet aggregation and diminished factor XII plasma levels in newborn infants, it has been suggested that no salicylate be ingested during the last month of pregnancy. Chronic high-dose therapy has been reported to increase the length of gestation and to prolong labor.

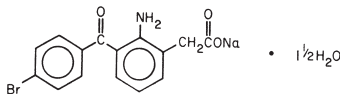
Several studies indicate that low doses of aspirin reduce the risk of myocardial infarction, stroke, and perhaps colon cancer.

Nonsalicylate Nonsteroidal Anti-Inflammatory Drugs

This group of NSAIDs include derivatives from propionic, acetic, and anthranilic acids, as well as oxicam. Little distinguishes the clinical profile of these NSAIDs from the others.

BROMFENAC SODIUM

Benezenacetic acid, 2-amino-3-(4-bromobenzoyl)-, monosodium salt, sesquihydrate; Duract



[12638-5-3] $C_{15}H_{11}BrNNaO_3.1\ 1/2H_2O$ (338.17).

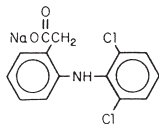
Preparation—From 2-amino-4′-bromobenzophenone and ethyl 2-(methylthio)acetate in the presence of *t*-butyl hypochlorite to form 3-(methylthio)-6-(*p*-bromobenzoyl)-2(1*H*)-indoline through the sulfonium ion intermediate, followed by rearrangement. The methylthio group is removed by catalytic reduction (Raney nickel) with subsequent hydrolysis of the resulting amide to yield the free acid. See *J Med Chem* 1984; 27:137.

Description—Orange crystals melting about 285° with decomposition.

Solubility—Soluble in water, alcohol, or dilute aqueous alkali; insoluble in organic solvents or dilute aqueous acid.

DICLOFENAC SODIUM

Benzeneacetic acid, 2-[(2,6-dichlorophenyl)amino]-, monosodium salt; Voltaren



[15307-79-6] (salt); [15307-86-5] (free acid) $C_{14}H_{10}Cl_2NNaO_2$ (318.13).

Preparation—Oxalyl chloride and 2,6-dichlorodiphenylamine are condensed to form the *N*, *N*-diphenyloxanilyl chloride that cyclizes under Friedel-Crafts conditions to yield 1-(2,6-diphenyl)isatin. Wolff-Kishner reduction of the 3-oxo group gives the lactam, which on hydrolysis affords the free acid. Neutralization with NaOH produces the salt; US Pat 3,558,690.

Description—White crystals; melts about 284°; pK_a 4.0.

Solubility—Soluble in water; insoluble in organic solvents.

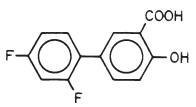
Comments—A pharmacological activity much like the other NSAIDs. As with other drugs in this group, diclofenac is thought to exert many of its effects as a result of its ability to inhibit prostaglandin synthesis.

Diclofenac is used as an anti-inflammatory, analgesic, and occasionally an antipyretic. Its anti-inflammatory action is similar to other NSAIDs with a potency, on weight basis, that is approximately 2.5 times that of indomethacin. On a weight basis, its analgesic potency is 8 to 16 times that of ibuprofen. It is used in the symptomatic relief of acute and chronic rheumatoid arthritis, osteoarthritis, and ankylosing spondylitis. It also has been used to relieve mild-to-moderate postoperative pain associated with dental, orthopedic, or postpartum procedures. It is also effective in relieving some cancer-related visceral pains. Diclofenac doses of 75 to 100 mg/day are equally effective in relieving pain as 0.9 to 2.7 g of aspirin or 1.2 g of ibuprofen. It is also effective in relieving some of the discomforts associated with dysmenorrhea.

Most of the adverse effects of diclofenac are similar to those of other NSAIDs and occur in several systems. The GI effects can include irritation, bleeding, ulceration, and eventually wall perforation. Such effects usually are associated with chronic, high-dose treatments. However, with usual therapeutic doses, diclofenac is less likely to cause serious GI problems than aspirin or naproxen. Diclofenac can cause headaches and dizziness in 3–9% and 1–3%, respectively, of patients. Use of this drug has been associated with renal impairment in less than 1% of patients. Severe hepatic reactions occur rarely, whereas 1–3% of patients may experience a rash or pruritus when using the drug. Tinnitus has been reported in 1–3% of patients using this drug, and fluid retention occurs in 3–9%. Because of its anticlotting actions, Diclofenac should be used with caution in patients who would be put at risk by prolonging bleeding time.

DIFLUNISAL

[1,1′-Biphenyl]-3-carboxylic acid, 2′,4′-difluoro-4-hydroxy-, Dolobid



[22494-42-4] $C_{13}H_8F_2O_3$ (250.20).

Preparation—Refer to US Pat 3,714,226.

Description—White crystals; melts at approximately 210°.

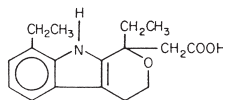
Solubility—Sparingly soluble in water; soluble in most organic solvents or dilute aqueous bases.

Comments—A prostaglandin inhibitor, nonsteroidal analgesic, and anti-inflammatory drug used in the management of mild-to-moderate pain and osteoarthritis. It also has measurable, but not clinically useful, antipyretic activity. Double-blind studies indicate that a 500-mg dose of the drug is more effective in the control of postoperative episiotomy pain than 600 mg of aspirin; in postoperative oral surgery 500 to 1000 mg of the drug was more potent than 600 mg of acetaminophen alone and comparable with 600 mg of acetaminophen with 60 mg of codeine, and more effective than 100 mg of propoxyphene napsylate. Moreover, it had a longer duration of action. After oral administration, peak plasma levels occur within 2 to 3 hr. Approximately 99% is bound to plasma proteins. Plasma half-life is 8 to 12 hr. Approximately 90% of the drug is excreted in the urine as two soluble glucuronide conjugates. Although it is a derivative of salicylic acid, it is not metabolized to salicylic acid.

The drug is contraindicated in patients in whom acute asthmatic attacks, urticaria, or rhinitis are precipitated by aspirin. It prolongs the clotting time in patients on anticoagulant therapy, significantly increases plasma levels of hydrochlorathiazide and acetaminophen, decreases the hyperuricemic effect of furosemide, and significantly decreases the urinary excretion of naproxen and its glucuronide metabolite. The most prominent side effects include nausea, dyspepsia, GI pain, and diarrhea; dizziness, headache, and rash also have been reported in 3–9% of patients. It appears to cause less GI bleeding than aspirin. Aspirin or acetaminophen should not be taken with this drug, except on professional advice.

ETODOLAC

Pyrano[3,4-*b*]indole-1-acetic acid, 1,8-diethyl-1,3,4,9-tetrahydro-, Lodine



[41340-25-4] $C_{17}H_{21}NO_3$ (287.36).

Preparation—See *J Med Chem* 19:391, 1976.

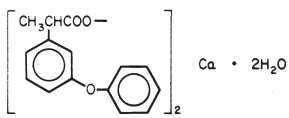
Description—White crystals; melts about 147°; pK_a 4.65.

Solubility—1 g in 10 mL water or 4 mL alcohol.

Comments—An *NSAID* used for osteoarthritis and rheumatoid arthritis.

FENOPROFEN CALCIUM

Benzeneacetic acid, (±)-α-methyl-3-phenoxy-, calcium salt (2:1), dihydrate; Nalfon



(±)-Calcium *m*-phenoxyhydratropate dihydrate [53746-45-5] $C_{30}H_{26}CaO_6.2H_2O$ (558.64); *anhydrous* [34597-40-5] (522.61).

Preparation—From *p*-phenoxyacetophenone by reduction of the phenone carbonyl group to the secondary alcohol; replacing the OH with Br using PBr_3; nucleophilic substitution of Br by CN followed by hydrolysis to the acid, which is converted to the calcium salt. *J Med Chem* 19:391, 1976.

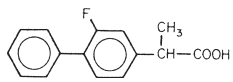
Description—White, crystalline powder; pK_a 4.5 (fenoprofen).

Solubility—Slightly soluble in water; sparingly soluble in alcohol.

Comments—An *NSAID* propionic acid derivative like *Ibuprofen*.

FLURBIPROFEN

(±)-[1,1′-Biphenyl]-4-acetic acid, 2-fluoro-α-methyl-, Ansaid



[5104-49-4] $C_{15}H_{13}FO_2$ (255.26)

Preparation—The Willgerodt reaction on 3-fluoro-4-phenylacetophenone yields the corresponding phenylacetic acid ester, which, with $NaOC_2H_5$ and ethyl carbonate, forms the substituted malonic ester. The ester is methylated by the classical method, hydrolyzed, and decarboxylated to the product; US Pat 3,755,427.

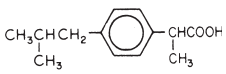
Description—White to slightly yellow powder; melts about 110°.

Solubility—Slightly soluble in water; soluble in dilute alkali; freely soluble in alcohol.

Comments—An *NSAID* used topically in ophthalmology to prevent miois during ocular surgery.

IBUPROFEN

Benzeneacetic acid, (±)-α-methyl-4-(2-methylpropyl)-, Rufen, Nuprin, Advil, Haltran, Motrin, Medipren



(±)-*p*-Isobutylhydratropic acid; (±)-2-(*p*-isobutylphenyl)propionic acid [15687-27-1] $C_{13}H_{18}O_2$ (206.28).

Preparation—Isobutylbenzene is acetylated in the *para* position by a Friedel-Crafts procedure on acetophenone, which is treated with HCN to yield the cyanohydrin. Heating with HI and red P hydrolyzes the nitrile to the acid and simultaneously reduces the hydroxyl group; *J Org Chem* 43:2936, 1978.

Description—White to off-white, crystalline powder; slight characteristic odor and taste; melts about 75°; apparent pK_a 5.2.

Solubility—Slightly soluble in water; soluble in alcohol or other organic solvents.

Comments—An *NSAID* that possesses *analgesic* and *antipyretic* activities. In mild-to-moderate pain, 200 mg appears to be as effective as 650 mg of aspirin. When used to relieve dysmenorrhea, it is as effective as mefenamic acid and more effective than aspirin or propoxyphene. Like other NSAIDs its mechanism of action likely relates to its inhibition of prostaglandin synthesis. Evidence that it does have a salutary effect in the treatment of chronic rheumatoid arthritis and osteoarthritis is shown by a reduction of joint swelling, decrease in pain, decrease in duration of morning stiffness, and improved functional capacity as indicated by an increase in grip strength, a delay in the time to onset of fatigue, and a decrease in the time to walk 50 ft.

The drug is absorbed rapidly after oral administration, and peak plasma serum levels generally are attained within 1 to 2 hr after oral administration. With single doses from 200 to 800 mg, a dose–response relation exists between the amount of drug administered and the integrated area under the serum drug concentration versus time curve. It is metabolized rapidly and eliminated in the urine; excretion virtually is complete 24 hr after the last dose of drug. The serum half-life is 1.8 to 2.0 hr.

It is indicated for relief of symptoms of rheumatoid arthritis and osteoarthritis. It also is indicated for the relief of mild-to-moderate pain, for the treatment of primary dysmenorrhea, and as an antipyretic. It is contraindicated in individuals sensitive to the drug or in individuals who have the syndrome of nasal polyps, angioedema, and bronchospastic reactivity to aspirin or other NSAIDs. Peptic ulceration and GI bleeding have been reported. Consequently, it should be given under close supervision to patients who have a history of upper GI tract disease. Blurred or diminished vision, scotomata, and other changes in color vision have been noted; should such occur, the drug should be discontinued and the patient given an ophthalmological examination.

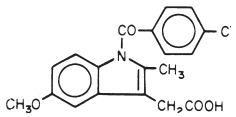
Patients should be cautioned to report signs or symptoms of GI ulceration or bleeding, blurred vision or other eye symptoms, skin rash, weight gain, or edema to their physicians. This drug, like aspirin and other NSAIDs, can inhibit platelet function and prolong bleeding time, but the effects are reversible and not as long lasting as those of aspirin. Nevertheless, it should be administered with caution to patients on anticoagulants. It is not recommended for use in pregnant women or nursing mothers.

Adverse reactions with an incidence greater than 1% may be categorized as *GI* (4–16%) (eg, nausea, epigastric pain, heartburn, diarrhea, abdominal distress, nausea and vomiting, indigestion, constipation and abdominal cramps, or pain), *CNS* [eg, dizziness (3–9%), headache, nervousness, and tinnitus], *dermatologic* [eg, rash (3–9%) and pruritus], and *metabolic* (eg, decreased appetite, edema, and fluid retention).

Adverse effects with an incidence of less than 1% include *GI* (gastric or duodenal ulcer with bleeding or perforation), *dermatologic* (vesiculobullous eruptions, urticaria, and erythema multiforme), *CNS* (depression or insomnia), *special senses* [amblyopia (blurred or diminished vision, scotomata, or other changes in vision)], *hematologic* (leukopenia and decreases in hemoglobin and hematocrit), and *cardiovascular* (congestive heart failure in patients who have marginal cardiac function and elevated blood pressure). Other reactions have been reported but under circumstances in which a causal relation could not be established.

INDOMETHACIN

1*H*-Indole-3-acetic acid, 1-(4-chlorobenzoyl)-5-methoxy-2-methyl-, Indocin, Indocin SR

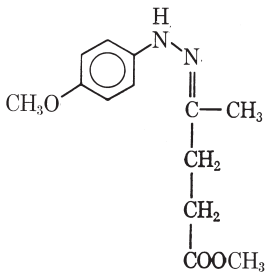


[53-86-1] $C_{19}H_{16}ClNO_4$ (357.79).

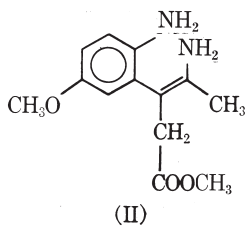
Preparation—*p*-Anisidine is diazotized and the diazonium compound reduced with sodium sulfite. The resulting *p*-methoxyphenylhydrazine undergoes the Fisher indole synthesis with methyl levulinate. The steps involved include formation of the hydrazone (I), rearrangement of I to the enamine compound II, and cyclization of II through loss of ammonia to form III. III is then hydrolyzed to the acid, which is re-esterified by means of the anhydride to give the *tert*-butyl ester. Acylation with *p*-chlorobenzoyl chloride followed by debutylation yields indomethacin. US Pat 3,161,654.

Description—Pale-yellow to yellow-tan, crystalline powder; odorless or a slight odor; slightly bitter taste; light sensitive, stable in air and stable in heat under the usual prevailing temperature conditions; one polymorphic form melts about 155°, the other about 162°.

Solubility—1 g in 50 mL alcohol, 30 mL chloroform, or 40 mL ether; practically soluble in water.



(I)



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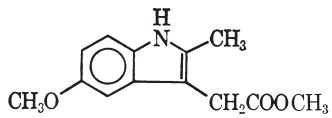


(III)

Comments—A nonsteroidal drug with anti-inflammatory, antipyretic, and analgesic properties. *It is not a simple analgesic and, because of its potential serious untoward effects, should not be used for trivial or minor problems*. It is indicated for the treatment of *rheumatoid arthritis*, *ankylosing (rheumatoid) spondylitis*, *osteoarthritis*, *bursitis*, *tendinitis*, *gouty arthritis*, and *patent ductus arteriosus in premature neonates*. The drug is absorbed rapidly after oral administration; peak plasma levels are reached in 2 hr; 97% of the drug is protein bound. It has a half-life of 2.6 to 11.2 hr; 10–20% of the drug is excreted unchanged in the urine. Because it is a potent drug and has a potential to cause severe adverse effects, it should be considered carefully for an active disease unresponsive to adequate trial with salicylates and other established measures, such as appropriate rest. The drug is contraindicated in children, pregnant women, and nursing mothers, patients who have GI problems, and patients who are allergic to aspirin.

The incidence of untoward effects has been reported to vary from a few percent to 75% of patients. Most frequent untoward actions include *GI* (single or multiple ulcerations, hemorrhage, GI bleeding, increased pain in ulcerative colitis, gastritis, nausea, vomiting, and epigastric distress), *eye reactions* (corneal deposits, retinal disturbances, and blurring of vision), *hepatic* [toxic hepatitis and jaundice (some fatalities have been reported)], *hematologic* (aplastic anemia, hemolytic anemia, depression of the bone marrow, agranulocytosis, leukopenia, and thrombocytopenia purpura), *hypersensitivity* [acute respiratory (including asthma and dys-

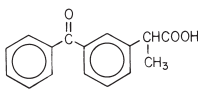
pnea), angiitis, pruritus, urticaria, skin rashes, etc.], *ear* [deafness (rarely) and tinnitus], *CNS* (psychotic disturbances, depersonalization, depression, mental confusion, coma, convulsions, peripheral neuropathy, drowsiness, lightheadedness, dizziness, and headache); *cardiovascular renal* (edema, hypertension, hematuria), *dermatologic* (loss of hair and erythema nodosum), *miscellaneous* (vaginal bleeding, hyperglycemia, glycosuria, ulcerative stomatitis, and epistaxis). Both the incidence and the severity of side effects appear to be dose related.

The high potential for dose-related adverse reactions (see above) makes it imperative that the smallest effective dosage be determined for each patient. GI reactions may be reduced if the patient takes the drug with food, immediately after meals, or with antacids. The occurrence of ocular or hematological disturbances in some patients on prolonged therapy with the drug indicates the need for periodic ophthalmological examination and appropriate blood tests. Whether the drug has any effect on anticoagulants is uncertain, but concurrent administration may be hazardous because of increased risk of GI bleeding.

It may aggravate psychiatric disturbances, epilepsy, and parkinsonism; it should be used with considerable caution in patients who have these conditions. Patients should be warned that ability to drive or perform other activities requiring alertness might be affected adversely. The drug should be discontinued if any of the untoward effects listed above occurs, pending consultation with the physician.

KETOPROFEN

Benzeneacetic acid, 3-benzoyl-α-methyl-, Orudis



[22071-15-4] $C_{16}H_{14}O_3$ (254.28).

Preparation—The diazonium salt prepared from 2-(*p*-aminophenyl)propionic acid is converted to the mercaptan (**I**) with potassium ethyl xanthate followed by hydrolysis. **I**, with *o*-iodobenzoic acid yields the corresponding diphenyl sulfide. The carboxyl group *ortho* to the sulfur atom cyclizes with the adjacent ring to form a thioxanthone configuration followed by desulfurization to reopen the ring and reform the benzophenone product; *Farmaco Ed Sci* 35:684, 1980.

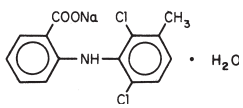
Description—White to off-white, odorless, crystalline, nonhygroscopic powder; melts about 95°.

Solubility—Practically insoluble in water; soluble in fixed bases; freely soluble in alcohol, chloroform, acetone, or ether.

Comments—An *NSAID* propionic derivative like *Ibuprofen*, but lower doses are needed and available.

MECLOFENAMATE SODIUM

Benzoic acid, 2-[(2,6-dichloro-3-methylphenyl)amino]-, monosodium salt, monohydrate



Monosodium *N*-(2,6-dichloro-*m*-tolyl)anthranilate monohydrate [6385-02-0] $C_{14}H_{10}Cl_2NNaO_2.H_2O$ (336.15).

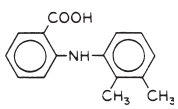
Preparation—By the Ullman condensation of *o*-iodobenzoic acid and 2,6-dichloro-*m*-toluidine in the presence of copper-bronze, *J Med Chem* 11:1009, 1968.

Description—White crystals; melts about 290°; a saturated solution in water (1 g in 65 mL) is slightly turbid; pH approximately 7.5.

Comments—An *NSAID* related to *Mefenamic Acid*.

MEFENAMIC ACID

Benzoic acid, 2-[(2,3-dimethylphenyl)amino]-, Ponstel



N-(2,3-Xylyl)anthranilic acid [61-68-7] $C_{15}H_{15}NO_2$ (241.29).

Preparation—*o*-Chlorobenzoic acid is condensed with 2,3-xylidine with the aid of potassium carbonate, and the resulting potassium salt is treated with mineral acid to liberate the desired acid. *J Med Chem* 11:111, 1968.

Description—White to off-white, crystalline powder; odorless; little initial taste, but a bitter aftertaste; darkens on prolonged exposure to light, nonhygroscopic; stable up to 45°; decarboxylates at temperature above its melting point (at 300°, 100% is decarboxylated in 3 min); melts about 230°.

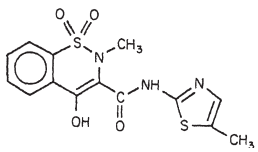
Solubility—1 g in 220 mL of alcohol; insoluble in water; sparingly soluble in chloroform or ether.

Comments—An analgesic drug used for the relief of moderately severe pain when *therapy will not exceed 1 wk* and for the treatment of *primary dysmenorrhea*. It also is indicated for the relief of pain resulting from postoperative pain. It is contraindicated in patients who have ulceration of the upper or lower intestinal tract, children younger than 14 yr, women during pregnancy, or patients known to be hypersensitive to the drug. Untoward effects include diarrhea, which may be severe and indicates the drug should be stopped; autoimmune hemolytic anemia; thrombocytopenic purpura; leukopenia; pancytopenia; agranulocytosis; and bone-marrow hypoplasia.

Minor reactions include drowsiness, GI discomfort, dizziness, headache, vomiting, urticaria, rash, eosinophilia, blurred vision, insomnia, and perspiration. Rarely, palpitations, facial edema, dyspnea, eye pain, ear pain, dysuria, hematuria, reversible loss of color vision, and increased insulin need in diabetic patients. Mild renal and hepatic toxicity also have been reported. As with all drugs, physicians would be well advised to consider its use only in cases that either cannot tolerate or do not respond to less-toxic agents.

MELOXICAM

2*H*-1,2-Benzothiazine-3-carboxamide, 4-hydroxy-2-methyl-*N*-(5-methyl-2-thiazolyl-, 1,1-dioxide; Mobic



[71125-38-7] $C_{14}H_{13}N_3O_4S_2$ (351.41).

Preparation—The imide of 2-carboxybenzenesulfonic acid and methyl chloroacetate are reacted in a modified Hinsberg reaction to yield the *N*-methoxy-carbonylmethyl derivative, which is isomerized by sodium methoxide in a mixture of toluene and *tert*-butyl alcohol to form the benzothiazine ring. Refluxing this latter compound with methyl iodide in methanol affords the *N*-methyl derivative (I). Compound I is refluxed with 2-amino-5-methylthiazole in xylene, with the reaction being driven by removal of the methanol formed using a molecular sieve in a Soxhlet apparatus. On cooling the product crystallizes. US Pat 4,233,299.

Description—Yellow solid melting about 254°. Log P approx. 0.1 (octanol/pH 7.4 buffer); pK_a 1.1 and 4.2.

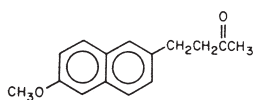
Solubility—Practically insoluble in water; more soluble at high or low pH; very slightly soluble in methanol.

Comments—A nonsteroidal anti-inflammatory drug (NSAID) that exhibits anti-inflammatory, analgesic, and antipyretic activities. Might have greater selectivity for COX-2. Clinical trials have demonstrated pain relief in osteoarthritis. Peak plasma levels occur about 4 to 5 hr after oral administration. It is ~99% bound to plasma protein. It is almost completely metabolized to four inactive metabolites (predominantly through P450 2C9 and 3A4) and eliminated in the urine and feces. The major metabolite is 5′-carboxy meloxicam. Half-life is about 15 to 20 hr. Patients with severe hepatic impairment have not been studied; it is not recommended in patients with advanced kidney disease.

It is contraindicated in patients with known hypersensitivity to it or demonstrated allergic-type reactions to NSAIDs. It has not been evaluated in persons under 18 yrs old.

NABUMETONE

2-Butanone, 4-(6-methoxy-2-naphthalenyl)-, Relafen



4-(6-Methoxy-2-naphthyl)-2-butanone; [42924-53-8] $C_{15}H_{16}O_2$ (228.29).

Preparation—Acetone and 6-methoxynaphthalenecarboxaldehyde are reacted in aldol fashion to form 5-(6-methoxy-2-naphthyl)-3-buten-2-one, which is reduced catalytically to nabumetone. See *J Med Chem* 21:1260, 1978.

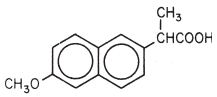
Description—White crystals; melts about 80°.

Solubility—Practically insoluble in water; sparingly soluble in alcohol.

Comments—An *NSAID* with a metabolite similar to *naproxen*.

NAPROXEN

2-Naphthaleneacetic acid, (+)-6-methoxy-α-methyl-, Equiproxen (Veterinary), Naprosyn



[22204-53-1] $C_{14}H_{14}O_3$ (230.26).

Preparation—6-Methoxynaphthalene is acetylated in the 2- position and the acetyl group is then converted to—$CH(CH_3)COOH$ by a sequence of reactions—Willgerodt-Kindler, esterification, alkylation and hydrolysis—yielding DL-naproxen (*CA 71:*91162j, 1969). Resolution of the racemate may be effected through precipitation of the more potent D-enantiomer as the cinchonidine salt (*J Med Chem 13:*203, 1970).

Description—White to off-white, crystalline powder; bitter taste; melts about 155°; apparent pK_a 4.15.

Solubility—Practically insoluble in water at pH 2; freely soluble in water at pH 8 or above; sparingly soluble in alcohol.

Comments—A propionic acid derivative that has anti-inflammatory, analgesic, and antipyretic activities. It is commercially available both as the acid and the sodium salt and is sold OTC. It is indicated for relief of symptoms of rheumatoid arthritis, both of acute flares and long-term management of the disease. Symptomatic improvement, when use of the drug is indicated, usually begins within 2 wk but a longer trial period may be necessary. It is comparable to aspirin in controlling disease symptoms, but with lesser frequency and severity of nervous system and milder GI adverse effects. It is used to relieve mild-to-moderate postoperative pain as well as postpartum pain, primary dysmenorrhea, orthopedic pain, headache, and visceral pain associated with cancer. Its analgesic effects are comparable with those of aspirin or indomethacin with usual doses.

It appears to be absorbed completely from the GI tract after oral administration. Peak plasma levels (approximately 55 mg/mL) are reached in 2 to 4 hr after a 500-mg dose, and steady-state levels are attained after 4 or 5 doses at 12-hr intervals. More than 99% is bound to serum albumin. The mean plasma half-life is approximately 13 hr. Approximately 95% of a dose is excreted in the urine, principally as conjugates of naproxen and its inactive metabolite 6-demethylnaproxen. The adverse effects, precautions, contraindications and drug interactions are essentially the same as for *Fenoprofen Calcium*.

NAPROXEN SODIUM

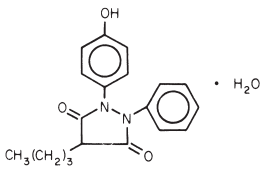
2-Naphthaleneacetic acid, 6-methoxy-α-methyl-, sodium salt; Anaprox

[26159-34-2] $C_{14}H_{13}NaO_3$ (252.24).

Comments—See *Naproxen*, above.

OXYPHENBUTAZONE

3,5-Pyrazolidinedione, 4-butyl-1-(4-hydroxyphenyl)-2-phenyl-, monohydrate



4-Butyl-1-(*p*-hydroxyphenyl)-2-phenyl-3,5-pyrazolidinedione monohydrate [7081-38-1] $C_{19}H_{20}N_2O_3.H_2O$ (342.39); *anhydrous* [129-20-4] (324.38).

Preparation—Diethyl butylmalonate is condensed with *p*-benzyloxyhydrazobenzene, with the aid of a solution of sodium ethoxide in anhydrous ethanol, to form 1-(*p*-benzyloxy)-2-phenyl-4-butyl-3,5- pyrazolidinedione (I). Completion of the reaction is effected by the addition of xylene and by heating of the mixture to about 140° for several hours, thus removing the alcohol released by the cyclizing condensation. Debenzylation of I is effected by Raney nickel hydrogenation at ambient temperature and pressure. Recrystallization of the initial product is from ether/petroleum ether. US Pat 2,745,783.

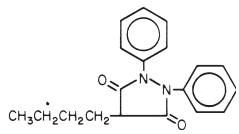
Description—White to yellowish white, odorless, crystalline powder; melts over a wide range between 85° and 100°.

Solubility—1 g in >10,000 mL water, 1.5 mL alcohol, 4 mL chloroform, 15 mL ether.

Comments—An *NSAID* propionic acid derivative.

PHENYLBUTAZONE

3,5-Pyrazolidinedione, 4-butyl-1,2-diphenyl-, Butazolidin



[50-33-9] $C_{19}H_{20}N_2O_2$ (308.38).

Preparation—Butylmalonyl chloride is condensed with hydrazobenzene in ether solution at 0° with the aid of pyridine. After extraction of the pyridine with aqueous HCl, the phenylbutazone is extracted with aqueous Na_2CO_3 and then precipitated by addition of HCl. US Pat 2,562,830.

Description—White to off-white, odorless, crystalline powder; melts about 105°.

Solubility—1 g in approximately 20 mL alcohol; slightly soluble in water; freely soluble in acetone or ether.

Comments—A synthetic pyrazolone derivative chemically related to aminopyrine and that has anti-inflammatory, antipyretic, analgesic, and mild uricosuric properties. Like other NSAIDs, these pharmacological effects likely relate to inhibition of prostaglandin synthesis caused by this drug. It is indicated for the symptomatic relief of *gout*, *rheumatoid arthritis*, *rheumatoid spondylitis*, *osteoarthritis*, *psoriatic arthritis*, *acute superficial thrombophlebitis*, and *painful shoulder*. Its anti-inflammatory and analgesic actions are comparable with that of usual doses of indomethacin, ibuprofen, or tolmetin. Because of the risk of agranulocytosis and aplastic anemia, it should be used only after other nonsteroidal and anti-inflammatory drugs have proved unsatisfactory; it is not recommended for use as a simple analgesic or antipyretic.

Therapy should not be started until the patient has been subjected to a complete physical and laboratory examination, including a hemogram and urinalysis, and has been adequately warned of potential adverse effects. In particular, it is contraindicated in patients who have severe renal, hepatic, or cardiac disease and should not be prescribed for those not available for frequent observation. Patients should be warned not to exceed the recommended dosage and to immediately report any fever, sore throat, or lesions in the mouth (symptoms of blood dyscrasia), dyspepsia, epigastric pain, symptoms of anemia, unusual bleeding, bruising, black or tarry stools (symptoms of intestinal lesions), and significant weight gain or anemia.

The goal of therapy should be *short-term* relief of *severe* symptoms to a level tolerable with the smallest possible drug dosage. If a favorable response is not observed within 1 wk, the drug should be discontinued. The drug is contraindicated in patients who have GI problems, have a history of drug allergy, and in children younger than 14 yr. It also is contraindicated in patients on other concurrent therapy, such as potent chemotherapeutic drugs and anticoagulant medication.

It is absorbed rapidly after oral administration and highly bound to plasma protein. Phenylbutazone's time to peak serum concentration is approximately 2.5 hr; however, the usual time for onset of antigout activity varies from 1 to 4 days and that for antirheumatic activity 3 to 7 days. Therapeutic serum concentrations average approximately 43 mg/mL; elimination half-life is approximately 84 hr. The drug (1%) and its major metabolite (oxyphenbutazone, 2%) are excreted by the kidneys.

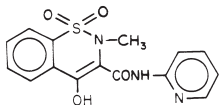
It produces untoward effects in approximately 40% of patients; approximately 15% have to discontinue the drug because of toxic effects. Consequently, the drug should be employed only in those patients who fail to respond adequately to less hazardous substances. The most frequently encountered untoward effects are water retention, nausea, rash, epigastric pain, vertigo, and stomatitis. Other less frequent but more severe effects include hepatitis, hypertension, transient psychosis, moderate leukopenia, agranulocytosis, and thrombocytopenia. CNS stimulation, visual symptoms, anemia, lethargy, constipation, diarrhea, GI hemorrhage, fever, and cardiac arrhythmias also have been observed.

Numerous drug interactions have been reported. Some of these interactions may be due to microsomal induction caused by phenylbutazone and its metabolite, oxyphenylbutazone. Generally, it should not be administered to patients taking anticoagulants, anti-inflammatory agents, bone-marrow depressants, digitoxin, hypoglycemics, methotrexate, phenytoin, or sulfonamides.

Because it is a potent drug and misuse can lead to serious results, physicians are well advised to familiarize themselves with its GI, acid-base balance, hepatic, dermatological, allergic, renal, cardiovascular, ocular, metabolic, and endocrine effects before prescribing this drug. It should be used with caution in pregnant women, nursing mothers, elderly patients, and patients known to have other illnesses. This drug should be taken with milk or with meals to minimize gastric irritation.

PIROXICAM

2*H*-1,2-Benzothiazine-3-carboxamide, 4-hydroxy-2-methyl-*N*-pyridinyl-, 1,1-dioxide; Feldene



[36322-90-4] $C_{15}H_{13}N_3O_4S$ (331.35).

Preparation—See *J Med Chem* 14:1171, 1971 and *Ibid* 15:848, 1972.

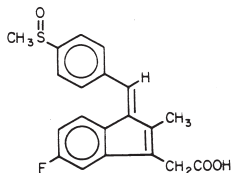
Description—White crystals; melts about 200° a saturated solution in dioxane:water (2:1) has a pK_a of approximately 6.3.

Solubility—Slightly soluble in water.

Comments—An *NSAID* structurally unrelated, but pharmacologically similar, to other NSAIDs.

SULINDAC

1*H*-Indene-3-acetic acid, (*Z*)-5-fluoro-2-methyl-1-[[4-(methylsulfinyl)phenyl] methylene]-, Clinoril



[38194-50-2] $C_{20}H_{17}FO_3S$ (356.41).

Preparation—The reaction of *p*-fluorobenzyl chloride with methylmalonic ester in the classic malonic ester synthetic route yields 3-(*p*-fluorophenyl)-2-methylpropanoic acid. Cyclization with polyphosphoric acid gives 6-fluoro-2-methylindanone which is reduced by means of a Reformatsky reaction to the alcohol, dehydrated to the indene, condensed with *p*-(methylthio)benzaldehyde to the 3-benzylidene derivative, the ester hydrolyzed and the thio group oxidized to the sulfoxide; *J Org Chem* 42:1914, 1977.

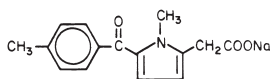
Description—Yellow crystals; melts at about 183° with decomposition; pK_a 4.5.

Solubility—Practically insoluble in water; sparingly soluble in alcohol.

Comments—An *NSAID* structurally related to *Indomethacin*.

TOLMETIN SODIUM

1*H*-Pyrrole-2-acetic acid, 1-methyl-5-(4-methylbenzoyl)-, sodium salt, dihydrate; Tolectin, Tolectin DS



[64490-92-2] $C_{15}H_{14}NNaO_3.2H_2O$ (315.31).

Preparation—The corresponding acetonitrile is obtained by a Friedel-Crafts reaction between 1-methylpyrrole-2-acetonitrile and *p*-methylbenzoyl chloride; after separation from the 4-aroyl isomer, produced simultaneously, by fractional crystallization or adsorption chromatography, the acetonitrile is converted to tolmetin by saponification and subsequently to its sodium salt (*J Med Chem* 14:646, 1971).

Description—Light yellow, crystalline powder; pK_a 3.5 (free acid).

Solubility—Freely soluble in water; slightly soluble in alcohol.

Comments—A nonsteroidal compound that has anti-inflammatory, analgesic, and antipyretic activities. Its mode of action is unknown, although inhibition of prostaglandin synthesis likely contributes to its anti-inflammatory action. In patients who have rheumatoid arthritis, various manifestations of its anti-inflammatory and analgesic actions are observed, but there is no evidence of alteration of the progressive course of the underlying disease.

The drug is absorbed rapidly and almost completely with peak plasma levels being reached within 30 to 60 min after an oral therapeutic dose. It is bound approximately 99% to plasma proteins; the mean plasma half-life is approximately 1 hr. Essentially, all of a dose is excreted in the urine within 24 hr, either as an inactive oxidative metabolite or as conjugates of tolmetin.

The drug is indicated for the relief of signs and symptoms of rheumatoid arthritis, both for acute flares and for long-term management of the disease. Safety and effectiveness in patients who are incapacitated, largely or wholly bedridden, or confined to a wheelchair, with little capacity for self-care have not been established. The drug is comparable with aspirin and with indomethacin in controlling disease activity; however, the frequency of the milder GI adverse effects is reported to be less than in aspirin-treated patients and the incidence of CNS adverse effects less than in indomethacin-treated patients. Concomitant administration of this drug and aspirin is not recommended because there does not appear to be any greater benefit from the combination over that achieved with aspirin alone and the potential for adverse reactions is increased.

It is contraindicated in patients demonstrated to be hypersensitive to the drug and also in those in whom aspirin and other NSAIDs induce symptoms of asthma, rhinitis, or urticaria. In patients who have active rheumatoid arthritis who also have an active peptic ulcer, treatment with nonulcerogenic drugs should be attempted; if it must be given, the patient should be observed closely for signs of ulcer perforation or severe GI bleeding. Because it is eliminated primarily by the kidneys, patients who have impaired renal function should be monitored closely and dosage reduced or discontinued if necessary. Because it prolongs bleeding time, patients who may be affected adversely should be observed carefully when treated with the drug. Patients who have compromised cardiac function should be treated with caution because the drug causes some retention of water and sodium, with a resultant mild peripheral edema.

The most frequent adverse reactions are GI in nature and include, in descending order of frequency, epigastric or abdominal pain or discomfort (approximately 1 of 6 patients), nausea, vomiting, indigestion, heartburn, constipation, and dyspepsia. The most common nervous system reactions are headache (1 of 15 patients), followed by dizziness and lightheadedness, tension and nervousness, and drowsiness. Tinnitus occurs in 1 of 40 patients. Mild edema is observed in approximately 1 of 50 patients. Rash, including maculopapular eruptions or urticaria, develops in 1 of 30 patients and pruritus in approximately 1 of 50 patients. Small and transient decreases in hemoglobin and hematocrit, not associated with GI bleeding, occur infrequently as also do a few cases of granulocytopenia.

Safe use in children younger than 2 yr has not been established, although the drug has been used safely and effectively in children older than 2 yr. Use of the drug in pregnancy is not recommended, and because it is secreted in human milk, its use by nursing mothers also is not recommended.

Selective COX-2 Inhibitors

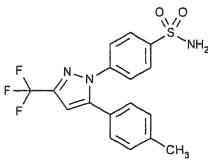
Whereas traditional NSAIDs block COX-1 and COX-2 isozymes non-selectively, the 'COX-2 inhibitors' inhibit COX-2 more selectively. The (simplified) concept is that COX-2 is induced during inflammation and pain and is not needed for protection of the GI mucosa, raising hopes that targeted therapy would have minimal impact on mucosal integrity and would reduce inflammation and relieve pain without producing GI bleeding. The ability to selectively inhibit the COX-2 isozyme is related to the difference in amino acids at position 523 of COX-1 and COX-2–isoleucine in COX-1, but valine in COX-2. The smaller valine forms a binding pocket in the channel leading to the catalytic site of the enzyme, which is believed to be a primary site of attachment of the selective COX-2 inhibitors.

The analgesic efficacy of the selective COX-2 inhibitors (the coxibs) is approximately equivalent to that of the traditional NSAIDs, and both have a relatively rapid onset of action. The adverse effects of COX-2 inhibition have yet to be fully characterized and are still somewhat controversial. It is unclear whether the adverse effects are specific to the individual agents currently marketed or will be observed with all COX-2 inhibitors (ie, are attributable to the mechanism of this class of agents).

Like other NSAIDs, the selective COX-2 inhibitors can cause renal toxicity (mainly edema and worsening of hypertension) and may decrease the antihypertensive effects of ACE inhibitors and diuretics. Unresolved at this time is the extent of sparing of GI ulcerations (with or without aspirin) and possible prothrombotic action that might increase cardiovascular risks.

CELECOXIB

Benzenesulfonamide, 4-[5-(4-methylphenyl)-3-(trifluoro-methyl)-1*H*-pyrazol-1-yl]-; Celebrex



p-[5-*p*-tolyl-3-(trifluoromethyl)pyrazol-1-yl]benzenesulfonamide [169590-42-5] $C_{17}H_{14}F_3N_3O_2S$ (381.38).

Preparation—Methyl trifluoroacetate and 4-methylbenzophenone are refluxed with sodium methoxide in methanol to yield 1-(*p*-tolyl)-4,4,4-trifluoro-1,3-butanedione. This latter compound is heated with *p*-hydrazinobenzenesulfonamide, closing the pyrazole ring forming the product. *Drugs of the Future* 1997; 22:71.

Description—Pale yellow crystals melting about 158°; pK_a 9.7.

Solubility—Sparingly soluble in water.

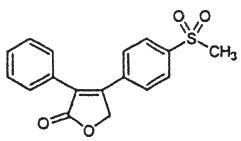
Comments—A nonsteroidal anti-inflammatory drug (NSAID) that exhibits anti-inflammatory, analgesic, and antipyretic activities. Its mode of action is due to inhibition of prostaglandin synthesis, primarily via inhibition of COX-2. Peak plasma levels occur about 3 hr after oral administration. It is ~97% bound to plasma protein. Its elimination is predominantly by hepatic metabolism and elimination in the urine and feces. The primary metabolites are the carboxylic acid and glucuronide. Half-life is about 11 hr. Dose should be reduced in patients with hepatic impairment and is not recommended in patients with severe renal insufficiency.

Clinical trials have demonstrated pain relief in osteo- and rheumatoid-arthritis and in acute analgesic models of post-oral surgery, post-orthopedic surgery, and primary dysmenorrhea.

It is contraindicated in patients with known hypersensitivity to it or demonstrated allergic-type reactions to sulfonamides or NSAIDs. Significant interactions may occur when administered together with drugs that inhibit P450 2C9; potentially with fluconazole, lithium, furosemide, or ACE inhibitors. It has not been evaluated in persons under 18 yrs old. Because of its lack of platelet inhibiting effects, it is not a substitute for aspirin for cardiovascular prophylaxis.

ROFECOXIB

2(5*H*)-Furanone, 4-[*p*-(methylsulfonyl)phenyl]-3-phenyl-



[162011-90-7] C17H14O4S (314.36).

Preparation—One method involves the Friedel-Crafts condensation of acetyl chloride and methylmercatobenzene to form 4-(methylthio)acetophenone which is then oxidized using hydrogen peroxide catalyzed by sodium tungstate yielding the sulfone(I). Bromination of I yields the phenacyl bromide derivative which, with sodium phenylacetate, undergoes nucleophilic displacement of bromine to produce the 4-(methylsulfonyl)phenacyl ester of phenylacetic acid. Heating this ester with diisopropylamine forms the 2(5*H*)-furanone ring, which is the product. *Drugs of the Future* 1287: 23, 1998.

Description—White to light yellow powder.

Solubility—Sparingly soluble in acetone; slightly soluble in methanol or isopropyl acetate; very slightly soluble in 1-octanol.

Comments—A nonsteroidal anti-inflammatory drug (NSAID) that exhibits anti-inflammatory, analgesic, and antipyretic activities. Its mode of action is due to inhibition of prostaglandin synthesis, primarily via inhibition of COX-2. The median time to peak plasma levels is 2 to 3 hr (range 2–9 hr) after oral administration. It is ~87% bound to plasma protein. Its metabolism is primarily mediated through reduction by cytosolic enzymes and elimination in the urine (~70–75%) and feces. The major metabolites are the *cis*- and *trans*-dihydro derivatives. The effective half-life (based on steady-state levels) is approximately 17 hr. Dose should be adjusted in patients with hepatic impairment and is not recommended in patients with advanced renal disease.

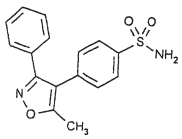
Clinical trials have demonstrated pain relief in osteo- and rheumatoid-arthritis and in acute analgesic models of post-oral surgery, post-orthopedic surgery, and primary dysmenorrhea.

It is contraindicated in patients with known hypersensitivity to it or demonstrated allergic-type reactions to sulfonamides or NSAIDs. It has not been evaluated in persons under 18 yrs old. Because of its lack of platelet inhibiting effects, it is not a substitute for aspirin for cardiovascular prophylaxis.

Note: Vioxx has been withdrawn from the market in October 2004.

VALDECOXIB

Benzenesulfonamide, 4-(5-methyl-3-phenyl-4-isooxazolyl-; Bextra



[181695-72-7] $C_{16}H_{14}N_2O_3S$ (314.36).

Preparation—One method involves conversion of benzyl phenyl ketone to the oxime which is deprotonated with butyl lithium and the product condensed with ethyl acetate to yield 3,4-diphenyl-5-methyl-4,5-dihydroisoxazolin-5-ol (I). Treatment of I with chloroformic acid followed by aqueous ammonia gives the product. *J Med Chem* 2000; 775: 43.

Description—Melts about 173°; pK_a 9.8.

Solubility—Insoluble in water; as with most sulfonamides it is more soluble in aqueous solution at high pH; soluble in most organic solvents.

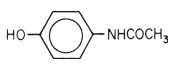
Comments—A nonsteroidal anti-inflammatory drug (NSAID) that exhibits anti-inflammatory, analgesic, and antipyretic activities. Its mode of action is due to inhibition of prostaglandin synthesis, primarily via inhibition of COX-2. Peak plasma levels occur about 3 hr after oral administration. It is ~98% bound to plasma protein. It undergoes extensive hepatic metabolism involving P450 isozymes (3A4 and 2C9) and non-P450 dependent pathways (eg, glucuronidation). Less than 5% is excreted unchanged in the urine. The mean half-life is about 8 to 11 hr and increases with age. It is not recommended in patients with severe hepatic impairment or advanced renal disease.

Clinical trials have demonstrated pain relief in osteo- and rheumatoid-arthritis and in primary dysmenorrhea.

It is contraindicated in patients with known hypersensitivity to it or demonstrated allergic-type reactions to sulfonamides or NSAIDs. It has not been evaluated in persons under 18 yrs old. Because of its lack of platelet inhibiting effects, it is not a substitute for aspirin for cardiovascular prophylaxis.

Acetaminophen

Acetamide, *N*-(4-hydroxyphenyl)-, *N*-Acetyl-*p*-aminophenol; *p*-Acetamidophenol



4′-Hydroxyacetanilide [103-90-2] $C_8H_9NO_2$ (151.16).

Preparation—*p*-Nitrophenol is reduced and the resulting *p*-aminophenol is acetylated by means of heating with a mixture of acetic anhydride and glacial acetic acid. The crude product may be purified by recrystallization from an ethanol–water mixture.

Description—White, odorless, crystalline powder; slightly bitter taste; melts about 170°; pH (saturated solution) 5.3 to 6.5; pK_a 9.51.

Solubility—1 g in 70 mL water, 20 mL boiling water, 10 mL alcohol, 50 mL chloroform, 40 mL glycerin; slightly soluble in ether.

Comments—The analgesic efficacy of acetaminophen is essentially equivalent to that of NSAIDDs, but a acetaminophen is not anti-inflammatory. The mechanism of action of acetaminophen is unknown, but the prevailing evidence suggests that involves a central component. Several possible actions have been proposed on the basis of *in vitro* studies. The oldest proposal is that acetaminophen inhibits COX-1, but rather than in the periphery. Another proposal is that acetaminophen inhibits a specific type of COX activity or under select conditions. Other reports suggest that descending modulatory mechanisms are involved, possibility involving 5-HT or endogenous opioid pathways. Taken together, the find-

ings suggest that acetaminophen has a direct action at the level of the spinal cord and in addition stimulates a supraspinal system that modulates neurotransmitters at the level of the spinal cord. This dual mechanism may explain why it has previously been so difficult to elucidate the basis for the analegesic effect of acetaminophen. It is effective in the treatment of a wide variety of arthritic and rheumatic conditions involving musculoskeletal pain as well as the headache pain, dysmenorrhea, myalgias, and neuralgias. It also is useful in diseases accompanied by pain, discomfort, and fever, such as the common cold and other viral infections. It is useful particularly as an analgesic-antipyretic in patients who experience untoward reactions to aspirin. It rarely induces untoward effects in therapeutic doses and usually is well tolerated by aspirin-sensitive patients. Rarely, a sensitivity reaction may occur; in this case the drug should be stopped. Acetaminophen frequently is combined with other drugs, such as caffeine, aspirin, and opiates, such as codeine and oxycodone. It lacks the anti-inflammatory action of the salicylates; hence, it is of only limited usefulness in inflammatory rheumatic disorders and is often not considered an NSAID agent. Unlike aspirin, acetaminophen does not antagonize the effects of uricosuric agents. Although large doses have been reported to potentiate anticoagulants, therapeutic doses have no effect on prothrombin time.

Absorption of the drug after oral administration is rapid and peak plasma levels are reached in 30 to 120 min. The therapeutic half-life is approximately 3 hr. Approximately 2% is excreted unchanged in the urine; the glucuronide and the sulfate conjugates are nontoxic and account for approximately 95% of the drug. A much smaller amount, estimated to be 3%, is oxidized via the hepatic cytochrome P-450 system to a chemically reactive intermediate that combines with liver glutathione to form a nontoxic substance. However, after massive single doses of the drug, the supply of liver glutathione is exhausted and the excess reactive arylating intermediate covalently binds to vital hepatocellular macromolecules, leading to necrosis. Hepatic necrosis and death have been observed after overdosage; hepatic damage is likely if an adult takes more than 10 to 15 g in a single dose or if a 2-year-old child takes more than 3 g.

Both *in vivo* and *in vitro* studies have shown that agents that stimulate metabolism, such as phenobarbital, phenytoin, and alcohol, potentiate acetaminophen-induced hepatotoxicity. The best indicator of potential liver injury is the half-life of its elimination. A half-life longer than 4 hr is associated uniformly with liver injury. Also, plasma levels greater than 300 mg/mL at 4 hr postingestion are consistent with liver injury, whereas levels less than 120mg/mL at 4 hr postingestion usually are not.

Treatment of overdosage includes administration of acetylcysteine to help conjugate the hepatotoxic metabolite plus symptomatic and supportive care. The label on its dosage forms carries the following (or equivalent) statement: *Warning—Do not use more than 10 days unless directed by a physician. Keep this medication out of reach of children*.

OTHER DRUGS TO RELIEVE PAIN (ADJUVANTS)

Certain drugs, although not classified as analgesics, are helpful in treating certain types of pain. Such drugs may be used alone or in concert with standard analgesics. Examples include antidepressants, α_2-adrenoceptor agonists, corticosteroids, anticonvulsants, agents related to γ-amino butyric acid (GABA), and calcitonin. In addition, muscle relaxants and benzodiazepines can relieve some musculoskeletal pains. The little that is known about the mechanisms by which these agents work to relieve pain is summarized in Table 83-2.

Table 83-2. Possible Mechanism(s) of Action of Some Adjuvants Used for Pain

ADJUVANT	POSSIBLE MECHANISM(S) OF ACTION
Antidepressants	Enhancement of descending modulatory pathways by inhibition of neuronal reuptake of norepinephrine and 5-HT. SSRI's are generally less effective than are non-selective agents.
α_2-adrenoceptor agonists	Potentiation of endogenous or exogenous opioid action at the level of the spinal cord.
Corticosteroids	Interruption of the inflammatory cascade by inhibition of cytokine production.
Anticonvulsants	Interruption of ectopic foci by action on ion channels.
GABA-related	Hyperpolarization of neurons by enhancement of Cl^- influx.
Calcitonin	Potentiation of amine reuptake; direct binding to CNS sites; release of endogenous opioids; decrease of Ca^{2+}.

GABA = γ-amino butyric acid; SSRI = selective serotonin reuptake inhibitor.

COMBINATIONS OF ANALGESICS

Analgesic combinations offer a potential benefit over individual agents, including increased compliance and reduced side-effects (if the same level of analgesia can be achieved with the lower doses of each component in the combination). Combining analgesics that have different mechanisms of action offers the additional potential advantage of being able to treat a broader spectrum of pain. Such an approach has been recommended by the World Health Organization (WHO). However, not all analgesic combinations lead to an improved clinical outcome. Therefore, each combination (and dose-ratio) must be evaluated independently. In addition, caution must be exercised to ensure that the maximum daily dose of either component of the combination is not exceeded. This is particularly important when one or both components are available separately OTC.

CHAPTER 84

Histamine and Antihistaminic Drugs

John E Hoover, BSc Pharm, RPh

Histamine is a physiologically active, endogenous substance (autocoid) that is produced within the body by the decarboxylation of the amino acid, histidine, and then stored in mast cells and basophils where it is protected from ubiquitous destructive enzymes, such as histaminase. It binds to and activates histamine H_1- and H_2-receptors in various sites in the body. H_3-receptors, which may be involved in the control of histamine synthesis, also have been described.

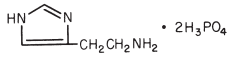
The action of histamine on the cells depends to some extent on the function of the cell as well as on the ratio of its H_1- and H_2-receptors. The cardiovascular effects of histamine include direct and indirect microvascular dilation (involving H_1- and H_2-receptors) and increased vascular permeability (probably involving H_1-receptors); as a result, intracutaneous injection of histamine produces a *triple response* characterized by local reddening, a bright halo or flare, and wheal formation. Histamine also binds to and activates specific receptors in the nose, eyes, respiratory tract, and skin, causing characteristic allergic signs and symptoms. Activation of H_1-receptors (H_1-antagonists) block these actions.

Historically, the term antihistamine has been used to describe drugs that act as H_1-receptor antagonists. Activation of H_2-receptors stimulates gastric acid secretion; drugs that antagonize H_2-receptors (eg, cimetidine/nizatidine, ranitidine, or famotidine) are referred to as H_2-receptors antagonists (see Chapter 66). The H_2-antagonists inhibit gastric secretion stimulated not only by histamine, but also by insulin, pentagastrin, food, or physiological vagal reflex.

Another amine, 5-hydroxytryptamine, also is distributed widely in animals and is present in some plants. This substance, discovered independently by three groups of workers, is also known as enteramine and serotonin. It is found in largest amounts in the brain, blood, spleen, stomach, intestine, lungs, and skin. It has been suggested that 5-hydroxytryptamine may be involved in the regulation of vascular tone, motor, and secretory activity of the gastrointestinal (GI) tract and kidney function. Serotonin also functions as a neurotransmitter in the brain, and drugs that prevent its reuptake (eg, fluoxetine) possess antidepressant activity. These observations and the demonstration that tumors of the argentaffin cells of the intestinal mucosa (argentaffinomas or carcinoids) secrete large amounts of 5-hydroxytryptamine have stimulated the search for 5-hydroxytryptamine antagonists. The pharmacological actions of 5-hydroxytryptamine are varied and complex. Liberation of excessive amounts in man, as in argentaffin cell tumors, produces episodic flushing, tachycardia, and hypertension followed by cyanosis, diarrhea, asthma, and pulmonary stenosis. 5- Hydroxytryptamine antagonists have been employed in the management of this malignancy, as well as certain skin diseases and psychoses. Several of the antihistamines described below possess both antihistaminergic and antiserotonergic activity. However, there are several clinically useful serotonin antagonists (granisetron hydrochloride, methysergide maleate, and ondansetron hydrochloride) that have been introduced into the clinical arena in recent years for the management of nausea or vomiting associated with carcinoid syndrome (granisetron, methysergide, and ondansetron) and vascular headache (methysergide). The remainder of this chapter is focused primarily on the role of histamine and uses of H_1-receptor antagonists.

HISTAMINE PHOSPHATE

1*H*-Imidazole-4-ethanamine, phosphate (1:2)



4-(2-Aminoethyl)imidazole phosphate (1:2) [51-74-1] $C_5H_9N_3 \cdot 2H_3PO_4$ (307.14).

Preparation—Histamine occurs in small amounts in ergot. It is among the products of bacterial decomposition of histidine, and this constitutes one of the methods for its production. It also is produced synthetically from imidazolylpropionic acid by several methods.

Description—Long prismatic crystals; colorless; odorless stable in air but affected by light; aqueous solutions are acid to litmus; when dried at 105° for 2 hr, melts at approximately 140°; pH (4.1% aq soln, iso-osmotic with serum) about 5.

Solubility—1 g in approximately 4 mL of water; slightly soluble in alcohol.

Pharmacology—Although many tissues contain a lethal amount of histamine in a bound or inactive form, no effect is produced until it is released in free form into body fluids as a result of certain stimuli. Because it is destroyed in the intestinal tract by the enzyme histaminase, it is ineffective when taken orally. After injection, it constricts certain smooth muscles such as the bronchi, uterus, and intestines and dilates the capillary bed. Characteristically, increased capillary permeability accompanies the dilation, and there is seepage of fluid, plasma, proteins, and even some cellular elements of the blood into extracellular spaces. Dilation of the capillaries and arterioles produces flushing of the face, fall in blood pressure, and increase in skin temperature.

It stimulates all types of glandular secretions—gastric, duodenal, salivary, and lacrimal. An important effect in man is the stimulation of the gastric glands, which increases the hydrochloric acid of the stomach. This effect of histamine was the basis of a diagnostic test that had been used in the past to differentiate between nonspecific hypochlorhydria and that caused by pernicious anemia. The preferred agent for this purpose is pentagastrin.

One highly characteristic effect of this agent is the *triple response* induced by the intracutaneous injection of small amounts of this agent.

It consists of

1. a local reddening at the site of the injection,
2. a wheal or patch of localized edema that obscures the original red spot, and
3. the scarlet flare that surrounds the wheal.

The initial red spot is due mostly to local capillary dilatation, and the wheal develops from arteriolar dilation and increased capillary permeability. The flare is a local phenomenon produced by an axon reflex involving peripheral sensory nerves. Because the flare does not appear in the presence of atrophy or degeneration of the nerve, this reaction has been used as a diagnostic test to distinguish between real and pseudoanesthesia.

When injected intravenously, it provokes an increased output of epinephrine from the adrenal medulla as indicated by a secondary rise in blood pressure. In the past, clinical use was made of this action on the adrenals by the use of it as a test agent in the diagnosis of pheochromocytoma. This test is now considered obsolete because of its hazardous nature and because chemical assays are now available for detecting and quantitating the levels of catecholamines and their metabolites in patients suspected of having pheochromocytoma.

Comments—Used primarily as a positive control in evaluation of allergenic skin testing. It has a few other minor diagnostic applications. Because the *flare* that results from intracutaneous injection of this agent is mediated by an axon reflex, this approach has been used as a test for the integrity of sensory nerves; the wheal that results has been used as a test for circulatory competency.

Adverse reactions are observed even after small doses, such as those employed in gastric analysis [0.01 mg/kg subcutaneously (SC)]. These include flushing, dizziness, headache, bronchial constriction, dyspnea, visual disturbances, faintness, syncope, urticaria, asthma, significant hypertension or hypotension, palpitation, tachycardia, nervousness, abdominal cramps, diarrhea, vomiting, metallic taste, allergic manifestations, or collapse with convulsions. The hypotension usually is postural and requires no treatment other than the patient's assuming a recumbent position. If treatment is required, epinephrine (0.3 mg SC) is an effective physiological antagonist.

ANTIHISTAMINES

All clinically available antihistamines antagonize histamine to approximately the same extent, regardless of their chemical class (ethanolamines, ethylenediamines, alkylamines, phenothiazines, or piperidines). They all induce some degree of sedation and anticholinergic activity. Only the ethanolamines and phenothiazines possess antiemetic properties. The clinical and pharmacological differences, therefore, are related chiefly to variations in adverse effects and to nonhistamine antagonizing actions, such as their atropine-like effects, central nervous system (CNS) effects (depression, stimulation, antiemetic, antitremor, and motion sickness), and local anesthetic properties. A knowledge of these factors is essential for proper drug selection.

All currently available antihistamines (H_1-receptor antagonists) act by competitively antagonizing the effects of histamine at receptor sites; they do not block the release of histamine and, hence, offer only palliative relief of allergic symptoms. After oral administration, effects are apparent within 15 to 30 min, are maximal within 1 hr, and persist for 4 to 6 hr. The liver is the principal site of metabolism; the agents are excreted in urine as unidentified metabolites.

Clinically, indications for the use of the various antihistaminic drugs vary considerably. The majority of these agents are *effective* for *perennial* and *seasonal allergic rhinitis, vasomotor rhinitis, allergic conjunctivitis, urticaria and angioedema, allergic reactions to blood and plasma, and dermographism* and as adjuncts to conventional therapy in *anaphylactic reactions*. A few antihistamines probably are effective in mild, local *allergic reactions to insect bites*; *physical allergy*; and minor *drug* and *serum* reactions characterized by *pruritus*. Selected antihistamines (eg, diphenhydramine hydrochloride) reduce rigidity and tremors in *paralysis agitans* (Parkinson's disease) and in *drug-induced extrapyramidal symptoms.* Some antihistamines (eg, buclizine, cyclizine, dimenhydrinate, diphenhydramine, meclizine) are also effective in the *active and prophylactic* management of *motion sickness.* More sedative agents (eg, diphenhydramine, doxylamine, promethazine) sometimes are used in *insomnia* and in *insomnia* predominant in certain medical disorders. Certain antihistamines, such as chlorpheniramine, doxylamine succinate, and pyrilamine maleate, are used in proprietary medication advertised as daytime sedatives and sleep aids. Methapyrilene, formerly used in virtually all nonprescription sleep aids in the US, was removed from these products in 1979 because of its possible carcinogenic properties.

The phenothiazine antihistamines possess other useful clinical properties not shared by conventional antihistamines. For example, promethazine hydrochloride is useful for *preoperative, postoperative*, and *obstetric sedation*; prevention and control of *nausea* and *vomiting* associated with certain types of anesthesia and surgery; and as *adjunctive therapy* to meperidine or other analgesics for the *control of postoperative pain.*

The usefulness of antihistamines in various other clinical conditions (eg, bronchial asthma, atopic dermatitis, neurodermatitis, allergic eczema, various contact and chemotoxic dermatitides, and generalized pruritus) and for cardiac arrhythmias, spasmolysis in GI allergies, prophylaxis of drug reactions, etc. must await further clinical investigation before a final assessment can be made. It is generally agreed that *most* antihistamines are *ineffective* in migraine and histamine headache; for prevention or reduction of the sequelae of pain, edema, and hemorrhage in oral surgery; and for potentiation of narcotic analgesic drugs, as antiemetics in postoperative patients and as antitussives or for treatment of nocturnal leg cramps, leg cramps of pregnancy, and functional dysmenorrhea.

The most common side effect of antihistamines is sedation, evidenced principally by drowsiness, plus a diminished alertness and ability to concentrate. Less-common effects—unless large doses are used—include dryness of the mouth, blurred vision, vertigo, and GI distress (see also above). The sedative effect of some antihistamines may be so intense as to impair driving ability and performance of duties that necessitate mental alertness. Other side effects elicited by these drugs include nausea, headache, and restiveness. Dermatological complications and skin eruptions have followed local application or oral administration of antihistamines. In a few individuals, certain antihistamines produce signs of central excitation such as insomnia and nervousness. Concurrent use of antihistamines and certain other CNS-active drugs should be avoided because the depressant effects of alcoholic beverages and other drugs that depress the CNS (tranquilizers, hypnotics, sedatives, antianxiety agents, depressants, analgesics, etc.) are increased by antihistamines. Patients being treated with monoamine oxidase inhibitors (MAOIs), or who have been treated with such drugs within the preceding 2 weeks, should not be given antihistamines.

Because of their drying effect on mucous membranes, antihistamines may exacerbate wheezing and therefore should not be used during an asthmatic attack. Because of the anticholinergic action of antihistamines, their use in the following diseases may be contraindicated or subject to great caution: narrow-angle glaucoma, prostatic hypertrophy, stenosing peptic ulcer, pyloroduodenal obstruction, bladder-neck obstruction, increased intraocular pressure, history of bronchial asthma, hyperthyroidism, cardiovascular disease, or hypertension. Antihistamines should not be given to premature or newborn infants and may be denied by the physician for patients breastfeeding infants.

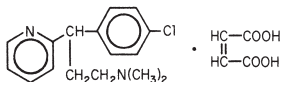
These brief observations call attention to the enormous number of clinical conditions for which antihistaminic drugs have been suggested. They also point up the fact that these drugs vary from *effective* to *ineffective* in these conditions.

When considering the multiplicity of available antihistamines, their numerous untoward reactions, and their propensity to induce sedation of variable intensity, one can appreciate the complex therapeutic problem that confronts both the patient and the physician in the selection of an antihistamine for

a particular patient with a histamine-related clinical condition. Three monographs that highlight prototype antihistamines of the alkylamine (chlorpheniramine), ethanolamine (diphenhydramine), and phenothiazine (promethazine) classes of antihistamines are presented below.

CHLORPHENIRAMINE MALEATE

2-Pyridinepropanamine, γ-(4-chlorophenyl)-*N*,*N*-dimethyl-, (*Z*)-2-butenedioate (1:1); Chlor-Trimeton



2-[*p*-Chloro-α-[2-(dimethylamino)ethyl]benzyl]pyridine maleate (1:1) [113-92-8] $C_{16}H_{19}ClN_2 \cdot C_4H_4O_4$ (390.87).

Preparation—By condensing 2-[*p*-chloro-α-(2-chloroethyl)benzyl]pyridine with dimethylamine in the presence of sodamide. Treatment of the base with an equimolar portion of maleic acid results in the formation of the maleate.

Description—White, crystalline powder; odorless; solutions are acid to litmus (pH 4 to 5); melts about 130° to 135°; pK_a 9.2.

Solubility—1 g in 4 mL water, 10 mL alcohol, or 10 mL chloroform; slightly soluble in ether or benzene.

Comments—An alkylamine antihistamine that is a common ingredient in over-the-counter (OTC) antitussive formulation. It has a mild sedative action and slight anticholinergic activity. It is probably effective in allergic and vasomotor rhinitis, allergic conjunctivitis, mild urticaria and angioedema, allergic reactions to blood and plasma in sensitive patients, and dermographism and as adjunct therapy in anaphylactic shock. It is used widely as an ingredient in proprietary antitussive formulations. It undergoes significant first-pass metabolism (40–55%). Peak plasma levels of 5.9 and 11 ng/mL are achieved in 2 to 6 hr. It has a low incidence of side effects; these side effects are similar to those induced by other antihistamines. See the introductory statement.

CHLORPHENIRAMINE TANNATE

ing of Tussizone-12, Rynatuss, Xiratuss, etc.

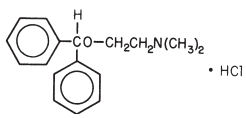
Preparation—US Pat 5,663,415 (1997); US Pat 6,455,727 (2002); see also *Carbetapentane tannate*.

Description—Tan solid of undetermined purity.

Comments—See Chlorpheniramine Maleate.

DIPHENHYDRAMINE HYDROCHLORIDE

Ethanamine, 2-(diphenylmethoxy)-*N*,*N*-dimethyl-, hydrochloride; Benadryl Hydrochloride



2-(Diphenylmethoxy)-*N*, *N*-dimethylethylamine hydrochloride [147-24-0] $C_{17}H_{21}NO \cdot HCl$ (291.82).

Preparation—By heating diphenylbromomethane, β-dimethylaminoethanol and sodium carbonate in toluene. After the toluene is distilled off, the purified diphenhydramine is converted to the hydrochloride with hydrogen chloride.

Description—White, crystalline powder; slowly darkens on exposure to light; solutions are practically neutral to litmus; melts about 167° to 172°.

Solubility—1 g in 1 mL water, 2 mL alcohol, 2 mL chloroform, or 50 mL acetone; slightly soluble in benzene or ether.

Comments—A potent ethanolamine antihistamine that possesses significant anticholinergic (drying), antitussive, antiemetic, and sedative effects. It is effective for use in perennial and seasonal allergic rhinitis; vasomotor rhinitis; allergic conjunctivitis caused by inhalant allergens and foods; mild, uncomplicated allergic skin manifestations of urticaria and angioedema; alleviation and prevention of allergic reactions to blood or plasma in patients who have a known history of such reactions; dermographism; therapy for anaphylactic reactions adjunctive to epinephrine and other standard measures after the acute manifestations have been controlled; parkinsonism (including drug induced) in the elderly unable to tolerate more potent agents; mild cases of parkinsonism (including drug induced) in other age groups; other cases of parkinsonism (including drug induced) in combination with centrally acting anticholinergic agents and active and prophylactic treatment of motion sickness. It also has significant antitussive activity; the syrup is used as a cough suppressant for the control of cough due to colds or allergy.

It is probably effective for use in mild, local allergic reactions to insect bites; physical allergy; minor drug and serum reactions characterized by pruritus; and intractable insomnia and insomnia dominant in certain medical disorders. Other suggested uses require further investigation. Although it is well absorbed after oral administration, first-pass metabolism is so extensive that only 40–60% reaches systemic circulation unchanged. Peak plasma concentrations are attained in 1 to 4 hr; 80–85% is bound to plasma protein; and elimination half- life ranges from 2.4 to 9.3 hr.

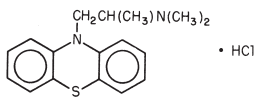
Patients, observed while on this drug, have shown numerous side effects such as drowsiness, confusion, restlessness, nausea, vomiting, diarrhea, blurring of vision, diplopia, difficulty in urination, constipation, nasal stuffiness, vertigo, palpitation, headache, and insomnia. Other side effects observed were urticaria, drug rash, photosensitivity, hemolytic anemia, hypotension, epigastric distress, anaphylactic shock, tightness of the chest and wheezing, thickening of bronchial secretions, dryness of the mouth, nose and throat and tingling, and heaviness and weakness of the hands.

Dimenhydrinate (Dramamine) contains approximately 50% diphenhydramine. The former agent is capable of masking symptoms of ototoxicity; therefore, dimenhydrinate and diphenhydramine should be used with caution in patients receiving aminoglycoside antibiotics (streptomycin, neomycin, or kanamycin) or other ototoxic drugs.

Because it has an atropine-like action, it should be used with caution in patients who have asthma. Likewise, patients should be cautioned about taking this drug with other depressant substances, because of the additive effect. Persons also should be advised not to operate a motor vehicle, fly an airplane, or operate hazardous machinery while on this drug. The incidence of side effects is approximately 30–60%.

PROMETHAZINE HYDROCHLORIDE

10*H*-Phenothiazine-10-ethanamine, *N*,*N*,α-trimethyl-, monohydrochloride; Phenergan



10-[2- (Dimethylamino)propyl]phenothiazine monohydrochloride [58-33-3] $C_{17}H_{20}N_2S \cdot HCl$ (320.88).

Preparation—By reacting phenothiazine with 1-chloro-2-(dimethylamino)propane hydrochloride in the presence of sodamide and sodium hydroxide in xylene. The base is extracted, purified, and converted to the hydrochloride.

Description—White to faint yellow, crystalline powder; practically odorless; slowly oxidized, particularly when moistened, on prolonged exposure to air, becoming blue in color; pH (1 in 20 solution) 4.0 to 5.0; melts within a 3° range between 215° and 225°; pK_a 9.1.

Solubility—Soluble in water, hot dehydrated alcohol, or chloroform; practically insoluble in ether, acetone, or ethyl acetate.

Comments—A phenothiazine antihistamine with significant sedation and antiemetic actions. It has significant anticholinergic activity. It has marked potency and prolonged duration of action. It is effective for use in perennial and seasonal allergic rhinitis; vasomotor rhinitis; allergic conjunctivitis caused by inhalant allergens and foods; mild, uncomplicated allergic skin manifestations of urticaria and angioedema; alleviation and prevention of allergic reactions to blood or plasma in patients who have a known history of such reactions; dermographism; therapy for anaphylactic reactions adjunctive to epinephrine and other standard measures after the acute manifestations have been controlled; preoperative, postoperative, or obstetric sedation; prevention and control of nausea and vomiting associated with certain types of anesthesia and surgery; therapy adjunctive to meperidine or other analgesics for control of postoperative pain; sedation in both children and adults as well as relief of apprehension and production of light sleep from which the patient can easily be aroused; active and prophylactic treatment of motion sickness; and antiemetic action in postoperative patients.

It is well absorbed, and peak effects occur within 20 min after oral, rectal, or intramucular (IM) administration; 76% to 80% is bound to plasma proteins; the duration of antihistaminic effect may persist for 12 hr or longer. The drug is excreted slowly in the urine and feces, primarily as inactive sulfoxides and glucuronides.

Untoward reactions include dryness of the mouth, blurring of vision, and, rarely, dizziness. Rare cases of leukopenia and one case of agranulocytosis have been reported. Minor increases in blood pressure and occasional mild hypotension have been documented. The appearance of photosensitivity may contraindicate further treatment. Excessive doses in adults have resulted in deep coma, sedation, and, rarely, convulsions; in children such doses have resulted in hyperexcitability and nightmares. See the introductory statement.

ANTIHISTAMINE COMBINATIONS

Typically, most antihistamine combinations include an antihistamine, a decongestant (eg, phenylephrine, or pseudoephadrine), a cough suppressant (eg, dextromethorphan, codeine, or hydrocodone), and an analgesic (eg, acetaminophen or aspirin). Because there are literally dozens of OTC and prescription antihistamine combinations available, it is recommended that the reader refer to a current *Facts and Comparisons Drug Information* or *Physicians' Desk Reference* (for both prescription and nonprescription drugs) for a listing of the available products, dosage, and suppliers.

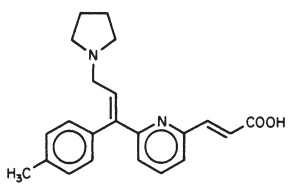
INHIBITORS OF HISTAMINE RELEASE

The antihistamines described in the previous section antagonize, in varying degrees, most but not all pharmacological effects of histamine. They appear to accomplish this by occupying the *receptor sites* on the effector cell to the exclusion of the agonist, histamine, without initiating a response. Typically, they are competitive antagonists and do not prevent the release of histamine in response to injury, drugs, or antigens. However, a more recently developed drug, cromolyn sodium, can prevent the release of histamine from mast cells that have been sensitized by specific antigens.

ASTEMIZOLE—see RPS-20, page 1467.

ACRIVASTINE

2-Propenoic acid, (*E*,*E*)-3-[6-[1-(4-methylphenyl)-3-(1-pyrrolidin-yl)-1-propenyl]-2-pyridinyl]-, ing of Semprex-D



[87848-99-5] $C_{22}H_{24}N_2O_2$ (348.44).

Preparation—A multistep procedure starting with 2-bromo-6-(p-toluoyl)pyridine, ethyl acrylate and triphenylphosphine with a Pd(II)acetate catalyst, under pressure to form a triphenyl-2-pyrrolidinoethylphosphonium bromide. This latter compound with butyl lithium, hot sulfuric acid and an elaborate clean-up procedure affords the product. US Pat 4,501,893(1985).

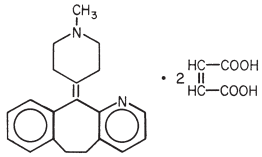
Description—Odorless white to cream-colored crystalline powder from 2-propanol.

Solubility—Soluble in chloroform and ethanol; slightly soluble in water.

Comments—Acrivastine, a structural analog of triprolidine hydrochloride, exhibits H_1-antihistamine activity in isolated tissues, animals, and humans, and has sedative effects in humans. The propionic acid derivative of acrivastine is a metabolite in several animal species (as well as man) and also exhibits H_1-antihistaminic activity. Pseudoephedrine hydrochloride is an indirect sympathomimetic agent. It releases norepinephrine from adrenergic nerves. *In vitro* tests and *in vivo* studies in animals of acrivastine and pseudoephedrine in combination failed to demonstrate evidence of any beneficial or deleterious pharmacologic interaction between the two agents.

AZATADINE MALEATE

5*H*-Benzo[5,6]cyclohepta[1,2-*b*]pyridine, 6,11-dihydro-11-(1-methyl-4-piperidinylidene)-, (*Z*)-2-butenedioate (1:2); ing of Trinalis



6,11-Dihydro-11-(1-methyl-4-piperidylidene)-5*H*-benzo[5,6]-cyclohepta[1,2-*b*]pyridine maleate (1:2) [3978-86-7] $C_{20}H_{22}N_2\ 2C_4H_4O_4$ (522.55).

Preparation—Azatadine is a chemical relative of cyproheptadine, differing from the latter in that a pyridine ring replaces one of the benzene rings of cyproheptadine and in the saturation of the cycloheptane ring of the latter compound. It may be prepared by dehydrating the condensation product formed in the presence of sodium and liquid ammonia from 4-chloro-*N*-methylpiperidine and 5,6-dihydro-11*H*-benzo-[5,6]cyclohepta[1,2-*b*]pyridine-11-one. Treatment of the base with a bimolar quantity of maleic acid forms the maleate salt. US Pat 3,326,924.

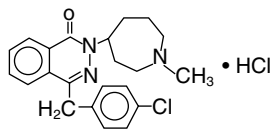
Description—White to off-white powder; non-hygroscopic; melts at approximately 153°; pK_a 8.4.

Solubility—1 g in 30 mL of water or 30 mL of alcohol.

Comments—An antihistamine structurally related to cyproheptadine with antiserotonin activity, mild to marked sedative action, and slight anticholinergic activity.

AZELASTINE HYDROCHLORIDE

1(2*H*)-Phthalazinone, (±)-4-[(4-chlorophenyl)methyl]-2-(hexahydro-1-methyl 1*H*-azepin-4-yl)-, monohydrochloride; Astelin; Optvar



[100643-71-8] $C_{22}H_{24}ClN_3.HCl$ (418.37).

Preparation—US Pat 3,813,384 (1974)

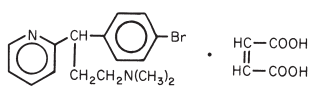
Description—A racemic mixture of white crystals melting about 225°–229° with a bitter taste; pH of a saturated aqueous solution between 5.0 and 5.4.

Solubility—Sparingly soluble in water, methanol, or propylene glycol: slightly soluble in ethanol, octanol, or glycerine.

Comments—A relatively selective histamine H_1 antagonist and an inhibitor of the release of histamine and other mediators from cells (eg, mast cells) involved in the allergic response. Based on in vitro studies using human cell lines, inhibition of other mediators involved in allergic reactions (eg, leukotrienes and PAF) has been demonstrated with this drug. Decreased chemotaxis and activation of eosinophils also has been demonstrated.

BROMPHENIRAMINE MALEATE

2-Pyridinepropanamine, γ-(4-bromophenyl-*N*,*N*-dimethyl-, (*Z*)-butenedioate (1:1); ing of Dimetapp



2-[*p*-Bromo-α-[2-(dimethylamino)ethyl]benzyl]pyridine maleate (1:1) [980-71-2] $C_{16}H_{19}BrN_2 \cdot C_4H_4O_4$ (435.32).

Preparation—α-(*p*-Bromophenyl)-2-pyridineacetonitrile is converted to its sodium derivative with sodium amide and condensed with 2-chloro-*N*, *N*-dimethylethylamine. The resulting nitrile is hydrolyzed to the corresponding acid, which is decarboxylated by treatment with H_2SO_4. The base, obtained on alkalinization, is solvent extracted and reacted with maleic acid.

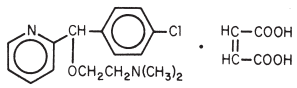
Description—White, crystalline powder; odorless; melts about 130° to 135°; pH (1 in 100 solution) 4.0 to 5.0; pK_a 3.9, 9.1.

Solubility—1 g in 5 mL water, 15 mL alcohol or 15 mL chloroform; slightly soluble in ether or benzene.

Comments—A mildly sedative bromine analog of chlorpheniramine with slight anticholinergic activity. It is an alkylamine derivative.

CARBINOXAMINE MALEATE

Ethanamine, 2-[(4-chlorophenyl)-2-pyridinylmethoxy]-*N*,*N*-dimethyl-, (*Z*)-2-butenedioate (1:1); ing of Rondec



2-[*p*-Chloro-α-[2-(dimethylamino)ethoxy]benzyl]pyridine maleate (1:1) [3505-38-2] $C_{16}H_{19}ClN_2O{\cdot}C_4H_4O_4$ (406.87).

Preparation—Picolinaldehyde and *p*-chlorophenylmagnesium bromide undergo a Grignard reaction to produce *p*-chloro-α-(2-pyridyl)benzyl alcohol. This is converted into its sodium alkoxide derivative with sodamide; β-Dimethylaminoethyl chloride is added to form carbinoxamine and the base converted into the maleate by reaction with maleic acid.

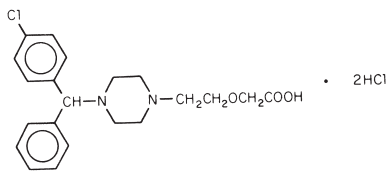
Description—White, crystalline powder; odorless; melts about 116° to 121°; pH (1 in 100 solution) 4.6 to 5.1; pK_a 8.7.

Solubility—1 g in <1 mL of water, 1.5 mL alcohol, 1.5 mL chloroform or 8300 mL ether.

Comments—An ethanolamine antiemetic with significant sedation and significant anticholinergic activity. It is useful for treating motion sickness.

CETIRIZINE HYDROCHLORIDE

Acetic acid, [2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]-ethoxy-, dihydrochloride; Zyrtec



[83881-52-1] $C_{21}H_{25}ClN_2O_3 \cdot 2HCl$ (461.82).

Preparation—Piperazine is condensed with 1 mol of 4-chlorobenzhydryl bromide under slightly alkaline conditions, and then the free secondary amine on the ring is further alkylated with 2-(2-chloroethoxy)acetamide to yield the amide of cetirizine that is hydrolyzed to the free acid. US Pat 4,525,358 (1985).

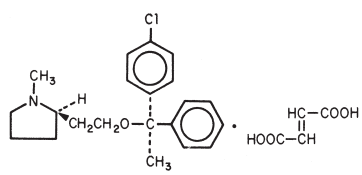
Description—Crystals that melt about 112° (base); dihydrochloride melts about 225°.

Solubility—Soluble in water.

Comments—A long-acting carboxylic acid metabolite of hydroxyzine with negligible anticholinergic activity. It is a piperazine derivative.

CLEMASTINE FUMARATE

Pyrrolidine, [*R*-(*R,*R**)]-2-[2-[1-(2-[2-[1-(4-chlorophenyl)-1-phenylethoxy]ethyl]-1-methyl-, (*E*)-2-butenedioate (1:1); Tavist**



(+)-(2*R*)-2-[2-[(*R*)-*p*-Chloro-α-methyl-α-phenylbenzyl)oxy]ethyl]-1-methylpyrrolidine fumarate (1:1) [14976-57-9] $C_{21}H_{26}ClNO \cdot C_4H_4O_4$ (459.97).

Preparation—Various benzhydryl ethers that have histamine-inhibiting action, clemastine being one, may be prepared by heating a mixture of the appropriate benzhydryl bromide and *N*-methyl-2-piperidylethanol in the presence of sodium carbonate. Details of the process, as well as of an alternate synthesis, are described in British patent 942,152 (see *CA 60*: 9250g, 1964).

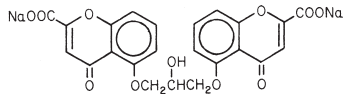
Description—White to faintly yellow, crystalline powder; practically odorless; melts 176° to 181° with decomposition.

Solubility—Slightly soluble in water, chloroform, or ether; slightly soluble in alcohol.

Comments—A long-acting ethanolamine antihistamine with slight anticholinergic activity. It has sedative and anticholinergic side effects.

CROMOLYN SODIUM

4*H*-1-Benzopyran-2-carboxylic acid, 5,5′-[(2-hydroxy-1,3-propanediyl)-bis[4-oxo-, disodium salt; DSCG; Sodium Chromoglycate; Crolom; Gastrocrom, Intal, Nasalcrom, Opticrom



[15826-37-6] $C_{23}H_{14}Na_2O_{11}$ (512.34).

Preparation—2,6-Dihydroxyacetophenone is reacted with epichlorohydrin in the presence of a basic catalyst to yield the diether, 2′, 2″-[(2-hydroxytrimethylene)dioxy]bis[6′-hydroxyacetophenone]. Reaction with diethyl oxalate affects dehydration and deethanolation of each hydroxyacetophenone portion, thus introducing the fused oxopyrancarboxylate groups as ethyl esters. This diester is then saponified with NaOH. US Pat 3,419,578.

Description—White, crystalline powder; odorless; tasteless but with a slightly bitter aftertaste; hygroscopic; pK_a believed by analogy with similar monochromes to be approximately 1.5 to 2; melts about 261°; does not exhibit polymorphism.

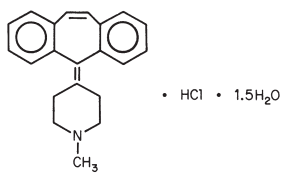
Solubility—1 g in 20 mL of water; insoluble in alcohol or chloroform.

Comments—An antiasthmatic, antiallergic, and mast-cell stabilizer used in the management of severe bronchial asthma; the prevention of exercise-induced and acute bronchospasm and allergic rhinitis; the treatment of allergic ocular disorders, such as vernal keratoconjunctivitis, vernal conjunctivitis, giant papillary conjunctivitis, vernal keratitis, and allergic keratoconjunctivitis; and in the management of mastocytosis. Animal studies show that it inhibits the degranulation of sensitized mast cells that occurs after exposure to specific antigens. Thus, it inhibits the release of histamine and SRS-A (slow-reacting substance of anaphylaxis) from the mast cell. It has no vasoconstrictor, antihistaminic, or anti-inflammatory activity.

It is absorbed poorly from the GI tract, lung (7–8%), or eye (0.03%). The systemically absorbed drug is excreted unchanged in the bile and the urine. Adverse reactions from the use of capsule and aerosol preparations include lacrimation, swollen parotid glands, nausea, dysuria, dizziness, headache, rash, urticaria, angioedema, joint swelling and pain; adverse reactions from the use of a nebulizer or nasal solutions are cough, nasal congestion, sneezing, nasal itching, epistaxis, postnasal drip, headache, and abdominal pain; and adverse reactions from ocular solutions include stinging or burning on instillation, puffy eyes, eye irritation, and styes. It is contraindicated in patients hypersensitive to cromolyn or any component of the product.

CYPROHEPTADINE HYDROCHLORIDE

Piperidine, 4-(5*H*-dibenzo[*a,d*]cyclohepten-5-ylidene)-1-methyl-, hydrochloride, sesquihydrate; Periactin



4-(5*H*-Dibenzo[*a,d*]cycloheptene-5-ylidene)-1-methylpiperidine hydrochloride sesquihydrate [41354-29-4] $C_{21}H_{21}N{\cdot}HCl{\cdot}1\ 1/2H_2O$ (350.89); *anhydrous* [969-33-5] (323.86).

Preparation—Phthalic anhydride is reacted with phenylacetic acid to form 3-benzylidenephthalide that, on isomerization and hydrogenation, gives 2-phenethylbenzoic acid. This is converted to its acid chloride, which then undergoes condensation to close the 7-membered ring and gives 10,11-dihydro-5*H*-dibenzo[*a,d*] cycloheptene-5-one. Bromination at the 10 position followed by dehydrobromination introduces the 10,11 double bond. Grignardization of this ketone with 4-chloro-1-methylpiperidine followed by dehydration of the resulting carbinol yields cyproheptadine (base), which, on reacting with an equimolar quantity of hydrogen chloride, forms the hydrochloride. US Pat 3,014,911.

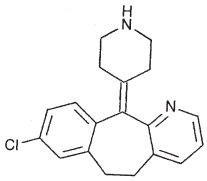
Description—White to slightly yellow, crystalline powder; odorless or practically odorless; slightly bitter taste; relatively stable in light, stable at room temperature; nonhygroscopic; sesquihydrate is stable in air; anhydrous form melts about 250° and sesquihydrate melts about 162°.

Solubility—1 g in 275 mL of water, 35 mL of alcohol, or 26 mL of chloroform; practically insoluble in ether.

Comments—An antihistamine with slight anticholinergic activity. It has mild sedative and antiserotonin activity.

DESLORATADINE

5*H*-Benzo[5,6]cyclohepta[1.2-*b*]pyridine, 8-chloro-6,11-dihydro-11-(4-piperidinylidene)-; Clarinex



[00643-71-8] $C_{19}H_{19}ClN_2$ (310.80).

Preparation—A multi-step synthesis starting with either 3-methylnicotinonitrile or ethyl nicotinate and 3-chlorophenylactonitrile. *Drugs of the Future* 2000; 25:339-346.

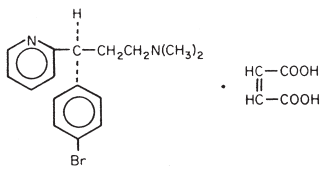
Description—Crystals, melting about 152°.

Solubility—Slightly soluble in water; very soluble in ethanol or propylene glycol.

Comments—A long-acting tricyclic histamine antagonist with selective histamine H_1 receptor e antagonist activity. Receptor binding data indicate that a concentration of 2–3 ng/mL (7 nanomolar), it shows significant interaction with the huma histamine H_1 receptor. It inhibited release from human mast cells in vitro.

DEXBROMPHENIRAMINE MALEATE

2-Pyridinepropanamine,(*S*)-γ-(4-bromophenyl)-*N*,*N*-dimethyl-, (*Z*)-2-butanedioate (1:1); ing of Drixoral



(+)-2-[*p*-Bromo-α-[2-dimethylamino)ethyl]benzyl]pyridine maleate (1:1). [2391-03-9] $C_{16}H_{19}BrN_2 \cdot C_4H_4O_4$ (435.32).

Preparation—As for *chlorpheniramide*, using the *p*-bromo derivative, rather than chloro. The racemic mixture produced is resolved to yield the product. See US Pats 2,676,964 and 3,061,517.

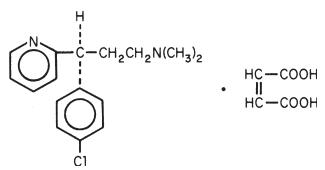
Description—White, crystalline powder; odorless; pH (1 in 100 solution) approximately 5; melts about 103° to 113°.

Solubility—1 g in 1.2 mL water, 2.5 mL alcohol, 2 mL chloroform, or 3000 mL ether.

Comments—The *d*-isomer of brompheniramine with slight anticholinergic activity. It is an alkylamine derivative.

DEXCHLORPHENIRAMINE MALEATE

2-Pyridinepropanamine, (*S*)-γ-(4-chlorophenyl)-*N*,*N*-dimethyl-, (*Z*)-2-butenedioate (1:1)



(+)-2-[*p*-Chloro-α-[2-(dimethylamino)ethyl]benzyl]pyridine maleate (1:1) [2438-32-6] $C_{16}H_{19}ClN_2 \cdot C_4H_4O_4$ (390.87).

Preparation—Racemic chlorpheniramine (see *Chlorpheniramine Maleate*) is resolved with the aid of (+)-phenylsuccinic acid. The (+)-enantiomorph of the base then is liberated from its (+)-phenylsuccinate salt by treatment with sodium hydroxide and reacted with an equimolar portion of maleic acid.

Description—White, crystalline powder; odorless; melts at 110 to 115°; pH (1 in 100 solution) 4.0 to 5.0.

Solubility—1 g in 1.1 mL water, 2 mL alcohol, 1.7 mL chloroform, or 2500 mL ether.

Comments—The *d*-isomer of chlorpheniramine with twice the potency and a wide margin of safety. It has minimal anticholinergic activity. It is an alkylamine derivative.

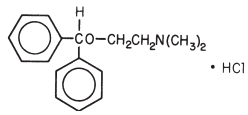
DIMENHYDRINATE

For the full monograph, see page 1310.

Comments—An ethanolamine antihistamine causing significant sedation. It is an antinauseant in motion sickness and vertigo associated with Meniere's syndrome. It has significant anticholinergic activity.

DIPHENHYDRAMINE HYDROCHLORIDE

Ethanamine, 2-(diphenylmethoxy)-*N*,*N*-dimethyl-, hydrochloride; Benadryl Hydrochloride



2-(Diphenylmethoxy)-*N*,*N*-dimethylethylamine hydrochloride [147-24-0] $C_{17}H_{21}NO.HCl$ (291.82).

Preparation—By heating diphenylbromomethane, β-dimethylamino-ethanol, and sodium carbonate in toluene. After distilling off the toluene, the purified diphenhydramine is converted to the hydrochloride with hydrogen chloride.

Description—White, crystalline powder; slowly darkens on exposure to light; solutions are practically neutral to litmus; melts 167° to 172°.

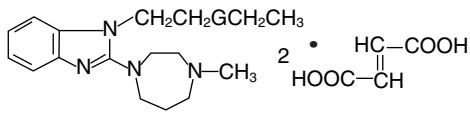
Solubility—1 g in 1 mL water, 2 mL alcohol, 2 mL chloroform, or 50 mL acetone; slightly soluble in benzene or ether.

Comments—An ethanolamine antihistamine with significant anticholinergic activity.

DOXYLAMINE SUCCINATE—see RPS-20, page 1469.

EMEDASTINE DIFUMARATE

1*H*-Benzimidazole, 1-(2-ethoxyethyl)-2-(hexahydro-4-methyl-1*H*-1,4diazepin-1-yl)-, (*E*)-2-butenedioate (1:2); Emadine



[87233-62-3] $C_{17}H_{26}N_4O.2C_4H_4O_4$ (534.57).

Preparation—1-Chloro-2-ethoxyethane and 2-chlorobenzimidazole are heated and stirred at 120° for 2 hrs. The mixture is made alkaline, extracted with ethyl acetate, dried, concentrated, and chromatographed to purify. The solvent is removed, the residue dissolved in hot ethanol, and fumaric acid added to yield the crystalline difumarate.

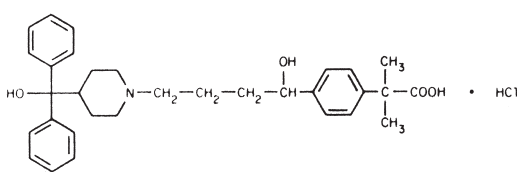
Description—Melts about 142°.

Solubility—Soluble in water.

Comments—A relatively selective, histamine H_1 receptor antagonist. In vitro examinations of emedastne's affinity for histamine receptors demonstrate relative selectivity for the H_1 histamine receptor. In vivo studies have shown concentration-dependent inhibition of histamine-stimulated vascular permeability in the conjunctiva following topical ocular administration. It appears to be devoid of effects on adrenergic, dopaminergic, and serotonin receptors.

FEXOFENADINE HYDROCHLORIDE

Benzeneacetic acid, (±)-4-[1-hydroxy-4-[4-hydroxydiphenylmethyl)-1-piperdinyl]butyl]-α,α-dimethyl-, hydrochloride; Allegra



[138452-21-8] $C_{32}H_{39}NO_4.HCl$ (538.13).

Preparation—One method involves reduction of 2-methyl-2-phenylpropanoic acid with $LiAlH_4$, esterification of the resulting alcohol with acetic anhydride to form the acetate, **I**. A Friedel-Crafts reaction of **I** with 4-chlorobutyryl chloride yields the *p*-(4-chlorobutyryl) derivative, **II**. *N*-Alkylation by **II** of α,α-diphenyl-4-piperidinemethanol in the pres-

ence of $KHCO_3$, followed by reduction of the carbonyl group to a secondary alcohol with $NaBH_4$ gives the methyl ester of fexofenadine. Hydrolysis with base affords the product, which is converted to the hydrochloride. *Arzneimittel-Forsch.* 1982; 32:1185.

Description—White crystals that melt about 143°.

Solubility—Freely soluble in ethanol or methanol; slightly soluble in chloroform or water; insoluble in hydrocarbon solvents.

Comments—An active metaboline of terfenadine without the cardiotoxic and drug-interaction potential. It has no anticholinergic activity. It is a piperidine derivative.

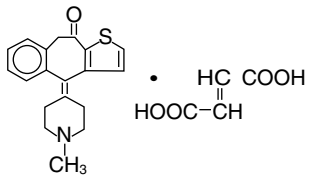
HYDROXYZINE HYDROCHLORIDE

For the full monograph, see page 1491.

Comments—A piperazine antihistamine with significant sedation often used as a preanesthetic. It has no anticholinergic activity.

KETOTIFEN FUMARATE

10*H*-Benzo[4,5]cyclohepta[1,2-*b*]thiophene-10-one, 4,9-dihydro-4-(1-methyl-4-piperidinylidene)-, (*E*)-2-butenedioate (1:1); Zaditor



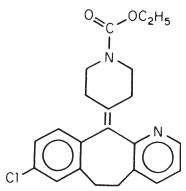
[34580-14-8] $C_{19}H_{19}NOS.C_4H_4O_4$ (425.51).

Preparation—A multi-step procedure starting with 9,10-dihydro-4*H*-benzo[4,5]cyclohepta[1,2-*b*]thiophen-4-one. *Helv chim Acta* 1976; 59:866. See also US Pat 3,682,930 (1971).

Description—Crystals from ethyl acetate. Melting point: base, 152–3°; fumarate, about 153°.

LORATADINE

1-Piperidinecarboxylic acid, 4-(8-chloro-5,6-dihydro-11*H*-benzo[5,6]-cyclohepta [1,2-*b*]pyridin-11-ylidene)-, Alavert; Claritin



[79794-75-5] $C_{22}H_{23}ClN_2O_2$ (382.89).

Preparation—*J Med Chem* 1972; 15:750. US Pat 4,282,233 (1981).

Description—Crystals that melt about 135°.

Comments—A long-acting, nonsedating tricyclic antihistamsine. It has no anticholinergic activity.

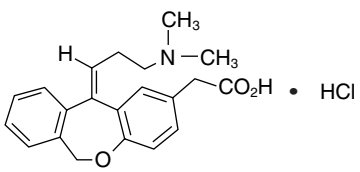
MECLIZINE HYDROCHLORIDE

For the full monograph, see page 1311.

Comments—A piperazine antihistamine with slight sedation. Its major use is for prophylactic treatment of motion sickness. It has no antichloinergic activity.

OLOPATADINE HYDROCHLORIDE

Dibenz[*b*,*e*]oxepin-2-acetic acid, *Z*-11-[3-(dimethylamino)-propylidene-6,11-dihydro-, hydrochloride; Patanol



[140462-76-6] $C_{21}H_{23}NO_3.HCl$ (373.88).

Preparation—By condensation of the sodium salt of methyl *p*-hydroxyphenyl acetate with phthalide to form the *o*-carboxyphenyl methyl ether. The ring is closed with trifluoroacetic anhydride and BF_3 in ether to yield the methyl ester of 10-oxobenz[*b*,*e*]oxapinacetic acid. Treatment with 3-dimethylaminopropyl triphenyl phosphonium bromide and hydrolysis of the ester which is formed, yields the product. *Drugs of the Future* 1993; 18:794.

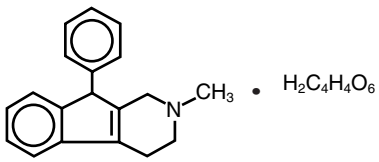
Description—White crystals, soluble in water. Melts about 248° (dec).

Solubility—Soluble in water.

Comments—An inhibitor of the release of histamine from the mast cell and a relatively selective histamine H_1 antagonist that inhibits the *in vivo* and *in vitro* type 1 immediate hypersensivity reaction including inhibition of histamine-induced effects on human conjunctival epithelial cells. It is devoid of effects on a-adrenergic, dopamine, and muscarinic type 1 and 2 receptors. Following topical ocular administration in humans, it was shown to have low systemic exposure.

PHENINDAMINE TARTRATE

1*H*-Indeno[2,1-*c*]pyridine-, 2,3,4,9-tetrahydro-3-methyl-9-phenyl-, [*R*-(*R,*R**)]-2,3dihydroxybutanedioate salt (1:1); Nolahist; Nolamine**



[569-59-5] $C_{19}H_{19}N.C_4H_6O_6$ (411.46).

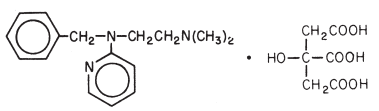
Preparation—Methylamine HCl, acetophenone and paraformaldehyde are refluxed in alcohol to form 3,3′-methyliminobispropiophenone HCl. Ring closure is achieved by heating with HBr to yield 2,3-dihydro-1-methyl-9-phenyl-1*H*-indeno[2,1-*c*]pyridine hydrobromide. Catalytic hydrogenation and treatment with alkali forms the base which is converted to the tartrate. US Pat 2,470,109 (1949).

Description—Creamy white powder; faint odor. Melts about 161° and on continued slow heating solidifies about 163° and melts again about 168° with decomposition.

Solubility—1 g in about 40 mL of water or 350 mL of alcohol; practically insoluble in chloroform, ether or benzene. Aqueous solutions are acid to litmus.

TRIPELENNAMINE CITRATE

1,2-Ethanediamine,*N*,*N*-dimethyl-N′-(phenylmethyl)-*N*′-2-pyridinyl-, 2-hydroxy-1,2,3-propanetricarboxylate (1:1); PBZ; Pyribenzamine



2-[Benzyl[2-(dimethylamino)ethyl]amino]pyridine citrate (1:1) [6138-56-3] $C_{16}H_{21}N_3 \cdot C_6H_8O_7$ (447.49).

Preparation—Tripelennamine is reacted with an equimolar portion of citric acid in a suitable volatile solvent. For the preparation of the base, see *Tripelennamine Hydrochloride*.

Description—White, crystalline powder; solutions are acid to litmus; melts about 107°.

Solubility—1 g in approximately 1 mL of water; freely soluble in alcohol; slightly soluble in ether; practically insoluble in chloroform or benzene.

Comments—An antihistamine said to be more palatable by the oral route of administration than the hydrochloride. Otherwise, its actions and uses are the same. See *Tripelennamine Hydrochloride*.

TRIPELENNAMINE HYDROCHLORIDE

1,2-Ethanediamine, *N*,*N*-dimethyl-*N*′-(phenylmethyl)-*N*′-2-pyridinyl-, monohydrochloride; PBZ; Pyribenzamine

2-[Benzyl[2-(dimethylamino)ethyl]amino]pyridine monohydrochloride [154-69-8] $C_{16}H_{21}N_3.HCl$ (291.82). For the structure of the base, see *Tripelennamine Citrate*.

Preparation—As follows: 2-aminopyridine, prepared by the action of sodamide on pyridine, is reacted with β-dimethylaminoethyl chloride in the presence of sodamide, and the resulting 2-[2-(dimethylamino)ethylamino]pyridine is condensed with benzyl bromide in the presence of sodamide. The hydrochloride is formed from the base by treatment with hydrogen chloride in an organic solvent.

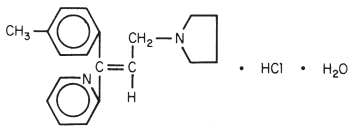
Description—White, crystalline powder; slowly darkens on exposure to light; solutions practically neutral to litmus; melts at 188° to 192°.

Solubility—1 g in 1 mL water, 6 mL alcohol, 6 mL chloroform, or about 350 mL acetone; insoluble in benzene, ether or ethyl acetate.

Comments—An ethylenediamine antihistamine with moderate sedation. It has slight anticholinergic activity.

TRIPROLIDINE HYDROCHLORIDE

Pyridine, *E*-2-[1-(4-methylphenyl)-3-(1-pyrrolidinyl)-1-propenyl]-monohydrochloride, monohydrate; ing of Actifed



[6138-79-0] $C_{19}H_{22}N_2.HCl.H_2O$ (332.87); *anhydrous* [550-70-9] (314.86).

Preparation—4′-Methylacetophenone is reacted with formaldehyde and pyrrolidine to form 3-(1-pyrrolidinyl)-4′-methylpropiophenone. Reaction with 2-pyridylsodium and subsequent hydrolysis produces the tertiary carbinol, α-[2-(1-pyrrolidinyl)ethyl]-α-*p*-tolyl-2-pyridinemethanol, which is dehydrated with sulfuric acid to introduce the propenyl double bond. Alkalinization liberates triprolidine, which is purified and reacted with an equimolar portion of HCl. US Pats 2,712,020 and 2,712,023.

Description—White, crystalline powder; no more than a slight, but unpleasant, odor; bitter taste; solutions are alkaline to litmus; melts about 115°; light sensitive; non-hygroscopic; stable to reasonable heat; pK_a 3.6, 9.3.

Solubility—1 g in 2.1 mL water, 1.8 mL alcohol, 1 mL chloroform, or 2000 mL of ether.

Comments—A propylamine antihistamine with a rapid onset and long duration of action found in OTC cold and sinus preparations. It has no anticholinergic activity.

CHAPTER 85

Central Nervous System Stimulants

Michael R Borenstein, PhD

Central nervous system (CNS) stimulants are substances that increase excitability within various regions of the brain or the spinal cord. The prominent effects produced by many of these drugs are arousal and increased motor function that result in subjective feelings of increased mental alertness, decreased fatigue, improved concentration, increased energy and motivation, and an elevation in mood. Excessive CNS excitation produced by these drugs can lead to dose-dependent adverse effects such as extreme nervousness, agitation, anxiety, and seizures.

Excitability of the CNS reflects an intricate balance between excitatory and inhibitory activity within the brain. Stimulants of the CNS directly or indirectly enhance excitatory activity or block inhibitory components. The excitatory transmitters, glutamate and aspartate, are important neurotransmitters at excitatory synapses where their actions are mediated through *N*-methyl-D-aspartate (NMDA) or non-NMDA (kainate or AMPA/quisqualate) receptors. In contrast, gamma-aminobutyric acid (GABA) and glycine are prominent inhibitory neurotransmitters. The neuromodulator, adenosine, also plays an important role in CNS excitation in that it can exert a depressant action, owing to its ability to decrease impulse-generated transmitter release and to limit excitation of postsynaptic elements by direct hyperpolarization of the neuronal membrane. Many CNS stimulants produce excitation through their antagonism at GABA, glycine, or adenosine receptors. The indirect-acting sympathomimetics, produce pronounced CNS stimulation by enhancing the actions of endogenous catecholamines because of their ability to increase release or prevent the uptake of endogenous catecholamines (Table 85-1).

The CNS stimulants are a diverse group of pharmacological agents. Many are used therapeutically and are prescription drugs (eg, the psychostimulant amphetamine). Others, such as the xanthine derivative, caffeine, are found predominately in nonprescription preparations or in common beverages. See Table 85-1 for classification of the CNS stimulants.

The xanthine derivatives (caffeine and theophylline) are mild CNS stimulants. Indeed, the ability of caffeine to increase alertness is one reason for the high consumption of caffeine-containing beverages. Of this class, only caffeine is used therapeutically for its stimulant effects. It is available in nonprescription preparations for use in promoting wakefulness. It is also found as an adjunct in various analgesic drug preparations, including prescription and nonprescription drugs, although its efficacy in the treatment of pain is not well established.

The indirect acting sympathomimetics (eg, methylphenidate and the amphetamines) are more potent CNS stimulants than caffeine but have limited therapeutic use. They are used in the treatment of attention deficit hyperactivity disorder (ADHD), narcolepsy, and obesity. However, because these CNS stimulants convey a sense of self-confidence, well-being, and euphoria, they are highly addictive and some are widely abused (eg, amphetamines, especially methamphetamine). Because of their abuse potential, the search continues to find alternative therapies for the potent CNS stimulants in these disorders. As relates to weight loss therapy, the amphetamines have limited usefulness because of the development of tolerance to their anorexic actions. Research in the area of obesity has revealed the role of various hormones and neuropeptides in lipid metabolism and satiety. It is likely that in the future, alternative therapeutics will be developed as more efficacious agents in the treatment of obesity.

CNS stimulation can be an adverse effect of some drugs at therapeutic doses. Common examples include sympathomimetic amines, nicotine, serotonin reuptake inhibitors, MAO inhibitors and various alkaloids. A number of agents are stimulant only at toxic doses. These include local anesthetics and salicylates. Only those drugs that have central stimulation as a predominant action are described in this section.

XANTHINE DERIVATIVES

Xanthine derivatives include caffeine, theophylline, theobromine, and several related synthetic derivatives, all of which have similar pharmacological properties but differ considerably in the intensity of their actions in various structures. For example, the stimulant effects of caffeine and theophylline on the CNS and on skeletal muscle are much greater than those of theobromine. However, theophylline surpasses caffeine in its diuretic, cardiac, and smooth muscular actions. Therefore, in the therapeutic application of these drugs for a specific effect, side effects can be minimized and the desired effect intensified by careful selection of the xanthine employed. For example, theophylline, but not caffeine, is used in the treatment of asthma because of its greater action on smooth muscle and its ability to alleviate bronchoconstriction. Because the principal therapeutic application of caffeine is as a CNS stimulant, its actions are discussed in this section. The principal therapeutic use of theophylline and related compounds is as a bronchodilator in the management of asthma; these drugs are discussed in Chapter 69.

AMINOPHYLLINE—page 1372.

CAFFEINE

1*H*-Purine-2,6-dione, 3,7-dihydro-1,3,7-trimethyl-, Theine: Nō Dōz; Tirent; Vivarin; Dexitac; Quick Pep

1,3,7-Trimethylxanthine [58-08-2] $C_8H_{10}N_4O_2$ (194.19); *monohydrate* [5743-12-4] (212.21).

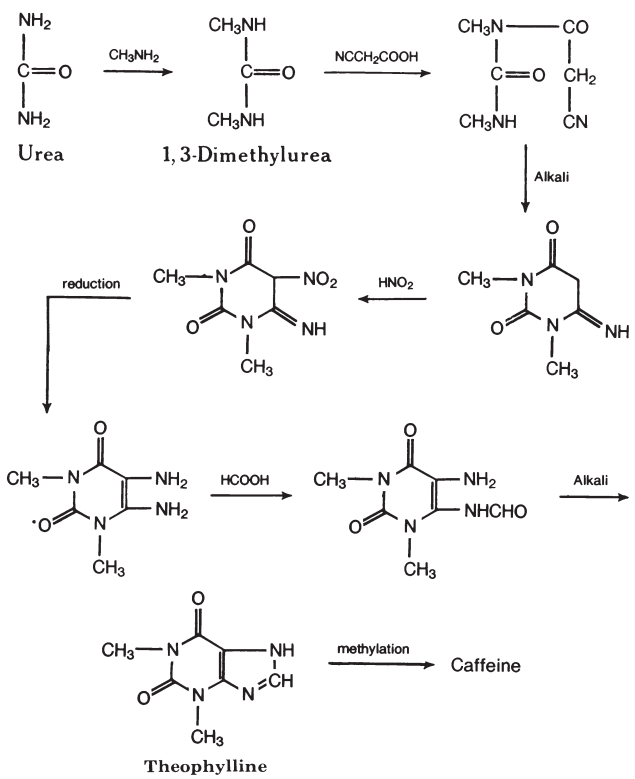
Preparation—Caffeine may be isolated from tea or coffee by boiling with water in the presence of lime or magnesium oxide, which

Table 85-1. Various Classes of CNS Stimulants and Representative Compounds

CLASS/COMPOUND	PRIMARY USE
Xanthines (adenosine antagonists)	
Caffeine	Stimulant
Theophylline	Bronchodilator
Psychostimulants[a]	
Amphetamine	Narcolepsy, ADHD
Methylphenidate	Narcolepsy, ADHD
Dexmethylphenidate	ADHD
Pemoline	Narcolepsy, ADHD
Benzphetamine	Weight control
Diethylpropion	Weight control
Mazindol	Weight control
Phendimetrazine	Weight control
Phentermine	Weight control
Sibutramine	Weight control
Cocaine	Drug of abuse
Methamphetamine	Drug of abuse
Modafinil[c]	Narcolepsy

[a] Increase aminergic activity by releasing monoamines or blocking their reuptake.
[b] Stimulates medullary respiratory centers.
[c] Mechanism unclear, possible adrenergic α-1B agonist.

serves to precipitate the tannins and some of the coloring matter. After filtration, the crude caffeine that separates is recrystallized from hot water after treatment with decolorizing charcoal. A source of the commercial supply is tea dust or sweepings. Increasing quantities of caffeine are now obtained as a byproduct in the manufacture of "decaffeinized coffee." It is also produced by methylation of theobromine (partial synthesis) and by total synthesis from urea or dimethylurea by variations of Traube's classic process (*Ber* 33:3052, 1900). The essential steps of a synthesis of theophylline and caffeine from urea are shown below:



Description—White powder or white, glistening needles, usually matted: odorless and has a bitter taste; pH (1% solution) 6.9; the hydrate is efflorescent in air and loses all its moisture at 80°; when rendered anhydrous by drying, it melts between 235° and 237.5°; pK_a 13.9.

Solubility—1 g of anhydrous caffeine dissolves in approximately 50 mL water, 6 mL of water at 80°, 75 mL alcohol, approximately 25 mL alcohol at 60°, approximately 6 mL chloroform, or 600 mL ether. Being a weak base, caffeine does not form stable salts, and even its salts of strong acids, such as the hydrochloride or hydrobromide, are hydrolyzed readily by water. The solubility of caffeine in water is increased by the presence of organic acids or their alkali salts, eg, benzoates, salicylates, cinnamates, or citrates, and this is the reason for the use of several such preparations.

Comments—None of the CNS stimulants are as widely used as is caffeine. The most prevalent sources of caffeine are beverages, which include coffee, tea, and many soft drinks. The caffeine content of tea leaves (2–3%) is higher than that of coffee beans (0.7–2.0%), but the beverages as finally prepared contain approximately equal amounts of this stimulant. The caffeine content (in 5 oz) is approximately 60 to 180 mg in brewed coffee, 30 to 120 mg in instant coffee, 20 to 110 mg in brewed tea, 25 to 50 mg in instant tea, 1 to 5 mg in decaffeinated coffee, and approximately 40 to 50 mg/12 oz in soft drinks. There is little doubt that the popularity of these beverages is due to the stimulant action of the caffeine that they contain. Caffeine is also found in oral nonprescription and prescription drugs.

Pharmacokinetics—Caffeine is absorbed readily after oral administration. After the oral administration of 100 mg of caffeine (amount contained in a cup of coffee), peak plasma levels of approximately 1.5 to 1.8 μg/mL are reached after 15 to 20 min. Plasma concentrations >20 μg/mL commonly produce adverse reactions. The lethal concentration is >100 μg/mL. Caffeine is distributed rapidly throughout all body tissues, readily crossing the placenta and the blood–brain barrier. Approximately 17% of the drug is bound to plasma proteins. Plasma half-life is 3 to 4 hr in adults; in preterm infants the half-life may be >100 hr. The longer half-life in infants is because of a much slower rate of metabolism because of the immaturity of the P-450-metabolizing systems. Therefore, if caffeine is used therapeutically in neonates (eg, in the treatment of prolonged apnea in preterm infants), dosing intervals need to be adjusted accordingly and its plasma concentration needs to be closely monitored. Caffeine is metabolized rapidly by the liver to 1-methyluric acid, 1-methylxanthine, and 7-methylxanthine. Less than 10% is excreted unchanged by the kidneys.

Pharmacology—Several mechanisms have been proposed for caffeine's stimulant actions. For many years it was thought that the stimulant action of caffeine was caused by its inhibition of the enzyme phosphodiesterase in the brain and the resulting accumulation and actions of cyclic 3′,5′-adenosine monophosphate (c-AMP). However, several compounds that are more potent than caffeine in inhibiting phosphodiesterase activity lack CNS-stimulant actions. Moreover, the concentration of caffeine needed to inhibit phosphodiesterase activity is 100 times greater than blood levels achieved after caffeine consumption. The more likely mechanism for the stimulant actions of caffeine is its blockade of adenosine receptors. Adenosine exerts prominent presynaptic and postsynaptic inhibition of neuronal activity. Blockade of this inhibition by caffeine would result in increased excitatory activity of neurons.

System Effects—Caffeine exerts effects on many systems. For example, in one double-blind clinical study, oral administration of 250 mg of the drug to nine healthy young noncoffee drinkers who had no coffee, tea, or cola in the previous 3 wk increased plasma renin activity (57%); plasma norepinephrine (75%); and plasma epinephrine by (207%); urinary normetanephrine and metanephrine were increased 52% and 100%, respectively; mean blood pressure increased 14/10 Torr within 1 hr; heart rate first decreased and then increased; and respiratory rate increased 20%.

- *CNS:* Caffeine stimulates all levels of the CNS. In oral doses of 100 to 200 mg, it stimulates the cerebral cortex, producing a more rapid and clear flow of thought, wakefulness, or arousal in fatigued patients, as well as improved psychomotor coordination. However, tasks requiring finite muscular coordination or timing may be adversely affected. Its cortical effects are milder and of shorter duration than those of the amphetamines. In larger doses, caffeine stimulates medullary vagal, vasomotor, and respiratory centers, inducing bradycardia, vasoconstriction, and an increased respiratory rate.
- *Cardiovascular:* In the heart, caffeine has a positive inotropic effect on the myocardium and a positive chronotropic effect on the sinoatrial node, causing a transient increase in heart rate, force of contraction, cardiac output, and work of the heart. In doses in excess of 250 mg, the centrally mediated vagal effects of caffeine may be masked by increased sinus rates; tachycardia, extrasystoles, or other ventricular arrhythmias may result. In the vasculature, caffeine, in normally ingested amounts, produces vasoconstriction of blood vessels, presumably by blocking adenosine receptors located in the smooth muscle of the vasculature. It is thought that the vasoconstriction of the cerebral blood vessels by caffeine contributes to its ability to relieve headaches. In the peripheral vasculature, caffeine ingestion results in increased vascular resistance and a slight increase in blood pressure, probably because of the action of caffeine on the smooth muscle of the vessels and on catecholamine release.

- *Skeletal Muscle:* Caffeine stimulates voluntary skeletal muscle, increasing the force of muscle contraction and decreasing muscular fatigue.
- *Gastrointestinal (GI):* Caffeine stimulation of parietal cells increases gastric acid secretion.
- *Renal:* Caffeine induces a mild diuresis by increasing renal blood flow and glomerular filtration rate and by decreasing proximal tubular reabsorption of sodium and water.
- *Metabolism:* Caffeine increases glycogenolysis and lipolysis, although the increases in blood glucose and plasma lipids usually are not of physiological consequence in healthy humans.

Adverse Effects—Dose-related adverse effects of caffeine include nervousness, anxiety, tremulousness, irritability, headache, excitation, restlessness, insomnia, tinnitus, GI irritation, nausea, vomiting, tachycardia, palpitations, and extrasystoles. Miscellaneous effects include hypersensitivity, urticaria, hyperglycemia, and diuresis.

Toxicity—Large doses are usually associated with GI pain, muscle twitching, facial flushing, dizziness, dyspnea, mild delirium, diuresis, dehydration, nausea, vomiting, and fever. More serious symptoms include cardiac arrhythmias and convulsions. The acute lethal dose of caffeine in adults appears to be approximately 5 to 10 g. Caffeine may aggravate diarrhea in patients who have irritable bowel, or it may exacerbate duodenal ulcers. Safety for pregnancy has not been established, but moderate intake does not appear to be harmful to the fetus.

Tolerance—Prolonged, high intake may produce tolerance to the diuretic, cardiovascular, and CNS system effects as well as physical dependence. Abrupt discontinuation of the stimulant may produce withdrawal symptoms of fatigue, headache, anxiety, nausea, vomiting, irritability, impaired psychomotor function, restlessness, lethargy, and less commonly, yawning and rhinorrhea. A typical symptom is headache that results from a rebound vasodilation of the brain vasculature upon withdrawal from caffeine. Symptoms appear within 24 hr after the last ingestion of caffeine, peak within 48 hr, and may persist for as long as 1 wk.

Drug Interactions—Caffeine and other xanthines may modify the effects of other drugs. These drugs can enhance the cardiac inotropic effects of beta-adrenergic stimulating agents and decrease the effect of benzodiazepines. Because caffeine ingestion results in reduced liver blood flow, the metabolism and elimination of drugs that are eliminated primarily by hepatic metabolism may be slowed.

Laboratory Tests—The ingestion of caffeine can cause a slight increase in urine levels of vanillylmandelic acid, catecholamines, and 5-hydroxyindoleacetic acid. Because high urine levels of vanillylmandelic acid or catecholamines may result in a false-positive diagnosis of pheochromocytoma or neuroblastoma, caffeine intake should be avoided during these tests.

Uses—Nonprescription caffeine preparations are used orally as a mild CNS stimulant to aid in staying awake and to restore mental alertness. Caffeine is the only stimulant approved by the Food and Drug Administration (FDA) for nonprescription use. Caffeine also is found in nonprescription drugs containing analgesics (acetaminophen, aspirin) for the treatment of mild pain, for relief from vascular headaches such as migraine and cluster headaches, and for the treatment of menstrual pain and discomfort (usual caffeine content of 30 to 65 mg/tablet). It is also a component in various cold remedies. Although the efficacy of caffeine in the analgesic preparations is controversial, results from some clinical studies indicate that the adjunct use of caffeine with analgesics may lower the amount of analgesic needed for pain relief. Caffeine is also used in combination with ergotamine in prescription drugs for migraine headaches, presumably because of its actions on extracranial vasculature and trigeminal afferents. Caffeine is used to treat preterm apnea in infants. However, the combination of caffeine with sodium benzoate is contraindicated for use in these infants because the benzoate can cause metabolic disturbances and bilirubinemia.

CAFFEINE, CITRATED

Xanthine, 1,3,5-trimethyl-, citrate salt; Cafcit

[69-22-7] Caffeine citrate

Preparation—Fifty grams each of caffeine and citric acid are dissolved in 100 mL of hot distilled water, the solution evaporated to dryness with constant stirring. It is usually prepared simply by dry-mixing equal quantities of each component.

Description—White, odorless powder; slightly bitter, acid taste; acid reaction. Solutions are adjusted to pH 4.7.

Solubility—1 g in approximately 4 mL warm water; the caffeine gradually precipitating on diluting the solution with an equal volume of water but redissolving on further dilution with sufficient water.

Incompatibilities—Neutralization of the citric acid by *alkalies* or *alkaline salts* causes precipitation of caffeine if in sufficient concentration. The alkali salts of organic acids may release either caffeine or the free organic acid. Generally, it displays the incompatibilities of the citric acid that it contains.

Comments—Approved by the FDA in 1999 as a solution for intravenous injection and oral administration for the short-term treatment of apnea of prematurity (AOP) in infants between 28 and <33 weeks gestational age.

Pharmacology—The mechanism of action of caffeine in AOP is not known but may be related to its following effects: stimulation of the respiratory center, increased minute ventilation, decreased threshold to hypercapnia, increased response to hypercapnia, increased skeletal muscle tone, decreased diaphragmatic fatigue, increased metabolic rate, and increased oxygen consumption.

Pharmacokinetics—Peak plasma levels of caffeine are reached 30 minutes to 2 hours following oral administration of 10 mg of caffeine base/kg to preterm neonates. The elimination of caffeine is much slower in infants compared to adults. Mean half-life in neonates is 3 to 4 days, and 86% is excreted unchanged.

Adverse Effects—Published long-term follow-up studies have not shown caffeine to adversely effect neurologic development or growth. Necrotizing enterocolitis, feeding intolerance, and the development of rash were the most commonly reported events, but the potential exist for CNS stimulation, cardiovascular and gastrointestinal effects, as well as alterations in metabolism and renal effects.

CAFFEINE AND SODIUM BENZOATE INJECTION

A sterile solution of caffeine and sodium benzoate in water for injection; contains an amount of anhydrous caffeine ($C_8H_{10}N_4O_2$) equivalent to 45% to 52%, and an amount of sodium benzoate ($C_7H_5NaO_2$) equivalent to 47.5% to 55.5%, of the labeled amounts of caffeine and sodium benzoate.

Description—pH between 6.5 and 8.5.

Comments—see *Caffeine* page 1551.

DYPHYLLINE—page 1373.
OXTRIPHYLLINE—page 1383.
THEOPHYLLINE—page 1373.
THEOPHYLLINE, EPHEDRINE HYDROCHLORIDE, AND PHENOBARBITAL—see RPS-19, page 973.

PSYCHOSTIMULANTS

Most of the compounds included under this heading are indirect-acting sympathomimetic drugs and are more potent central stimulants than the xanthine derivatives. These compounds do not stimulate monoaminergic receptors directly, but rather they increase the actions of endogenous monoamines. This is because of their ability to inhibit the uptake of the catecholamine from the synaptic cleft after release (eg, cocaine, methylphenidate, mazindol, or sibutramine) or to cause catecholamine release (amphetamine and congeners). The actions of diethylpropion and phentermine are primarily on adrenergic neurotransmission, pemoline on dopaminergic neurotransmission, and those of mazindol and sibutramine increase adrenergic, dopaminergic, and serotonergic activity. Because of their propensity to produce euphoria, many of these drugs are widely abused and are controlled substances. Given the abuse liability and dependence potential of many of these compounds, the therapeutic use of these drugs needs to be monitored closely. Other compounds in this category (eg, cocaine, methamphetamine) have limited therapeutic use but are some of the most widely abused drugs in the world.

Many drugs in this class are used in the treatment of ADHD in children and adults. This is a disorder characterized by a variety of symptoms, including an unacceptable degree of hyperactivity, inability to concentrate, short attention span, difficulty in learning, emotional lability, and compulsiveness. Paradoxically, CNS stimulants can be beneficial in the treatment of this disorder although the mechanisms by which they provide benefit is unknown. Although their use remains controversial, there is a patient group with severe, persistent hyperactivity, and a short attention span that benefit from treatment with these agents. Drug treatment is not indicated for all children who have this disorder; stimulants are not indicated for the child who exhibits symptoms secondary to environmental factors or primary psychiatric disorders. Consequently, these should be ruled out and remedial psychological, educational, and social resources should be used before drug therapy

is instituted. In the adult population, cardiovascular effects of these stimulants often preclude their use. The psychostimulants most frequently used for this purpose are amphetamine and methylphenidate; pemoline is also used but is not the first choice of drug for treatment.

Narcolepsy is another condition that requires long-term treatment. This disorder, characterized by sleep attacks, cataplexy (loss of muscle tone), hypnagogic hallucinations, sleep paralysis, and nocturnal sleep disruption, may result from an impairment in catecholamine neurotransmission. The psychostimulants are effective in preventing the daytime symptoms (sleep attacks and cataplexy), although they can also interfere with nighttime sleep. In the US, the drugs approved for use for narcolepsy are amphetamine, methylphenidate, pemoline, and modafinil.

Obesity is the only other condition for which the psychostimulants are approved for use. Amphetamine and its analogs have significant anorexic effects. The mechanisms by which these drugs reduce appetite are not fully established, but it is thought that stimulation of satiety centers in the hypothalamus and limbic areas is involved. However, tolerance readily develops to this action within a few weeks. Because of the development of tolerance, the production of undesirable side effects, and the high abuse potential of the amphetamines, many in the medical field believe that the use of these drugs for weight reduction purposes is inappropriate. Others would argue that their use is appropriate when all other approaches have failed and if drug use is carefully monitored. The drugs primarily used as appetite suppressants are benzphetamine, diethylpropion, mazindol, methamphetamine, sibutramine, phendimetrazine, and phentermine. Although these drugs may differ in potency and some of their adverse effects, their qualitative pharmacological effects are similar.

The psychostimulants can improve psychomotor performance and enhance wakefulness, although it is questionable whether concentration in complex learning situations or judgment is improved. Their effects are thought to be mediated through cortical stimulation and possibly through stimulation of the reticular activating system. For the amphetamines, the (*S*), (+), or dextro- isomers are somewhat more potent than the (*R*), (−), or levo- isomers (eg, amphetamine isomer effects differ by 3- to 4-fold) in elicitation of CNS responses the dextro enantiomer of methylphenidate is also the more potent isomer. The alerting effect of the psychostimulants, their anorectic effect, and their locomotor-stimulating action are likely mediated by enhancement of the actions of norepinephrine and dopamine in various brain regions. Euphoric effects are likely related to actions on dopamine within the limbic system. That the CNS-stimulating effects of these compounds are mediated through the catecholamines is suggested by animal studies findings that the inhibition of catecholamine synthesis prevents the behavioral activation produced by the drugs.

Adverse effects of the psychostimulant drugs are generally extensions of their therapeutic actions but may differ somewhat with the individual agents owing to their differences in potency and the specificity of their pharmacological action. In general, adverse effects include nervousness, insomnia, anorexia, nausea, palpitations, headache, dyskinesias, blood pressure and pulse changes, tachycardia, angina, cardiac arrhythmias, abdominal pain, weight loss, and hypersensitivity reactions. Acute CNS toxicity with these agents can produce restlessness, dizziness, tremor, hyperactive reflexes, talkativeness, irritability, weakness, insomnia, and fever. Larger doses can produce confusion, increased libido, anxiety, panic states, hallucinations, psychotic behavior, and seizures. Some of these effects may also be caused by the ability of these drugs to enhance the actions of 5-hydroxytryptamine (5-HT) from serotonergic neurons. In addition, there may be pronounced cardiovascular and GI effects. Symptoms of overdose may include vomiting, agitation, tremors, hyperreflexia, muscle twitching, convulsions (may be followed by coma), euphoria, confusion, hallucinations, delirium, sweating, hyperpyrexia, tachycardia, palpitations, cardiac arrhythmias, hypertension, mydriasis, and dryness of the mucous membranes. Tolerance, psychological dependence, abnormal behavior, and physical dependence can occur with the psychostimulants. Characteristics of high-dose use that may emerge include severe dermatoses, significant insomnia, irritability, hyperactivity, personality changes, disorganized thought, poor concentration, compulsivity, hallucinations, and possibly, a severe psychotic state resembling paranoid schizophrenia.

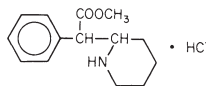
Severe *drug interactions* may occur between the psychostimulants and other drugs, especially those that also have actions on monoaminergic neurons. For example the psychostimulants and selective serotonin-reuptake inhibitors (eg, fluoxetine, paroxetine, sertraline, or fluvoxamine) may result in a group of symptoms (termed *serotonin syndrome*) which include excitation, hypomania, restlessness, loss of consciousness, confusion, disorientation, anxiety, agitation, motor weakness, myoclonus, tremor, hemiballismus, hyperreflexia, ataxia, dysarthria, hyperthermia, shivering, diaphoresis, emesis, and tachycardia. Similarly, the use of psychostimulants in patients being treated with monoamine oxidase inhibitors (MAOIs) is contraindicated. Because of their cardiovascular effects, stimulants are contraindicated in patients who have a history of coronary heart disease, chronic heart failure, arrhythmias, stroke, or glaucoma. In addition, the psychostimulants need to be used cautiously in patients being treated with other drugs that affect cardiovascular function, including nonprescription drugs containing phenylpropanolamine, ephedrine, or pseudoephedrine. The use of psychostimulants is not recommended for patients taking antidepressants, lithium, sumatriptan, tryptophan, or dihydroergotamine. In general, psychostimulants are contraindicated in patients who have agitation, cardiovascular disorders, hypertension, hyperthyroidism, glaucoma, hypersensitivities to the drugs, motor tics, a diagnosis of or family history of Tourette's syndrome, a history of epilepsy or abnormal EEGs, or a history of drug abuse because their use could exacerbate the symptoms associated with these disorders or disease states. The safe use of the psychostimulants in children younger than 6 yrs. of age has not been established. See Chapter 70 for additional discussion of the amphetamines, contraindications for use, and drug interactions.

Cocaine is also a potent sympathomimetic CNS stimulant with actions similar to those of the amphetamines but with a much shorter duration of action. In contrast to the amphetamines, which cause monoamine release, cocaine's actions are thought to be mediated primarily by its blockade of the reuptake of released monoamines. Cocaine has local anesthetic actions; however, its use for this purpose is limited, having been replaced by synthetic local anesthetics that have little CNS stimulation. The importance of cocaine lies in its abuse potential; it is currently one of the most widely abused drugs in the United States.

AMPHETAMINE SULFATE—see RPS-19, page 986.
BENZPHETAMINE HYDROCHLORIDE—see RPS-19, page 987.
COCAINE—page 1484.
DEXTROAMPHETAMINE SULFATE—see RPS-19, page 987.
DIETHYLPROPION—see RPS-19, page 987.
MAZINDOL—see RPS-19, page 992.
METHAMPHETAMINE—see RPS-19, page 994.

METHYLPHENIDATE HYDROCHLORIDE

2-Piperidineacetic acid, (*R*,R)-(±)-α-phenyl-, methyl ester, hydrochloride, Ritalin; Concerta**



[298-59-9] $C_{14}H_{19}NO_2.HCl$ (269.77).

Preparation—2-Chloropyridine is condensed with phenylacetonitrile and the resulting α-phenyl-2-pyridineacetonitrile is hydrated to its corresponding amide. The pyridine ring then is hydrogenated catalytically and the amide converted to its corresponding carboxylic acid. Esterification with methanol, with the aid of HCl, yields the final product.

Description—White, odorless, fine, crystalline powder; melts about 75°; solutions are acid to litmus, pK_a 8.9.

Solubility—Freely soluble in water or methanol; soluble in alcohol; slightly soluble in chloroform or acetone.

Comments—A mild *CNS stimulant* with a potency intermediate to caffeine and amphetamine. It is effective as adjunctive therapy to other remedial measures (psychological, educational, and social) in the management of ADHD. It is also effective in the treatment of narcolepsy and possibly effective in mild depression and in apathetic or withdrawn senile behavior. Methylphenidate also shares the abuse potential of the amphetamines. The drug should not be used to alleviate normal fatigue.

Pharmacokinetics—Methylphenidate is readily absorbed from the GI tract. Peak blood levels are reached in 1 to 3 hr, and the plasma half-life ranges from 1 to 3 hr. The pharmacological effects persist from 4 to 6 hr after oral administration of conventional tablets and approximately 8 hr for extended-release preparations. Approximately 80% of an oral dose is metabolized to ritalinic acid and excreted in the urine.

Pharmacology—Its pharmacological properties are essentially the same as those of the amphetamines. Its actions appear to be mediated by blockade of norepinephrine and dopamine into the presynaptic neuron and increase the release of these monoamines into the extraneuronal.

See the general statement for effects, adverse effects, and contraindications for use of methylphenidate. Additional adverse reactions reported with methylphenidate use include leukopenia and anemia, and a few cases of scalp hair loss have been reported with methylphenidate.

Drug Interactions—In addition to above discussion of drug interactions, human studies indicate methylphenidate may inhibit metabolism of coumarin anticoagulants, anticonvulsants, and tricyclic antidepressants. Dosage of these agents may require downward adjustment when given concomitantly with this drug.

DEXMETHYLPHENIDATE HYDROCHLORIDE

2-Piperidineacetic acid, (*R,*R**)-(+)-α-phenyl-, methyl ester, hydrochloride, Focalin**

[40431-64-9] $C_{14}H_{19}NO_2$.HCl (269.77).

Preparation—See US Pat 6,162,919 (1998).

Description—The *d-threo* isomer of methylphenidate, which is a racemic mixture of the d-threo and l-threo isomers. White to off white powder; solutions are acid to litmus.

Solubility—Freely soluble in water or methanol; soluble in alcohol; slightly soluble in chloroform or acetone.

Comments—Dexmethylphenidate was approved by the FDA in 2001 for treatment of ADHD in children greater than 6 years of age. It is the d-threo enantiomer (the more pharmacologically active enantiomer) of racemic methylphenidate hydrochloride. It is not approved for use in narcolepsy.

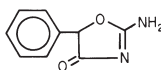
Pharmacokinetics—Dexmethylphenidate is readily absorbed following oral administration, reaching a maximum concentration 1 to 1.5 hours post dose. The mean plasma elimination half-life is approximately 2.2 hours.

Pharmacology—See methylphenidate.

Drug Interactions—See methylphenidate

PEMOLINE

4(5*H*)-Oxazolone, 2-amino-5-phenyl-, Cylert



[2152-34-3] $C_9H_8N_2O_2$ (176.17).

Preparation—Ethyl mandelate, $C_6H_5CH(OH)COOC_2H_5$, is reacted with guanidine, $HN{=}C(NH_2)_2$, in boiling alcoholic solution. US Pat 2,892,753.

Description—White, crystalline powder; odorless and tasteless; melts about 256° with decomposition.

Solubility—Practically insoluble in water, chloroform, dilute HCl, or ether; slightly soluble in alcohol or propylene glycol.

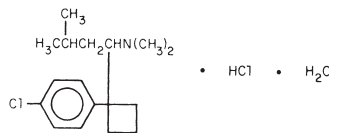
Comments—A CNS stimulant that is structurally different from the amphetamines and methylphenidate. It has less abuse potential than the amphetamines and is classified as a *Schedule IV* drug (amphetamines are *Schedule II* drugs). Although laboratory studies indicate that pemoline may act through dopaminergic mechanisms, the mechanism and site of action in man are not known. It is used in the treatment of narcolepsy and as adjunctive therapy in children who have attention deficit disorder; however, its efficacy is less than that of amphetamine or methylphenidate. It also has less sympathomimetic effects than the amphetamines. Pemoline has been used in the treatment of fatigue, mental depression, chronic schizophrenia, and as a mild stimulant in geriatric patients; however, clinical benefits from such use are minimal. It should not be used for the prevention or the treatment of normal fatigue.

Pharmacokinetics—Peak serum levels of the drug are reached 2 to 4 hr after ingestion of a single oral dose; the serum half-life is approximately 12 hr, and a steady-state level is reached in 2 to 3 days of multiple dosage. Approximately 50% of the drug is bound to serum proteins. Approximately 75% of an oral dose is excreted in the urine within 24 hr, approximately 43% is excreted unchanged, and 22% is excreted as pemoline conjugates.

Adverse Effects and Toxicity—In addition to adverse effects common to the psychostimulants, pemoline use can produce dyskinetic movements of the tongue, lips, face, and extremities as well as abnormal oculogyric function (nystagmus and oculogyric crises). Pemoline has been associated with life-threatening hepatic failure and, for this reason, it is not recommended as the first choice of drug in treatment.

SIBUTRAMINE HYDROCHLORIDE

(±)-Cyclobutanemethanamine, 1-(4-chlorophenyl)-*N*,*N*-dimethyl-α-(2-methylpropyl)-, hydrochloride, monohydrate; Meridia; Reductil



[125494-59-9] $C_{17}H_{26}ClN.HCl.2H_2O$ (334.33).

Preparation—See US Pat 4,929,629 (1987).

Description—White crystals melting about 193° to 196°.

Solubility—Moderately soluble in water.

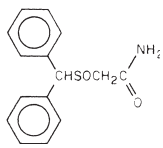
Comments—An appetite-suppressant drug that was approved by the FDA in 1997. It can be considered a prodrug because its pharmacological activity actually resides in two of its desmethylated metabolites (formed from CYP-$3A_4$ metabolism of the parent drug). The pharmacological effects of the active sibutramine metabolites block the uptake of all three monoamines but with a slightly greater potency on norepinephrine and dopamine uptake than on serotonin uptake.

Pharmacokinetics—The drug is rapidly absorbed after oral administration. Sibutramine undergoes extensive first-pass metabolism (half-life is approximately 1 hr). Concentrations of the active metabolites peak at 3 to 4 hr and have half-lives of 14 to 16 hr. These metabolites are further metabolized by hydroxylation and conjugation to inactive substances and excreted in the urine.

Adverse Effects and Contraindication—Similar to other psychostimulants.

MODAFINIL

Acetamide, 2-[(diphenylmethyl)sulfinyl]-, Provigil



[68693-11-8] $C_{15}H_{15}NO_2S$ (273.35).

Preparation—See US Pat 4,177,290 (1978).

Description—White crystals melting about 164° to 166°.

Comments—Modafinil is a psychostimulant with a mechanism of action distinct from other agents in this class. It is approved for use in the US for the treatment of the symptoms of daytime sleepiness in narcolepsy and other sleep disorders. Modafinil is a drug that possesses alerting properties (eugerioc), although its precise mechanism of action is not known. Psychometric, psychobiological tests, and electroencephalogram (EEG) profiles show changes that are viewed as improvements in vigilance. There is some suggestion that modafinil may be somewhat less effective than amphetamine or methylphenidate. However, unlike the amphetamines, modafinil does not reduce Stage 2 rapid eye movement (REM) sleep or alter heart rate or blood pressure.

Pharmacology—The exact mechanism of antinarcoleptic action is unknown. Limited studies have indicated that it may increase glutaminergic transmission in the thalamus and hypothalamus or have an agonist effect at central alpha 1-B adrenergic receptors.

Pharmacokinetics—Peak plasma concentrations are reached 2 to 3 hr after oral administration of the drug. Plasma half-life is 8 to 10 hr.

Adverse Effects—Dose-related adverse effects include dry mouth, dry eyes, nausea, inner tension, sleep disturbances, sweating, headache, dizziness, hot flashes, and gastralgia. Other effects include tachycardia, hypersalivation, anorexia, anxiety, choking, dysphoria, bad temper, hypertension, excitation, fatigue, sexual hyperactivity, weight gain, euphoria, and motor excitation.

CHAPTER 86

Antineoplastic Drugs

Jean M Scholtz, BS, PharmD, BCPS

Before the 1940s the principal nonsurgical treatment of neoplasms was radiograph and radium therapy, although certain arsenicals and urethane were also in use. During the 1940s, there were three main developments: radioisotopes, nitrogen mustards, and antifolic acid agents. The use of sex hormones for the treatment of certain types of neoplasms and of adrenal corticoids and adrenocorticotropic hormone (ACTH) for the treatment of leukemia also developed considerably during these years.

Much excitement was generated by these early developments in antineoplastic therapy, but it was later tempered by the realization not only that the drugs were not curative but also that, for the most part, life-expectancy was negligibly increased, the drugs being mainly palliative. Subsequently, there has been a great proliferation in both the number and the classes of anticancer drugs and in the theory of cell kinetics and cancer at the molecular level. Recent progress in the understanding of oncogenes and tumor-suppressor, and their role in pathogenesis of cancer have led to the development of new classes of drugs. Long-term cures and disease-free remissions continue to be achieved with various combinations of these drugs, with more research being performed in the chemoprevention arena.

Tumor Growth and Kinetics

The principal difference between mature normal tissues and tumors is not in the rate of cell replication but in that the rate of proliferation for most normal tissues equals the rate of cell death, whereas in neoplasms, proliferation exceeds the death rate. Proliferation in normal tissue responds to subtle signals that indicate when proliferation is needed for repair, regeneration or growth, and development. Neoplasms seem to lack such an autoregulation of proliferation, and the cell-replication rate appears to depend mostly on an intrinsic rate modulated by the adequacy of the vascular supply.

EXPONENTIAL GROWTH AND DOUBLING TIMES— In the early stages, the growth of a tumor is approximately constant. The doubling time is the mean (*average*) interval between successive mitoses. It is characteristic of the particular type of tumor cell. Doubling time varies significantly among various kinds of tumors. In Burkitt's tumor, it is approximately 24 hours; in acute leukemia, 2 weeks; in breast cancer, 3 months; and in multiple myeloma, 6 to 12 months. Contrary to common belief, these doubling times are within the range of those for normal tissues. For example, white-cell precursors divide approximately every 12 hours and mucosal cells of the rectum every 24 hours.

A tumor becomes detectable when the number of cells reaches approximately 10^9 to 10^{10} cells. This requires 30 to 33 doubling times. The neoplasm becomes lethal when the population reaches approximately 5×10^{11} to 5×10^{12} cells, after 39 to 42 doubling times.

PHASES OF THE CELL CYCLE— Some drugs can exert a lethal action only when a cell is in a particular stage of activity and growth. Therefore, a knowledge of cell kinetics will be useful. After mitosis and cell division, the new daughter cells are in a resting state, terms phase G_0 (G for gap). The length of time spent in G_0 depends on both the type of cell and the autoregulatory factors. In some tissues, such as bone marrow, gastrointestinal (GI) mucosa, and skin, G_0 is prolonged only moderately during maturation and aging, whereas with others, such as nerve and skeletal muscle cells, G_0 becomes essentially infinitely long well in advance of maturity. In solid tumors, G_0 is longer when the cell mass is large than when small, because the vascular supply cannot keep pace with the rate of growth. Ultimately, the cell enters a postresting phase, called G_1. In this phase, metabolism appears to be normal, but the cell is committed to divide. After a latency period, the cell enters the S-phase, in which DNA synthesis is activated, in preparation for mitosis. The cell then enters another phase, G_2, the premitotic phase, in which DNA synthesis is essentially at rest but protein synthesis and other metabolic activities are increased and the cell volume grows. Finally, the cell undergoes mitosis (phase M) and cellular fission.

The cell cycle can be thought of as existing in two superstages: G_0 as one, and all of $G_1 + S + G_2 + M$ as the other, the latter comprising all phases committed to cellular division. The entity $(G_1 + S + G_2 + M)/(G_0 + G_1 + S + G_2 + M)$ is known as the growth fraction. In tumors, it usually lies between 0.2 and 0.7. Although the growth fraction tends to be greater in the more rapidly proliferating tissues and tumors, this is not always the case. The proliferation of normal cells is tightly controlled by proto-oncogenes and tumor-suppressor genes. These provide stimulatory and inhibitory signals, respectively, which regulate the cell cycle. The evolution of cells through the cell cycle is a tightly-regulated process. Various proteins, called cyclins, along with enzymes called cyclin-dependent kinases (CDKs), regulate movement of cells through the cell cycle. Various gene mutations, such as loss or mutation of tumor suppressor gene p53, result in excessive cell proliferation. Apoptosis and senescence (aging) are other mechanisms that control excessive cell division. Research is ongoing to discover genes, proteins, and receptors involved in the growth of cancer cells, and strategies or agents to alter their effects on the cell cycle and cell growth.

Chemotherapeutic Intervention

PHASE SPECIFICITY— Antineoplastic drugs are of two general categories: (1) those that can act on the cell throughout its cycle (such drugs are said to be phase nonspecific) and (2) those that act preferentially during one or more of the nonresting phases (these drugs tend to be ineffective if delivered to the cell during the wrong phase). Even phase-nonspecific drugs

have greater activity during the growth phases. The particular phase during which a drug acts depends on the lethal mechanism. Those that combine irreversibly with DNA can do so at any time and hence are phase nonspecific. However, more DNA is exposed during the growth phases than during G_0, so that even these drugs have some phase selectivity. Drugs that interfere with DNA synthesis are specific to the S phase; those that block protein synthesis are specific mainly to phases S and G2; and those that inhibit microtubule assembly are specific mainly to M.

TUMOR SELECTIVITY AND RESPONSE—Especially for phase-specific drugs, the probability of a lethal action on a tumor cell (or normal cell) is directly proportional to the percent of time spent in the vulnerable phase. It follows that the percent of time spent in the vulnerable phase is an important determinant of the susceptibility of tumors of different cell types. Even without reference to any particular growth phase, the generality that those tumors with a large growth fraction are more susceptible to chemotherapy than those with a low fraction is an important precept. Examples of tumors with high growth fractions that respond well to chemotherapy are acute leukemia in children, Burkitt's lymphoma, choriocarcinoma, chronic myelogenous leukemia (these last three now are considered curable), lymphocytic leukemia, Hodgkin's disease, Wilms' tumor, and breast cancer. Examples of neoplasms that respond poorly are malignant melanoma, carcinoma of the GI tract, bronchogenic carcinoma, and tumors of the uterus and cervix.

Because growth fractions are higher in small, recent tumors, it follows that efficacy is enhanced by early treatment. Different cell types spend different proportions of time in one as opposed to another phase (ie, more in G_2 than S, etc.). Therefore, the most effective drug would be expected to be of a type that is specific to the phase of longest duration. In part, this may account for the differences in efficacy among drugs of different mechanisms and phase specificity.

There has been interest in and investigation of the possibility of *synchronizing* tumor cells so that all cells are in the same phase of the cycle. If the cells were synchronized and the host cells were not, then the tumor could be made more vulnerable to appropriate drugs given at the proper time, and the therapeutic index could be increased. Synchronization is attempted by a holding *pulse* of a mitostatic or some other drug that holds the cells in a given phase until the out-of-phase cells also come into that phase. Discontinuation of the synchronizing drug simultaneously releases the cells to resume their cycle, all starting from the same phase. In combination chemotherapy, drugs often are administered in sequence, rather than simultaneously; the first-given drug sometimes serves as a synchronizing drug.

DETERMINANTS OF SENSITIVITY AND SELECTIVITY—In addition to the growth fraction or vulnerable phase time of a tumor, other factors also determine the selectivity of drugs for certain cell types. The demand for nutrients varies among tumor types but also differs between tumor cells and normal cells. For example, many tumors require more asparagine than normal cells, so that if the plasma asparagine is destroyed enzymatically (see *Asparaginase,* page 1562, the tumor cells are selectively *starved* to death.

Some drugs are metabolized in the peripheral cells as well as in the liver, and the different cell types differ in their ability to metabolize these drugs. For example, with bleomycin, there is evidence to suggest that the drug is metabolized less in susceptible tumor cells than in other cells, thus permitting higher local concentrations. Several drugs are converted to active metabolites by the target cells (*lethal synthesis*), and differences in the rates of conversion may contribute to selectivity.

Differences in penetrance account for some differences among drugs; lipid-soluble antineoplastic drugs are more effective than water-soluble ones for neoplasms in the central nervous system (CNS). With some drugs, active transport into tumor cells is greater than into normal cells; with other drugs, there are differences in outward transport. An unassessed factor in selectivity is that of effects on the immune system. There are not only tumor-cell-attacking *killer* T cells but also suppressor T cells and blocking factors from B cells that protect certain neoplastic cells from immune attack. According to which immune cells are the most suppressed, some antineoplastic drugs might antagonize the immune response to neoplastic cells, and other drugs augment it.

REQUIREMENTS FOR "KILL"—A remission usually can be achieved with a kill of 90% to 99% of the neoplastic cells. A kill of 99% would leave at least 10^7 to 10^8 surviving cells to carry on tumor growth, and the remission would last only 3 to 4 doubling times. With those neoplasms against which the immune system is ineffective, a 100% kill is necessary to effect a true cure, because it has been shown experimentally that a single implanted neoplastic cell can develop into a tumor. However, a true cure may not always be necessary. For example, with a tumor, the doubling time of which is 12 months, a kill of 99.99% (which would leave perhaps 10^6 surviving cells) would require approximately 13 years for the tumor cell population to recover to the number extant at the time of treatment.

A second course of an appropriate chemotherapy might add another 13 years, which, with middle-aged or elderly patients, might be beyond the normal life expectancy. However, with a rapidly doubling tumor such as Burkitt's tumor, the survival time in the untreated patient is measured in days, not years; even if all but a single cell were killed by an antineoplastic drug, survival would be prolonged less than 2 months; therefore, either a complete kill or sustained or frequently repeated courses are imperative. Fortunately, 50% to 60% of Burkitt's tumor cells are in the S phase and are thus highly susceptible to drugs that are S-phase specific.

COMBINATION CHEMOTHERAPY—One way of increasing the percent of kill is to combine two or more antineoplastic drugs. Radiation also is a modality that often can be combined effectively with drugs. There are four criteria to optimize such combinations:

1. Each component drug must have some efficacy by itself.
2. Each component drug should have a different mechanism of cytotoxic activity and, preferably, phase specificity.
3. Each component drug should have a different spectrum of toxicity than the other components, in order to avoid overwhelming toxicity of a given type.
4. The mechanism of resistance to each component should be different to that of the other components.

LOG CELL-KILL PRINCIPLE—Antineoplastic drugs may be characterized by their log cell-kill index, that is, by the negative log of the fraction of the tumor cell population that survives a single course of treatment. Thus a drug that kills 99.99% of the tumor cell population, ie, leaves 0.0001 (or $1/10^4$) of the population, is known as a 4-log drug; a second drug that kills 99.9% is known as a 3-log drug. The log cell-kill index is a tenuous number, but it is useful in predicting the effects of combinations that meet criteria 1 and 2. The predicted effect of a combination is obtained by addition of the indices of the component drugs. Theoretically, a 4-log drug plus a 3-log drug should provide a 7-log combination, that is, kills 99.99999% or leaves $1/10^7$ of the population. A third drug that kills 99% (2-log drug) would further reduce the remaining population to $1/10^9$, which comes close to complete eradication of a tumor caught early.

DRUG RESISTANCE—Some tumor populations appear to be heterogeneous by the time the tumor is discovered, some of the cells being resistant to certain drugs at the outset of treatment. This is well established for adrenal, colon, jejunal, kidney, and liver carcinomas. As many as four different cancer cell types have been identified in a single tumor. Differences among some of these cell types do not represent different genes necessarily but rather, sometimes, differences in the number of copies of a single gene. Resistance in cancer cells can occur de novo or develop during treatment as a result of cell mutation. The resistant daughter cells then can proliferate in the environment of the drug. Whatever the cause, resistance often terminates the usefulness of an antineoplastic drug.

Various mechanisms of resistance have been identified, and include the following:

1. Improved proficiency in the repair of potentially lethal DNA damage
2. Loss of a transport system essential for the permeation of the drug into the tumor cell, as happens with methotrexate.
3. Increases or decreases in the amounts or binding affinity of target enzymes necessary for the intratumor *lethal synthesis* of an essential active metabolite (DHFR, topoisomerase II)
4. An increase in outward active transport or efflux of the drug, so that effective intracellular concentrations cannot be achieved or maintained (multidrug or pleiotropic drug-resistance)
5. Overexpression of metallothionine (resistance to platinum-containing and certain alkylating antineoplastics)
6. Antibody formation (eg, interferons)
7. Membrane changes that confer resistance to natural killer (NK) cells
8. Increased glutathione synthesis in cancer cells treated with anthracyclinedione cells

Lipophilic anticancer drugs such as the vinca alkaloids, certain alkylaminoanthraquinones actinomycin-D, colchicine, verapamil, and probably other drugs are transported outwardly by an adenosine-triphosphate-(ATP-)–dependent pump, known as *P*-glycoprotein. This is produced excessively by some tumor cells, and accounts for the primary mechanism of multiple drug resistance. Various drugs, such as verapamil, cyclosporine, and quinidine, compete for this pump, thereby inhibiting P-glycoprotein. However, the concentrations of these agents required to inhibit P-glycoprotein results in excessive toxicity, and thus their use continues to be examined. Studies with new more potent agents are being performed.

TOXICITY—Neoplastic cells have compositions and activities very much like those of the host cells. This has made it impossible thus far to design antineoplastic drugs that also do not attack normal cells. Every antineoplastic drug has a therapeutic index less than 1.0. This may be changing with some of the new *targeted therapies,* although many of these new therapeutic agents lack significant cytotoxicity when used independently. The principles that apply to antitumor efficacy also apply to the toxicity. Thus the tissues most affected are those with high growth fractions, and the integrity of the highly proliferative tissues can be disturbed considerably. Consequently, the bone marrow, lymphoblasts, mucous membranes, skin, and gonads are affected to a greater extent than other cells. Because the myelogenous leukocyte turnover is faster and the growth fraction is greater than those of erythrocytes, *bone-marrow depression* usually causes a more severe neutropenia and thrombocytopenia than anemia. Bone-marrow depression is a major adverse effect of antineoplastic drugs.

Suppression of proliferation of mucosal cells causes mucositis, characterized by aphthous and gastrointestinal ulceration or mucositis. Arrest of the proliferation of the cutaneous epithelial cells may cause alopecia, scaliness of the skin, sometimes even desquamation. Some drugs that lack significant dermatological actions may nevertheless recall cutaneous toxicities induced by previous drugs or radiation.

Aspermia may result from actions on the seminiferous tubules and amenorrhea from actions on the ovaries (where the growth fraction but not the turnover rate is high). The immune cells have a rapid turnover and are highly susceptible to certain cytotoxic agents. *Immunosuppression* makes the patient more vulnerable to *infection*; it is noteworthy that 50% of cancer patients die of intercurrent infections rather than from the terminal phases of the neoplastic disease.

Immunosuppression probably enhances the growth of certain neoplasms. Because they interfere with genetic mechanisms, certain antineoplastic drugs are mutagenic and carcinogenic, and the patient is subjected to the risk of future neoplasia. The incidences of acute leukemia and bone sarcoma are considerably higher in persons who have been treated with antineoplastic drugs than in the general population. Theoretical considerations predict that all neoplastic drugs are teratogenic, and teratogenic activity has been shown with some.

There are also other toxicities related to antineoplastic actions. For example, massive cell destruction results in the release of large quantities of purine from the nucleic acids of the dead cells; these purine bases are metabolized to uric acid. Hyperuricemia, renal damage consequent to hyperuricuria and also some neurological damage may result. Hence, it is common to give allopurinol along with antineoplastic drugs. Massive destruction of certain leukemic cells may also cause an acute hypotensive crisis that sometimes is called *anaphylaxis* despite its not being a true allergic response. For reasons not understood, treatment of breast cancer is thrombogenic in approximately 7% of cases, irrespective of the drug used.

Some of the local adverse effects also are related to the antineoplastic mechanisms. Extravasation, or leakage of the drug out of the vein, may present high concentrations to the cells in the local area, leading to vesication, ulceration, sloughing, or tissue necrosis. Other drugs may cause phlebitis, or pain and irritation, along the vein during or following administration. Gastrointestinal toxicity may cause nausea, vomiting, diarrhea, cramping, or constipation.

Other toxicities may not be seen immediately, but weeks or months after chemotherapy is initiated. These include pulmonary fibrosis, cardiac toxicity, liver and renal toxicity. The specific toxicities are discussed under the specific agents listed below. A few of these may be minimized or prevented by using various antidotes including amofostine, dexrazoxane, and mesna.

PRECAUTIONS AND CONTRAINDICATIONS—With all drugs that cause bone-marrow depression, it is essential to monitor the blood cell count, which may serve both as a guide to adequate dosage and as a precaution against overdoses. The minimum advisable leukocyte and platelet count varies somewhat among the drugs but is usually 3000 to 4000 leukocytes and 20,000 to 100,000 platelets. When the count falls below these limits, the drug dosage should be reduced or the drug discontinued until there is recovery. It usually is not advisable to begin treatment with a bone-marrow depressant drug within 4 weeks of the administration of another bone-marrow depressant drug or radiation therapy. The use of colony stimulating factors, which stimulate the bone marrow to produce granulocytes, have greatly improved the morbidity and delays in treatment due to chemotherapy-induced bone marrow suppression. In most malignancies, chemotherapy cannot be administered if the blood cell count is < 2500 leucocytes.

Antineoplastic drugs are teratogenic, and should not be used during pregnancy unless the risk-benefit ratio has been discussed. Because most antineoplastic drugs can be found in breast milk, infants must not be nursed during antineoplastic therapy. Studies have shown that improper handling during mixing or administration of anticancer drugs may result in urine mutagenicity and chromosomal damage, and although controversial, are thought to be due to exposure to cytotoxic agents. They are fetotoxic in pregnant nurses that handle such drugs. All antineoplastic agents must be handled with proper attention to aseptic techniques during preparation and administration, as well as proper disposable.

CLASSES AND MECHANISMS OF DRUGS—Antineoplastic drugs may be conveniently grouped into several categories. Some of the categories are based on chemical and mechanistic properties and others on the origins of natural products.

Alkylating Agents—The subgroups of the alkylating agents include: nitrogen mustards, nitrosoureas, methylhydrazines, ethylenimines, platinum analogues, and alkylsulfonates. The nitrogen mustards are all bis(β-chloroethyl)amines. The mustards are important drugs in treatment regimens; cyclophosphamide, the most useful alkylating agent, is a member of this class.

The ethylenimines contain three ethylenimine groups per molecule, and the alkylsulfonates are bismethylsulfonates. Thus these compounds are all polyfunctional alkylating agents, a fact that relates importantly to the mechanism of action. The alkylating groups react with nucleophilic centers in many

different kinds of molecules; guanine is the most reactive target in DNA. However, their bifunctional or trifunctional character allows them to cross-link double-stranded DNA, thus preventing the strands from separating for replication. The platinum analogs are alkylating-like agents in which the chloride atoms are lost intracellularly resulting in a reactive electrophile. This covalently binds to DNA forming intra- and inter- strand crosslinks.

Nitrosoureas—These usually are classified as alkylating agents. Carmustine is bifunctional and may be able to cross-link double-stranded DNA. Lomustine contains a single β-chloroethyl group but can cross-link DNA by use of the nitroso group as a second electrophilic group. Streptozocin lacks a bifunctional alkylating moiety. Carbamoylation of the nucleoside bases in nucleic acids has been suggested as a possible mechanism of action. However, the nitroso group is also a free radical and an ion generator, which could confer radiomimetic properties.

Methylhydrazines—Procarbazine and dacarbazine sometimes are classified as alkylating agents, because an *alkylating* moiety is liberated within the target cell. However, like other hydrazines, they generate free hydroxyl radicals and ions and thus also are considered radiomimetic.

Antimetabolites—There are three subcategories of antimetabolites: purine analogs, pyrimidine analogs, and folinic acid analogs. The purine analogs are incorporated into DNA as the deoxyribotides and into RNA as the ribotides, where they interfere with coding and replication. They also act like the natural purine bases in inhibiting synthesis of purine bases by acting through the allosteric feedback systems (pseudofeedback). The pyrimidine analogs inhibit enzymes in the biosynthetic pathways for pyrimidine ribotides and deoxyribotides; thymidylate synthetase, orotic acid decarboxylase, aspartate carbamoyltransferase, dihydroorotase, and DNA polymerase are inhibited. Methotrexate and trimetrexate bind very tightly to dihydrofolate reductase and thereby prevent the conversion of dihydrofolate (folinate) to tetrahydrofolate.

Antibiotics and Natural Products—This is a miscellaneous group of drugs with respect to mechanism of action. Mitomycin appears to be an alkylating agent, the anthracyclines and epipodophyllotoxins act therapeutically by inhibiting topoisomerase II, and the vinca alkaloids and taxols interfere with microspindle function. Dactinomycin binds to DNA and inhibits DNA synthesis, and mithramycin inhibits DNA-dependent RNA polymerase. Bleomycin both acts as an antimetabolite of thymidine and causes fragmentation of DNA.

Steroid Hormones—The steroid hormones are transported to the cell nucleus, where they attach to chromatin and usually stimulate transcription and, hence, protein synthesis. However, the glucocorticoids suppress mitosis in lymphocytes, and fibroblasts and appear to inhibit transcription. This so-called lympholytic effect is employed in the chemotherapy of the lymphocytic leukemias and in immunosuppression.

The estrogens, progestins, and androgens also probably inhibit transcription and prevent mitosis in those cell types that are derived from normal cells that are suppressed by these hormones in the natural hormonal physiology. Thus, the normal prostate gland is suppressed by estrogens, apparently by a comparative antagonism of androgens, and estrogens are used to treat cancer of the prostate gland, etc. Similarly, androgens exert an antiestrogen effect on certain breast tumors; only tumors of a cell type that contain estrogen receptors are responsive. Antiestrogens also are used to suppress such tumors. Estrogens also suppress the growth of some breast tumors, but the mechanism of the effect is understood poorly. Luteinizing hormone releasing hormone (LHRH) analogs act centrally to inhibit androgen and estrogen synthesis. Progestins behave as antiestrogens in the endometrium and, hence, may be employed in the chemotherapy of endometrial carcinoma.

Monoclonal Antibodies—These agents directly target receptors that are overexpressed in tumor cells. Rituximab is directed against CD20 on B lymphocytes, thus binding to the antigen and activating complement dependent cytoxicity. Gemtuzumab is directed against CD33, which is expressed on leukemic blasts.

Miscellaneous—Porfimer is a photosensitizing agent used in the photodynamic therapy. Isotretinoin is a differentiating agent useful in the treatment of leukemias.

KINETICS AND REGIMENS—With drugs with phase-specific actions, the temporal window of vulnerability is the duration of the vulnerable phase of the cell cycle. With rapidly proliferating cells, this may be only a few hours for any given cell. If the cell cycles are synchronized, only a brief exposure to the drug may be needed to accomplish a high degree of cell kill; the optimal drug would be one with a half-life such that it does not persist in the body beyond the time necessary to act upon the tumor cells, so that there would be the least necessary exposure of normal cells to the drug. However, the synchronization of cell cycles is yet in its infancy, and most regimens attack a tumor cell population that randomly is in various phases of the cell cycle. In this case, it is optimal to keep the drug in the body for slightly longer than the duration of the entire cell cycle.

In the case of Burkitt's lymphoma, with a doubling time of 24 hours, exposure to drug should be approximately a day to effect the greatest tumor cell kill. Unfortunately, white-cell stem cells have a doubling time of only 12 hours and GI cells approximately 24 hours, so that it is not possible to expose Burkitt's lymphoma cells for the duration of an entire cell cycle without causing a life-threatening kill of certain kinds of normal cells. The clinical problem, then, is to devise a regimen that is more sparing of normal cells yet causes an adequate remission, though not complete elimination of the tumor. This is possible, despite the shorter cell cycles of certain normal cells, because the normal cells spend more time in G_0 than do Burkitt's lymphoma cells. Problems of this kind usually are resolved by repeating courses of submaximal tumor-killing doses.

It is much more difficult to devise an effective yet safe regimen for the treatment of tumors with long doubling times, because the tumor doubling time may be many times longer than the hematopoietic stem, immune, and mucosal cells. Long, multicourse combination treatments are the rule. Most are quite empirical with respect to kinetic considerations. In these, because the duration of a course is inevitably longer than the elimination lifetime of the drugs in use, a regimen needs maintenance dosing or constant infusion. One example of this is the prolonged, low-dose infusions of 5-fluorouracil over several months.

Site-directed administration of antineoplastic drugs by intra-arterial infusion is advantageous to intravenous administration only if the concentration of drug in the blood in systemic circulation is substantially lower than that infused into the artery. This is thought to occur when a high rate of systemic clearance of the drug exists, so that toxic amounts of the drug do not accumulate. However, experience with intra-arterial fluorouracil, a drug with a half-life of less than 20 minutes, has been disappointing. It has been explained that the local extraction ratio of fluorouracil during prolonged intra-arterial infusion is sufficiently low that there is not a sufficiently selective uptake into the target to gain much advantage by local infusion.

In contrast, the nitrosourea, carmustine has a high extraction ratio by the intracarotid arterial route and, consequently, is advantageous by this route (for CNS tumors), even though there is considerable local toxicity. Similarly, diaziquone has a high local extraction ratio and is advantageous by the intra-arterial route. The local clearance of an intra-arterially infused drug of low extraction ratio may be increased by decreasing the rate of blood flow with a vasoconstrictor. Although most regimens are largely empirical, improvisation, or failure to follow the regimen as recommended, is a common cause of early relapse, especially in pediatrics.

Circadian rhythms may not only affect the metabolism of many drugs but also the susceptibility of the patient to the toxic effects of antineoplastic drugs. Many studies have been per-

formed, and the effects shown. However, the data does not warrant clinical changes in anticancer regimens at this time based on circadian kinetics.

As among drugs in general, various antineoplastic drugs are involved in pharmacokinetic drug interactions. For example, cisplatin and daunorubicin induce the hepatic enzymes for the metabolism of carbamazepine, phenytoin, and valproate. Verapamil competes for the active transport of lipophilic anticancer drugs out of cells. Some of these interactions are due to biochemical modulation. Methotrexate and leucovorin cause this effect. Sequential methotrexate, followed by 5-fluorouracil, results in increased activation of 5-fluorouracil to the active moiety, FUTP, leading to increased cell kill due to increased concentrations in RNA. The combination of leucovorin with 5-fluorouracil causes increased cell death by providing an exogenous source of reduced folate, thus increasing the binding of FdUMP to thymidylate synthetase.

IMMUNOACTIVE DRUGS

The immune system is quite complex. Several types of cells are involved. These are cells, the ancestral line of which has derived from bone marrow stem cells. Some of the descendants of the stem cells migrate to sites elsewhere in the body, where they become small lymphocytes. There are two general types of lymphocytes involved in the immune responses: the B cells and the T cells. The B lymphocytes get the designation B from the fact that in birds they derive from stem-cell clones in the bursa of Fabricus; in man, the location of analogous clones may be in the intestinal mucosal Peyer's patches. The T cells get their designation from the fact that they are derived from stem cells cloned in the thymus gland. Undifferentiated lymphocytes take up residence in lymph tissue in the spleen, tonsils, intestines, and other sites.

B and T cells respond to antigen by cellular transformation, proliferation, and differentiation. Proliferation increases the population of immunocompetent cells and differentiation creates cells with various roles to play in the immune response. Both B and T cells differentiate into what broadly may be termed effector cells and memory cells. The memory cells revert to an inactive state (G_0) but respond to later immune challenge by accelerated proliferation, differentiation, and activity. During their residence in the bursa equivalent, the future effector B cells become programmed to respond to an antigen by transformation into plasma cells, which produce antibodies (immunoglobulins I_A, I_D, I_E, I_G, and I_M), the role of which is to combine with circulating antigens. The immunity conferred by B cells is known as humoral immunity.

Hypersensitivity mediated through the humoral immune system is called immediate hypersensitivity, because the response is rapid. T cells become programmed in the thymus to respond in various ways to antigen that has become fixed to cell surfaces or engulfed by macrophages. The cytotoxic T cell (effector cell, *killer* cell), with the aid of complement, attacks and lyses those cells to which the offending antigen is attached. There are different cytotoxic T cells for different antigens. There are also helper T cells, which promote B-cell activity, and suppressor T cells, which restrain both the cytotoxic T cells and the B cells. Helper and suppressor B cells also exist. T-cell-mediated immunity is known as cell-mediated immunity. This is the immune response involved in graft rejection, autoimmunity, and delayed hypersensitivity.

The priming of lymphocytes in response to antigen is known as the primary response. The final effector response is known as the secondary, or efferent, response.

There are other bone-marrow, stem-cell-derived cells, such as macrophages and K cells, that participate in the immune response. In the primary response, the macrophages engulf antigens, process them, and present the processed antigen to helper T lymphocytes, which initiate the recruitment of other lymphocytes. Thus the macrophages are an integral part of the afferent limb of the primary response. They also appear to be involved in the efferent response; they fix and alter antigen prior to its recognition by the T cells. Details of the immune system may be found in Chapter 89.

OTHER IMMUNOMODULATORS—Because immunosuppression is a common adverse effect of antineoplastic drugs and also because many immunosuppressive drugs have come from among the antineoplastics, it is common to believe that antineoplastic cytotoxicity automatically suppresses the immune system. However, the immune system has helper, suppressor, and killer components, so that the net effect depends on which components are affected most. IL-2 (interleukin-2) is used for its direct stimulation of T lymphocytes. Indeed, there is thought to be immunostimulatory components to the actions of some antineoplastic drugs.

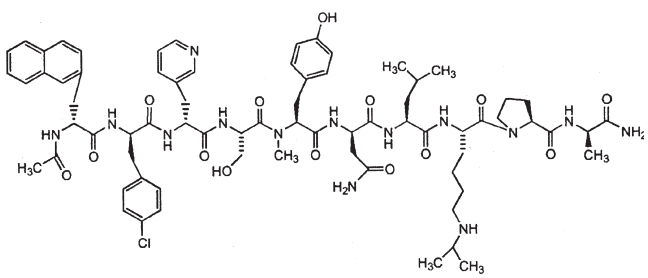
Conversely, the situation is analogous with the so-called immunostimulants, because the net effect on any given immune response depends on which of the sundry participating cells are stimulated most. For example, levamisole is called an immunostimulant, but it either can augment or suppress an immune response depending on factors such the type of response, dose, and timing. T-lymphocyte function is augmented more than B-lymphocyte function. The drug tends to normalize a disturbed immune system. A similar bifunctionalism exists among the various cytokines. Interferons, for example, stimulate some immune cells and suppress others. Diethyl dithiocarbamate, however, is nearly a pure immunostimulant; it induces the recruitment of T lymphocytes and promotes cytotoxicity. Every vaccine is an immunostimulant and often selective. However, some, such as staphage lysate, cause rather general immunostimulation and may be used to confer varying degrees of immunity to various nonbacterial invaders.

It is now known that certain autonomic and CNS transmitters and neuromodulators also have influences on the immune system. Enkephalins and endorphins stimulate B-lymphocyte proliferation and antibody production and promote T-lymphocyte and natural killer-cell cytotoxicity. Opioid drugs mimic some of the immunomodulatory actions of the peptides. It is believed that these peptides are part of a neuroendocrine-immune system loop. Histamine stimulates suppressor T lymphocytes and thus tends to limit immune responses. The action is mediated through H_2-receptors. Consequently, H_2-antagonists, such as cimetidine and ranitidine, tend to augment the efferent immune response. Various immune cells also possess alpha- and beta-adrenoreceptors, through which immune functions can be affected by circulation of epinephrine and sympathetically released norepinephrine and their antagonists. The overall effect of alpha-agonism is immunosuppression but that of beta-agonism varies according to the immune status under various conditions.

ANTINEOPLASTIC DRUGS

ABARELIX

D-Alaninamide, *N*-acetyl-3-(2-naphthalenyl)-D-alanyl-4-chloro-D-phenylalanyl-3-(3-pyridinyl)-D-alanyl-L-seryl-*N*-methyl-L-tyrosyl-D-asparaginyl-L-leucyl-*N* ^{6}-(1-methylethyl)-L-lysyl-L-prolyl-, Plenaxis



[183552-38-7] $C_{72}H_{95}ClN_{14}O_{14}$ (1416.08).

Preparation—A synthetic decapeptide initially manufactured as an acetate-water complex, then converted into a carboxymethylcellulose complex to prepare the drug product. The reconstituted injection (with normal saline) has a pH of 5 ± 1.

Description—White to off-white powder.

Comments—Acts by directly suppressing luteinizing hormone and follicle stimulating hormone secretion and thereby reducing the secretion of testosterone by the testes. Used for palliative treatment of men with advanced symptomatic *prostate cancer*. May prolong QTc interval, therefore may interact with Class I and III antiarrythymic agents. It is highly protein bound (96–99%). The most common side effects experienced in clinical trials were serious allergic reactions (including loss of consciousness), hot flashes, sleep disturbances, pain, including back pain, breast enlargement or pain, and constipation.

ALDESLEUKIN

Interleukin-2 Recombinant; Proleukin

2-133-Interleukin 2 (human reduced) [110942-02-4] $C_{690}H_{1115}N_{177}O_{203}S_6$ (15,600).

Preparation—A continuous chain of 133 amino acid residues; a product of recombinant DNA technology with genetically engineered *E coli* strains containing an analog of the human IL-2 gene.

Comments—Identical to a cytokine, IL-2, secreted by activated helper T lymphocytes that is a colony-stimulating factor for active T lymphocytes, immature thymocytes, natural killer (NK) cells, antigen-activated B lymphocytes, and probably other cells of the immune system. The ability to stimulate proliferation of cytotoxic T lymphocytes and NK cells has led to clinical trials against several kinds of cancer. It is approved for *metastatic renal cancer and metastatic melanoma.* Treatment consists of the administration of IL-2 alone, prior to, and along with, autologous lymphokine-activated killer (LAK) cells; the IL-2 for the purpose of encouraging the proliferation of LAK cells. At present, the combination has been found effective in some cases of *colorectal carcinoma* and *Hodgkin's disease,* but treatment of other cancers is under active investigation. It is also under investigation as an antiinfective agent; it is in Phase II trials for use in AIDS.

Common adverse effects attributable to IL-2 are nausea, vomiting, diarrhea, fever, malaise, pruritus, severe anemia, hyperbilirubinemia, and elevated plasma creatinine. Less-common effects are elevated capillary permeability with pulmonary edema, fluid retention, hypotension, cardiac dysrhythmias, thrombocytopenia, and disorientation, even coma. Approximately 20% of patients treated with IL-2 and LAK cells develop hypothyroidism. It is contraindicated in patients with an abnormal thallium stress test or abnormal pulmonary function tests and those with organ allografts. Treatment is prohibitively expensive. The peptide nature of IL-2 requires parenteral administration. The half-life is less than 1 hr, and is administered by a 15-minute infusion every 8 hours for a maximum of 14 doses. Following 9 days of rest, the schedule may be repeated as tolerated for a maximum of 28 doses per course with a 7-week break between each course of treatment.

ALEMTUZUMAB

Immunoglobulin G 1 (human-rat monoclonalCAMPATH-1H 1-chain anti-human antigen CD52), disulfidewith human-rat monoclonal CAMPATH-1H light chain, dimer; CamPath

[CAS-216503-57-0]

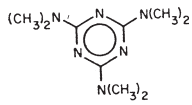
Preparation—It is produced in a mammalian cell (Chinese hamster ovary) suspension culture in a medium containing neomycin. Neomycin is not detectable in the final product. A recombinant DNA-derived humanized monoclonal antibody (Campath-1H) that is directed against the 21–28 kD cell surface glycoprotein, CD52. that is expressed on the surface of normal and malignant B and T lymphocytes, NK cells, monocytes, macrophages, and tissues of the male reproductive system. The Campath-1H antibody is an IgG1 kappa with human variable framework and constant regions, and complementarity-determining regions from a murine (rat) monoclonal antibody (Campath-1G). The Campath-1H antibody has an approximate molecular weight of 150 kDa. US Pat 5,846,534 (1998).

Description—Campath is a sterile, clear, colorless, isotonic solution for injection; pH 6.8–7.4.

Comments—A recombinant DNA-derived human monoclonal antibody that is indicated for the treatment of *B-cell chronic leukemia* in patients who have failed fludarabine therapy. It acts against the 21–28 kD by binding to cell surface glycoprotein, CD52, that is expressed on the surface of normal and malignant B and T lymphocytes. This agent causes myelosuppression, which may result in severe, and sometimes fatal, pancytopenia or serious opportunistic and bacterial infections. Other side effects include nausea and vomiting, rash, and pneumonia. Gradual dose escalation is recommended to reduce the incidence of infusion-related reactions, including hypotension, rigors, fever, shortness of breath, bronchospasm, chills, and/or rash. The average half-life is about 12 days, and it is administered by intravenous infusion over a two hour period three times weekly.

ALTRETAMINE

1,3,5-Triazine-2,4,6-triamine, *N,N,N′,N′,N ″,N ″*-hexamethyl-, Hexamethylmelamine; Hexalen



[645-05-6] $C_9H_{18}N_6$ (210.28).

Preparation—*J Am Chem Soc* 73:2984, 1951.

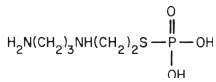
Description—White needles; melts about 173°.

Solubility—Practically insoluble in water; increasingly soluble at pH less than 3.

Comments—A Group C oral alkylating agent related to triethylenemelamine, an early alkylating agent. It is one of several secondary drugs for treatment of *ovarian tumors.* It is approved as a single agent for *refractory ovarian cancer.* It also has proved useful in the treatment of both *Hodgkin's* and *non-Hodgkin's lymphomas, oat-cell bronchogenic carcinoma,* and *breast tumor.* Nausea and vomiting are the main acute adverse effects. Delayed toxicity includes bone-marrow depression, CNS depression, peripheral neuritis, ataxia, hallucinations, psychoses, pruritus, and dermatitis. The drug is metabolized in the liver. The terminal half-life is 4.7 to 10.2 hr, which may increase with concomitant cimetidine therapy. Phenobarbital may decrease the half-life, and severe hypotension may occur with concomitant MAO inhibitor agents.

AMIFOSTINE

Ethanethiol, (*S*)-2-[(3-aminopropyl)amino]-, dihydrogen phosphate (ester); Ethiotos; Ethyol



[20537-88-6] $C_5H_{15}N_2O_3PS$ (214.21).

Preparation—1,3-Propanediamine is monoalkylated with 2-chloroethanol to form 2-[3-(aminopropyl)amino]ethanol and the free OH converted to Br by use of HBr. Treating the resulting alkyl bromide with sodium thiophosphate (Na_3PO_3S), followed by acidification affords the product. *J Med Chem* 1969; 12:236. US Pat 3,892,824 (1973).

Description—White crystalline solid melting about 161° (dec).

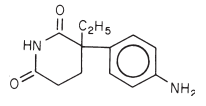
Solubility—Freely soluble in water; $pK_{a1} < 2.0$; pK_{a2} 4.2; pK_{a3} 9.0; pK_{a4} 11.7.

Comments—Approved for reduction of renal toxicity caused by repeated administration of cisplatin. It is a thiophosphate prodrug that once dephosphorylized provides a reduced thiol. It is indicated to reduce cumulative renal toxicity associated with repeated doses of cisplatin for the treatment of advanced ovarian cancer or non-small cell lung cancer. It also reduces the incidence of xerostomia in patients with head and neck cancer undergoing post-operative radiation treatments involving the parotid gland. It has been used to treat myelodysplasia and may protect against cisplatin and paclitaxel induced neurotoxicity.

It is rapidly metabolized and after only 6 min, less than 10% remains in the plasma. The thiol metabolite is distributed rapidly throughout the body. Approximately 62% of treated patients experienced hypotension, 19% experienced severe nausea and vomiting. Administration should be interrupted if systolic blood pressure drops significantly. Antiemetics should be coadministered, including a 5HT3 receptor antagonist. Hypersensitivity reactions also were reported.

AMINOGLUTETHIMIDE

2,6-Piperidinedione, 3-(4-aminophenyl)-3-ethyl-, Cytadren



2-(*p*-Aminophenyl)-2-ethylglutaramide [125-84-8]$C_{13}H_{16}N_2O_2$ (232.28).

Preparation—By a procedure similar to *Glutethimide* with nitration of the α-ethylbenzyl cyanide to the *p*-nitro derivative. This then, is reduced to the amine after ring closure. US Pat 2,848,455.

Description—White crystals; melts about 150°.

Solubility—Slightly soluble in water; freely soluble in many organic solvents.

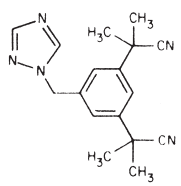
Comments—Inhibits the first step in adrenalcorticoid biosynthesis by inhibiting the conversion of cholesterol to Δ5-pregrenolone. It also inhibits the aromatase that converts androstenedione to estrone and estradiol, thus eliminating the adrenal source, the only source of estrogens in postmenopausal and oophorectomized women. It is approved for *suppression of adrenalcorticoid production* in selected Cushing's syndrome patients. Treatment with aminoglutethimide is preferred to adrenalectomy in postmenopausal women who have *estrogen receptor-positive breast carcinoma.* Hydrocortisone is administered concomitantly to suppress the counterproductive, counterregulatory increase in ACTH release that accrues to the drug-induced lowering of plasma hydrocortisone. The regimen, however, causes more adverse effects than does tamoxifen and hence is a second-choice treatment. It also is useful in the management of certain cases of *Cushing's syndrome and prostate cancer.*

Early adverse effects include lethargy (40% of recipients), ataxia (10% of recipients), nausea, vomiting, and anorexia, and morbilliform rash; tolerance to this effects develops in 1 to 6 wk. Delayed adverse effects mostly relate to mineralocorticoid insufficiency and include orthostatic hypotension (10% of recipients; symptoms are dizziness and weakness) so that mineralocorticoids may require supplementation. Occasional adverse effects include pruritus, myalgia, headache, masculinization and hirsuitism in women, precocious sexual development in boys, hypothyroidism with goiters after long-term use, leukopenia, thrombocytopenia, granulocytopenia, and pancytopenia. Alkaline phosphatase and serum glutamic oxaloacetic transminase (SGOT) activities in serum frequently occur, and cholestatic jaundice occurs rarely. Aminoglutethimide induces the metabolism of dexamethasone, thus that particular glucocorticoid should not be used concomitantly. It also enhances the clearance of digitoxin, theophylline, and warfarin.

Aminoglutethimide is well absorbed orally. Initially, approximately 50% is excreted in the urine unchanged, but induction of liver metabolism diminishes the importance of renal elimination. The elimination half-life is initially approximately 13 hr but decreases to approximately 7 hr after 1 to 2 wk.

ANASTRAZOLE

1,3-Benzenediacetonitrile, α,α,α′,α′-tetramethyl-5-(1*H*-1,2,4-triazol-1-ylmethyl)-, Arimidex



[120511-73-1] $C_{17}H_{19}N_5$ (293.37).

Preparation—A mixture of α,α′-dibromomesitylene, tetra-(*t*-butyl) ammonium bromide, and KCN in methylene chloride or methylene chloride/water is heated to produce 5-methyl-1,3-phenylenebisacetonitrile. Refluxing this latter compound with methyl iodide and NaH in DMF yields the α,α-dimethyl derivative of both nitrile side chains. Further treatment with NBS and benzoyl peroxide brominates the free aryl methyl group, and reaction with sodiated 1,2,4-triazole forms the product. US Pat 4,935,437 (1990).

Description—Off-white crystals melting about 82°.

Solubility—Freely soluble in methanol, ethanol, acetone, or tetrahydrofuran (THF); soluble in acetonitrile; soluble in 0.5 mg/mL water.

Comments—Approved for use in postmenopausal women with hormone receptor positive or hormone receptor unknown locally advanced or metastatic breast cancer or those who have advanced breast cancer with disease progression after tamoxifen therapy. It is a potent nonsteroidal inhibitor of aromatase, and, as such, inhibits conversion of androstenedione to estrone. It significantly reduces levels of circulating estradiol up to 80% after daily dosing with no detectable effect on adrenal corticosteroids of aldosterone. In clinical trials it proved similar in efficacy to megosterol in objective response and stabilization of disease in postmenopausal (primarily ER-positive) women who had progressing breast cancer, evidencing progression after tamoxifen therapy. ER-negative breast cancer rarely responds to anastrozole.

It is well absorbed when taken orally with or without food. Approximately 85% of the dose can be recovered from the urine and the feces. Approximaely 85% of the dose is eliminated by means of hepatic metabolism and another 11% by means of renal excretion. The major circulating metabolite has no pharmacological activity. It has a terminal half-life of approximately 50 hr, concordantly steady-state levels are reached after 7 days of dosing.

Hepatic function is important for its clearance; clearance was reduced as much as 30% in patients who have cirrhosis of the liver. Vaginal bleeding occurs infrequently in the first weeks after the switch to therapy with this drug.

ARSENIC TRIOXIDE

Arsenic trioxide; Trisenox

Arsenous acid, arsenous oxide [13276-53-3] As_4O_6 (395.68).

Preparation—Occurs naturally in the mineral claudetite.

Description—Odorless, transparent crystals or white powder. Melts about 315° (with sublimation) and boils about 465°. Sp gr 3.74.

Solubility—Reported from 1.2 to 3.7 g/100 mL, at 20° in various references.

Comments—Used for remission, induction, and consolidation of the acute promyelocytic (M3) subtype of acute myeloid (myelogenous, nonlymphocytic) leukemia (AML, ANLL) with the t(15:17) chromosomal translocation that is refractory to retinoid and anthracycline therapy or has relapsed despite such therapy. Extensively metabolized via reduction by arsenate reductase and methylation (mainly in the liver) by methyltransferases, widely distributed throughout the body, and eliminated principally by metabolism and urinary excretion. Acts by inducing differentiation through degradation of the chimeric PML/RAR-alpha protein, and also induces apoptosis through a mitochondrion-dependent process, resulting in subsequent release of cytochrome C with caspase activation. The main toxicities are fatigue, electrocardiographic changes with QT prolongation, arrhythmias, and a syndrome characterized by fever, dyspnea, skin rash, fluid retention, and weight gain. Should be used caution in patients receiving drugs that may prolong the QT interval or those that may cause electrolyte abnormalities.

ASPARAGINASE

L-Asparagine amidohydrolase; E.C. 3.5.1.1.; Elspar

L-Asparaginase [9015-68-3], an enzyme of molecular weight 133,000 ± 5000, believed to consist of four equivalent subunits.

Preparation—L-Asparaginase, an enzyme that catalyzes hydrolysis of L-asparagine to l-aspartate and ammonia, occurs in many species. Isolated in pure form from several sources, it usually is obtained from *E coli* or *Erwinia caratovora,* which produces also an asparaginase devoid of antileukemic activity, that is removed on purification of the enzyme. See Mashburn and Wriston, *Arch Biochem Biophys* 105:450, 1964.

Description—White, crystalline powder.

Solubility—Freely soluble in water; practically insoluble in chloroform or in methanol.

Comments—Protein synthesis in several normal as well as malignant cell types depends partly on exogenous asparagine, and, in a few cells, such as lymphoblasts and certain other leukemic cells, essentially is dependent totally. The enzymatic destruction of asparagine by asparaginase injected into plasma deprives the dependent cells of the essential asparagine and, thus, not only arrests their growth but also might even result in some cell death and tumor regression. It is approved for use in *acute lymphocytic leukemia.*

Currently, it is used mainly in chemotherapy of acute lymphocytic leukemia, T-cell leukemias, and lymphomas in sequential combinations with other drugs. When it is administered immediately after a course of vincristine and a glucocorticoid (usually prednisone or dexamethasone) for the induction of the first remission in children, the median duration of remission is more than doubled. Addition of doxorubicin and intrathecal cytarabine further prolongs survival. Some studies indicate a small increase in the incidence of complete remissions. The enzyme also is useful for induction of remission in children who have relapsed acute lymphocytic leukemia. It is not recommended for maintenance. Asparaginase protects some tissues and cancers from some antimetabolites (eg, methotrexate, cytarabine), probably by preventing DNA synthesis. Such interactions, especially with methotrexate, should be anticipated. In patients allergic to asparaginase, pegaspargase, a polyethylene-glycol (PEG) conjugated l-asparaginase preparation is available. Also, Erwinia asparaginase is an orphan drug for use in patients allergic to asparaginase from *E coli.*

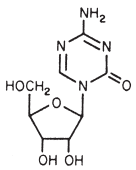
Sixty to 90% of recipients of asparaginase show laboratory evidence of an impairment of liver function, such that plasma fibrinogen and other clotting factors may be diminished, and most patients have a considerable elevation of blood ammonia. Effects on the pancreas also are common; insulin production is diminished; there may be hyperglycemia; serum amylase activity may increase; and acute pancreatitis, sometimes hemorrhagic, may occur in as many as 5% of recipients. There also

are actions on the CNS to cause impairment of the sensorium, mental depression, and rare coma. Nausea, vomiting, chills, and fever also occur frequently. Hypersensitivity reactions, ranging from mild rash to anaphylaxis and death, occur in 5% to 20% of recipients, so that sensitivity testing before administration is necessary and desensitization may be necessary before a second course is administered. *Erwinia* (Porton) asparaginase is less sensitizing than that from *E. coli.* Both enzymes also have immunosuppressant activity.

It must be administered parenterally. The rate of clearance varies considerably between preparations. Its half-life is approximately 16 hr.

AZACITIDINE

1,3,5-Triazin-2(1*H*)-one, 4-amino-1-β-D-ribofuranosyl-, Mylosar, Vidaza



[320-67-2] $C_8H_{12}N_4O_5$ (244.20).

Preparation—A ring analog of cytidine, obtained by synthesis or produced microbiologically. US Pat 3,350,388.

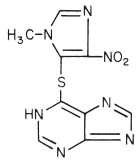
Description—White powder that melts about 229°.

Solubility—1 g in 25 mL water or 1000 mL alcohol. Reconstituted intravenous solutions are not stable for more than a few hours.

Comments—A pyrimidine nucleoside analog of cytidine, this antimetabolite is used to treat patients with various myelodysplastic syndromes subtypes including refractory anemias with sideroblasts or excess blasts and chronic myelomonocytic leukemia. It causes acute nausea, vomiting, diarrhea, and fever. Delayed toxicity, which is not dose-related, includes prolonged leukopenia, thrombocytopenia, and hepatotoxicity. The mortality rate has been reported to be approximately 6%. It should not be used in patients with severe hepatic impairment. It is administered subcutaneously once daily for seven days at 4-week intervals. Metabolites are excreted primarily by the kidneys, and dosage adjustments are required with impaired renal function.

AZATHIOPRINE

1*H*-Purine, 6-[(1-methyl-4-nitro-1*H*-imidazol-5-yl)thiol]-, Imuran



6-[(1-Methyl-4-nitroimidazol-5-yl)thio]purine [446-86-6] $C_9H_7N_7O_2S$ (277.26).

Preparation—*N,N′*-Dimethyloxaldiamide is reacted with phosphorus pentachloride to give 5-chloro-1-methylimidazole. This is nitrated, and the resulting 5-chloro-1-methyl-4-nitroimidazole condensed with purine-6-thiol (mercaptopurine) in an appropriate dehydrohalogenating environment. US Pat 3,056,785.

Description—Yellow, matted powder that is odorless and has a slightly bitter taste; light sensitive, nonhygroscopic, and stable to reasonable temperatures; decomposes at approximately 245°.

Solubility—Insoluble in water; slightly soluble in alcohol or chloroform; soluble in dilute solutions of alkali hydroxides (unstable); sparingly soluble in dilute mineral acids.

Comments—Approved for prevention of renal transplant rejection. It is a derivative of *Mercaptopurine* into which it largely is converted in the body, but not all of its actions are those of mercaptopurine. It is used only as an *immunosuppressive* drug. It suppresses T-lymphocyte and monocyte (hence macrophage) production more than B-lymphocyte production. It probably has been used more than any other immunosuppressive drug in *kidney transplantations.* Currently, approximately one-half of kidney transplants survive for longer than 3 yr when azathioprine is used, but other measures also contribute to this rate of success. It also is used in other organ transplantations.

Azathioprine works in the afferent and not the efferent immune phase and hence does not suppress ongoing graft rejection. It appears to bring about a satisfactory response in a high percentage of patients who have *ulcerative colitis, regional enteritis, polymyositis,* or *refractory idiopathic thrombocytopenic purpura* but induces considerable toxicity. In *rheumatoid arthritis,* it is used when conventional therapy fails. It is almost as effective as gold, penicillamine, or cyclophosphamide and less toxic than penicillamine or cyclophosphamide. It may improve metabolic control in recent-onset diabetes mellitus. It is usually of little benefit in *systemic lupus erythematosus.*

Nausea and vomiting are frequent. Other toxicity or intercurrent infection (see the introductory statement) occurs in approximately one-third of patients under immunosuppressive treatment with the drug. Bone-marrow depression is the most frequent, occurring in approximately 11% of patients; leukopenia (28 to more than 50%, as much as 16% serious), thrombocytopenia, and, to a lesser extent, anemia or pancytopenia are manifested.

In antiarthritic doses, infections are not increased, and other adverse effects are less frequent and less severe. Pancreatitis, alopecia, arthralgia, skin rashes, serum sickness, stomatitis, esophagitis, steatorrhea, retinopathy, peritoneal hemorrhage, and pulmonary edema also may occur in a small percentage of cases. Occasionally, hepatic damage, with elevation of the plasma content of liver enzymes and jaundice, is seen, but damage seems slight and seems to disappear during the course of treatment. However, in the presence of liver dysfunction the drug should be withheld. Although the incidence is rare, an increase in reticulum cell sarcoma and lymphoma has been noted in transplant patients receiving azathioprine; it is unclear whether this is from immunosuppression or from the successfully sustained transplant. However, the drug is carcinogenic in experimental animals.

Although it is degraded rapidly in the liver, it is important that the kidney regulates the plasma concentration of the effective metabolites, so that toxicity is greatly increased in the presence of allopurinol or renal impairment, unless the dosage is properly adjusted. It should not be used during pregnancy if possible.

It is metabolized rapidly to 6-MP, so that its useful half-life is that of 6-MP. Because allopurinol inhibits the metabolism of 6-MP, the dosage of this drug must be reduced to approximately one-third of the usual dose when allopurinol is used concurrently. Hepatic insufficiency diminishes efficacy.

BCG VACCINE

TICE BCG; TheraCys, BCG Live (intravesical)

Preparation—TICE is an attenuated live culture preparation of the Bacillus of Calmette and Guerin (BCG) strain *Mycobacterium.* The culture is grown on a medium containing glycerin, asparagine, citric acid, potassium phosphate, magnesium sulfate, and iron ammonium citrate. Prior to freeze-drying lactose is added. Each 10^8 colony-forming units (CFU) is equivalent to approximately 50 mg net weight.

TheraCys is a freeze-dried suspension of the same bacterium grown on Sauton medium (potato and glycerin based). Each approx 10^9 CFU weighs approximately 80 mg.

See, Guerin C, *The History of BCG in BCG Vaccines: Tuberculosis-Cancer,* Rosenthal SR, ed. Littleton, MA: PSG, 1980.

Comments—Approved for treatment of primary cancer of the urinary bladder. TICE BCG is freeze dried and (attenuated), whereas TheraCys is live, but both are used by intravenous instillation into the urinary bladder. The exact mechanism is unknown, but BCG instillation elicits an inflammatory response with leukocytic infiltration into the bladder. This is associated with an eradication or reduction of superficial carcinoma lesions. In clinical trials approximately 50% of patients treated with TICE BCG showed complete responses and appeared disease-free; approximately 75% showed positive response. In patients who have *in situ* carcinoma and are treated with TheraCys, approximately 71% showed good clinical response. Following bladder instillation, the drug is retained for 2 hours and then voided. Bladder irritability occurs in 50% of patients in the following 24 to 72 hours.

BCG should not be given to patients who have compromised immune systems or who are receiving immunosuppressants, antimicrobial agents, or radiation therapy. Deaths have occurred owing to systemic infections, and therapy should be interrupted if patients show high or persistent fever and malaise.

BEVACIZUMAB

Immunoglobulin G1 (human mouse monoclonal rhuMAb-VEGF γ-chain anti-human vascular endothelial growth factor), disulfide with human-mouse monoclonal rhuMAb-VEGF light chain dimer; Avastin

[216974-75-3] $C_{6638}H_{10160}N_{1720}O_{2109}S_{44}$ (149,214.2).

Preparation—Produced in a Chinese Hamster Ovary mammalian cell expression system in a nutrient medium containing gentamycin.

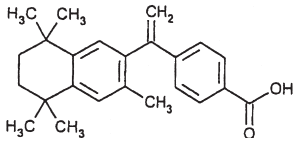
Description—Clear to slightly opalescent, colorless to pale brown in the sterile, IV infusion; pH 6.2.

Comments—recombinant humanized monoclonal IgG1 antibody that binds to and inhibits a natural protein called human vascular endothelial growth factor (VEGF) which plays a role in the formation and maintenance of tumor blood vessels. This monoclonal antibody belongs to a new class of drugs called angiogenesis inhibitors, and is believed to work by targeting and inhibiting the function of a natural protein called "vascular endothelial growth factor" (VEGF) that stimulates new blood vessel formation or angiogenesis. When this binding occurs, the tumor cannot stimulate the growth of blood vessels, thus denying tumors blood, oxygen, and other nutrients needed for growth. Indicated in combination with intravenous 5-fluorouracil—based chemotherapy for first-line treatment of patients with metastatic carcinoma of the colon or rectum.

Common side effects include hypertension, tiredness, blood clots, diarrhea, leukopenia, headache, anorexia, stomatitis, constipation, upper respiratory infection, epistaxis, dyspnea, exfoliative dermatitis, and proteinuria. Serious, but uncommon side effects include gastrointestinal perforation (sometimes leading to intra-abdominal infections), impaired wound healing, and internal bleeding.

BEXAROTENE

Benzoic acid, 4-[1-(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl)ethenyl]-, Targretin



[153539-49-0] $C_{24}H_{28}O_2$ (348.48).

Preparation—US Pat 5,466,861(1995).

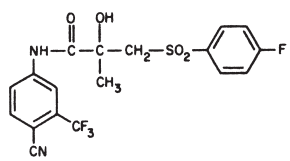
Description—White to off-white powder from methylene chloride melting about 231°.

Solubility—Insoluble in water; soluble in ethanol or vegetable oils.

Comments—a synthetic retinoid analog, is an antineoplastic agent that selectively binds with and activates retinoid X receptor (RXR) subtypes (RXR_α, RXR_β, and RXR_γ). Bexarotene is an oral orphan drug for the treatment of skin manifestations of cutaneous T-cell lymphoma (CTCL) in patients who are refractory to at least one prior systemic therapy. Metabolized through oxidation by the cytochrome P-450 (CYP) 3A4 isoenzyme and primarily eliminated by biliary excretion with a terminal half-life of 7 hrs. Plasma concentrations after a 300-mg dose increased by approximately 48% after a meal containing fat compared with a glucose solution. Adverse reactions include skin rash, dry skin, flu-like symptoms, anemia, fever, hyperlipemia, hypothyroidism, leukopenia, peripheral edema, photosensitivity, and increased liver function tests. Drug interactions may occur with protein bound drugs, gemfibrozil, hormonal contraceptives, tamoxifen, oral hypoglycemic agents, or inhibitors or inducers of the cytochrome P-450 system.

BICALUTAMIDE

Propanamide, (±)-*N*-[4-cyano-3-(trifluoromethyl)phenyl]-3-[4-(fluorophenyl)sulfonyl]-2-hydroxy-2-methyl-, Casodex



[90357-06-5] $C_{18}H_{14}N_2O_4S$ (430.38).

Preparation—Thiophenol is reacted with methyl 2,3-epoxy-2-methylpropanoate and NaH in THF to yield the methyl ester of 2-hydroxy-2-methyl-3-(phenylthio)propionic acid (I). Saponification of I, to form the acid, followed by treatment with thionyl chloride, and the acyl chloride reacted with 4-amino-3-(trifluoromethyl)benzonitrile, produces the corresponding amide. Oxidation of the thio ether linkage with 3-chloroperbenzoic acid gives the title compound.

Description—White to off-white crystals that melt about 192°. It is a racemic mixture and the *S*-isomer is essentially inactive; $pK_a \sim 12$.

Solubility—Soluble in 5 mg/mL water; soluble in acetone or in THF; slightly soluble in chloroform or anhydrous alcohol; sparingly soluble in methanol.

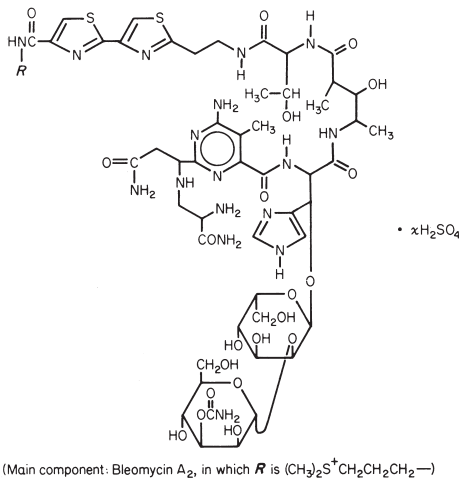
Comments—Approved for use in advanced prostate cancer in combination with LHRH analogs. It is a nonsteroidal antiandrogen that acts by inhibiting androgen uptake or nuclear binding target tissues. When 50 mg of this drug was given once a day, it proved no different from flutamide 250 mg tid in patients who had either leuprolide or goserelin depot or implants. Time to treatment failure was no different.

Bicalutamide is well absorbed orally with or without meals. The active (*R*) isomer is inactivated largely by oxidation followed by glucuronidation. The (*S*) isomer is cleared rapidly, and does not contribute significantly to steady-state plasma levels. Peak levels are reached approximately 3 hr after a single dose and exhibit a half-life of 5.8 days. Mean steady-state plasma concentration in cancer patients is 8.9 mcg/mL. Renal and hepatic function impairment did not affect the affect the drug's elimination.

Elevations in plasma testosterone and estradiol levels are noted when bicalutamide is used as a single agent. Gynecomastia and breast pain were reported in approximately 38% of treated patients. The most frequent adverse reaction was hot flashes reported in 49% of patients. Diarrhea was also reported. It can displace coumarin anticoagulants from plasma protein binding sites, thus caution should be exercised when treatment is started in patient being treated with anticoagulants. Patients should be monitored for possible increases in liver enzymes, as rare cases of death due to hepatotoxicity have occurred.

BLEOMYCIN SULFATE

Blenoxane



(Main component: Bleomycin A_2, in which ***R*** is $(CH_3)_2S^+CH_2CH_2CH_2$—)

Bleomycin Sulfate (salt) [9041-93-4].

A mixture of the sulfate salts of a group of related basic glycopeptide antibiotics, notably bleomycin A_2 and bleomycin B_2, obtained from cultures of Streptomyces verticillus; bleomycin A_2 is the main component of the bleomycin used clinically.

Preparation—For the purification and separation of the bleomycins see Umezawa et al. *J Antibiot* 1966; 19:200, 210, also Takita. *J Antibiot* 1968; 21:79, and 1969; 22:237.

Description—Cream-colored, hygroscopic powder.

Solubility—Soluble in water; sparingly soluble in alcohol.

Comments—Causes fragmentation of DNA and also inhibits incorporation of thymidine into DNA. It stops the progression of cells through the G_2 and the M phases of the cell cycle. Despite these actions, it has little effect on bone marrow, a circumstance that gives it a special usefulness in drug combinations. Its selectivity appears to be related to distribution. It is approved as palliative treatment of *lymphomas, testicular carcinoma,* and *squamous cell carcinoma.* A component of all three preferred combinations is used for the treatment of *testicular carcinoma* and of two for cervical cancer. It is included in one of two preferred combinations to treat *squamous cell carcinoma of the head and neck.* It also has been used successfully in the treatment of squamous cell carcinomas of the skin, penis, and vulva. It is in two of five preferred for *Hodgkin's disease.* It is a component of four of seven preferred combinations to treat diffuse lymphocytic lymphoma. It has shown efficacy against reticulum cell sarcoma, lymphosarcoma, chloriocarcinoma, teratocarcinoma, and AIDS related Kaposi's sarcoma. It is also sometimes used intrapleurally for sclerotherapy in the management of malignant pleural effusions and is also effective against *common warts.*

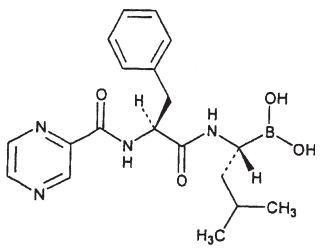
It is toxic, and 10% to 40% of patients develop a pneumonitis that progresses to pulmonary fibrosis: 1% of bleomycin-treated patients die of pulmonary complications. The effect is most likely to occur in elderly patients or those who have received a total of 400 Units. The drug must be used extremely cautiously in the presence of pulmonary disease. Acute hyper-

pyrexia and cardiorespiratory collapse also occur, especially in patients who have lymphomas; for this reason, patients who have lymphomas are given two test doses of 5 U or less and are observed for a day before treatment is begun. Anticalmodulin drugs (eg, trifluperazine) enhance lethal toxicity. Bleomycin commonly causes nausea, vomiting, chills, and fever, and in half the patients, it causes erythema and hyperkeratosis, which sometimes progresses to vesication. Other occasional adverse effects are cutaneous desquamation, hyperesthesia, confusion, vertigo, pruritus, tenderness, alopecia, and aphthous ulcers. Cutaneous toxicity is most likely to occur when the total cumulative dose exceeds 150 U.

It is absorbed poorly orally and also is inactivated in the gut and the liver. Consequently, it must be administered parenterally. Higher concentrations are reached in certain neoplasms (carcinomas more than sarcomas), lungs, and skin than in other tissues, which accounts for the selectivity and the loci of toxicities. In the tissues, the drug appears to be deaminated and, possibly, also hydrolyzed by peptidases. The enzymatic destruction is less in those tissues in which the higher concentrations are reached. Sixty to 70% is excreted in the urine. In patients who have normal renal function, the elimination half-life is approximately 2 hr; in renal failure the half-life may be as long as 21 hr. Care must be exercised in the presence of renal impairment.

BORTEZOMIB

Boronic acid, [(1*R*)-3-methyl-1-[[(2*S*)-1-oxo-3-phenyl-2-[(pyrazinylcarbonyl)amino]propyl]amino]butyl]-, Velcade



[179324-69-7] $C_{19}H_{25}BN_4O_4$ (328.24).

Preparation—The pinanediol ester of leucineboronic acid is coupled with an *N*-Boc protected amino acid in the presence of TBTU (*O*-(benzotriazol-1-yl)-*N,N,N′,N′*-tetramethyluronium tetrafluoroborate). Deprotection and *N*-acetyl-ation yields the dipeptideboronic ester. *Biorg Med Chem Lett,* 1998; 8:336 and US Pat 4,499,087 (1985) in *Chem Abstr* 1985; 103:71709.

Description—The pure drug substance exists in the cyclic anhydride form as a trimeric boroxine. The injectable exists as a mannitol boronic ester which, after reconstitution, is in equilibrium with the monoboronic acid, the hydrolysis product.

Solubility—In water; 3.3 to 3.8 mg/mL in a pH range of 2 to 6.5.

Comments—reversible inhibitor of the chymotrypsin-like activity of the 26S proteasome (large protein complex that degrades ubiquitinated proteins). The ubiquitin-proteasome pathway are essential in regulating the intracellular concentration of specific proteins, thereby maintaining homeostasis within cells. Inhibition of the 26S proteasome prevents this targeted proteolysis which can affect multiple signaling cascades within the cell. This disruption of normal homeostatic mechanisms can lead to cell death**. I**ndicated for multiple myeloma in patients who have received at least two prior chemotherapy regimens and experienced disease progression. Adverse effects may be severe and life-threatening, and include peripheral neuropathy (paresthesias and/or loss of reflexes), asthenia, hypotension, diarrhea, constipation, vomiting, thrombocytopenia, neutropenia, or fever.

In vitro studies with human liver microsomes and human cDNA-expressed cytochrome P450 isozymes indicate that bortezomib is primarily oxidatively metabolized via cytochrome P450 enzymes, 3A4, 2D6, 2C19, 2C9, and 1A2. The major metabolic pathway is deboronation to form two deboronated metabolites that subsequently undergo hydroxylation to several metabolites. Deboronated-bortezomib metabolites are inactive as 26S proteasome inhibitors.

BROMOCRIPTINE—page 1418.

BUSULFAN

1,4-Butanediol, dimethanesulfonate; Tetramethylene Dimethanesulfonate; Myleran
$CH_3SO_2O(CH_2)_4OSO_2CH_3$

1,5-Butanediol dimethanesulfonate [55-98-1] $C_6H_{14}O_6S_2$ (246.29).

Preparation—By esterifying 1,4-butanediol with methanesulfonyl chloride in the presence of pyridine.

Description—White, crystalline powder; melting about 116°.

Solubility—Slightly soluble in water; slightly soluble in alcohol; 1 g in approximately 45 mL acetone.

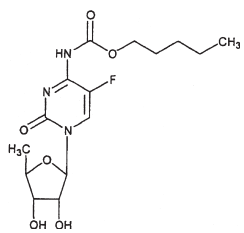
Comments—An alkylating agent that is efficacious as an *antineoplastic* drug in certain cases. It is phase nonspecific. Its principal distinction is that in the usual doses it exerts little action on rapidly proliferative tissues other than bone marrow. With low doses, granulocytopoiesis can be suppressed selectively without affecting erythropoiesis. Thus, it is approved for the palliative treatment of *chronic granulocytic* (myelogenous, myeloid, myelocytic) *leukemia;* for this type of leukemia, it is one of two drugs of choice. It is not to be used in terminal or acute phases of the disease. It is also quite effective in the treatment of *polycythemia vera* and *primary thrombocytosis.* Because it has little effect on lymphopoiesis, it is of no value in lymphocytic leukemia, Hodgkin's disease, or malignant lymphoma. It is useless against solid tumors, but is used in high dosages for pretransplant conditioning regimens in patients undergoing autologous or allogeneic bone marrow transplantation for acute or chronic leukemias.

Its principal toxicity is pancytopenia and long-lasting thrombocytopenia. Lymphocytopenia is uncommon. A complete differential blood count (including thrombocytes) once a week is mandatory. Nausea, vomiting, diarrhea, impotence, amenorrhea, sterility, and fetal malformation occasionally occur. Granulocyte destruction results in a high rate of excretion of urates, the precipitation of which may cause renal damage; cotreatment with allopurinol may avoid such damage. It also sometimes causes cheilosis, glossitis, interstitial pulmonary fibrosis, anhidrosis, skin pigmentation (which may be the result of adrenalcortical hypofunction), alopecia, and gynecomastia.

It is not immunosuppressive. It is rapidly and completely absorbed, and metabolized in the liver mainly by glutathione conjugation (spontaneous and glutathione *S*-transferase-mediated). The glutathione conjugate is then further metabolized in the liver by oxidation with an elimination half-life is 2 to 3 hr.

CAPECITABINE

Carbamic acid, [1-(5-deoxy-β-D-ribofuranosyl)-5-fluoro-1,2-di-hydro-2-oxo-4-pyrimidinyl]-, pentyl ester; Xeloda



[154361-50-9] $C_{15}H_{22}FN_3O_6$ (359.35).

Preparation—5′-Deoxy-5-fluorocytidine is acetylated with acetic anhydride to form the 2′,3′-diacetate, which on treatment with *n*-pentyl chloroformate yields the N^4-propxycarbonyl derivative. The esters are saponified using dilute NaOH to give the product. US Pat 5,472,949 (1995).

Description—Off-white crystalline powder or crystals from ethyl acetate, melting about 110–120°. It is the prodrug of doxifluridine and is designed to be metabolized in the body to 5-fluorouracil.

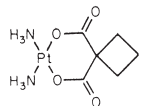
Solubility—Water; 26 mg/mL at 20°.

Comments—A fluoropyrimidine carbamate prodrug indicated for the treatment of metastatic breast cancer and colorectal cancer. It undergoes extensive metabolism in the liver by the enzyme carboxylesterase to an intermediate, 5′-deoxy-5-fluorocytidine, which is converted to 5′-deoxy-5-fluorouridine by the enzyme cytidine deaminase. The 5′-deoxy-5-fluorouridine metabolite is then hydrolyzed by thymidine phosphorylase to fluorouracil in the tumor. Peak plasma levels are achieved in about 1.5 hours, and peak fluorouracil levels are reached at 2 hours after oral administration and oral bioavailability is about 70% to 80%.

The main toxicities consist of diarrhea, hand-and-foot syndrome, myelosuppression, nausea, and vomiting. Myelosuppression, nausea and vomiting, and mucositis occur at a significantly less incidence than that seen with intravenous fluorouracil. Its toxicity may be increased with concomitant administration of leucovorin. Drug interactions may occur resulting in increased phenytoin levels or increased bleeding with warfarin.

CARBOPLATIN

Platinum, diammine [1,1-cyclobutanedicarboxylato(2-)-*O,O′*]-, CBDCA, Paraplatin



[41575-94-4] $C_6H_{12}N_2O_4Pt$ (371.25).

Preparation—Silver sulfate is reacted with *cis*-diammine platinum diiodide to yield the diaquodiammine platinum sulfate. Interaction with barium 1,1-cyclobutanedicarboxylate precipitates $BaSO_4$, and forms the product. *Inorg Chem Acta* 1980; 46:L15.

Description—White crystals.

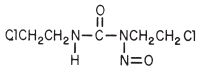
Solubility—1 g in approximately 10 mL water or 1000 mL alcohol.

Comments—Its *antineoplastic* activity results from binding to DNA and inhibiting DNA synthesis. Specifically, bidentate dicarboxylate ligands of carboplatin are displaced by water (aquation), forming positively charged platinum complexes that react with nucleophilic sites on DNA. Cisplatin has the same mechanism of action providing the same clinical antitumor spectrum. Carboplatin and cisplatin are activated by an initial aquation reaction, carboplatin is a more stable compound and is activated more slowly than cisplatin Carboplatin produces predominantly DNA intrastrand cross-links from the formation of adducts between the activated platinum complexes of the drug and the N-7 atom on guanine. Interstrand cross-linking within the DNA helix also occurs which are stable bonds that do not dissociate easily. Higher concentrations of carboplatin than cisplatin are required to produce equivalent levels of DNA binding

Carboplatin is less nephrotoxic and ototoxic compared to cisplatin. It is approved as palliative relief for *ovarian cancer.* It is presently an alternative drug for treatment of *small-cell* and *non–small-cell lung cancer, ovarian, head and neck, Wilms' tumor, brain, bladder* and *testicular carcinomas.* Immediate adverse effects are nausea and vomiting. Delayed toxicity includes myelosuppression with sometimes pronounced thrombocytopenia, renal, and otic toxicities. The drug is not effective orally. In plasma, less than 10% is protein bound. The elimination half-life is 3 to 7 hr. Dosage adjustments are required based on renal function.

CARMUSTINE

Urea, *N,N′*-bis(2-chloroethyl)-*N*-nitroso-, BiCNU



1,3-Bis(2-chloroethyl)-1-nitrosourea [154-93-8] $C_5H_9Cl_2N_3O_2$ (214.05).

Preparation—Like other cytotoxic nitrosoureas, it may be synthesized by nitrosation with sodium nitrite of the appropriate substituted urea—in this case 1,3-bis(2-chloroethyl)urea—in a cold, acid medium (eg, formic acid). Methods of synthesis of nitrosoureas have been published by Johnston et al. *J Med Chem* 1963; 6:669.

Description—White or light yellow powder; melts, with decomposition, to an oily liquid about 30°.

Solubility—Slightly soluble in water; freely soluble in alcohol; highly soluble in lipids; decomposes rapidly in acid or aqueous solutions with a pH greater than 7.

Comments—Although this is an alkylating drug, it also carbamoylates amino and other groups. Its cytotoxic effect is likely due to its ability to cross-link cellular DNA. Synthesis of DNA and RNA is inhibited. It is phase nonspecific. Carmustine is approved for intravenous use in *brain tumors, multiple myeloma, Hodgkin's disease,* and *non-Hodgkin's lymphomas.* The drug is used mainly in the treatment of *brain glioblastoma* (for which it shares drug-of-choice status with its congener lomustine), *Hodgkin's disease* and other *lymphomas;* it is a component of a first-choice combination for *myeloma.* It has been reported to have a high efficacy against *Burkitt's tumor.* Although it has activity against various other carcinomas, including melanoma and renal cell carcinoma, it is not among the usual choices for such diseases. It usually is given in combination with radiotherapy in the treatment of brain tumors and with vincristine, procarbazine, and glucocorticoids (eg, prednisone) in the treatment of the various lymphomas and multiple myeloma. An intracranial carmustine wafer implant is available as an adjunct to surgery in palliative treatment of recurrent glioblastoma multiforme in patients for whom surgical resection is indicated. It is also effective topically for the palliative treatment of cutaneous T-cell lymphoma (mycosis fungoides).

Within 2 hr after administration and lasting for 4 to 6 hr, nausea and vomiting occur frequently and usually severely. Rapid intravenous infusion causes intense flushing and conjunctival suffusion with a similar time course. There may be a burning sensation but rarely thrombosis at the site of injection. Delayed bone-marrow toxicity occurs; also, thrombocytopenia that reaches a nadir in approximately 4 wk and a less severe leukepenia in approximately 6 wk occur, each lasting 2 to 7 wk; mild anemia may occur. With repeated doses, bone-marrow depression is cumulative. Leukocyte and platelet counts and signs of intercurrent infections should be monitored carefully throughout treatment. Severe dyspnea and a sometimes fatal interstitial pulmonary fibrosis occasionally occur. There also may be a mild, reversible hepatotoxicity in approximately 25% of recipients. Other adverse effects include slight nephrotoxocity [with a transient elevation of blood urea nitrogen (BUN)] to severe nephrotoxicity and renal failure, and with large cumulative doses, vertigo and ataxia occur. There is an increased risk of nonlymphocytic leukemia.

By the oral route, it is metabolized almost completely as it passes through the liver; consequently, it must be given intravenously. After intravenous administration, its plasma half-life is short, reported variously as from 3 to 30 min. Because the drug is highly lipid soluble, it readily passes the blood-brain barrier, and concentrations of metabolites in the cerebrospinal fluid range from approximately 50% to 115% of those in plasma.

CETUXIMAB

Immunoglobulin G1, anti-(human epidermal growth factor receptor) (human-mouse monoclonal C225γ-chain), disulfide with human-mouse monoclonal C225 K-chain, dimer; Erbitux

[205923-56-4] Molecular weight is approximately 170,000 daltons.

Preparation—Produced in mammalian (murine myeloma) cell cultures. Also US 6,645,990 and US Pat Appl 0040096890 (2004).

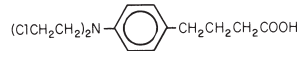
Description—White, amorphous particulate.

Comments—Recombinant, human/mouse chimeric monoclonal antibody that targets a natural protein called "epidermal growth factor receptor" (EGFR) on the surface of cancer cells, thus interfering with their growth. This binding to EGFR blocks phosphorylation and activation of receptor-associated kinases, resulting in inhibition of cell growth, induction of apoptosis, and decreased matrix metalloproteinase and vascular endothelial growth factor production. In vitro assays and in vivo animal studies have shown that only the growth and survival of tumor cells that over-express the EGFR are inhibited. Approved as a single agent is indicated for the treatment of EGFR-expressing, metastatic colorectal carcinoma in patients who are intolerant to irinotecan-based chemotherapy, or in combination with irinotecan, for the treatment of EGFR-expressing, metastatic colorectal carcinoma in patients who are refractory to irinotecan-based chemotherapy.

Common side effects include acne-like rash, dry skin, tiredness or weakness, fever, constipation, and abdominal pain. Severe infusion reactions occurred in approximately 3% of patients, rarely with fatal outcome (<1 in 1000). Approximately 90% of severe infusion reactions were associated with the first infusion. Severe infusion reactions are characterized by rapid onset of airway obstruction (bronchospasm, stridor, hoarseness), urticaria, and hypotension. Other less common but more serious events are interstitial lung disease, pulmonary emboli, and sepsis. Studies have shown a mean half-life was 114 hours (range, 75–188 hours).

CHLORAMBUCIL

Benzenebutanoic acid, 4-[bis(2-chloroethyl)amino]-, Leukeran



4-[*p*-[Bis(2-chloroethyl)amino]phenyl]butyric acid [305-03-3] $C_{14}H_{19}Cl_2NO_2$ (304.22).

Preparation—4-Phenylbutyric acid is nitrated and the resulting p-nitric acid is esterified with isopropyl alcohol. The nitro ester then is hydrogenated to the aminoester. Reaction with ethylene oxide converts the—NH_2 into—$N(CH_2CH_2OH)_2$, which then is converted into—$N(CH_2CH_2Cl)_2$ by treatment with $POCl_3$. Hydrolysis of the ester yields the acid, chlorambucil.

Description—Off-white, slightly granular powder.

Solubility—Slightly soluble in water; soluble in dilute alkali; 1 g in 2 mL acetone.

Comments—An alkylating agent effective by the oral route. It is approved for and is the agent of choice in the treatment of *chronic lymphocytic leukemia.* It also is effective in the treatment of *Waldenstrom's macroglobulinemia, multiple myeloma, lymphosarcoma, giant-cell follicular lymphoma,* and, to a lesser degree, in *choriocarcinoma, Hodgkin's disease,* and *ovarian and testicular tumors.* As an immunosuppressant it is considered of value in the treatment of the nephrotic syndrome and vasculitis associated with *systemic lupus erythematosus, Wegner's granulomatosis, idiopathic membranous nephropathy,* and *Behçet's disease.*

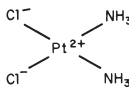
It is the slowest-acting and least toxic of currently used nitrogen mustards. Its toxicity is manifested mainly as bone-marrow depression, although in therapeutic doses it generally is moderate and reversible. Most patients have some neutropenia after the third week of treatment until approximately 10 days after discontinuation of treatment. Slowly progressing lymphopenia also occurs, but it repairs itself quickly after treatment. Thrombocytopenia and anemia also occur sometimes. When the total accumulated dose exceeds 6.5 mg/kg the incidence of severe bone-marrow damage becomes high, and even irreversible toxicity may occur. It is mandatory that hemoglobin, leukocyte and platelet counts be monitored closely. It is contraindicated for 4 wk after radiotherapy or other drugs that depress bone marrow. If possible, it should be avoided during the first trimester of pregnancy.

It is adsorbed well by the oral route. It is degraded extensively in the body. The elimination half-life is approximately 1.5 hr.

CHLOROQUINE PHOSPHATE—page 1666.

CISPLATIN

Platinum, diamminedichloro-, (*SP*-4-2), Platinol



cis-Diamminedichloroplatinum [15663-27-1]$Cl_2H_6N_2Pt$ (300.06).

Preparation—A solution of potassium tetrachloroplatinate(II), which is prepared by reduction of the hexachloroplatinate(II) salt with hydrazine, is neutralized with ammonium chloride and ammonium hydroxide. The cis-isomer precipitates (*Inorg Synth* 1963, 7:239).

Description—White, lyophylized powder; melts about 207°.

Solubility—1 g in approximately 1000 mL of water or normal saline; 1 g in approximately 42 mL of dimethylformamide.

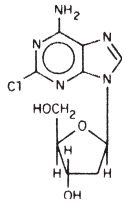
Comments—Cross-links DNA and hence acts like alkylating antineoplastic agents. It is approved as palliative relief for metastatic testicular and ovarian tumors and for advanced bladder cancer. It is used in various first-choice combinations for the treatment of metastatic carcinomas of the testes, ovary, prostate, and cervix; squamous cell carcinoma of the head and neck; small-oat-cell and non-small-cell cancer of the lung; advanced cancer of the bladder, medulloblastoma, and retinoblastoma that has proved refractory to surgery or radiation. It also is used alone in the treatment of bladder cancer.

Acute toxicity includes severe nausea, vomiting, and anorexia, which occurs in almost all recipients but can be controlled largely with antiemetics. Occasional anaphylactoid reactions occur. Delayed toxicity includes ototoxicity (tinnitus or hearing loss in approximately 30% of patients), which requires audiometric monitoring. Nephrotoxicity, which requires monitoring of serum creatinine, urate, and BUN and avoidance of other nephrotoxic drugs, is a serious side effect in all patients and is controlled by forced diuresis (administration of mannitol and saline) and hydration prior to and following administration. Use of prophylactic amifostine, a phosphorylated sulfhydryl compound, decreases the incidence and severity of nephrotoxicity and is administered immediately prior to cisplatin administration. Bone-marrow depression occurs in 25% to 30% of recipients, typically at the higher dosages. Peripheral neuropathies, loss of taste, and convulsions are other side effects experienced. In studies of patients with advanced ovarian cancer, the incidence and severity of cisplatin-induced neurotoxicity appeared to be reduced in patients who received prophylactic amifostine. Electrolyte deficits, perhaps from hemodilution by fluids, have been reported, and consist primarily of hypomagnesemia, hypokalemia, and hypocalcemia. It combines tightly with various proteins, which stimulates the immune system to produce various antibodies; the adverse effect of such immune stimulation are not known.

It is not absorbed orally and must be given intravenously. Intra-arterial and peritoneal administration has shown to be effective in select patients. Approximately 90% is bound to plasma proteins. It does not cross the blood-brain barrier. Elimination is mainly renal, partly by tubular secretion; excretion is nonlinear. It is contraindicated in patients with poor renal function. The distribution half-life of the unbound drug is 25 to 49 min and the elimination half-life of total platinum is normally 58 to 73 hr but may be as long as 240 hr in anuria. However, platinum can be identified in tissues, especially liver, kidney, testes, and intestine, for prolonged periods of time. Sodium thiosulfate decomposes the drug and complexes platinum and thus protects against renal damage and certain other toxicity.

CLADRIBINE

Adenosine, 2-chloro-2′-deoxy-, Leustatin



[4291-63-8] $C_{10}H_{12}ClN_5O_3$ (285.69).

Preparation—By condensing 2,6-dichloropurine with 1-chloro-2-deoxy-3,5-di-*O*-(*p*-tolyl)-α-D-*erythro*-pentofuranose in acetonitrile, the product(s) purified and separated by chromatography and the 7- substituted isomer heated with ammonia-saturated methanol, whereby the free chloro group is replaced by amino, to give the product.

Description—White crystals melting about 212°; solidifies and does not remelt below 300°.

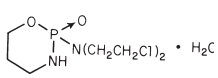
Solubility—Soluble in water and DMF.

Comments—Approved for use in hairy-cell leukemia and is used in the treatment of chronic lymphocytic leukemia and low-grade non-Hodgkin's lymphoma. It is a synthetic antimetabolite that passively crosses the plasma membrane and is activated by deoxycytidine kinase to 2-CdAMP. It is both incorporated into DNA and inhibits DNA single-strand-break repair. Poly adenosine diphosphate-(ADP-) ribosylation of the damaged DNA depletes cellular NAD and ATP and disrupts cell cycling. In clinical trials, 92% of previously untreated patients and 84% of previously treated patients displayed positive clinical responses to a single course of 0.09 mg/kg/day administered for 7 consecutive days.

It is usually administered by continuous intravenous infusion. It has a terminal half-life of elimination of approximately 5.4 hr. It is cleared mainly by the kidney. In patients who have normal renal function, no accumulation of the drug is seen after the normal 7-day course of therapy. Severe neutropenia is seen in approximately 70% of treated patients starting therapy. This is frequently accompanied by fever or infection. Severe anemia appeared in approximately 12% of patients. Headache and rash are also common side effects. A prolonged bone-marrow hypocellularity has been noted in 34% of treated patients. This condition may last for as long as 3 yr, although its significance is unknown. At high doses, it may cause severe, irreversible neurotoxicity, acute nephrotoxicity, and severe bone marrow suppression.

CYCLOPHOSPHAMIDE

2*H*-1,3,2-Oxazaphosphorin-2-amine, *N,N*-bis(2-chloroethyl)-tetrahydro-, 2-oxide, monohydrate; Cytoxan; Neosar



[6055-19-2] $C_7H_{15}Cl_2N_2O_2P.H_2O$ (279.10); anhydrous [50-18-0] (261.09).

Preparation—3-Amino-1-propanol is condensed with *N,N*-bis(2-chloroethyl)phosphoramidic dichloride [$(ClCH_2CH_2CH_2)_2N–POCl_2$] in dioxane solution under the catalytic influence of triethylamine. The condensation is double, involving both the hydroxyl and the amino groups, thus effecting the cyclization.

Description—White, crystalline powder; liquefies on loss of its water of crystallization.

Solubility—1 g in approximately 25 mL water; soluble in alcohol.

Comments—An alkylating agent. Unlike other β-chloroethylamino alkylators, it does not cyclize readily to the active ethyleneimonium form until activated by hepatic enzymes. The liver is protected by the further metabolism of activated metabolites to inactive end products. Thus, the substance is stable in the GI tract, tolerated well, and effec-

tive by the oral and parenteral routes; it does not cause local vesication, necrosis, phlebitis, or even pain.

Cyclophosphamide is approved for *Stage III and IV, malignant lymphomas, multiple myeloma, leukemias, mycosis fungoides, neuroblastoma, retinoblastoma,* and *carcinoma of the breast.* Alone or in combination, it is the drug of choice for treatment of Burkitt's and non-Hodgkin's lymphomas. It is a component of various first-choice combinations for treatment of Hodgkin's disease, follicular lymphoma, diffuse histiocytic lymphoma, multiple myeloma, squamous cell, and large-cell anaplastic carcinomas, and adenocarcinoma of the lung, small- (oat-) cell lung cancer, soft-tissue sarcomas, embryonal rhabdomyosarcoma, osteogenic sarcoma, retinoblastoma, neuroblastoma, pediatric solid tumors, Ewing's sarcoma, breast tumor, ovarian tumors, and testicular tumors. In combination, it shares alternative drug status with various other drugs for chemotherapy of acute lymphocytic leukemia, testicular cancer, Wilms' tumor, glioblastoma, cervical cancer, head and neck squamous cell carcinoma, islet cell carcinoma, Kaposi's sarcoma, and chronic lymphocytic leukemia. Active metabolites appear in cerebrospinal fluid but in insufficient quantities to treat meningeal leukemia. It is used in high dosages in combination with busulfan as a conditioning regimen prior to allogeneic hematopoietic progenitor cell transplantation in leukemias.

It is an immunosuppressive drug. It has been shown to be of value in the treatment of rheumatoid arthritis, Wegner's granulomatosis, hemophilia A with factor VIII destruction, idiopathic thrombocytopenic purpura (alone or in combination), erythroid aplasia, childhood nephrotic syndrome, pemphigus and vulgaris and dermatomyositis (in combination). It appears to be erratic against systemic lupus erythematosus. It possibly may be efficacious in the management of uveitis. In combination with radiation treatment, it improves the survival of bone marrow and probably of heart transplants. The long-term toxicities of cyclophosphamide should be considered if the drug is to be used as other than a cancer chemotherapeutic agent.

Alopecia occurs in approximately 50% of patients receiving maximal prolonged treatment. Leukopenia is the inevitable side effect and is used as an index of dosage. Other side effects include sterile hemorrhagic cystitis in 20% of those receiving treatment, anorexia, nausea, and vomiting (regardless of route of administration), anaphylactoid reactions, fever, hemolytic-uremic reaction, pulmonary infiltrates and fibrosis, mucosal ulcerations, dizziness, occasional thrombocytopenia, hypoprothrombinemia, nail ridging, cutaneous pigmentation, water intoxication, aspermia in males (3–6 months or longer in onset), anovulation in 30% to 50% of females, and occasional hepatic dysfunction. Bladder telangiectasis and abnormal urinary cytology occur; in long-term use, bladder fibrosis and transitional cell carcinoma occasionally occur. Sodium 2-mercaptoethanesulfonate (Mesna), a synthetic sulfhydryl compound, interacts with acrolein and other metabolites to decrease the incidence and severity of hemorrhagic cystitis. The blood count should be monitored closely during induction and at least weekly thereafter. Cyclophosphamide is relatively platelet sparing; cyclophosphamide is carcinogenic.

It is absorbed orally. It is distributed to the tissues with a volume of distribution greater than the total body water. The drug is metabolized by the hepatic microsomal system to alkylating metabolites that, in turn, are converted to phosphoramide mustard and acrolein. High doses rapidly induce the metabolism of the drug. The plasma half-life is 4 to 6 hr. Although the clinical significance has not been clearly elucidated, caution should be used with concomitant therapy with drugs which induce liver microsomal enzymes, as this may result in an increased pharmacologic effect and toxicity of cyclophosphamide because of increased conversion to active metabolites.

CYCLOSPORINE

For the full monograph, see page 1590.

Comments—Suppresses helper T lymphocytes without significantly affecting suppressor T or B lymphocytes. Thus, it is a selective immunosuppressive drug without the cytotoxicity characteristic of most other immunosuppressive drugs. Because it works only in the primary (afferent) immune phase, it must be administered before exposure to the attacking antigen. It has a modest effect to suppress some humoral immunity.

It is the most efficacious immunosuppressive and is approved for prevention of graft rejection in allogenic transplantation of kidney, liver, or heart. It is less successful in pancreatic, lung, or bone-marrow transplantation. It also is used in the management of severe aplastic anemia, some cases of myasthenia gravis, childhood diabetes (Type I) of recent onset, Graves' disease, Crohn's disease, multiple sclerosis, pemphigus and pemphigoid, dermatomyositis, polymyositis, atopic dermatitis, severe psoriasis, Behçet's disease, uveitis, biliary cirrhosis, and pulmonary sarcoidosis. It usually is employed in combination with a glucocorticoid. Although combination with other immunosuppressives usually is avoided, in bone-marrow transplantation it commonly is combined with methotrexate.

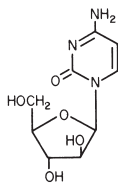
Nephrotoxicity is a common, serious adverse effect, occurring with an incidence of approximately 25% in renal and 40% in heart transplantations. In renal transplantation, nephrotoxicity is difficult to distinguish from graft rejection. Nonsteroidal anti-inflammatory drugs (NSAIDs), aminoglycosides, trimethoprim, or sulfamethoxozole favor nephrotoxicity. Hepatotoxicity occurs in 4 to 7% of cases. Hypertension occurs in approximately 26% of cases. Benign breast tumors and lymphoproliferative disorders may occur; the latter usually remit after the drug is discontinued.

CNS toxicity includes headache, parethesias (50%), lethargy, weakness, loquaciousness, sleep disorders, confusion, depression, blurred vision, tremors (12%), ataxia, quadraplegia, coma, hallucinations, mania, and convulsions. Severe CNS effects have been associated with low plasma cholesterol, hypomagnesemia, hypokalemia, high-dose methylprednisolone, aluminum overload (from dialysis), and hypertension.

Hirsutism occurs with an incidence of 21% and acne with an incidence of 6%. Gum hyperplasia and diarrhea occur in 3% to 4% of cases. Leukopenia, anemia, and thromboembolism occur rarely. Insulin-dependent diabetes may result from cyclosporine-glucocorticoid combination. Rare anaphylactoid reactions occur during intravenous infusion; polyoxyethylated castor oil in the injection is the usual culprit. There is a danger of severe infection, especially when other immunosuppressives or verapamil are used concurrently. It is teratogenic. It also is exceedingly expensive, which leads some authorities to doubt the cost-effectiveness of the drug. The systemic bioavailability by the oral route averages 27% but varies greatly; the intravenous dose is approximately 1/3 the oral dose. Plasma levels peak in approximately 3.5 hr. In plasma, approximately 90% is protein bound. The pharmacokinetics are multicompartmental. The volume of distribution is 1 to 13 (av 4) L/kg; it is concentration dependent. Nearly all of the drug is metabolized by cytochrome P-450 III in the liver; 94% of the metabolites are excreted into the bile, and 6% are excreted into the urine. The elimination half-life is 10 to 27 hr; there is a circadian periodicity to the elimination rate, the rate being faster in the morning. In infants and children, the volume of distribution and clearance are greater than in adults. Androgens, cimetidine, danazol, erythromycin, ketoconazole, and miconazole each slows the elimination rate and increases plasma levels. Trough plasma levels should be monitored as should be renal function, because many treatment failures result from low concentrations.

CYTARABINE

2(1*H*)-Pyrimidinone, 4-amino-1-β-D-arabinofuranosyl- Cytosine Arabinoside; Cytarabine; Cytosar-U; DepoCyt; Alexan; Arabitin; Aracytin; Aracytine; Citarabina; Iretin; Laracit; Novumtrax; Udicil; Udicil CS



1-β-D-Arabinofuranosylcytosine [147-94-4] $C_9H_{13}N_3O_5$ (243.22).

Preparation—Cytidine is reacted with fuming HNO_3 and the resulting cytidine 2′,3′,5′-trinitrate is boiled in alcohol containing dilute alkali hydroxide to form the inverted 2′-hydroxy compound. Remaining nitrate groups are removed by means of saponification. *CA* 1971; 75:130077q.

Description—White to off-white, odorless, crystalline powder; nonhygroscopic and stable at 40°; melts about 216°.

Solubility—1 g in 5 mL water, 500 mL alcohol, 1000 mL chloroform, or 300 mL methanol.

Comments—A pyrimidine nucleoside antimetabolite that is cytotoxic to a number of cell types. Incorporation of the nucleotidase into DNA inhibits polymerization by termination of strand synthesis. It is S-phase specific. It is approved for use in *acute lymphocytic leukemia.* It is a component of first-choice combinations to treat both *acute* and *chronic myeloblastic leukemias* and *non-Hodgkin's* and *Burkitt's lymphomas.* By the intraventricular route, it is the first alternate to methotrexate to treat *leukemic metastases in the CNS* and also other meningeal soft-tissue metastases. With other drugs it shares alternative-drug status for treatment of *acute lymphocytic leukemia* and *diffuse histiocytic lymphoma.* There does not appear to be cross refractoriness to mercaptopurine, methotrexate, or prednisone. By constant intravenous infusion, or with frequent low doses, it is also effective in the treatment of *preleukemic syndromes.*

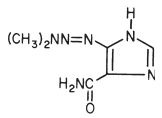
This drug is not absorbed sufficiently orally to be maximally effective by this route. Oral bioavailability is less than 0.2. However, it does penetrate into the cerebrospinal fluid and reaches a concentration of as much as 40% of that in plasma. Conversely, intrathecal administration can result in systemic toxicity. In the body, 90% is destroyed by deamination; the plasma elimination half-life is 1 to 3 hr. The elimination half-life in the cerebrospinal fluid is approximately 3.5 hr. Because detoxification takes place throughout the body, the drug may be given in the presence of renal impairment, but the dose should be reduced in hepatic failure.

The primary adverse effects are leukopenia (66%), thrombocytopenia (62%), and, less frequently, anemia and megaloblastosis, which are actually closely related to the therapeutic response and hence, are essentially unavoidable. Bone-marrow depression is more severe when the drug is given in high-dose regimens (15 times the usual dose) and by continuous intravenous infusion than by single injection. However, there are indications that with low rates of infusion an antineoplastic effect can be achieved without serious immunosuppression.

Other side effects are nausea, vomiting (especially after intravenous administration), diarrhea, aphthous ulceration, abdominal pain and bowel necrosis, esophagitis, chest pain, thrombophlebitis at the site of injection, neuritis, arthalgias, flushing, rash, alopecia, sepsis, and teratogenicity. Liver damage may occur. It should be given cautiously and in reduced doses to patients who have liver impairment or bone-marrow depression. It must not be given in combination with methotrexate. Leukocyte and platelet counts should be made daily during the initial course of treatment and at regular intervals during maintenance. High-dose treatment may cause serious neurotoxicity (in peripheral nerves, mood, ideation, memory, cerebellum, and seizures) and skin and ocular toxicities.

DACARBAZINE

1*H*-Imidazole-4-carboxamide, 5-(3,3-dimethyl-l-triazenyl)-, DIC; DTIC-Dome



5-(3,3-Dimethyl-l-triazeno)imidazole-4-carboxamide [4342-03-4] $C_6H_{10}N_6O$ (182.18).

Preparation—5-Diazoimidazole-4-carboxamide, obtained by reaction between 5-aminoimidazole-4-carboxamide and sodium nitrite in acid solution, is reacted with an anhydrous solution of dimethylamine in methanol at 5 to produce dacarbazine (Shealy et al. *J Org Chem* 1962; 17:2150).

Description—Colorless to ivory-colored microcrystalline powder; sensitive to light and heat; reported to melt at 205° and decompose explosively at 250° to 255°; pKa 4.42.

Solubility—Slightly soluble in water or alcohol.

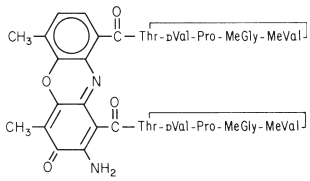
Comments—It is converted in the body to an alkylating metabolite that primarily impairs DNA. It is approved for the treatment of *metastatic malignant melanoma.* The objective response rate is approximately only 20%. It is also a component of first-choice combinations for *Hodgkin's lymphoma* [adriamycin, bleomycin, vinblastine, dacarbazine (ABVD)], and is useful in some adult soft-tissue tumors. With several drugs it shares alternative status for *islet-cell carcinoma* and *neuroblastoma.*

The most serious adverse effect is bone-marrow depression, which occasionally is fatal; leukocytes and platelets are the most affected, anemia being mild, when it occurs. Careful monitoring of leukocytes, platelets, and erythrocytes is required. If there is preexisting bone-marrow depression, or if another bone-marrow suppressant drug is in use or has been used within 4 wk, the dose must be reduced. Anorexia, nausea, and vomiting lasting 1 to 12 hr occur in more than 90% of recipients of the drug, thus aggressive antiemetic therapy is required. A flu-like syndrome accompanied by fever as high as 39° can occur; myalgia and malaise sometimes occurs approximately 1 wk after large doses and may continue for 1 to 3 wk. Facial flushing, facial paresthesias, and alopecia also have been observed. Abnormalities in liver or renal function have been reported, and the drug should be used cautiously in patients who have liver or renal damage. Extravasation of dacarbazine may cause pain and local necrosis. The drug is mutagenic and teratogenic.

It is eliminated with a terminal half-life of 5 hr. Dacarbazine requires initial activation by the cytochrome P450 system of the liver through an *N*-demethylation reaction. Approximately 50% of an intravenous dose is metabolized in the liver; by the oral route, little remains unchanged, thus making the intravenous route necessary. Approximately 40% of the drug appears unchanged in the urine within 6 hr. The unmetabolized drug is excreted in the urine by tubular secretion. The volume of distribution is larger than total body water.

DACTINOMYCIN

2-bis[Cyclo(N-methyl-L-valyl-sarcosyl-L-prolyl-D-valyl-L-threonyl)]-1,9 dimethyl-4,6 3H-phenoxazinone; Dactinomycin; Meractinomycin; Cosmegen; Actinomycin-D; Lyovac; Ac-De; Dacmozen



Actinomycin D [50-76-0]; $C_{62}H_{86}N_{12}O_{16}$ (1255.43).

Caution—Handle with exceptional care, to prevent inhaling particles of it and exposing the skin to it.

Preparation—Elaborated during the culture of *Streptomyces parvulus.* After extracting from the fermentation broth, it is purified through chromatographic and crystallization processes. US Pat 2,378,876.

Description—Bright-red crystalline powder; light sensitive and should be protected appropriately; should be protected from excessive heat and moisture; melts about 246° with the decomposition; contains in each milligram an amount of antibiotic activity of not less than 900 μg of dactinomycin.

Solubility—1 g in approximately 8 mL alcohol, 25 mL water (at 10°), 1000 mL water (at 37°), or approximately 1666 mL ether.

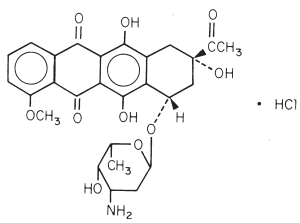
Comments—An antineoplastic drug that inhibits DNA-dependent RNA polymerase, approved for use in *Wilms' tumor, rhabdomyosarcoma, Ewing's sarcoma*, and *carcinoma of the testis and the uterus.* It is a component of first-choice combinations for treatment of *choriocarcinoma, embryonal rhabdomyosarcoma,* and *Wilms' tumor.* Tumors that fail to respond to systemic treatment sometimes respond to local perfusion. Dactinomycin potentiates radiotherapy (*radiation recall*) and is a secondary immunosuppressive.

Nausea and vomiting are usual and occur within the first few hours after administration of dactinomycin and require antiemetic therapy. Anorexia, abdominal pain, diarrhea, proctitis, and GI ulceration follow. The patient also may experience malaise, fatigue, lethargy, myalgia, and fever. Cheilitis, ulcerative stomatitis, pharyngitis, esophagitis, and proctitis are common. Because agranulocytosis, leukopenia, pancytopenia, thrombocytopenia, and anemia frequently occur, and *must be monitored closely.* Cutaneous eruptions, alopecia, hyperpigmentation, and erythema also occur. Anaphylaxis has been reported. Side effects appear to be reversible. The drug is toxic locally, and phlebitis and cellulitis may occur at the site of injection; extravasation may cause serious local tissue damage. Venous thrombosis also may result from local effects.

Half of the dose is excreted intact into the bile and 10% into the urine; the half-life is approximately 36 hr. The drug does not pass the blood–brain barrier.

DAUNORUBICIN HYDROCHLORIDE

5,12-Naphthacenedione, (8*S-cis*)-8-acetyl-10-[(3-amino-2,3,6-trideoxy-α-L-*lyxo*-hexanopyranosyl)oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-10-methoxy-, hydrochloride; Cerubidine; Daunomycin HCl; Daunoblastin; Daunoblastina; Rubilem; Trixilem



[23541-50-6] $C_{27}H_{29}NO_{10}.HCl$ (563.99).

Preparation—An antibiotic produced by *S peuceticus* or *S coeruleorubidus.*

Description—Red needles decomposing about 190°; pH (aqueous solution containing 5 mg/mL) 4.5 to 6.5.

Comments—Intercalates into DNA, inhibits topoisomerase II, produces oxygen radicals, and inhibits DNA synthesis. It can prevent cell division in doses that do not interfere with nucleic acid synthesis.

It is approved for use in acute *nonlymphocytic leukemia* in adults and for *acute lymphocytic leukemia* in adults and in children. In combination with other drugs it is included in the first-choice chemotherapy of *acute myelocytic leukemia* in adults (for induction of remission), *acute lymphocytic leukemia,* and the *acute phase of chronic myelocytic leukemia.* The drug is not given as a single agent.

Acutely, it causes nausea, vomiting and fever; rarely, it causes convulsions, cardiac dysrhythmias, S-T depression, and pulmonary edema; occasionally, it is fatal. Phlebitis at the site of injection or tissue necrosis from extravasation may occur. It also colors the urine red for 1 to 2 days. Delayed toxicity includes frequent bone-marrow depression (with leukopenia and thrombocytopenia), which may be severe, and a dose-limiting, irreversible congestive heart failure (CHF). Other toxicities include stomatitis and aphthous ulceration, anorexia, hemorrhagic mucositis enterocolitis, abdominal pain, fever, rashes, usually reversible alopecia (80% of recipients), renal tubular damage, and hematuria. Cardiotoxicity also may be delayed. Rhythm disturbances are not related to cumulative dose, but a late CHF is frequent when the cumulative dose exceeds 550 mg/m^2. The onset of failure may occur as long as 1 to 6 months after discontinuation of treatment. Daunorubicin is teratogenic, mutagenic, and carcinogenic. Monitoring of blood-cell counts, renal function, and electrocardiogram (ECG) is required.

Oral absorption is poor, and it must be given intravenously. The half-life of distribution is 45 min and of elimination, approximately 19 hr. The half-life of its active metabolite, daunorubicinol, is approximately 27 hr. Daunorubicin is metabolized mostly in the liver and also secreted into the bile (ca 40%). Dosage must be reduced in liver or renal insufficiencies.

DAUNORUBICIN CITRATE LIPOSOMAL

DaunoXome

Preparation—See *Stealth Liposomes*, D Lasic & F Martin, CRC Press, Boca Raton, FL, 1995.

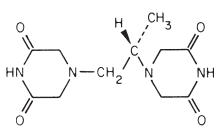
Description—*Daunorubicin*, as the citrate salt, encapsulated in liposomes.

Comments—A liposomal preparation formulated to maximize the delivery and selectivity of daunorubicin to solid tumors *in situ.* Indicated as a first line cytotoxic therapy for advanced HIV-associated Kaposi's sarcoma. While in the circulation, the liposome formulation protects the drug from chemical and enzymatic degradation, minimizes protein binding, and generally decreases uptake by normal (non-reticuloendothelial system) tissues. Increased cytoctoxicity may also be due to increased permeability of the tumor neovasculature to some particles in the size range of daunorubicin citrate liposome. Once within the tumor environment, daunorubicin is released over time enabling it to exert its antineoplastic activity. Liposomal encapsulation substantially affects the functional properties relative to those of the unencapsulated drug.

Primary toxicities of daunorubicin citrate liposome are myelosuppression, mainly of the granulocytes (which may be severe), and cardiac toxicity, which is usually cardiomyopathy associated with a decrease of the left ventricular ejection fraction (LVEF). Measurement of LVEF should be performed at total cumulative doses of 320 mg/m^2, 480 mg/m^2 and every 240 mg/m^2 thereafter. A triad of back pain, flushing, and chest tightness has been reported in 13.8% of the patients (16/116) treated in the randomized clinical trial and in 2.7% of treatment cycles (27/994). Dosage should be reduced in patients with impaired hepatic function. Pharmacokinetics of liposomal daunorubicin differs significantly from conventional daunorubicin hydrochloride. The liposomal form has has smaller steady-state volume of distribution 6.4 L and clearance of 17 ml/min. These differences result in a higher daunorubicin exposure (in terms of plasma AUC) from the liposomal form. The apparent elimination half-life of daunorubicin citrate liposome is 4.4 hours.

DEXRAZOXANE

2,6-Piperazinedione, (*S*)-4,4′-(1-methyl-1,2-ethanediyl)bis-, Zinecard, Razoxin



[24584-09-6] $C_{11}H_{16}N_4O_4$ (268.27).

Preparation—The *S*-isomer of propane-1,2-diamine is treated with excess chloroacetic acid to yield the tetra-carboxymethyl derivative, which is cyclized with formamide at each pair of acetic acid fragments to form a bis-imide (2,6-piperazinedione), the title product. US Pat 3,941,791 (1976).

Description—White crystals that melt at approximately 194°. Octanol-water partition coefficient 0.025; pK_a 2.1.

Solubility—In milligrams per milliliter: water, 10 to 12; 0.1 *N* HCl, 35 to 43; 0.1 *N* NaOH, 25 to 34; 10% alcohol, 6.7 to 10; methanol, 1; 0.1 *M* citrate buffer pH 4, 9.7 to 14.5; 0.1 *M* borate buffer pH 9, 8.7 to 13. Practically insoluble in nonpolar organic solvents. If the pH is greater than 7, it rapidly degrades.

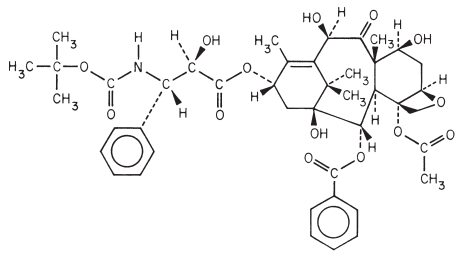
Comments—Approved for reduction of the incidence or severity of cardiomyopathy associated with doxorubicin use in women who have breast cancer and whose total doxorubicin dose has reached 300 mg/m^2. It is a cyclic ethylenediamine tetra-acetic acid (EDTA) derivative that penetrates cell membranes. Intracellularly, the ring opens and it chelated iron, thereby interfering with the free-radical generation that contributes to doxorubicin cardiomyopathy.

Peak plasma concentrations are reached 15 to 30 min after a 15-min infusion of a 500-mg/m^2 dose. It is not bound to plasma proteins, and approximately 42% of the above dose is cleared in the urine. When started with the seventh course of 5-FU, adriamycin, cyclophosphamide (FAC) therapy in patients continuing the therapy, it reduced the incidence of CHF from 22% to 3%. In other studies, it was shown to reduce loss of cardiac function and the risk of heart attack.

It may add to the myelosuppressive action of anticancer regimens. Evidence also exists that this drug will reduce the efficacy of FAC therapy if used too early. It should be used only in patients who have received a cumulative dose of 300 mg/m^2. The recommended dosage ratio of dexrazoxane:doxorubicin is 10:1 (eg, 500 mg/m$_2$ dexrazoxane:50 mg/m$_2$ doxorubicin) given by slow IV push or IV infusion. Proper administration is required for maximum protective effect. After completing the infusion of dexrazoxane, and prior to a total elapsed time of 30 minutes (from the beginning of the dexrazoxane infusion), the IV injection of doxorubicin should be given.

DOCETAXEL

(2*R*,3*S*)-*N*-Carboxy-3-phenylisoserine, *N*-*tert*-butyl ester, 13-ester with 5β,20-epoxy-1,2α,4,7β,10β,13α-hexahydroxytax-11-en-9-one 4-acetate-2-benzoate; Taxotere; Daxotel; Dexotel; Oncodocel



[114977-28-5] $C_{43}H_{53}NO_{14}$ (807.89).

Preparation—Complex synthesis with a precursor obtained from the needles of the yew plant. US Pat 4,814,470 (1989); *J Org Chem* 1991; 56:6939.

Description—White to off-white powder that melts about 232°.

Solubility—Practically insoluble in water; highly lipophilic.

Comments—Active as a single agent for treatment of locally advanced or metastatic breast cancer after failing anthracycline-based therapy or in locally advanced or metastatic non-small lung cancer failing platinum-based chemotherapy. It induced clinical response in approximately 45% of patients who had advanced breast cancer and who progressed after anthracycline treatment with approximately 2% complete responses. Also approved combined with cisplatin as first-line therapy for unresectable, locally advanced or metastatic non-small cell lung cancer and in combination with prednisone for hormone refractory metastatic prostate cancer. It promotes the inappropriate assembly of microtubules and prevents their disassembly. Cells experiencing this, arrest in mitosis.

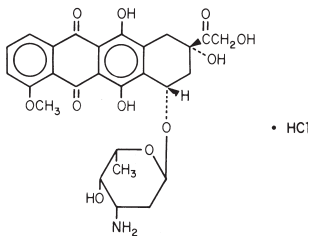
After a 1-hr infusion, its distribution is characterized by three compartments with half-lives of 4 min, 36 min, and 11.1 hr. In the blood, it is approximately 94% protein bound. Approximately 80% of an administered dose is excreted after 1 wk, with approximately 75% appearing in the feces. The excreted drug is primarily the major metabolite that is produced by cytochrome P-450 oxidation of the tertbutyl ester group. In patients who have moderate hepatic impairment, total clearance of the drug reduced 27%, increasing the AUC 38%.

Neutropenia is the major toxicity and occurs in virtually every patient. Deaths due to sepsis are the most common drug-related lethality,

as high as 11% in patients who have abnormal liver function. Frequent monitoring of blood counts is essential so that doses can be adjusted. The drug should not be administered to patients who have neutrophil counts less than 1500/mm^3. Deaths due to thrombocytopenia and bleeding were seen in patients who had severe liver function impairment. Pain, paresthesia, and asthenia are reported frequently, and nausea and vomiting is mild to moderate. Hypersensivity reactions (characterized by hypotension and/or bronchospasm, or generalized rash/-erythema) and severe fluid retention may occur; therefore, all patients require a 3 to 5-day dexamethasone regimen beginning one day prior to initiation of therapy.

DOXORUBICIN HYDROCHLORIDE

5,12-Naphthacenedione, (8*S-cis*)-10-[(3-amino-2,3,6-trideoxy-α-L-*lyxo*-hexopyransoyl)oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(hydroxyacetyl)-1-methoxy-, hydrochloride; Hydroxydaunorubicin Hydrochloride; Adriamycin; Rubex; Doxorubicin



14-Hydroxydaunorubicin hydrochloride [25316-40-9] $C_{27}H_{29}NO_{11}$.HCl (579.99).

Preparation—An anthracycline antibiotic isolated from cultures of *Streptomyces peucetius var caesius* (US Pat 3,590,028). It differs from *Daunorubicin* only in having a hydroxyacetyl group in place of the acetyl group in daunorubicin, in position 8.

Description—Red-orange, crystalline powder; almost odorless; hygroscopic; melts about 205° with decomposition; pKa 8.22.

Solubility—1 g dissolves in approximately 10 mL water or approximately 2000 mL alcohol.

Comments—Approved for use in *acute lymphoblastic* and *myeloblastic leukemias; Hodgkin's* and *non-Hodgkin's lymphomas; Wilms' tumor; neuroblastoma; sarcomas,* and *breast, ovarian, transitional cell, bronchogenic, gastric,* and *thyroid carcinomas.* It has the widest anti neoplastic spectrum and usefulness of the antineoplastic drugs. It intercalates the base pairs of the DNA double helix, thus inhibiting nucleic acid synthesis, inhibiting topoisomerase II and produceing oxygen radicals. Administered alone, it is the drug of first choice for the treatment of *thyroid adenoma* and *primary hepatocellular carcinoma.* It is a component of 31 first-choice combinations for the treatment of *ovarian, endometrial,* and *breast tumors; bronchogenic oat-cell carcinoma, non-small-cell lung carcinoma; gastric adenocarcinoma; retinoblastoma; neuroblastoma; mycosis fungoides; pancreatic carcinoma; prostatic carcinoma; bladder carcinoma; myeloma; diffuse histiocytic lymphoma; Wilms' tumor; Hodgkin's disease; adrenal tumors; osteogenic sarcoma; soft-tissue sarcoma; Ewing's sarcoma; rhabdomyosarcoma;* and *acute lymhocytic leukemia.* It is an alternative drug for the treatment of *islet cell, cervical, testicular,* and *adrenocortical cancer.* It is also an immunosuppressant, but its status remains to be determined. Tumor resistance to this drug may be suppressed by verapamil.

There is a high incidence of bone-marrow depression, which manifests itself mainly as a neutropenia that is most severe 10 to 14 days after treatment and lasts approximately 7 days; a white-cell count as low as 1000/mm^3 is to be expected. Monitoring of leukocytes and erythrocytes and signs of intercurrent infection is mandatory. Other frequent adverse effects are nausea and vomiting and reversible alopecia. Stomatitis and esophagitis may occur 5 to 10 days after treatment. Anorexia and diarrhea occur occasionally. Rarely, there may be hypersensitivity (fever, chills, urticaria), hyperpigmentation of the nails, lacrimation, conjunctivitis, and recurrence of skin reactions caused by previous radiotherapy. Hyperuricemia from rapid lysis of neoplastic cells may occur.

A serious toxicity is acute left-ventricular irreversible cardiomyopathy, which may be treated with digitalis. An early change in ECG patterns is not prodromal of the more serious CHF. This cardiotoxicity is most likely to occur with patients in whom the cumulated dose is 550 mg/m^2. Prior radiotherapy to the chest, concomitant cyclophasphamide therapy, or hyperthermia may cause the cardiomyopathy to occur with a total dose as low as 400 mg/m^2. Antineoplastic activity has been dissociated from cardiotoxicity in certain chemical congeners that may eventually replace this drug. Toxicity appears to result from oxidant and free-radical metabolites. Certain antioxidants, such as dexrazoxane (ICRF-187), protect against cardiotoxicity.

It is locally toxic and causes venous streaking, and extravasation results in pain, cellulitis, and sloughing. Its natural color may cause the urine and other body secretions to be red. It may potentiate hemorrhagic cystitis caused by cyclophosphamide, mucositis by radiotherapy, hepatotoxicity by 6-MP and the bone-marrow depressant actions of other antineoplastic drugs.

It is absorbed poorly and must be administered intravenously. The pharmacokinetics are multicompartmental. Distribution phases have half-lives of 12 min and 3.3 hr. The elimination half-life is approximately 30 hr. Forty to 50% is secreted into the bile. Most of the remainder is metabolized in the liver, partly to an active metabolite (doxorubicinol), but a few percent is excreted into the urine. In the presence of liver impairment, the dose should be reduced.

DOXORUBICIN HYDROCHLORIDE LIPOSOMAL

Doxil

Preparation—See *Stealth Liposomes*, D Lasic & F Martin, CRC Press, Boca Raton, FL, 1995.

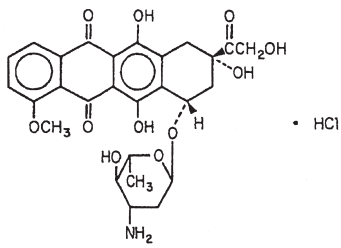
Description—*Doxorubicin hydrochloride* encapsulated in liposomes.

Comments—A liposomal coated core of doxorubicin coated with a polyethylene glycol derivative. The polymer coating masks recognition by the reticuloendothelial cells, resulting in increased blood circulation time and half-life. Active for AIDS-related Kaposi's sarcoma in patients with disease that has progressed on prior therapy or who are intolerant to therapy. Also indicated for treatment of metastatic ovarian cancer refractory to paclitaxel and platinum-based therapy.

Adverse reactions are similar to doxorubicin. Dose limiting effect is severe myelosuppression. Palmar-plantar erythrodysesthesia is cumulative and consists of painful red palms and soles progressing to ulceration if doses are not reduced. Acute infusion-related reactions (flushing, shortness of breath, facial swelling, headache, chills, back pain, tightness in the chest or throat, and/or hypotension) have occurred in up to 10% of treated patients. Cardiomyopathy may be lessened, but not eliminated. Dosage must be reduced with impaired hepatic function.

EPIRUBUCIN HYDROCHLORIDE

5,12-Naphthacenedione, 10-[3-amino-2,3,6-trideoxy-α-L-*ara-bino*-exopyranosyl)oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(hydroxyacetyl)-1-methoxy-, hydrochloride; Ellence, Pharmorubicin



[56390-09-1] $C_{27}H_{29}NO_{11}$.HCl (579.98).

Preparation—*J Med Chem*, 1977; 18:703 and US Pat 4,058,519 (1977).

Description—Orange-red solid melting about 185° (dec). $[\alpha]^{20}{}_D$ + 274° (c = 0.01, methanol). It is the 4′-epimer of doxorubicin.

Solubility—Solutions are light sensitive.

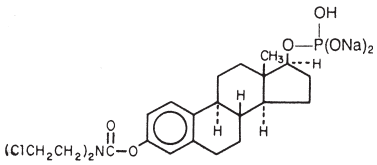
Comments—Anthracycline agent that forms a complex with DNA by intercalation between base pairs triggering DNA cleavage by topoisomerase II, thus causing inhibition of DNA and protein synthesis. Indicated as a component of adjuvant therapy in patients with evidence of axillary node tumor involvement following resection of primary breast cancer. Also shown to be effective in the treatment of small cell lung cancer, non-small cell lung cancer, non-Hodgkin's lymphoma, Hodgkin's disease, gastric cancer, bladder cancer, ovarian cancer, prostatic cancer, and primary hepatocelluar carcinoma.

Extensively and rapidly metabolized by the liver; dosage adjustments required with liver or severe renal impairment. Primary dose limiting toxicity consists of dose-dependent, reversible leukopenia and/or neutropenia, with nadir reached 10 to 14 days from drug administration. Other adverse effects include acute (sinus tachycardia and/or ECG abnormalities) or delayed cardiotoxicity (decreased left ventricular ejection fraction and/or signs and symptoms of congestive heart failure). Life-threatening cardiotoxicity is dependent on the cumulative dose of epirubicin, and usually occurs late in therapy or within 2 to 3 months after completion of treatment. The estimated risk of epirubicin-treated patients developing clinically evident CHF was 0.9% at a cumulative

dose of 550 mg/m^2, 1.6% at 700 mg/m^2, and 3.3% at 900 mg/m^2. The risk increases steeply after 900 mg/m^2. Other adverse effects include hair loss, nausea, vomiting, diarrhea, mouth sores.

ESTRAMUSTINE PHOSPHATE SODIUM

Estra-1,3,5(10)-triene-3,17-diol(17β), 3-[bis(2-chloroethyl)carbamate] 17-, (dihydrogen phosphate), disodium salt; Emcyt; Estracyte



[52205-73-9] $C_{23}H_{30}Cl_2NNa_2O_6P$ (564.35).

Preparation—A compound of estradiol with a nitrogen mustard moiety.

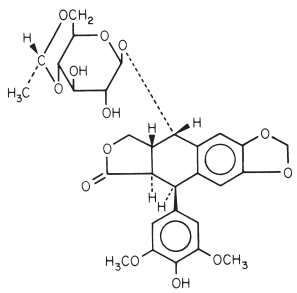
Description—Off-white powder.

Solubility—Freely soluble in water or in methanol; slightly soluble in chloroform or in anhydrous ethanol; pH of 0.5% solution, 8.5 to 10.

Comments—An alkylating agent that is approved for metastatic and/or progressive cancer of the prostate, but is also active for advanced breast cancer. It causes nausea and vomiting, delayed bone-marrow depression, mild gynecomastia, perianal anesthesia, thrombophlebitis, occasional myocardial infarction, hypertension, hypoglycemia, and hepatotoxicity. It is nearly 75% absorbed orally and metabolized in the liver. It is excreted in the urine, bile, and feces with a prolonged half-life of about 20–24 hr.

ETOPOSIDE

Vepesid, VP16



9-[(4,6-*O*-Ethylidene-β-D-glucopyranosyl)oxy]-5,8,8a,9-tetrahydro-5-(4-hydroxy-3,5-dimethoxyphenyl)furo[3′,4′:6,7]-naphtho[2,3-*d*]-1,3-dioxol-6(5a*H*)-one [33419-42-0] $C_{29}H_{32}O_{13}$ (588.56).

Preparation—A semisynthetic derivative of podophyllotoxin. See *J Med Chem* 1971, 14:936.

Description—White to yellow-brown powder; melts about 221°.

Solubility—Soluble in methanol or in chloroform; slightly soluble in ethanol; sparingly soluble in water or in ether.

Comments—Damages DNA, most likely by means of topoisomerase II cleavage, and arrests the cell cycle primarily in phase G_2, although it has some action in late S and M. It is approved for *refractory testicular tumors* and *small-cell lung cancer.* Alone, it is one of two drugs of choice for the treatment of *Kaposi's sarcoma* and one of three for *non-Hodgkin's lymphoma.* It also is a component of first-choice combinations to treat *oat-cell bronchogenic carcinoma* and *refractory disseminated germ-cell tumors.* It is an alternative drug for use against *acute lymphocytic leukemia, acute myelocytic leukemia, Hodgkin's disease, Wilms' tumor, choriocarcinoma, diffuse histiocytic lymphoma, Ewing's sarcoma, hepatocellular carcinoma, neuroblastoma, non-Hodgkin's lymphoma,* and *non-small cell bronchogenic carcinoma.*

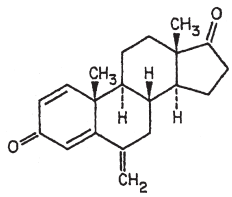
Acute adverse effects of mild nausea and vomiting, chills and fever; postural hypotension, tachycardia, palpitations, and bronchospasm occur during and after rapid intravenous infusion. Delayed toxicity includes leukopenia (60–90%), thrombocytopenia (28–41%), anemia (≤ 33%), diarrhea, fever, alopecia, rash, stomatitis, Stevens-Johnson syndrome, various other allergic responses, hepatotoxicity (3%), and peripheral neuropathy. It increases the hypoprothrombopenic affects of warfarin.

Oral absorption is 25% to 75%. In plasma, approximately 94% is protein bound, and the concentration in the cerebrospinal fluid is less than 10% of that in plasma. Distribution is slow; the initial half-life being approximately 1.5 hr. Approximately 35% is excreted unchanged in the urine and approximately 6% into bile. A hydroxyacid metabolite is excreted in the bile, and the sulfate and glucuronide metabolites are excreted in urine. The elimination half-life is 4 to 11 hr. Dosage reduction is required for elevated bilirubin or liver impairment.

ETRETINATE—page 1291.

EXEMESTANE

Androsta-1,4-diene-3,17-dione, 6-methylene-, Aromasin



[107868-30-4] $C_{20}H_{24}O_2$ (296.41).

Preparation—US Pat 3,622,841 (1987).

Description—White to slightly yellow crystalline powder melting about 190°.

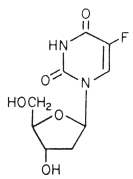
Solubility—Freely soluble in DMF; soluble in methanol; practically insoluble in water.

Comments—irreversible, selective aromatase inhibitor that acts as false substrate for aromatase converting reactive alkylating intermediates that bind covalently to the substrate binding site of the enzyme thus inactivating it. Used in the treatment of advanced breast cancer in postmenopausal women whose disease has progressed following tamoxifen therapy.

Exemestane selectively inhibits the conversion of androgens to estrogens and does not affect synthesis of adrenal corticosteroid, aldosterone, or thyroid hormone. Adverse effects include hot flushes (flashes), nausea, fatigue, increased sweating, increased appetite, excessive weight gain, and increases in liver function tests.

FLOXURIDINE

Uridine, 2′-deoxy-5-fluoro-, FUDR



[50-91-9] $C_9H_{11}FN_2O_5$ (246.19).

Preparation—*J Am Chem Soc* 1959; 81:4112.

Description—White to off-white, odorless solid; melts about 151°.

Solubility—1 g in 3 mL water, 12 mL alcohol, or more than 10,000 mL chloroform or ether; pH of 2% solution, 4.0 to 5.5.

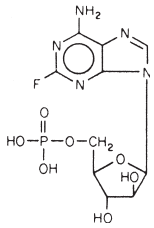
Comments—In the body it is converted into a false nucleotide that interferes with the synthesis of DNA. It also is converted to fluorouracil, so that it potentially has all the actions and uses of Fluorouracil. It is approved for *GI adenocarcinoma with metastasis to the liver.* However, currently, its use is restricted to regional intraarterial infusion of carcinomas that are judged incurable by surgery or other chemotherapy, mainly *colorectal cancer metastatic to the liver* and *hepatocellular carcinoma.* In these uses, it does not appear to be superior to fluorouracil.

The most frequent adverse effects are nausea, vomiting, diarrhea, enteritis, localized erythema along the course of infused artery, leukopenia, and elevation in serum transaminase, alkaline phosphatase, bilirubin, and lactic dehydrogenase. Other effects are abdominal cramps, anorexia, duodenal ulcer, duodenitis, gastroenteritis, pharyngitis, glossitis, gastritis, alopecia, dermititis, hyperpigmentation, edema, peeling of the skin, pruritus, various rashes and skin ulceration, abscesses, ataxia, blurred vision, convulsions, depression, hemiplegia, hiccoughs, lethargy, nystagmus, malaise, pain, vertigo, asthenia, dysuria, fever, hypoadrenalism, thrombocytopenia, prothrombinopenia, hypoproteinemia, and aberrations in the sedimentation rate and BSP test.

It is contraindicated in patients who have cachexia, potentially serious infections, or bone-marrow depression. The drug is metabolized mainly in the body, but some is excreted unchanged in the urine.

FLUDARABINE PHOSPHATE

9*H*-Purin-6-amine, 2-fluoro-9-(5-*O*-phosphono-β-D-arabinofuranosyl)-, Fludara



[75607-67-9] $C_{10}H_{13}FN_5O_7P$ (365.21).

Preparation—US Pat 4,357,324.

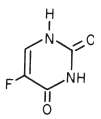
Description—White powder.

Solubility—Soluble in water.

Comments—Supplied as the monophosphate but is rapidly dephosphorylated *in vivo* to yield the free nucleoside that is actively transported into susceptible cells. Once rephosphorylated and part of the nucleotide pool of the cell, fludarabine is a potent inhibitor of DNA and RNA synthesis, by inhibition of many enzymes involved in nucleic acid synthesis. The synthesis of DNA appears to be inhibited at lower intracellular concentrations of fludarabine nucleotides. Fludarabine is approved for use in *chronic lymphocytic leukemia* that has proved refractory to at least one alkylating agent. It also has activity against *Hodgkin's* and *non-Hodgkin's lymphomas, mycosis fungoides,* and *macroglobulinemia.* Fludarabine, administered IV, has a short initial half-live of approximately 80 min. The most severe adverse effects involve a CNS syndrome and suppression of the hematopoietic system. The CNS syndrome includes a delayed blindness, coma, and death that appear at high doses. This syndrome is rare in patients receiving the recommended dose for chronic lymphocytic leukemia. Severe bone-marrow suppression results in decreased counts of neutrophil (< 500/μl in 59% of patients), hematocrit, and platelets in 50 to 60% of patients. The myelosuppression may be cumulative. It also is reported to cause pulmonary dysfunction, skin rashes, and pruritus.

FLUOROURACIL

2,4(1*H*,3*H*)-Pyrimidinedione, 5-fluoro-, 5-FU; Adrucil; Efudex; Fluoroplex



5-Fluorouracil [51-21-8] $C_4H_3FN_2O_2$ (130.08).

Preparation—Potassium fluoroacetate is reacted with methyl bromide to form methyl fluoroacetate that is then subjected to a Claisen condensation with methyl formate and sodium ethoxide to produce the potassium enolate of the methyl ester of α-fluoromalonaldehydic acid (I). Cyclization of I is affected through condensation under anhydrous conditions with *S*-benzylisothiourea. The resulting 2-(benzylthio) compound is hydrolyzed readily in the presence of acid to form fluorouracil. US Pat 2,802,005.

Description—White to practically white, practically odorless, crystalline powder; stable when exposed to air; decomposes about 282°.

Solubility—1 g in 80 mL water, 170 mL alcohol, or 55 mL methanol; practically insoluble in chloroform, ether, or benzene; solubility in aqueous solutions increases with increasing pH.

Comments—A congener of uracil that acts both as a surrogate and as an antimetabolite of that nucleotide. Its metabolite, 5-fluorodeoxyuridine-5'-monophosphate (FUMP), blocks the synthesis of thymidylic acid and hence of deoxyribonucleic acid; it also is incorporated into RNA. Uracil is used preferentially by neoplastic tissue; thus the antimetabolite has some degree of selectivity for the neoplasm. It is approved for palliative treatment of *cancer of the colon, rectum, stomach, breast,* and *pancreas.* It is not curative, but it may bring approximately regression of a number of neoplasms. It is the antineoplastic of choice of the treatment of *colorectal cancer.*

In combination with other drugs it provides chemotherapy of first choice in the treatment of *breast cancer, islet-cell tumors, squamous cell carcinoma* of the *head* and *neck, non-small-cell carcinoma* of the *lung, pancreatic* and *gastric carcinomas, primary hepatocellular carcinoma, testicular* and *prostatic carcinomas,* and *bladder tumors.* It shares alternative-drug status for the treatment of *endometrial carcinoma; squamous cell tumors of the head, neck, and cervix; and ovarian tumors.* It may be useful in the treatment of *neoplasms of the gallbladder* and, to a lesser extent, those of the esophagus, larynx, thyroid, and pharynx. Remissions of as long as 4 yr have been noted in a few instances, although the average is a few months.

The drug also is used topically in the treatment of precancerous dermatoses, especially *actinic keratosis,* for which it is the treatment of choice if the lesions are multiple. Even lesions that are not clinically discernible respond. For this reason, the drug is applied to the entire affected area. Healing continues for 1 to 2 months after treatment. The drug does not affect nonkeratotic lesions. It is a secondary (efferent) immunosuppressive agent and therefore has not been used in organ transplantation.

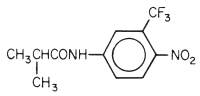
The drug is toxic, approximately two-thirds of patients showing signs of toxicity; the mortality rate is approximately 3% when treatment is initiated by daily doses. When the drug is administered by intravenous bolus, leukopenia is the principal adverse effect, usually occurring between day 7 and day 14, with a nadir at days 21 to 25. Leucocytes readily recover if the dose is lowered promptly. Thrombocytopenia is less frequent, with a nadir occurring between day 7 and day 17. Aphthous ulceration may occur or the appearance of diarrhea are signs that therapy should be discontinued temporarily. Other toxic effects include vomiting, nausea, GI ulceration (the dose-limiting effect of constant infusion), alopecia, dermatitis, hyperpigmentation, pharyngitis, esophagitis, cerebellar ataxia (sometimes irreversible), and epistaxis. Lassitude and asthenia, lasting from 12 to 35 hr after an injection, may occur; severe CNS depression may occur in patients who have familial pyrimidinemia. When the drug is administered as a continuous low-dose protracted infusion, the dose-limiting toxicity is hand-foot syndrome, which involves painful and erythematous desquamation of the palms and soles. Topically, it may induce photosensitization and always erythema, scaling, fissuring, tenderness, and usually erosion, ulceration, necrosis, and re-epithelialization as the result of the therapeutic action, although some persons appear to be resistant to this effect. The antineoplastic effect as well as the toxicities are potentiated by concomitant administration with leucovorin (folinic acid).

By the oral route, there is poor absorption and variable first-pass elimination of the drug by the gut and liver, so that intravenous administration is required. At least 60% is metabolized to CO_2, but more than 15% is excreted into the urine. The drug enters the cerebrospinal fluid and effusions. The plasma half-life is approximately 10 min, but the active metabolite, FUMP, may be detectable for days.

FLUOXYMESTERONE—page 1471.

FLUTAMIDE

Propaneamide, 2-methyl-*N*-[4-fluoro-3-(trifluoromethyl)phenyl]-, Eulexin



[13311-84-7] $C_{11}H_{11}F_3N_2O_3$ (276.21).

Preparation—See *J Med Chem* 1967; 10:93.

Description—Yellow crystals melting about 110°.

Solubility—Practically insoluble in water.

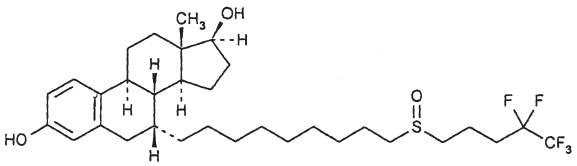
Comments—Approved for use in Stage D or metastatic prostate cancer in combination with LHRH analogs. It is a nonsteroidal antiandrogen that acts by inhibiting androgen uptake or nuclear binding at target tissues. When used with goserelin or leuprolide an radiation, in patients who have fairly advanced prostate cancer (StageB2-C), this drug significantly lowered local failure rate against radiation alone and with hormonal therapy reduced distant metastasis from 36% to 16%; it also increased disease-free survival time in patients receiving complete hormone therapy to 4.4 yr versus 2.6 yr for those receiving radiation alone.

It is absorbed rapidly and completely when taken orally; it is also metabolized rapidly. The major plasma metabolite is the pharmacologically active alpha hydroxylate, which accounts for 23% of the dose 1 hr after administration. The half-life of this metabolite is approximately 6 hr in normal healthy volunteers, approximately 9 hr at steady state in the elderly. The drug itself accounts for approximately only 2.5% of the drug in plasma 1 hr after administration. Both flutamide and the alpha hydroxylate are >90% plasma protein bound. In patients who have renal impairment, the half-life of the major metabolite was slightly prolonged.

Hepatotoxicity has been noted with the use of flutamide, and hepatic function should be monitored. Treatment should be discontinued if serum transaminase levels exceed 2 or 3 times the normal upper limit. Likewise, methemoglobinemia, hemolytic anemia, and cholestatic jaundice have been noted. Malignant breast neoplasms and gynecomastia have occurred in male patients taking drug. Urine discoloration and photosensitivity also occur with drug intake.

FULVESTRANT

Estra-1,3,5(10)-triene-3,17-diol, (7α,17β)-7-[9-[(4,4,5,5,5-pentafluoropentyl)sulfinyl]nonyl]-, Faslodex



129453-61-8] $C_{32}H_{47}F_5O_3S$ (606.77).

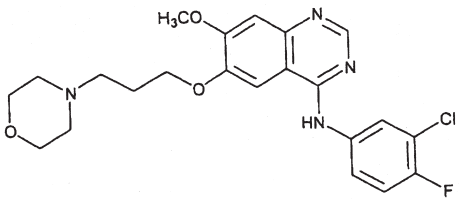
Preparation—*J Med Chem*, 1991; 34:1624-30.

Description—White powder.

Comments—an estrogen antagonist without known agonist effects that competitively binds to and downregulates estrogen receptors in human breast cancer cells. It inhibits the growth of tamoxifen-resistant as well as estrogen-sensitive human breast cancer (MCF-7) cell lines in vitro and in vivo. It does not appear to exhibit peripheral steroidal effects as there are no changes in concentrations of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) in post-menopausal women receiving 250 mg of fulvestrant IM monthly. Peak plasma concentrations of fulvestrant are attained approximately 7 days after IM administration and persist for at least 1 month. Steady-state plasma fulvestrant concentrations usually are achieved within 3 to 6 months after administration of once-monthly IM injections. The drug is approximately 99% bound to plasma proteins and is extensively metabolized in the liver with an elimination half-life of about 40 days. Metabolism of fulvestrant appears to involve a combination of various biotransformation pathways (eg, oxidation, aromatic hydroxylation, conjugation), but it does not appear to substantially inhibit any of the major cytochrome P-450 (CYP) isoenzymes, including 1A2, 2C9, 2C19, 2D6, and 3A4 in vitro. Main side effects include gastrointestinal effects, headache, back pain, vasodilation (hot flushes), and pharyngitis.

GEFITINIB

Quinazolinamine, *N*-(3-chloro-4-fluorophenyl)-7-meth-oxy-6-[3-(4-morpholinyl)propoxy]-, Iressa



[184475-35-2] $C_{22}H_{24}ClFN_4O_3$ (446.91).

Preparation—*J Med Chem* 2002; 45:3772 and *J Med Chem* 1999; 42:1803.

Description—White to off-white powder; pK_{a1} 5.4; pK_{a2} 7.2.

Solubility—Freely soluble in glacial acetic acid or DMSO; soluble in pyridine; sparingly soluble in THF; slightly in methanol, anhydrous alcohol, 2-propanol or aceetonitrile.

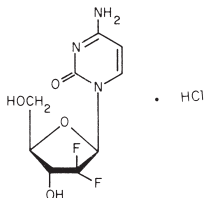
Solubility—Sparingly soluble at pH1, almost insoluble above pH 7, with solubility dropping sharply between pH 4 and pH 6. In nonaqueous solvents, gefitinib is freely soluble in glacial acetic acid and dimethylsulphoxide, soluble in pyridine, sparingly soluble in tetrahydrofuran, and slightly soluble in methanol, ethanol (99.5%), ethyl acetate, propan-2-ol and acetonitrile.

Comments—An inhibitor of epidermal growth factor receptor (EGFR) tyrosine kinase . Effective orally as monotherapy in patients with locally advanced or metastatic non-small cell lung cancer in patients failing platinum-based and docetaxel regimens. Inhibits the intracellular phosphorylation of numerous tyrosine kinases associated with transmembrane cell surface receptors, including the tyrosine kinases associated with the EGFR (which are expressed on cell surfaces on normal cells and cancer cells). Activation of EGFR tyrosine kinase appears to initiate a cascade of intracellular signaling events leading to cell proliferation and influencing processes critical to cell survival and tumor progression (eg, angiogenesis, apoptosis, metastasis); however, the precise mechanism of antineoplastic activity of gefitinib has not been fully elucidated. Undergoes extensive hepatic metabolism, mainly by CYP3A4. If used concomitantly with potent cytochrome P-450 (CYP) isoenzyme 3A4 inducers (eg, rifampin, phenytoin), the dosage of gefitinib must be increased.

Adverse effects occurring in 5% or more of patients receiving gefitinib (250 mg once daily) during clinical trials include diarrhea, rash, acne, dry skin, nausea, vomiting, pruritus, anorexia, and asthenia. Gefitinib-associated pulmonary toxicity has been described as interstitial pneumonia, pneumonitis, and alveolitis at an incidence of 1%.

GEMCITABINE HYDROCHLORIDE

Cytidine, 2′-deoxy-2′,2′-difluoro-, monohydrochloride; Gemzar



[122111-03-9] $C_9H_{11}F_2N_3O_4.HCl$ (299.66).

Preparation—The acetonide of 2,3-dihydroxypropanal (chiron—from mannitol) undergoes a Reformatsky reaction with ethyl 2,2-dibromo-2-fluoroacetate to yield the classic alcohol product, which is then benzylated to protect the generated OH group. Treatment with acid removes the acetonide group and the resulting diol forms a lactone with the γ-OH function. The free OH is benzylated (protection) and the lactone carbonyl reduced to form a mixture of isomers of 3,3-difluoro-4,5-di(benzyloxy)-2-furanol and the free OH is converted to a mesyl ester (**I**) with methanesulfonyl chloride and base. Cysteine is reacted with trimethylsilyl chloride to silylate the hydroxyl and amino groups (**II**). Compound **I** reacts with **II,** accompanied by loss of the mesyl group and, after removal of the benzyloxy groups with ammonia, yields the title compound.

Description—White to off-white powder that melts about 290° (dec).

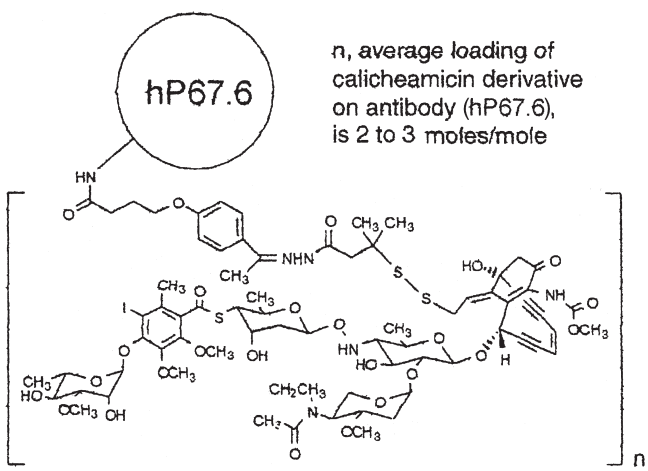
Solubility—Soluble in water; slightly soluble in methanol; practically insoluble in ethanol or in polar organic solvents.

Comments—Indicated as first-line treatment for Stage II or above adenocarcinoma of the pancreas or in patients previously treated with 5-FU. Also active for colon cancer and in combination with cisplatin for the first-line treatment of inoperable, locally advanced or metastatic non-small cell lung cancer. After uptake into the cellular phosphoneucleotide pool, its triphosphate salt serves as a substrate for DNA polymerase but results in inhibition of DNA strand elongation. Clinical trials have shown that this drug yielded significant improvement over 5-FU for previously untreated pancreatic cancer, both with respect to time to disease progression and survival. The volume of distribution increases with duration of infusion, indicating that shorter infusions do not reach maximal distribution. It is eliminated by the kidneys, with no drug accumulating after weekly dosing.

Nausea and vomiting are relatively common adverse reactions, although myelosuppression is dose-limiting toxicity. Approximately 19% of patients required red-blood-cell (RBC) transfusions, and 16% suffered mild hemorrhage. Dyspnea was reported in 235 of the patients.

GEMTUZUMAB OZOGAMICIN

Mylotarg



[220578-59-6]

Preparation—Isolated from the fermentation of *Micromonospora echinospora* ssp. *calichensis.*

Description—A recombinant humanized IgG4 kappa antibody conjugated with a cytotoxic antitumor antibiotic, calicheamicin. Drug product is light sensitive and solutions should be protected from UV light. The drug product is a sterile, white, preservative-free lyophilized powder.

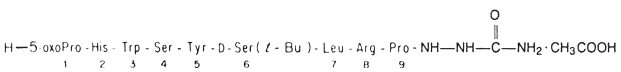
Comments—Recombinant DNA-derived humanized anti-CD33 monoclonal antibody. Effective for the treatment of patients with CD33-positive acute myeloid leukemia (AML) in first relapse who are 60 years of age or older and who are not considered candidates for other cytotoxic chemotherapy. The antibody component is an IgG_4 kappa immunoglobulin that is conjugated with the cytotoxic antitumor antibiotic calicheamicin. It binds specifically to antigen CD33, a sialic acid-dependent adhesion protein that is expressed on leukemic blasts in more than 80% of patients with acute myeloid leukemia (AML). Following binding, a complex is formed that is internalized by the myeloid cell. Calicheamicin is released (presumably via hydrolysis) within the lysosomes of the myeloid cell and binds to DNA in the minor groove, resulting in double strand breaks and cell death.

Severe myelosuppression (neutropenia, thrombocytopenia, anemia) occurs in all patients, with a median recovery pf neutrophils occurring 40.5 days after the first dose. Severe hypersensitivity reactions, including infrequently fatal anaphylaxis, have occurred. Acute infusion reactions, including shaking chills, fever, nausea, vomiting, headache, hypotension, hypertension, hypoxia, dyspnea, hyperglycemia, and anaphylaxis, may occur during the first 24 hours after administration. Severe adverse pulmonary events, including dyspnea, pulmonary infiltrates, pleural effusions, noncardiogenic pulmonary edema, pulmonary insufficiency and hypoxia, and acute respiratory distress syndrome, have occurred as sequelae of infusion reactions and infrequently were fatal. Severe hepatotoxicity, including hepatic veno-occlusive disease (VOD) and hepatic failure, has occurred and sometimes resulted in death.

GOLD AU—See page 367.

GOSERELIN ACETATE

Luteinizing hormone-releasing factor (pig) 6-[*O*-(1,1-dimethylethyl)-D-serine]-10-deglycinamide-, 2-(aminocarbonyl)hydrazide, acetate salt; Zoladex



[65807-02-5 (goserelin)] $C_{59}H_{84}N_{18}O_{14}.C_2H_4O_2$ (1329.48).

Preparation—*J Med Chem* 1978; 21:1018.

Description—White to off-white powder.

Solubility—Soluble in water, dilute acids, or bases; aqueous solution pH approximately 6.0.

Comments—A synthetic LHRH (GnRH) analog that acts as a potent inhibitor of pituitary gonadotropin secretion. Proliferation of prostatic cells and usually prostatic neoplastic cells are simulated by dihydortestosterone generated locally from circulating testosterone (80%); hence it is directly under the control of LH-RH/FSH/RH. Like the natural releasing hormone, treatment with this drug initially causes an acceleration of the growth of prostatic tumors; however, it later causes a decline in tumor growth rate, as a result of down regulation (densensitization) of LH-RH/FSH-RH receptors in the anterior hypophysis and androgen receptors in prostatic tumor cells. It is approved for palliative treatment of *prostatic carcinoma;* however, it is active against *estrogen receptor positive breast cancer.*

Recipients often experience an exacerbation of the cancer during the first few weeks of treatment. This results in temporarily increased bone destruction and pain in approximately 8% of cases; hypercalcemia, renal insufficiency, and urinary obstruction may occur. The concurrent use of the antiandrogen and flutamide, prevents these flareups. As downregulation develops and androgen-estrogen blood levels decline to castration levels, approximately 60% of the patients have hot flashes that gradually recede. In male patients, loss of libido and sexual dysfunction are common. Plasma levels of phosphatase and appropriate sex hormone should be monitored; hormone levels reach castration values in approximately 2 wk; and phosphatase returns to baseline levels in 4 wk.

HYDROXYPROGESTERONE CAPROATED—see RPS-19, page 1095.

HYDROXYUREA

Hydroxycarbamide; Mylocel

[127-07-1] $CH_4N_2O_2$ (76.05).

Preparation—By interaction of hydroxylamine hydrochloride and potassium cyanide.

Description—White powder; odorless; essentially tasteless; melts about 135°.

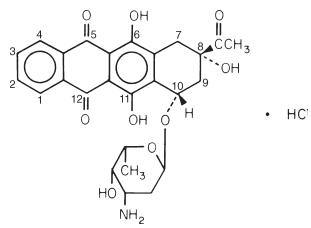
Solubility—Freely soluble in water.

Comments—Inhibits synthesis of DNA but not of RNA. It is lethal to cells in the S phase and also holds cells in the G_1 phase in which they are more sensitive to irradiation. It shares first-choice status with busulfan for the treatment of the *chronic phase* of *chronic myelocytic leukemia.* The value of either drug as a backup drug for the other may be limited by cross resistance. It sometimes is combined with radiation to treat squamous cell carcinoma of the head and neck or used alone to treat inoperable ovarian carcinoma or malignant melanoma in which it has erratic palliative actions; superior chemotherapy is retiring it from such uses. Hydroxyurea is also approved for the treatment of adult patients with sickle cell disease. The drug reduces the number of painful crises, the frequency of acute chest syndrome and hospitalization, and the need for blood transfusion

As an *immunosuppressant,* it may be used in the treatment of *psoriasis.* It appears to improve the condition of the patient in a high percentage of cases, but the quality of the response may not be as good as with some other drugs. Adverse effects include severe bone barrow suppression (leukopenia, thrombocytopenia, anemia), maculopapular rash, elevation of hepatic enzymes, and gastrointestinal toxicity (nausea, vomiting, diarrhea, mucositis).

IDARUBICIN HYDROCHLORIDE

5,12-Naphthacenedione, (7*S-cis*)-9-acetyl-7-[(3-amino-2,3,6-trideoxy-α-L-*lyxo*-hexopyranosyl)oxy]-7,8,9,10-tetrahydroxy-, hydrochloride; Idamycin; Zavedos



[57852-57-0] $C_{26}H_{27}NO_9.HCl$ (533.96).

Preparation—See US Pat 4,046,879 (1977).

Description—Orange crystals that melt about 184° (or 173°).

Comments—Approved for use with other approved drugs for the treatment of acute myelogenous leukemia (AML) in adults. Clinical trials showed it to be superior to daunorubicin when used with cytarabine in the induction and the duration of remissions in previously untreated AML. It is also active for the blast phase of chronic myelogenous leukemia and acute lymphocytic leukemia. It is a highly lipohilic synthetic anthracycline. Its cellular uptake is increased over other anthracyclines, although it shares the topoisomerase II cellular target. It exhibits high levels of tissue binding and undergoes extensive extrahepatic metabolism. Elimination is primarily by means of biliary and secondarily by means of renal excretion of the biologically active major metabolite idarubicinol (13-dehydroidarubicin). It is thought to penetrate into the cerebrospinal fluid, and both idarubicin and idarubicinol are approximately 95° bound to plasma proteins.

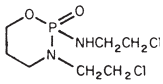
The terminal half-life of elimination for idarubicin varies widely, but averages approximately 22 hr. The half-life for elimination of idarubicinol is longer than 45 hr; thus it accumulates to higher levels than idarubicin and may contribute significantly to the therapeutic effect. Patients who have moderate levels of hepatic dysfunction exhibit elevated levels of circulating drug, so care must be taken in treating such patients. The drug should not be administered if bilirubin levels are higher than 5 mg/dL.

Myelosuppression is the major toxicity resulting from idarubicin administration; care should be taken when the drug is administered to patients who have low WBC counts or who previously have received radiation therapy. Bleeding and infection have followed therapy. Caution must be taken during administration to avoid extravasation as this agent is a tissue vesicant. Cardiotoxicity resembling CHF is common, and is the primary dose-limiting toxicity. Although difficult to predict, cardiotoxicity is associated with a decrease in left ventricular end vol-

ume. Administration necessitates close monitoring of the patient for blood counts and cardiac, renal, and hepatic function.

IFOSFAMIDE

2*H*-1,3,2-Oxazaphosphorin-2-amine, *N*,3-bis(2-chloroethyl)-tetrahydro-, 2-oxide; Ifex



[3778-73-2] $C_7H_{15}C_{12}N_2O_2P$ (261.09).

Preparation—Reaction of 3-(chloromethylamino)-1-propanol with $POCl_3$ yields the *N*-(2-chloroethyl)-*P*-chlorooxaphosphorane oxide, which with 2-chloroethylamine yields the product. US Pat 3,732,340.

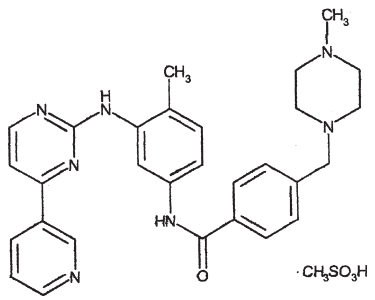
Description—White crystals that melt about 40°.

Solubility—Soluble in water.

Comments—An alkylating agent isomeric with cyclophosphamide. It is a component of a first-choice combination for the treatment of adult soft-tissue sarcomas and *testicular cancer.* It is an alternative drug for the treatment of *acute lymphocytic leukemia, acute myelocytic leukemia, breast carcinoma, Burkitt's lymphoma, colorectal carcinoma, diffuse histiocytic lymphoma, bone and soft tissue sarcoma, melanoma, non-small-cell lung carcinoma, oat-cell carcinoma, pancreatic carcinoma, testicular carcinoma, ovarian carcinoma,* and *Wilms' tumor.* Nausea and vomiting occur acutely. Delayed toxicity includes bone-marrow depression, hemorrhagic cystitis, alopecia, and a usually temporary sterility. It is converted slowly to an active metabolite, the half-life being approximately 15 hr. The active metabolites are rapidly bound to proteins. The volume of distribution is larger than that of total body water. To avoid bladder toxicity, it must be given with extensive hydration and a cytotoxic protector, such as mesna. Neurologic toxicity (lethargy, ataxia, stupor, somnolence, disorientation, seizures) occurs at a higher incidence in patients receiving high doses or with impaired renal function.

IMATINIB MESYLATE

***p*-Toluidide, α-(4-methyl)-1-piperazinyl-3′-[[4-(3-pyridyl)-2-pyrimidinyl]amino]-*p*-tolu-*p*-toluidide; Gleevec**



[152459-95-5] $C_{29}H_{31}N_7O.CH_4SO_3$ (589.71).

Preparation—*Tetr Lett*, 2001; 3: 2273 and US Pat 5,521,184 (1996).

Description—(Salt) White to off-white to brownish or yellow tinged crystalline powder; α-form melts about 226°, β-form melts about 217°. (Base) Melts about 211°; pK_{a1} 8.07, pK_{a2} 3.73, pK_{a3} 2.56, pK_{a4} 1.52.

Solubility—(Salt) Very soluble in water or aqueous buffers ≤ pH 5.5: soluble 100g/L at pH 4 and 49 mg/L at pH 7. Soluble to some extent in DMSO, methanol or ethanol; insoluble in 1-octanol, acetone or acetonitrile.

Comments—Protein-tyrosine kinase inhibitor that inhibits the Bcr-Abl tyrosine kinase, the constitutive abnormal tyrosine kinase created by the Philadelphia chromosome abnormality in chronic myeloid leukemia (CML). It inhibits proliferation and induces apoptosis in Bcr-Abl positive cell lines as well as fresh leukemic cells from Philadelphia chromosome positive chronic myeloid leukemia. Also an inhibitor of the receptor tyrosine kinases for platelet-derived growth factor (PDGF) and stem cell factor (SCF), c-kit, and inhibits PDGF- and SCF-mediated cellular events. In vitro, inhibits proliferation and induces apoptosis in gastrointestinal stromal tumor (GIST) cells, which express an activating c-kit mutation. Indicated for the treatment of newly diagnosed adult patients with Philadelphia chromosome positive CML in chronic phase, patients with Philadelphia chromosome positive CML in blast crisis, accelerated phase, or in chronic phase after failure of interferon-alpha therapy and pediatric patients with Ph^+ chronic phase CML whose disease has recurred after stem cell transplant or who are resistant to interferon alpha therapy. Also indicated for the treatment of patients with Kit (CD117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumors.

Well absorbed after oral administration (oral bioavailability 98%) with C_{max} achieved within 2 to 4 hours post-dose. Hepatic metabolism, primarily by CYP3A4, with elimination half-lives of imatinib and major active metabolite, the N-desmethyl derivative, are approximately 18 and 40 hours, respectively. Binding to plasma proteins in vitro approximately 95%, mostly to albumin and α_1-acid glycoprotein. Dosage adjustments are required with liver dysfunction. Altered metabolism may occur when administered with cytochrome P-450 (CYP) isoenzyme 3A4 (CYP3A4) inhibitors (eg, clarithromycin, erythromycin, itraconazole, ketoconazole) and inducers (eg, carbamazepine, dexamethasone, phenobarbital, phenytoin, rifampin, St John's wort). Imatinib appears to inhibit CYP3A4, thus may increase plasma CYP3A4-substrate concentrations when used with CYP3A4 substrates (eg, cyclosporine, pimozide, triazolo-benzodiazepines, dihydropyridine calcium-channel blockers, certain HMG-CoA reductase inhibitors). Also appears to inhibit CYP2C9 resulting in increased anticoagulant effect and inhibits CYP2D6.

Main toxicities associated with this drug include fluid retention/edema which could be severe resulting in pleural effusion, pericardial effusion, pulmonary edema, ascites, and superficial edema (ie, rapid weight gain, anasarca). Also hematologic effects (Grade 3 or 4 neutropenia, anemia, or thrombocytopenia occurred in up to 30–40% of patients), increases in liver enzymes (Grade 3 or 4 hyperbilirubinemia occurred in up to 4% of patients), nausea, vomiting, muscle cramps, diarrhea, rash, myalgias, headache, and hypokalemia may occur.

INTERFERON ALFA-2A, RECOMBINANT

Comments—Identical to one of the human alpha-interferons. Interferons and other cytokines are discussed in Chapter 60. It increases class I histocompatibility molecules on lymphocytes, enhances the production of ILs-1 and -2 (which mediate much of the toxic and therapeutic effects), modulates antibody responses, and enhances NK cell activity. It also inhibits tumor-cell growth by its ability to inhibit protein synthesis. It also is antiproliferative and thus can be immunosuppressive. The action on NK cells is the most important for its *antineoplastic* action. It is approved for use in *hairy-cell leukemia* and *AIDS-related Kaposi's sarcoma.* It shares first-choice status for the treatment of *hairy-cell leukemia* and *Kaposi's sarcoma* and is the drug of choice for treatment of *renal cell carcinoma.* It also is an alternative drug for use against *chronic myelocytic leukemia multiple myeloma* (21% respond), *melanoma* (13–23% respond), and *advanced cutaneous T-cell lymphomas.* Preliminary trials also show promising efficacy against ovarian carcinoma, non-Hodgkin's lymphoma, and metastatic carcinoid tumor.

It has *antiviral* activity, especially against RNA viruses. It has been shown to be effective in the treatment of varicella in immunocompromised children, non-A and non-B hepatitis, genital warts, and lymphoproliferative disorders caused by Epstein-Barr virus and in the prevention of cytomegalovirus, rhinoviral colds, and even possibly opportunistic bacterial infections in renal and other transplant recipients. Other investigations are in progress.

It enhances the targeting of monoclonal antibody-tethered cytotoxic drugs to cancer cells.

Toxicity varies directly with the dose and the rate of absorption. Antiviral effects, without toxicity, can be achieved with 3×10^5 IU. No adverse effects accrue to intranasal doses of 2.5×10^7 IU.

Antibodies to rIFN-αA develop, which may cause refractoriness to occur.

The following adverse effects with antineoplastic doses have incidences of 75% through 98% (in order of decreasing incidence): fever (IL-1-mediated), fatigue, elevated SGOT, and myalgias; 50% through 74%: headache, leukopenia, chills, neutropenia, and hypocalcemia; 25% through 49%: proteinuria, elevated alkaline phosphatase, anorexia, thrombocytopenia, nausea, hyperglycemia, hyperbilirubinemia, diarrhea, and proteinuria; 10% through 24%: dizziness, rash, hyperphosphatemia, oropharyngeal inflammation, hyperuricemia, weight loss, pruritus, dry skin, and azotemia; 5% through 9%: anemia, emesis, confusion, arthralgia, sweating, alopecia, paresthesias, numbness, lethargy, and hypotension; less than 5%: lethargy, nervousness, night sweats, conjunctivitis, sleep disturbances, edema, dysrhythmias and chest pain, decreased libido, impotence, etc. Interstitial nephritis and renal failure rarely occur. Many of the adverse effects diminish after several days of continued treatment. Interferons are expensive.

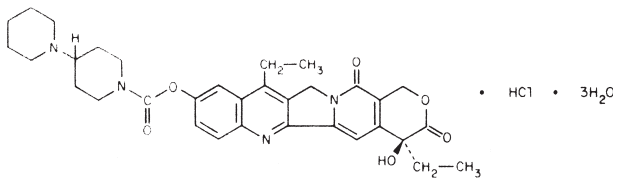
It is not absorbed orally. By the intravenous route, it entirely disappears within 4 hr, but by the intramuscular or subcutaneous route disapperance takes 6 to 7 hr.

INTERFERON ALFA-2B, RECOMBINANT

Comments—It is approved for use in *hairy-cell leukemia, AIDS-related Kaposi's sarcoma, chronic myelogenous leukemia, melanoma, condylomata acuminata,* and *chronic hepatitis.* Its actions are nearly those of rIFN-αA, and the uses are presently the same, except that it appears to be somewhat less effective against melanoma, and antibody formation is less. Neither alpha interferon has been studied in a sufficient number of cases to ascertain whether adverse effects differ substantially; they seem to be qualitatively the same but perhaps of slightly lower incidence and severity with rIFN-α-2.

IRINOTECAN HYDROCHLORIDE TRIHYDRATE

[1,4′-Bipiperidine]-1′-carboxylic acid, 4,11-diethyl-3,4,12,14-tetra-hydro-4-hydroxy-3,14-dioxo-1*H*-pyrano[3′,4′:6,7]indolizino-[1,2-*b*]quinolin-9-yl ester, monohydrochloride, trihydrate; Camptosar; CPT-11



[136572-09-3] $C_{33}H_{38}N_4O_6.HCl.3H_2O$ (677.20).

Preparation—A semisynthetic derivative of camptothecin, an alkaloid derived from plants (eg, *Camptotheca acuminata*). US Pat 4,604,463 (1986).

Description—Pale yellow needles that melt about 257°.

Solubility—Slightly soluble in water or organic solvents; pH of a 2% aq solution is 4.

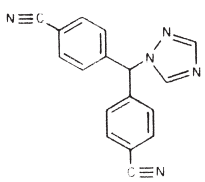
Comments—Indicated in as first-line therapy in combination with 5-fluorouracil/leucovorin of metastatic carcinoma of the colon or the rectum or for metastatic carcinoma of the colon or the rectum in patients failing 5-FU therapy. It is a prodrug that is converted to the active metabolite, SN-38, in vivo. This conversion is attributed primarily to carboxylesterase enzymes located in the liver and is linear with dose. The activating enzymes do not appear to be saturable or inducible. SN-38 is a potent inhibitor of topoisomerase I. It causes the enzyme to freeze at a step in catalysis where it exists as a covalent adduct to a nicked strand of the DNA helix. Cancer-cell resistance to SN-38 may arise from lowered levels of topoisomerase I or from specific topoisomerase I mutations.

SN-38 is inactivated largely by glucuronidation. Urinary excretion of irinotecan accounts for approximately 15% of the dose. Very little SN-38 is eliminated via the kidney, but 3% of the dose appears in the urine as the SN-38-glucuronide. Cumulative urinary and biliary excretion over 48 hr ranges from 25% to 50%. After IV infusion, drug levels in plasma drop in a multiexponential manner with a terminal half-life of approximately 6 hr. The terminal half-life for SN-38 is approximately 10 hr. Maximal concentrations of SN-38 are generally seen 1 hr after a 90-min infusion of the drug. After a 125-mg/m^2 infusion. Maximal plasma concentrations of irinotecan equal approximately 1660 ng/mL, whereas maximal SN-38 concentrations equal approximately 26 ng/mL.

This drug can induce early and late forms of diarrhea, which must be treated promptly. The early form is transient and is cholinergic in derivation. The later form of diarrhea, due to cytotoxic effects on gut lining, can be prolonged and can result in dehydration or electrolyte imbalance. Severe myelosuppression and death due to sepsis have followed its administration. Therapy should be discontinued temporarily if neutropenic fever occurs or if the neutrophil count drops to less than 500/mm^3 or if total WBC count drops to less than 2000/mm^3. Patients previously receiving pelvic or abdominal irradiation are at particular risk for myelosuppression. This drug may harm the fetus and may be excreted in breast milk.

LETROZOLE

Benzonitrile, 4,4′-(1*H*-1,2,4-triazol-1-ylmethylene)bis-, Femara



[112809-51-5] $C_{17}H_{11}N_5$ (285.31).

Preparation—A mixture of α-bromo-*p*-tolunitrile and 1,2,4-triazole in chloroform and acetonitrile is stirred to give 1-(*p*-cyanotolyl)-1,2,4-triazole which is then treated with α-fluoro-*p*-tolunitrile and potassium *t*-butoxide to yield the product. US Pat 4,978,672 (1990) and US Pat 5,473,078 (1995).

Description—White to yellowish-white, practically odorless, crystalline powder melting about 185°.

Solubility—Freely soluble in methylene dichloride; slightly soluble in ethanol; practically insoluble in water.

Comments—Approved for first-line treatment of hormone receptor-positive or hormone receptor-unknown locally advanced or metastatic breast cancer in postmenopausal women as well as use in postmenopausal women who have breast cancer that has progressed after antiestrogen therapy. It is a nonsteroidal inhibitor of aromatase. It binds the heme portion of the P-450 subunit of the enzyme and reduces the production of estrogen in all tissues. Treatment with this drug significantly lowers serum estrone and estradiol. It is effective as ovarectomy at raising serum luteinizing hormone (LH) while not increasing follicle-stimulating hormone (FSH). It causes regression of estrogen-stimulated neoplasia.

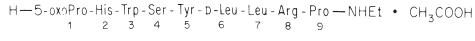
It is rapidly and completely absorbed from the GI tract. Its absorption is unaffected by coadministration wit food. Plateau blood levels are reached after 2 wk daily dosing with 25-mg tablets. It has a large volume of distribution and displays a terminal half-life for elimination of approximately 2 days. The major pathway for elimination is by means of metabolism to an inactive carbinol metabolite and the renal clearance of the glucuronide conjugate of the carbinol. Approximately 90% of the drug appears in the urine, approximately 75% of it as the conjugated metabolite. Cytochrome P-450 enzymes are likely responsible for the metabolism, and the drug is known to inhibit some of these enzymes. Renal dysfunction was not found to affect circulating drug levels, while moderate hepatic dysfunction increased levels of circulating drug 37%.

In clinical studies, approximately 3% of patients discontinued therapy for reasons other than cancer progression. A minor incidence of thromboembolism and vaginal bleeding was observed. Patients receiving the drug did not require replacement corticoid therapy. The most frequently reported adverse experiences were bone pain, hot flushes, back pain, nausea, arthralgia and dyspnea.

LEUCOVORIN CALCIUM—page 1705.

LEUPROLIDE ACETATE

6-D-Leucine-9-(*N*-ethyl-L-prolinamide)-10-deglycinamide-, monoacetate salt; Lupron



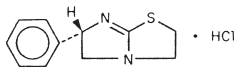
Leuprorelin; LH releasing factor (pig). [74381-53-6] $C_{59}H_{84}N_{16}O_{12}.C_2H_4O_2$ (1269.47).

Comments—An analog of the gonadotropin-releasing hormone, LH-RH/FSH-RH. Proliferation of prostatic and usually of prostatic neoplastic cells is stimulated by dihydrotestosterone generated locally from circulating testosterone (80%); hence it is indirectly under the control of LH-RH/FSH/RH. Like the natural releasing hormone, treatment with this drug initially causes an acceleration of the growth of prostatic tumors; however, it later causes a decline in tumor growth rate, as the result of downregulation (densensitization) of LH-RH/FSH-RH receptors in the anterior hypophysis and androgen receptors in prostatic tumor cells. It is approved for use only for palliative treatment of *prostatic carcinoma* when orchiectomy or estrogen therapy is rejected by the patient; however, it is analogously active against estrogen receptor-positive breast cancer. Metabolism and elimination have not been fully elucidated to date, but studies show an elimination half-life of about 3 hours following IV administration.

Recipients often experience an exacerbation of the cancer during the first few weeks of treatment. This results in temporarily increased bone destruction and pain in 3% to 10% of cases, and hypercalcemia and urinary obstruction may occur. The concurrent use of the antiandrogen, flutamide, prevents these flareups. As downregulation develops and androgen-estrogen blood levels decline to castration levels, approximately half of the patients have hot flashes which gradually recede. In male patients there is commonly loss of libido, impotence, and gynecomastia. Nausea and vomiting, edema, changes in bone density and thrombophlebitis are uncommon complications. Plasma levels of phosphatase and appropriate sex hormone should be monitored; hormone levels reach castration values in approximately 2 wk and phosphatase to baseline levels in 4 wk.

LEVAMISOLE HYDROCHLORIDE

Imidazo[2,1-*b*]thiazole, (*S*)-2,3,5,6-tetrahydro-6-phenyl-, monohydrochloride; Ergamisol



[16595-8-5] $C_{11}H_{12}N_2S.HCl$ (240.75).

Preparation—US Pat 3,274,209 or 3,579,530.

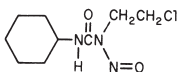
Description—White to cream-colored crystals.

Solubility—1 g in 2 mL water or 5 mL methanol; practically insoluble in ether.

Comments—A drug that predominantly stimulates, but also suppresses, immune responses to a variety of antigens, depending on dose and timing of administration. It acts upon T lymphocytes, B lymphocytes, monocytes, macrophages, and neutrophils to modify their proliferation, mobility, and factor-release. It does not act on killer or NK cells. An increase in monocyte chemotaxis is thought to be the most important action. Its effects on T lymphocytes are more pronounced than those on B lymphocytes. Clinical interest focuses on the immune stimulatory effects, especially in the treatment of cancer. Indicated as adjuvant treatment in combination with fluorouracil after surgical resection in patients with Dukes' stage C colon cancer. It is most ineffective in the induction of tumor regression, although it may be occasionally effective against breast carcinoma, ovarian carcinoma, and AML. It is most useful for the *stabilization of remission in breast carcinoma, bronchogenic carcinomas, squamous cell sarcomas of the head and neck, gastric carcinoma, leukemias, and myeloma.* It has been reported to be effective in the management of certain immune disorders, namely, erythema multiforme, lupus erythematosis, and *rheumatoid arthritis,* against which it seems to be as effective as penicillamine. There also are reports of anti-infectious activity against aphthous stomatitis, chronic brucellosis, leprosy, and staphylococcal infections. Adverse effects are usually mild and infrequent. They include vertigo (especially with ethanol), nausea, vomiting, headache, fever, dermatitis, and granulocytopenia. It readily is absorbed orally. It is metabolized nearly entirely in the liver. The elimination half-life is approximately 4 hr.

LOMUSTINE

Urea, *N*-(2-chloroethyl)-*N′*-cyclohexyl-*N*-nitroso-, CCNU; CeeNU



1-(2-Chloroethyl)-3-cyclohexyl-1-nitrosourea [13010-47-4] $C_9H_{16}ClN_3O_2$ (233.70).

Preparation—This drug, a cytotoxic nitrosourea, may be prepared by nitrosation of its substituted urea moiety (see preparation of *Carmustine*), page ____.

Description—Yellow powder.

Solubility—Practically insoluble in water, soluble in alcohol; highly soluble in lipids.

Comments—It has been approved for use in *brain cancer* and *Hodgkin's disease.* A chemical congener of *Carmustine* and has similar mechanisms of action and shares some of the same uses. Like carmustine, it reaches high concentrations in the cerebrospinal fluid and hence shares with carmustine a first-choice status for the treatment of *glioblastoma.* It has alternative drug status for treatment of *Hodgkin's* and *diffuse histiocytic lymphomas, multiple myeloma, non-small-cell lung cancer,* and *renal carcinoma.* It also is used in *bone-marrow transplantation* in Hodgkin's disease.

The adverse effects are similar to those of carmustine except that there may be rare interstitial pulmonary fibrosis (may occur at any dosage, but typically with cumulative doses exceeding 1100 mg/m^2). Nausea and vomiting occur later (3–6 hr) and last longer (24 hr). Thrombocytopenia and leukopenia reach nadirs in 4 and 6 weeks, respectively, and last 1 to 2 wk. Stomatitis, alopecia, anemia, and mild, transient hepatotoxicity occasionally occur. Dysarthria, ataxia, lethargy, and disorientation have been reported. Monitoring of leukocyte counts is required. When other myelosuppressive drugs are in use or have been used within the previous 4 wk, the dose of lomustine should be reduced.

Lomustine is absorbed well orally and survives the first pass through the liver to be effective by the oral route. It is distributed among the tissues with a volume of distribution greater than total body water. In the cerebrospinal fluid, the concentration of metabolites reaches 150% of that in plasma. Biotransformation occurs throughout the body; the half-life is approximately 15 min; the half-lives of metabolites are 48 hr. The dosage is 100–130 mg/M^2 as a single oral dose every 6 weeks.

LYMPHOCYTE IMMUNE ANTI-THYMOCYTE GLOBULIN (EQUINE)

Atgam

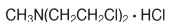
A preparation of equine immunoglobulin containing antibodies (primarily IgG) prepared from the hyperimmune serum of horses immunized with human thymus lymphocytes.

Description—Transparent to slightly opalescent (pink) aqueous solution of the protein.

Comments—Attacks T lymphocytes but not B lymphocytes. Its approved use is the *prevention of allograft rejection* in renal transplantation. Efficacy is enhanced and adverse effects are attenuated when the globulin is used in combination with other immunosuppressive agents. The globulin also has been reported to be of value in the treatment of T-cell leukemias, graft-versus-host disease, and selected cases of aplastic anemia. Frequent adverse effects include chills, fever, urticaria, pruritus, generalized rashes, leukopenia, and thrombocytopenia. Less frequently experienced adverse effects are nausea, vomiting, stomatitis, diarrhea, hypotension, chest pain, back pain, night sweats, pain at the injection site, and peripheral thrombophlebitis. Rarely there may be tachycardia, myalgias, pulmonary edema, serum sickness, anaphylaxis, laryngospasm, local and systemic infections, and activation of herpes simplex infections. Prior to use, a skin test for sensitivity to horse serum is advisable. The half-life 3 to 9 days.

MECHLORETHAMINE HYDROCHLORIDE

Ethanamine, 2-chloro-*N*-(2-chloroethyl)-*N*-methyl-, hydrochloride; Nitrogen Mustard: HN2; Mustargen



2,2′-Dichloro-*N*-methyldiethylamine hydrochloride [55-86-7] $C_5H_{11}Cl_2N.HCl$ (192.52).

History—The medical uses for nitrogen mustards were discovered as a result of chemical warfare research on vesicant agents during World War II. After noting that these agents brought about dissolution of lymphoid tissue, L Goodman, A Gilman, and T Dougherty were prompted to study the effect of nitrogen mustards on transplanted lymphosarcoma in mice. The first clinical trial with these agents was conducted in 1942.

Preparation—Among other ways, the base may be synthesized by reacting methylamine with a double equimolar portion of ethylene oxide to produce *N*-methyldiethanolamine, which then is reacted with thionly chloride. After purification, the base then may be converted conveniently to the hydrochloride by dissolving it in a suitable organic solvent and passing HCl into the solution.

Description—White, crystalline, hygroscopic powder that melts about 109°; pH (1:500 aqueous solution) 3 to 5.

Solubility—Soluble in water; soluble in alcohol.

Comments—The prototype of a series of alkylating agents called the nitrogen mustards. The β-chloroethyl groups lose chloride ions to generate carbonium and azaridium (ethylenimonium) ions, which are extremely reactive and alkylate many biologically important chemical groups. In DNA they alkylate guanine groups; if one *arm* alkylates one guanine moiety and the second arm another guanine on the opposing strand of double-stranded DNA, the DNA becomes irreversibly crosslinked. This inhibits mitosis and also may cause chromosomal breakage. Relatively undifferentiated germinal cells are nonproliferative and hypertrophied during exposure to the drug, but the more differentiated germinal cells disintegrate. Certain neoplastic growths, particularly of the lymph nodes and bone marrow, are somewhat more sensitive to the drug than are the normal more slowly proliferative tissues. It is approved for use in *Hodgkin's disease, lymphosarcoma, chronic lymphocytic* and *myelocytic leukemia, polycythemia vera, mycosis fungoides,* and *bronchogenic carcinoma.*

Although this was the drug that ushered in the era of cancer chemotherapy, it is still used today. The combinations known as MOPP (mechlorethamine, vincristine, procarbazine, prednisone) and MOP (MOPP without prednisone) offer options for treatment of *Hodgkin's disease.* It is also a component of first-choice combinations to treat *medulloblastoma* and *diffuse histiocytic lymphoma.* Mechlorethamine's only other therapeutic status of note is as the drug of choice in the topical treatment of mycosis fungoides and intraplueral, intrapericardial, or intraperitoneal palliative treatment of effusions resulting from metastatic carcinomas. In *polycythemia vera,* remissions of several months to 2 yr have been achieved. All of the above diseases eventually develop resistance to nitrogen mustards.

It is an immunosuppressive drug, but the requirement for intravenous administration and its high toxicity have discouraged its use. In the treatment of *"malignant" rheumatoid arthritis* it effects a good initial response in nearly all patients; maintenance is carried on with cyclophosphamide or other immunosuppressive drugs. It also has been

reported to improve the condition of a high percentage of patients who have *ulcerative colitis.*

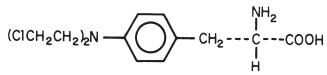
Nausea and vomiting commonly occur within 30 to 180 min after administration, but sedative and antiemetic agents greatly diminish the incidence of such untoward actions originating centrally. Diarrhea also occurs frequently. Bone-marrow depression may result in lymphocytopenia followed by leukopenia and occasionally thrombocytopenia and thus in bleeding tendencies. Serious and potentially lethal hematological responses mainly occur when the total accumulated dose in a course of therapy exceeds 0.4 mg (400 μg)/kg. Skin eruptions are noted rarely, but herpes zoster (shingles) commonly occurs, especially in the treatment of malignant lymphoma. Sometimes temporary menstrual irregularities occur in females. In patients who have large tumor masses which involute rapidly with treatment, there may be hyperuricemia, and adequate fluid intake and allopurinol are needed to prevent crystalluria and kidney damage. Alopecia, metallic taste, headache, drowsiness, asthenia, tinnitus, and deafness sometimes occur.

It is teratogenic and carcinogenic and should not be used during the first trimester of pregnancy. Several local reactions to mechlorethamine, as well as rapid chemical breakdown of the drug, require that therapy be limited to the intravenous route; even so, extravasation may cause tender local induration and tissue necrosis, and irritation from within the lumen of the vessel may cause phlebothrombosis or thrombophlebitis, especially if the infusion rate is too rapid or the concentration of solution is too high. Extravasation should be treated with 1/6 *M* sodium thiosulfate solution.

MEDROXYPROGESTERONE ACETATE—page 1467.

MELPHALAN

L-Phenylalanine, 4-[bis(2-chloroethyl)amino]-, Alkeran, L-PAM, Phenylalanine mustard; L-sarcolysin



[148-82-3] $C_{13}H_{18}Cl_2N_2O_2$ (305.20).

Preparation—L-3-Phenylalanine is nitrated and the *p*-nitro compound is reduced to L-3-(*p*-aminophenyl)alanine. This is reacted with ethylene oxide to form the corresponding bis(2-hydroxy-ethyl)-amino compound that then is treated with phosphoryl chloride to yield the drug.

Description—Off-white to buff powder having a faint odor; sensitive to light, heat, and moisture; melts about 180° with decomposition.

Solubility—Practically insoluble in water, chloroform, or ether; slightly soluble in alcohol; soluble in dilute mineral acids.

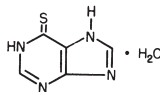
Comments—An alkylating agent of the bischloroethylamine type. Cytotoxicity appears to be related to the extent of its interstrand cross-linking with DNA, probably by binding at the N^7 position of guanine. It is approved for use in *multiple myeloma* and *nonresectable epithelial carcinoma of the ovary.* In combination with prednisone either it or cyclophosphamide is the drug of choice for treatment of *multiple myeloma.* Seventy to 80% of patients show subjective improvement; 33% to 50% show objective improvement for periods from 6 months to 2 yr; and life expectancy may be increased even when no objective signs of improvement are obtained. It is a component of the combination of choice against *ovarian carcinoma.* It is used occasionally in the *treatment of tumors of the testis, osteogenic sarcoma, non-small cell lung cancer,* and *chronic granulocytic leukemia.*

Adverse effects include mild nausea and vomiting after large doses, bone-marrow depression with anemia, neutropenia, thrombocytopenia, and occasional azotemia. Aphthous ulceration, GI hemorrhage, skin eruptions, and bronchopulmonary dyplasia also occur occasionally. Regular blood-cell counts are required. It should be given cautiously if the patient has been receiving radiation or other cancer chemotherapy. It is contraindicated in thrombocytopenia, anemia, and leukopenia and during the first trimester of pregnancy. In the presence of impaired renal function the drug should be used cautiously. IV melphalan may cause anaphylaxis, diaphoresis, hypotension, tachycardia, bronchospasm, dyspnea, and cardiac arrest.

It is absorbed well by the oral route, being as efficacious as by the intravenous route. It is transformed into active metabolites in probably all tissues. The elimination half-life is approximately 1 to 3 hr. Following IV administration, drug plasma concentrations declined rapidly in a biexponential manner with distribution phase and terminal elimination phase half-lives of approximately 10 and 75 minutes, respectively. Estimates of average total body clearance varied among studies, but typical values of approximately 7–9 ml/min/kg (250–325 ml/min/m^2) were observed with mean (±SD) peak melphalan plasma concentrations in myeloma patients given IV melphalan at doses of 10 or 20 mg/m^2 were 1.2 ± 0.4 and 2.8 ± 1.9 ug/ml, respectively. The steady-state volume of distribution of melphalan is 0.5 L/kg, with plasma protein binding ranging from 60% to 90%.

MERCAPTOPURINE

6*H*-Purine-6-thione, 1,7-dihydro-, monohydrate; Purinethol; 6-MP



Purine-6-thiol monohydrate (tautomer) [6112-76-1] $C_5H_4N_4S.H_2O$ (170.19); *anhydrous* [50-44-2] (152.17).

Preparation—Thiourea and ethyl cyanoacetate are reacted in the presence of sodium methylate to give 2-thiol-4-amino-6-hydroxypyrimidine (I) that then is converted to the 5-nitroso derivative (II) by treatment with sodium nitrite and acetic acid. Reduction of II with sodium hydrosulfite yields the corresponding diamino compound (III) which then is desulfurized by hydrogenolysis in the presence of Raney nickel to yield 4,5-diamino-6-hydroxypyrimidine (IV). The imidazole ring closure then is effected by double condensation of IV with formic acid (V), and the resulting hypoxanthine is thiolated with P_2S_5.

Description—Yellow, crystalline powder; odorless or practically odorless; melts with decomposition at temperatures above 308°.

Solubility—Insoluble in water, acetone, or ether; soluble in hot alcohol or in dilute aqueous alkali; slightly soluble in diluted H_2SO_4.

Comments—It is converted to 6-thioinosinic acid, which acts as an antimetabolite to inhibit synthesis of adenine and guanine and also to prevent conversion of purine bases into nucleotides. It also mimics inosinic acid in exerting a negative feedback suppression of the synthesis of inosinic acid. Some mercaptopurine also is converted to thioguanine, which is incorporated into both DNA and RNA to generate defective nucleic acids. Thus nucleic acid synthesis and functions are impaired several ways. Cell mitosis is inhibited.

In combination with methotrexate it provides a combination of first choice in the *maintenance chemotherapy of acute lymphocytic leukemia* (this is its approved use). It is an alternative drug for the treatment of *stable chronic myelocytic leukemia;* the remission rate is approximately 80% if the disease is caught early, but cures are not achieved. Induction sometimes is accomplished with busulfan and maintenance with mercaptopurine. There is no cross resistance between this drug and nonpurine antineoplastic drugs.

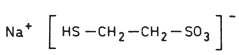
It is mostly a secondary (efferent) *immunosuppressive* drug that is capable of eliciting a high percentage of favorable responses in *ulcerative colitis* and *psoriatic arthritis.* It also is moderately effective in the treatment of *systemic lupus erythematosus, dermatomyositis,* and *polymyositis.* However, it probably will not become the drug of choice for any of these disorders. Immunosuppression predisposes to intercurrent infections.

Bone-marrow depression occurs during treatment. Leukopenia and thrombocytopenia (with hemorrhage) are common and may be severe, but anemia is rare. Frequent monitoring of the blood-cell population is mandatory. Nausea, vomiting, and anorexia may occur; they signal onset of GI toxicity, which may take the form of mucositis and ulceration. Oral, pharyngeal, and esophageal mucositis may also occur, with thrushlike stomatitis or aphthous ulceration. Diarrhea and spruelike symptoms occasionally occur. There also may be jaundice in 10% to 40% of patients who have acute leukemia due to hepatic injury which can occur with any dosage, but seems to occur when doses of more than 2.5 mg/kg/day. The histologic pattern of mercaptopurine hepatotoxicity includes features of both intrahepatic cholestasis and parenchymal cell necrosis. In patients who have high WBC counts or massive disease, cellular destruction leads to hyperuricemia and sometimes to tubular clogging with urate crystals and consequent oliguria, thus necessitating use of allopurinol.

The systemic bioavailability by the oral route ranges from 5% to 37%, owing to first-pass metabolism in the intestinal mucosa and liver. Both oxidation by xanthine oxidase and *S*-methylation occur. The xanthine oxidase inhibitor, allopurinol, considerably increases plasma levels from oral, but not from intravenous, drug, so that only approximately one-third of the usual oral dose should be given in the presence of allopurinol. Approximately 20% of the drug in plasma is protein bound, and the volume of distribution is larger than the extracellular space; however, the access to cerebrospinal fluid is slight. The half-life averages 47 min in adults and 21 min in children. Inhibition of the anticoagulant effect of warfarin, when given with mercaptopurine, has been reported.

MESNA

Ethanesulfonic acid, monosodium salt; Mesnex



[19767-45-4] $C_2H_5NaO_3S_2$ (164.17).

Preparation—Reaction of sodium vinylsulfonate with NaSH or H_2S, in an anti-Markovnikov addition yields the product.

Description—White crystalline powder with a "rotten egg" odor.

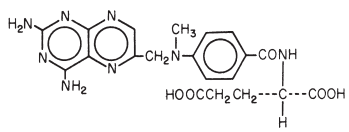
Solubility—Freely soluble in water; sparingly soluble in organic solvents.

Comments—Approved for prevention of ifosfamide-induced hemorrhagic cystitis. It is a mercaptan which scavenges and inactivates reactive molecules such as acrolein produced by ifosfamide activation. In clinical trials, patients treated with ifosfamide and traditional protective strategies (diuretics and alkalinization of urine) suffered approximately 20% hematuria. Those treated with this drug suffered none. It is eliminated rapidly by the kidneys. Approximately 33% of a dose appears in the urine within 24 hr, the largest fraction within the first 4 hr. The half-life ranges from 1.2–8.3 hours following oral administration of the drug, with a volume of distribution of approximately 0.65 L/kg.

It should not be used in patients hypersensitive to thiol-containing agents. Adverse reactions include nausea, vomiting, and diarrhea. The drug may cause a false positive test for urinary ketones.

METHOTREXATE

L-Glutamic acid, *N*-[4-[[(2,4-diamino-6-pteridinyl)methyl]methylamino]benzoyl]-, Folex: Methotrexate; Mexate



4-Amino-10-methylfolic acid; [59-05-2]; a mixture of 4-amino-10-methylfolic acid and closely related compounds and contains not less than 85.0% of $C_{20}H_{22}N_8O_5$ (454.44).

Preparation—2,3-Dibromopropionaldehyde (I) is condensed in an aqueous medium with 2,4,5,6-tetraminopyrimidine (II). The condensation is multiple, consisting of (a) dehydrobromination, involving a hydrogen of the 5-amino group and the 2-bromine; (b) dehydration, involving two hydrogens of the 6-amino group and the oxygen in II; and (c) dehydrogenation, involving the remaining hydrogen of the 5-amino group and the 2-hydrogen of II. The dehydrogenation in step (c) is brought approximately by another molecule of II that, by effecting the dehydrogenation, is reduced to 2,3-dibromo-1-propanol. The overall effect of these condensations is the cyclization of I with II to produce 6-bromomethyl-2,4-diaminopteridine (III). Further condensation (dehydrobromination involving the bromine in III and the hydrogen of the methylamino group in *N*-[*p*-(methylamino)benzoyl]glutamic acid) yields the crude drug, which is purified.

Description—Orange-brown, crystalline powder.

Solubility—Practically insoluble in water, alcohol, chloroform, or ether; freely soluble in dilute solutions of alkali hydroxides or carbonates; slightly soluble in dilute hydrochloric acid.

Comments—Inhibits dihydrofolate reductase, and thus prevents conversion of deoxyuridylate to thymidylate and blocks the synthesis of new DNA needed for cellular replication. Methotrexate is approved for use, and is the drug of choice, in *trophoblastic tumors* such as choriocarcinoma, *hydatidiform mole,* and *chorioadenoma destruens.* It also is approved for *prophylaxis of and treatment of meningeal leukemias* and for *breast cancer* and *nonmetastatic osteosarcoma.* It sometimes is combined with dactinomycin in these uses. When given intrathecally, it is the drug of choice for *CNS prophylaxis in acute lymphocytic leukemia.* In combination with other drugs it provides the therapy of choice. It is a component of first-choice combinations for induction and maintenance in *acute lymphocytic leukemia, diffuse histiocytic leukemia, cervical cancer, medulloblastoma, osteogenic sarcoma, breast cancer, non-Hodgkin's lymphomas, Burkitt's lymphoma, bladder carcinoma, squamous cell carcinoma of the head and neck, oat-cell* and *non-small-cell lung cancers.* It is an alternative drug for treatment of *adult soft-tissue sarcoma, follicular lymphoma, embryonal rhabdomyosarcoma,* and *colorectal carcinoma.* It also is used sequentially with fluorouracil in the treatment of node-negative breast cancer.

It may be given by intra-arterial infusion into the affected region in the treatment of a variety of carcinomata of the head, neck, pelvis, and limbs; the local concentrations achieved may be high enough to be effective and yet low enough in the rest of the body not to be toxic. The endocellular transport competitor, folinic acid (leucovorin), is also often given systematically to prevent generalized toxicity.

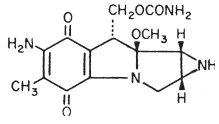
It is a secondary (efferent) immunosuppressive drug. It is one of a few drugs used to treat *Reiter's syndrome,* although results range from poor to good. It is employed to treat *psoriasis* refractory to other drugs; with methotrexate, approximately 50% of affected joints and 65% of skin lesions improve. It is used successfully to treat severe, progressive, refractory *rheumatoid arthritis* and glucocorticoid-dependent asthma. It has provided improvement in *dermatomyositis* and *polymyositis* (40–100% improvement), *Wegner's granulomatosis, pemphigus vulgaris, pityriasis rubra pilaris, bullous pemphigoid,* and *thrombocytopenic purpura,* but other drugs appear to be equal or superior.

The toxic effects are extensions of its antimetabolite effects; sometimes toxicity occurs first. They include bone-marrow hypoplasia with leukopenia, thrombocytopenia (with hemorrhage), and anemia. Depression of cellular proliferation along the GI tract results in diarrhea, ulcerative stomatitis, hemorrhagic enteritis, and perforation. Alopecia also may occur. Dosage schedules in which methotrexate is given chronically daily may cause liver damage. The drug must not be used when there is preexisting liver damage or bone-marrow depression, or during pregnancy. Daily blood counts and triweekly creatinine determinations are mandatory. The toxicity and therapeutic effects may be antagonized by leucovorin (leucovorin or thymidine *rescue*); if the leucovorin is given after an appropriate delay, it can prevent the toxic but not the therapeutic effect on certain tumors or the immune system. The drug is concentrated in the urine, and precipitation may cause renal failure; alkalinization and high water intake help protect the kidneys. Nitrous oxide, often used in pediatric oncology units, increases its cytotoxicity and probably its efficacy.

In doses less than 30 mg/m^2, it is absorbed well by the oral route; but approximately 1/3 of an oral dose is metabolized by intestinal bacteria, and antibiotics affect the amount absorbed. In doses greater than 80 mg/m^2, the amount absorbed is reduced further by 30 to 50%. Only approximately 50% of the drug is bound to plasma protein, but it does not gain much access to the cerebrospinal fluid because it is strongly ionized and outwardly transported at the choroid plexus; consequently, it must be administered intrathecally for use in the CNS. In the usual doses, it actively is transported into all tissues, but it is transported preferentially into responsive neoplastic cells. Intensification of therapy, alternating with or followed by leucovorin rescue, may achieve sufficient plasma levels (1 μM) to effect meningeal leukemias and lymphomas without intrathecal administration. Plasma clearance is triexponential, with a distribution half-life of approximately 45 min, a second phase of approximately 3.5 hr (possibly an enterohepatic component, because 10% of the drug is secreted into bile), and an elimination half-life of 6 to 69 hr. Renal tubular secretion accounts for approximately 80% of elimination, and probenecid, salicylate, and other NSAIDs, etc, interfere with excretion. Because methotrexate is partly bound to serum proteins, its toxicity may be increased as a result of displacement by certain drugs such as salicylates, sulfonamides, sulfonylureas, phenytoin, phenylbutazone, tetracyclines, chloramphenicol, and aminobenzoic acid. The dose must be adjusted in renal failure.

MITOMYCIN

Azirino[2′,3′:3,4]pyrrolo[1,2-*a*]indole-4,7-dione, [1a*R*-(1aα,8β,8aα,8bα)]-6-amino-8-[[(aminocarbonyl)oxy]methyl]-1,1a,2,8,8a,8b-hexahydro-8a-methoxy-5-methyl-, Mitocin-C; Mutamycin



Mitomycin C [50-07-7] $C_{15}H_{18}N_4O_5$ (334.33).

Preparation—One of three closely related entities isolated from the antibiotic complex produced by *Streptomyces caespitosus,* an organism from Japanese soil.

Description—Blue-violet, crystalline powder.

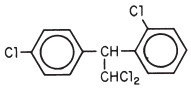
Solubility—Soluble in water and in common organic solvents.

Comments—Inhibits DNA synthesis by cross-linking double-stranded DNA through guanine and cytosine. It is approved for palliative treatment of *disseminated adenocarcinoma of the stomach and the pancreas that have failed other treatments.* It is a component of second-line combinations for the treatment of *cervical, gastric,* and *pancreatic carcinomas* and *non-small-cell bronchogenic carcinoma.* It is instilled into the bladder in *papilloma.* It is an alternative drug for use against

head and *neck squamous cell carcinoma, bladder carcinoma,* and *osteogenic sarcoma.* Acute adverse effects occur in approximately 14% of patients; they include nausea, vomiting, anorexia, fever, local irritation, and cellulites or tissue necrosis from extravasation at the site of injection. Delayed toxicity includes cumulative, frequently irreversible, bone-marrow depression (64% of recipients), stomatitis, alopecia, and renal impairment (20% of recipients). Pulmonary toxicity with hemoptysis, dyspnea, coughing, and pneumonia and hemolytic uremic syndrome occur infrequently, but may be severe.

MITOTANE

Benzene, 1-chloro-2[2,2-dichloro-1-(4-chlorohenyl)ethyl]-, *o,p′*-DDD; Lysodren



1,1-Dichloro-2-(*o*-chlorophenyl)-2-(*p*-chlorophenyl)ethane [53-19-0] $C_{14}H_{10}Cl_4$ (320.05).

Preparation—Chlorobenzene is condensed with 2,2-dichloro-1- (*o*-chlorophenyl)ethanol with the aid of H_2SO_4.

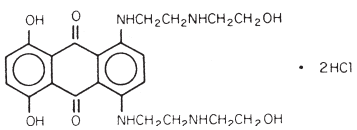
Description—White, tasteless, crystalline powder; slight aromatic odor; stable in light, air, and heat; melts about 78°.

Solubility—Practically insoluble in water; soluble in alcohol, ether, solvent hexane, or fixed oils or fats.

Comments—Because it is toxic to the adrenal cortex, it is approved for the treatment of *inoperable adrenal cortical carcinoma.* Nearly 50% of patients respond to treatment. It also is used to treat *Cushing's syndrome* and *Leydig carcinoma of the testicle.* Causes focal degeneration in the zona fasciculata and reticularis of the adrenal cortex with resultant atrophy and usually causes only minimal degeneration in the zona glomerulosa (site of aldosterone biosynthesis). Adverse effects of adrenal insufficiency may necessitate adrenal steroid replacement; these effects include anorexia, nausea, vomiting (in 80%), diarrhea, lethargy, somnolence (25%), dizziness (15%), headache, confusion, asthenia, tremors, ataxia, speech difficulties, neuropathies, dermatitis (15%), hypersensitivity, flushing, hyperpyrexia, postural hypotension, alopecia, pigmentation, leukopenia, thrombocytopenia, hyperbilirubinemia, albuminuria, hemorrhagic cystitis, elevated serum transaminase, blurred vision, diplopia, lens opacities, and retinopathy. The drug should be used with caution in the presence of liver damage, bone-marrow depression, dermatitis, or neuropathy. It is metabolized in the liver and reported to increase the metabolism of warfarin through induction of hepatic microsomal enzymes.

MITOXANTRONE HYDROCHLORIDE

9,10-Anthracenedione, 1,4-dihydroxy-5,8-bis-[[2-[(2-hydroxyethyl)-amino]ethyl]amino]-, dihydrochloride; Novantrone



Mitozantrone [70476-82-3] $C_{22}H_{28}N_4O_6.2HCl$ (517.41).

Preparation—*J Med Chem* 1978, 21:291.

Description—Blue-black solid; hygroscopic; melts about 161°; pKa 5.99, 8.13.

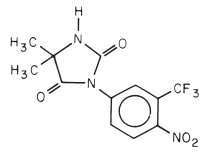
Solubility—Sparingly soluble in water; slightly soluble in methanol.

Comments—An alkylaminoanthraquinone antineoplastic drug related to doxorubicin. It is approved for the treatment of *acute nonlymphocytic leukemia* when combined with other agents and in combination with a corticosteroid in the palliative treatment of advanced, symptomatic (ie, painful) *hormone-refractory prostate cancer*. It is also indicated for reducing neurologic disability and/or the frequency of clinical relapses in patients with secondary (chronic) progressive, progressive relapsing, or worsening relapsing-remitting multiple sclerosis (ie, patients whose neurologic status is significantly abnormal between relapses), but not for treatment of patients with primary progressive multiple sclerosis. It is an alternative drug for the treatment of *acute lymphoblastic leukemia, chronic myelogenous leukemia, ovarian* and *breast carcinoma.* Immediate adverse effects include nausea, vomiting, and phlebitis. Tissue necrosis and sloughing result from extravasation. Delayed adverse effects include myelosuppression and cardiac, renal, and hepatic toxicities. The *N*-substitution on the aminosugar decreases the cardiotoxicity. The drug is not absorbed orally. It is eliminated mostly in the bile and has a half-life of 20 to 36 hr.

Myocardial toxicity, manifested in its most severe form by potentially fatal congestive heart failure (CHF), may occur either during therapy with mitoxantrone or months to years after termination of therapy. In cancer patients, the risk of symptomatic CHF was estimated to be 2.6% for patients receiving up to a cumulative dose of 140 mg/m^2. Cardiovascular disease, prior or concomitant radiotherapy to the mediastinal/pericardial area, previous therapy with other anthracyclines or anthracenediones, or concomitant use of other cardiotoxic drugs may increase the risk of cardiac toxicity.

NILUTAMIDE

2,4-Imidazolidindione, 5,5-dimethyl-3-[4-nitro-3-(trifluoromethyl)-phenyl]-, Nilandron; Anandron



[63612-50-0] $C_{12}H_{10}F_3N_3O_4$ (317.23).

Preparation—By reaction of 5,5-dimethylhydantoin with 5-chloro-2-nitro-α,α,α-trifluorotoluene in diphenyl ether or diglyme at 200° with CuO, Cu_2O, or NaOH as the condensing agent. US Pat 5,166,358 (1992).

Description—Microcrystalline, off-white powder that melts about 154°.

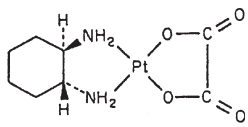
Solubility—Freely soluble in ethyl acetate, acetone, chloroform, ethanol, methylene chloride, or methanol; slightly soluble in water (<0.1% at 25°).

Comments—Approved for use in metastatic prostate cancer (Stage D) in combination with castration. It is a nonsteroidal antiandrogen that interacts with the testosterone receptor and prevents its response or nuclear binding at target tissues. It is absorbed rapidly and completely after oral administration. After a detectable distribution phase, it is metabolized extensively, less than 2% is excreted unchanged in the urine within 5 days. Several metabolites have been identified, one with 25% to 50% of the activity of the parent drug. The majority of the administered doses (62%) appears in the urine within 120 hr of administration. The average half-life is approximately 45 hr after a single dose. During multiple dosing (3 × 50 mg twice a day), steady-state levels were reached in 2 to 4 wk. It is bound by plasma proteins. Severe hepatic impairment is a contraindication for this drug.

Interstitial pneumonitis had been reported in 2% of patients receiving the drug. Signs of pneumonitis most often appeared within the first 3 months of treatment. Serum increases in hepatic enzymes led to discontinuation of the drug in 1% of patients. The drug should be discontinued if liver serum enzyme levels increase to 2- or 3-fold the normal upper limit. As many as half the patients report a delay in adapting to the dark; wearing tinted glasses seems to help in this respect. It inhibits several P-450 enzymes and care should be taken to monitor coadministered drugs that necessitate liver metabolism.

OXALIPLATIN

Platinum, [*SP*-4-2-(1*R-trans*)]-(1,2-cyclohexanediamine-*N,N′*) [ethanedioato(2-)-*O,O′*]-, Eloxatin



[61825-94-3] $C_8H_{14}N_2O_4Pt$ (397.30).

Preparation—*J Med Chem*, 1978; 21:1315.

Description—Colorless plates.

Solubility—6 mg/mL in water; very slightly soluble in methanol and practically insoluble in ethanol or acetone.

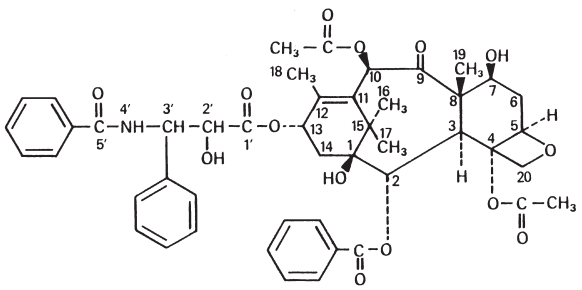
Comments—undergoes nonenzymatic conversion forming several transient reactive species, including monoaquo and diaquo DACH platinum, which covalently bind with macromolecules. Both inter- and intra-strand Pt-DNA cross-links are formed. Crosslinks are formed between the *N*7 positions of two adjacent guanines (GG), adjacent adenine-guanines (AG), and guanines separated by an intervening nucleotide (GNG). These crosslinks inhibit DNA replication and transcription. It is indicated in combination with fluorouracil and leucovorin, for the treatment of metastatic cancer of the colon or rectum in

patients whose disease has recurred or progressed during or within 6 months following first-line therapy with the combination regimen of fluorouracil, leucovorin, and irinotecan. It also has shown activity in ovarian cancer, germ-cell cancer, and cervical cancer.

Pharmacokinetics of oxaliplatin are triexponential with short initial α and β distribution phases (0.28 hour and 16.3 hours, respectively) and a long terminal γ phase (273 hours). Approximately 80% of oxaliplatin is bound to plasma proteins, and it undergoes extensive biotransformation, and has a very large volume of distribution. Over 5 days, approximately 50% will be excreted in the urine, and only 5% will be excreted in the feces. The dose-limiting toxicity of oxaliplatin is a peripheral neuropathy that is often triggered by exposure to cold, and manifests as paresthesias and/or dysesthesias in the upper and lower extremities, mouth, and throat. The peripheral neuropathy is cumulative; 75% of patients receiving a cumulative dose of 1560 mg/m^2 experience some neurotoxicity. Hematologic toxicity is mild to moderate, and nausea is well controlled with antiemetics. Anaphylactic-like reactions to oxaliplatin have been reported.

PACLITAXEL

5β,20-Epoxy-1,2α,4,7β,10β,13α-hexahydroxytax-11-en-9-one 4,10-diacetate 2-benzoate 13-ester with (*2R,3S*)-*N*-benzoyl-3-phenylisoserine; FK + 506; Taxol; Anzatax; Biotax; Bristaxol; Ifaxol; Intaxel; Medixel; Onxol; Parexel; Paxene; Praxel



[33069-62-4] $C_{47}H_{51}NO_{14}$ (853.92).

Preparation—Extracted from the bark of the Pacific yew tree (*Taxus brevifolia, Taxaceae*).

Description—White needles that melt about 215° with decomposition.

Solubility—Highly lipophilic and insoluble in water

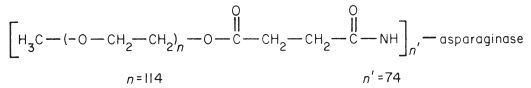
Comments—Inhibits mitosis by stabilizing mitotic spindles by preventing depolymerization and promoting their formation. This causes inhibition of the normal dynamic reorganization of the microtubule network that is essential for interphase and mitotic cellular functions. May induce cell death by triggering apoptosis. Taxol is approved as first-line and subsequent therapy for use in *ovarian cancer* and as adjuvant treatment of *node-positive or metastatic breast cancer given sequentially to doxorubicin-containing regimen*. It is also indicated in combination with cisplatin as first line treatment for non-small cell lung cancer in patients who cannot tolerate surgery and/or radiation therapy and for second-line treatment of AIDS-related Kaposi's sarcoma. It has shown activity in malignant melanoma, gastric cancer, and acute leukemia.

Following IV administration, paclitaxel is widely distributed into body fluids and tissues with the mean apparent volume of distribution at steady state ranging from 227–688 L/m^2 with 88% to 98% bound to plasma proteins. The average distribution half-life ($t_{1/2\alpha}$) is 0.27 to 0.34 hours, and an average elimination half-life ($t_{1/2\beta}$) is 2.33 to 5.8 hours, depending on infusion time. It is extensively metabolized in the liver to its major metabolite, 6α-hydroxypaclitaxel, which is mediated by cytochrome P-450 isoenzyme CYP2C8.

Bone marrow suppression (primarily neutropenia), peripheral neuropathies (62% incidence consisting of numbness, tingling, and pain in hands and feet), and mucositis are dose-dependent and the dose-limiting toxicities. Anaphylaxis and severe hypersensitivity reactions consisting of dyspnea and hypotension requiring treatment, angioedema, and generalized urticaria have occurred in 2% to 4% of patients in clinical trials. All patients must be pretreated with corticosteroids, diphenhydramine, and H_2 antagonists. Severe cardiac changes (bradycardia, hypotension, chest pain, tachycardia, complete AV block) have been documented in <1% of patients during therapy. The drug is an irritant and potentially a vesicant. It also causes alopecia, facial flushing, and elevations in liver enzymes.

PEGASPARGASE

(Monomethoxypolyethylene glycol succinimidyl)$_{74}$-L-asparaginase; Oncaspar



[130167-69-0].

Preparation—See US Pat 4,179,337 (1979).

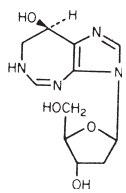
Description—The reaction product of L-asparaginase (derived from *E coli*) with succinic anhydride and esters with polyethylene glycol monomethyl ether. Its molecular weight is about 5000.

Comments—Approved for patients who have acute lymphoblastic leukemia who require, but who have developed hypersensitivity to, L-asparaginase. It generally is used in combination with other drugs. It is the enzyme L-asparaginase, obtained from *E coli,* that has been modified covalently by the addition of methoxypolyethylene glycol (mol wt 5000 daltons). Rapid depletion of asparagine by the administration of pegaspargase kills leukemia cells hat rely on exogenous sources of asparagine for growth. In asparaginase-hypersensitive patients, 93% of whom had relapsed from previous therapy, 50% evidenced reinduction after multiple injections of pegasparagase, 36% showing complete remissions.

The half-life of this drug in the blood is 3 to 6 days, with the volume of distribution approximating plasma volume. L-asparaginase is detectable in the blood 15 days after an administration of pegaspargase. Adverse reactions were relatively minor with elevations of liver enzymes, thrombosis, hyperglycemia, and pancreatitis being reported in less than 5% of patients. Allergic reactions, including rash and bronchospasm, were reported in greater than 5% of patients. Pegaspargase was administered intravenously and intramuscularly to 48 and 126 patients respectively. The incidence of hypersensitivity reactions when pegaspargase was administered intramuscularly was 30% in patients who were previously hypersensitive to native L-asparaginase and 11% in non-hypersensitive patients. The incidence of hypersensitivity reactions when pegaspargase was administered intravenously was 60% in patients who were previously hypersensitive to native L-asparaginase and 12% in non-hypersensitive patients.

PENTOSTATIN

Imidazo[4,5-*d*][1,3]diazepin-8-ol, (*R*)-3-(2-deoxy-β-D-*erythro*-pentofuranosyl)-3,6,7,8-tetrahydro-, Nipent, 2′-deoxycoformycin (DCF)



[63677-95-2] $C_{11}H_{16}N_4O_4$ (268.27).

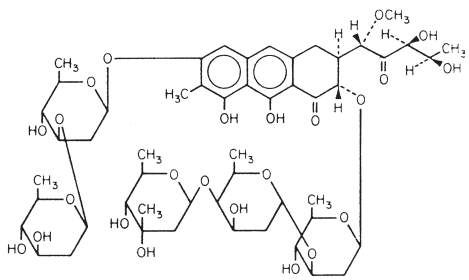
Preparation—*J Org Chem* 1982, 47, 3457. Usually isolated from *Streptomyces antibioticus.*

Description—White crystals that melt about 223°; pKa 5.2.

Comments—Inhibits adenosine deaminase, thus leading to an accumulation of 2′-deoxyATP. Inhibition of cell proliferation results. Lymphocytes are especially sensitive to this drug. It is approved for use in α-*interferon refractory hairy-cell leukemia.* It is an alternative drug for use against chronic *lymphocytic leukemia, mycosis fungoides, acute lymphoblastic leukemia.* Adverse effects include myelosuppression sometimes with severe lymphopenia, conjuctivitis, panserositis, lethargy, coma, pulmonary toxicity, hyperuricemia and immunosuppression; various infections may occur, herpes simplex infections being the most common.

PLICAMYCIN

Aureolic acid; Mithramycin; Mithracin



[18378-89-7] $C_{52}H_{76}O_{24}$ (1085.16).

Preparation—Produced by cultures of *Streptomyces argillaceus, S plicatus,* and *S tanashiensis.*

Description—Yellow, crystalline powder; odorless; hygroscopic; melts about 182°.

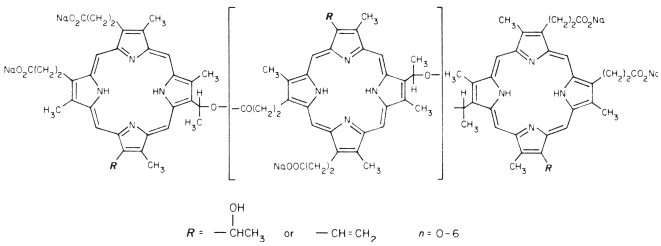
Solubility—Slightly soluble in water, slightly soluble in alcohol; freely soluble in ethyl acetate.

Comments—An antibiotic elaborated during culture of certain strains of *Streptomyces.* A yellow, crystalline powder; odorless; hygroscopic; slightly soluble in water; slightly soluble in alcohol. It has various uses: Binds to guanine-rich DNA and thus inhibits DNA-dependent RNA polymerase. It acts mainly during the S phase. It is approved for and used to treat *carcinoma* of the *testes*, but use has been replaced by other more effective agents. It also is an alternative drug for *blast phase* of *chronic myelogenous leukemia,* especially in combination with hydroxyurea. Because it suppresses osteoclast activity, it often is used to treat *malignant hypercalcemia* (neoplasms that cause dissolution of bone salts) unresponsive to conventional treatment and *Paget's disease* of the bone..

It is toxic, and drug-induced mortality ranges from 0.09% to 0.7%, depending on dose. Death results from hemorrhagic diatheses resulting from hypoprothrombinemia,, thrombocytopenia, increased clotting and bleeding times, and abnormal clot retraction. The hemorrhagic episode usually begins with nosebleed, but it may begin with hematemesis. The most common untoward effects are nausea, vomiting, diarrhea, anorexia, and stomatitis. Less frequently there occur fever, facial flushing, rash, phlebitis, malaise, headache, drowsiness, asthenia, lethargy, depression, hepatic dysfunction, renal insufficiency, hypocalciuria, hypokalemia, hypophosphatemia, and leukopenia. The hemorrhagic syndrome occurs in approximately 5% of patients who receive no more than 30 μg/kg/day for no more than 10 doses, whereas it is approximately 12% for higher doses. It is locally toxic and can cause necrosis and sloughing if extravasated.

PORFIMER SODIUM

Polymorphin oligomer containing ester and ether linkages; Photofrin



[87806-31-1].

Preparation—See US Pat 4,649,151 (1987).

Description—The purified product as a mixture of oligomers formed by ester and ether linkages to as many as eight porphyrin units with aggregates of a combined molecular weight of approximately 10^5.

Solubility—The reconstituted product should be protected from heat and light and used immediately. ***DO NOT MIX*** with other drugs in the same solution.

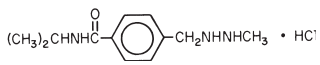
Comments—Approved for photodynamic therapy of obstructive esophageal cancer and for the treatment of microinvasive endobronchial NSCLC in patients for whom surgery and radiotherapy are not indicated. It is injected intravenously after which 40 to 70 hr are allowed for clearance. It is retained in a few tissues, notably spleen, liver, and skin, and tumor. Laser light at 630-nm wavelength then is used to irradiate the esophagus. The drug that is present is excited by the light to initiate the production of reactive oxygen species. These are tissues damaging on their own but, in addition, they induce necrosis in the tumor by means of ischemia mediated by the production of thromboxane A2 and vascular occlusion. In a clinical trial of 17 patients who have obstructive esophageal cancer, 93% showed objective response after therapy, and 65% received clinically important benefit.

After a 2-mg/kg dose the half-life for elimination was 250 hr. It is approximately 90% protein bound in the serum. Patients treated with this drug are photosensitive and should take care to remain protected from sunlight and bright indoor light for a minimum of 30 days. Serious side effects were noted in less than 5% of patients and were primarily related to inflammation at the illumination site.

PREDNISONE—page 1448.

PROCARBAZINE HYDROCHLORIDE

Benzamide, *N*-(1-methylethyl)-4-[(2-methylhydrazino)methyl]-, monohydrochloride; Matulane



N-Isopropyl-α-(2-methylhydrazino)-*p*-toluamide monohydrochloride [366-70-1] $C_{12}H_{19}N_3O.HCl$ (257.76).

Preparation—1,2-Bis(carbobenzoxy)-1-methylhydrazine is reacted with 4-(bromoethyl)benzoic acid methyl ester ultimately to yield 4-[[2-methyl-1,2-di(carbobenzoxy)hydrazino]methyl]benzoic acid. Thionyl chloride is used to obtain the acid chloride which is reacted with isopropylamine to give the *N*-isopropylamide compound. Treatment with 33% HBr in glacial acetic acid removes the protecting carbobenzoxy groups, and thus resulting hydrobromide may be converted to the hydrochloride by the usual process. US Pat 3,520,926.

Description—White to pale yellow, crystalline powder; slight odor and a bitter taste; solutions are acid to litmus; stable in light, slowly oxidized in air, and stable at room temperature (in the presence of oxygen, oxidation is accelerated by increased temperature); melts about 223° with decomposition; pK_a (at room temperature) 6.8.

Solubility—1 g in 7 mL water or 100 mL alcohol; slightly soluble in chloroform; insoluble in ether.

Comments—Unstable in aqueous solutions, it breaks down to form the methylazoxy derivative, the active form of the drug. It generates hydrogen peroxide, hydroxyl, and methyl-free radicals, the latter being thought to alkylate DNA, resulting in degradation and chromosomal breaks; DNA synthesis, and hence protein synthesis, is impaired. It is approved as part of a combination therapy for *Hodgkin's disease.* The most important use of procarbazine is as a component of several combinations of choice for *Hodgkin's disease, nonHodgkin's lymphoma, mycosis fungoides, multiple myeloma,* and *medulloblastoma.* It is an alternative drug to treat non-small-cell *bronchogenic carcinoma;* it is rarely used alone. Cross resistance with other agents or radiation apparently does not occur.

Untoward reactions include frequent leukopenia, thrombocytopenia, anemia, less frequent nausea, and vomiting; rare reactions are anorexia, dry mouth, stomatitis, dysphagia, diarrhea, constipation, myalgia and arthralgia, chills and fever, sweating, fatigue, asthenia, lethargy, and drowsiness. Ascites, edema, effusions, cough, intercurrent infections, epistaxis, hemorrhaging, melena, pruritus, allergic dermatitis, allergic pneumonitis, flushing, alopecia, pigmentation, herpes, jaundice, headache, vertigo, depression, paresthesias, neuropathies, insomnia, nightmares, ataxia, confusion, coma, tremors, and convulsions may occur. Rarely, there may be hoarseness, hypotension, tachycardia, syncope, hemolysis, nystagmus, photophobia, photosensitivity, retinal hemorrhage, diplopia, papilledema, impaired hearing, and slurred speech. It is mutagenic, teratogenic, and carcinogenic in experimental animals. Thus, it must be regarded as a dangerous drug.

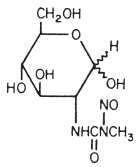
CNS depressants should not be given at the same time, except under supervision. Because the drug is a monoamine oxidase inhibitor, tricyclic antidepressants, various sympathomimetics and tyramine-containing foods should be avoided. Because it has disulfiram-like activity, patients should be warned against ingestion of alcoholic beverages. Caution must be exercised in the presence of liver damage, respiratory disorders, renal impairment, or bone-marrow depression.

It is absorbed almost completely by the oral route. It penetrates readily into the cerebrospinal fluid. Peak plasma and cerebrospinal fluid levels occur approximately 60 min after an oral dose. It is metabolized rapidly and auto-oxidized, with an elimination half-life of only approximately 7 min. Almost none is excreted unchanged.

SODIUM IODIDE I 131—See Chapter 29
SODIUM PHOSPHATE P 32—See Chapter 29.

STREPTOZOCIN

D-Glucopyranose, 2-deoxy-2[[(methylnitrosoamino)carbonyl]amino]-, Streptozocin; Zanosar



[18883-66-4] $C_8H_{15}N_3O_7$ (265.22).

Preparation—A nitrosourea antibiotic isolated from *Streptomyces achromogenes* fermentation broth; also synthesized; *J Am Chem Soc* 1969; 52:2555.

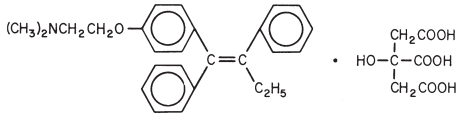
Description—Plates or prisms; melts about 115° with decomposition.

Solubility—Soluble in water or in alcohol.

Comments—It is approved for and has become the drug of first choice (in combination with fluorouracil) for treatment of *islet-cell carcinoma.* It also is used with fluorouracil and mitomycin for *pancreatic carcinoma.* It is an alternative drug for use against *malignant carcinoid tumors, non-small cell lung cancer, squamous cell carcinoma of the oral cavity,* and *hepatomae.* Acute adverse effects include severe nausea and vomiting, proteinuria, local pain at the site of administration, and chills. Renal damage is the principal delayed toxicity, but hepatotoxicity also occurs. Bone-marrow depression occurs in approximately 20% of recipients. The drug is mainly metabolized; its half-life is approximately 15 min. Dosage adjustments are recommended with decreased renal function.

TAMOXIFEN CITRATE

(*Z*)-2-[4-(1,2-diphenyl-1-butenyl)phenoxy]-*N*,*N*-dimethyl-, Nolvadex



(*Z*)-2- [p - (1,2-Diphenyl-1-butenyl)phenoxy]-*N*,*N*-dimethylethylamine citrate (1:1) [54965-24-1] $C_{26}H_{29}NO.C_6H_8O_7$ (563.65).

Preparation—4-β-Dimethylaminoethoxy-α-ethyldesoxybenzoin by reaction with phenylmagnesium bromide or phenyl lithium is converted to 1-(4-β-dimethylaminoethoxyphenyl)-1,2-diphenyl butanol, which on dehydration yields a mixture of tamoxifen and its cis-isomer that may be separated with petroleum ether; tamoxifen is converted to the 1:1 citrate for dispensing use. See *Nature* 1966; 212:733; *CA* 1967; 67:90515g.

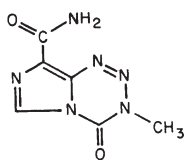
Description—White, crystalline powder; melts about 140°.

Comments—A nonsteroidal antiestrogen approved for palliative therapy of breast cancer in men and postmenopausal women. It is also effective as adjuvant therapy in axillary node-negative or node-positive breast cancer following total mastectomy, axillary dissection, and breast irradiation. The drug competes with estrogens for cytosol estrogen receptors and thus blocks estrogen effects in the target tissue. Tumors with negative receptor assays do not respond to it. Adverse effects frequently reported are hot flashes, nausea, and vomiting. The drug also can cause weight gain, vaginal bleeding and discharge, rashes, transient leukopenia, increased hepatic enzymes, and thrombocytopenia. Increased bone and tumor pain may occur. Infrequent side effects are deep vein thrombosis and hypercalcemia.

The oral bioavailability is 25% to 100%. The half-life of a single dose is 18 hr, but it is only 7 hr at steady state.

TEMOZOLOMIDE

Imidazo[5,1-*d*]-*as*-tetrazine-8-carboxamide, 3,4-dihydro-3-methyl-4-oxo-,Temodar



[85622-93-1] $C_6H_6N_6O2$ (194.15).

Preparation—The dimethyl ester of 4-aminopyrazole-3,5-dicarboxylic acid is diazotized with sodium nitrite and HCl and the diazonium salt treated with methylamine to yield the product. *J Med Chem* 1995; 38:1496

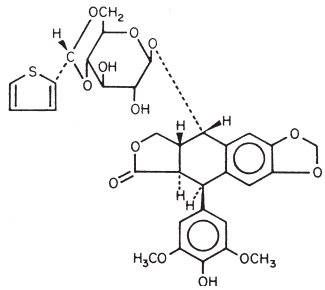
Description—White to light tan powder melting about 180°. It is the prodrug for *dacarbazine* which is formed by hydrolysis of the amide group (carbonyl and adjacent *N*-atom bearing the methyl group) in the tetrazine ring. The molecule is stable below pH 5 but rapidly transforms to *dacarbazine* at pH >7; $[\alpha]^{20}_D$ +43 ± 2°, c = 1, water).

Solubility—(mg/mL) Water (3), ethanol(1), DMSO(22–25),

Comments—Undergoes rapid non-enzymatic conversion at physiologic pH to the reactive ompound, 3-methyl-(triazen-1-yl)imidazole-4-carboxamide(MTIC), whick alkylates DNA. Alkylation (methylation) occurs mainly at the O^6 and N^7 positions of guanine. Indicated for the treatment of adults with refractory anaplastic astrocytoma who have experienced disease progression on a drug regimen containing a nitrosourea and procarbazine. Completely absorbed after oral administration; food reduces the rate and extent of absorption. Rapidly eliminated with a mean elimination half-life of 1.8 hours and mean apparent volume of distribution of 0.4 L/kg (%CV=13%). It is weakly bound to human plasma proteins, with an overall clearance of about 5.5 L/h/m^2. Most frequently occurring adverse effects were nausea and vomiting, fatigue, headache, and dose-limiting myelosuppression (thrombocytopenia and neutropenia).

TENIPOSIDE

Furo[3′,4′:6,7]naphtho[2,3-*d*]-1,3-dioxol-6(5a*H*)-one, [5*R*-[5α,5aβ,8aα,9β(*R)]]-5,8,8a,9-tetrahydro-5-(4-hydroxy-3,5-dimethoxyphenyl)-9-[[4,6-*O*-(2-thienylmethylene)-β-D-glucopyranosyl]oxy]-, VM-26; Vumon**



[29767-20-2] $C_{32}H_{32}O_{13}S$ (656.66).

Preparation—A semisynthetic derivative of podophyllotoxin.

Description—White crystals that melt about 245°.

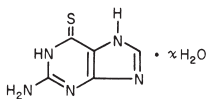
Comments—A drug related to podophyllotoxin and similar to etoposide in antieoplastic activity. It arrests the cell cycle in late S and G_2 phases. It is approved for use in *relapsed or refractory acute lymphocytic leukemia in children.* It is an alternative drug for the treatment of *cutaneous T-cell lymphoma, Kaposi's sarcoma,* and *small cell lung brain metastases.* The principal adverse effects (leukopenia, thrombocytopenia, etc) result from myelosuppression, but hypotension, thrombophlebitis, and anaphylaxis also occur. The drug is not absorbed orally. In plasma it is almost completely protein bound. It is eliminated mainly by hepatic metabolism, with a half-life of 8 to 24 hr.

TESTOLACTONE—see RPS-19, page 1104.

TESTOSTERONE PROPIONATE—see RPS-19, page 1105.

THIOGUANINE

6*H*-Purine-6-thione, 2-amino-1,7-dihydro-, Tabloid



2-Aminopurine-6(1*H*)-thione [154-42-7] $C_5H_5N_5S$ (167.19); *hemihydrate* [50322-14-0] (176.20).

Preparation—By thionation of guanine with phosphorus pentasulfide. US Pat 2,884,667.

Description—Pale yellow, crystalline powder, odorless or practically odorless.

Solubility—Insoluble in water, alcohol, or chloroform; freely soluble in dilute solutions of alkali hydroxides.

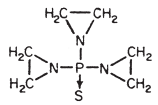
Comments—An antimetabolite of guanine which is converted into 6-thioguanine-ribose-phosphate; this not only is incorporated into DNA and RNA but also interferes with guanine synthesis. It acts mainly in the S phase of the cell cycle, but cell replication ultimately is prevented. It also promotes differentiation of some cancer cells. Its actions are very similar to those of mercaptopurine, some of which is converted to thioguanine and cross resistance occurs between the two drugs; however, its actions and uses are not identical. It is approved for *acute nonlymphocytic leukemia.* With other drugs, thioguanine is a component of combinations that are treatments of choice for *AMLs* and the *acute phase of chronic granulocytic leukemia.* It is an alternative drug for use against *acute lymphocytic leukemia.* It sometimes is used in the stable phase of *chronic myelocytic leukemia.* It also is a potent *immunosuppressive drug,* but its status has yet to be settled. It has been used especially in the treatment of *nephrosis* and *collagen-vascular disorders.*

Its adverse effects are virtually the same as those for mercaptopurine (see page 1497), except that the incidence of GI toxicity is less and there is no adverse interaction with allopurinol.

It is metabolized nearly completely in the body; the 6-thiol group is methylated and the 8-amino group removed to yield 6-methyl-mercaptopurine. Xanthine oxidase is not involved.

THIOTEPA

Aziridine, 1,1′,1″-phosphinothioylidynetris-, Triethylenephosphoramide; Thioplex



[52-24-4] $C_6H_{12}N_3PS$ (189.2).

Preparation—By condensing ethylenimine with thiophosphorylchloride ($PSCl_3$) in the presence of triethylamine as the acid receptor.

Description—Fine, white, crystalline flakes; faint odor; melts about 54°.

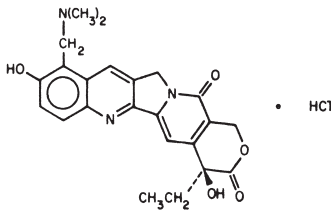
Solubility—1 g in 13 mL water, 8.3 mL alcohol, 1.9 mL chloroform, or 4.1 mL ether.

Comments—An alkylating agent. However, it has a much lower chemical reactivity than the β-chloroethylamines and hence has a low degree of local irritancy and lacks the vesicant properties. For this reason it currently is used mainly for local application, where appropriate. It is approved for use in *adenocarcinoma of the breast and ovary.* Local instillation into the urinary bladder for *papillary carcinoma* is sometimes effective. It also may be instilled into other cavities (ie, intrathecally) to control serous infusions consequent to certain neoplasms. It occasionally may be infiltered directly into tumors, especially obstructive lesions. Given systemically, its bone-marrow toxicity is unpredictable, so that such use is dangerous; consequently, it is nearing obsolescence for systemic treatment. The neoplasm for which it is still a possible desperation choice is *embryonal rhabdomyosarcoma.*

Local adverse effects include local pain, weeping, and occasional perforation through the lesion. The most serious systemic adverse effect is bone-marrow depression, characterized by neutropenia, thrombocytopenia, and usually low-grade anemia. It is mandatory to monitor the blood-cell counts. The effects may not appear for 5 to 30 days, which complicates management. Anorexia, nausea, and vomiting are not as common as with other alkylating agents. Headache, dizziness, fever, and tightness in the throat may occur. Hyperuricemia may result from massive cell destruction, and crystalluria and oliguria are possible. Hypersensitivity is uncommon, but hives, skin rash, and even anaphylaxis can occur. Depression of spermatogenesis and ovarian function have been reported. Systemic side effects from local instillation can occur. It is excreted mostly unchanged, so that the dose should be reduced in renal failure. It is contraindicated if there is previous bone-marrow depression or pregnancy.

TOPOTECAN HYDROCHLORIDE

1*H*-Pyrano[3′,4′:6,7]indolizino[1,2-*b*]quinoline-3,14(4*H*,12*H*)-dione, 10-[(dimethylamino)methyl]-4-ethyl-4,9-dihydroxy-, monohydrochloride; Hycamtin



[119413-54-6] $C_{23}H_{23}N_3O_5.HCl$ (457.92).

Preparation—Semisynthetic derivative of camptothecin derived from *Camptotheca acuminata. J Med Chem* 1991; 34:98.

Description—Light yellow to greenish-yellow crystals that melt about 215° (dec).

Solubility—Soluble 1 mg/mL in water.

Comments—Indicated in metastatic ovarian cancer that has failed at least one round of alternative therapy. It is a potent inhibitor of topoisomerase I. It causes the enzyme to freeze at a step in catalysis where it exists as a covalent adduct to a nicked strand of the DNA helix. Cancer-cell resistance to this drug may arise from lowered levels of topoisomerase I or from specific topoisomerase I mutations.

It undergoes reversible hydrolysis of the lactose moiety to yield a pharmacologically inactive ring-opened form. Liver metabolism plays only a minor role in inactivation of the drug. Approximately 30% of the drug is excreted in the urine; thus renal clearance is important. It exhibits multiexponential elimination from the plasma with a terminal half-life of approximately 2.5 hr. Approximately 35% is bound to plasma proteins. It is given by IV infusion over 30 minutes for 5 days every 21 days.

Bone-marrow suppression is its dose-limiting toxicity, most commonly neutropenia. The drug should not be administered if baseline neutrophil counts are less than 1500/mm^3 or platelet counts less than 100,000/mm^3. Neutropenia is most common during the first course of treatment, approximately a 60% frequency, but occurs during all courses at approximately a 40% frequency. The nadir of the neutrophil count is approximately 11 days. Thrombocytopenia occurs in approximately 25% of patients. Anemia occurs in approximately 40% of patients, with the nadir in RBC count at approximately day 15. It may harm the fetus and may appear in breast milk. Nausea and vomiting and total alopecia are noted in approximately 50% of patients.

TRETINOIN

Vesanoid

See page 1288 for full monograph.

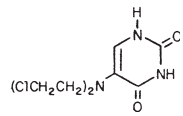
Comments—Approved for induction of remission in patients who have acute promyelocytic leukemia displaying the t(15;17) translocation and who are refractory or who have relapsed from anthracycline therapy. It is a transretinoic acid related to vitamin A. It induces differentiation of promyelocytic cell and can induce complete remissions. Administered daily for as long as 90 days, it induced complete remissions in 50% to 80% of relapsed patients. It induces leukocytosis in approximately 40% of patients.

A single 45-mg/m^2 oral dose yields peak blood concentrations in approximately 1.5 hr; it is >95% bound to plasma proteins, largely albumin. Approximately 65% of a dose appears in the urine within 72 hr; approximately 30% appears in the feces within for 6 days. Cytochrome P-450 is involved in the metabolic activation of this drug, and several metabolites have been identified. This metabolism in inducible, and blood levels decrease by approximately one third after a 1-wk continuous treatment. Ketoconazole pretreatment led to a 72% increase in tretinoin AUC.

Almost all patients experience adverse reactions characteristic of high-dose vitamin A ingestion. Fever, headache, skin dryness, bone pain, malaise, chest discomfort, edema, DIC, etc. It can induce benign intracranial hypertension. Symptoms include headache, nausea, and visual disturbances. GI hemorrhage, pain, diarrhea, and constipation have been reported.

URACIL MUSTARD

2,4(1*H*, 3*H*)-Pyrimidinedione, 5-[bis(2-chloroethyl)amino-, Uramustine; Uracil Mustard



5-[Bis(2-chlorethyl)amino]uracil [66-75-1] $C_8H_{11}Cl_2N_3O_2$ (252.10).

Preparation—Using 5-aminouracil, ethylene oxide and thionyl chloride as reactants.

Description—Off-white, crystalline powder; odorless; melts about 200° with decomposition. Unstable in high humidity or aqueous vehicles.

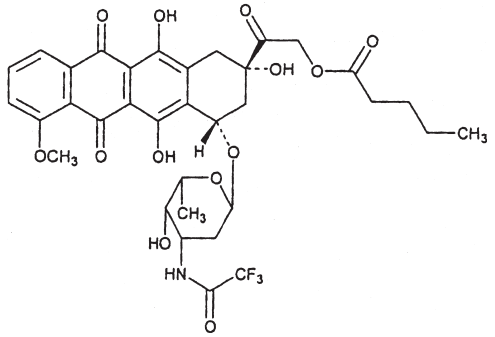
Solubility—1 g in more than 1000 mL water or in 50 mL alcohol.

Comments—An alkylating agent of the nitrogen-mustard-type. It is essentially an obsolete drug, having been displaced by the more efficacious and less toxic chlorambucil. However, this drug still may have a special use in the treatment of *primary thrombocytosis.* Other neoplasms for which the drug is used occasionally are non-Hodgkin's lymphomas, chronic lymphocytic leukemia, chronic myelocytic leukemia, mycosis fungoides, and polycythemia vera. The most common untoward effects are nausea, vomiting, and diarrhea. Pruritus, dermatitis, and partial alopecia do occur, but less frequently than with cyclophosphamide. Nervousness, irritability, depression, amenorrhea, and oligospermia occur infrequently. Bone-marrow depression with leukopenia, thrombocytopenia, and even anemia may occur, and the blood counts must be monitored twice a week during the first month of treatment. The bone-marrow damage may become irreversible when

the cumulative dose approaches 1 mg/kg. Rapid involution of tumors may cause hyperuricemia and consequent nephropathy and renal failure, so that plasma uric acid levels should be determined regularly and the patients should drink a lot of water.

VALRUBICIN

Pentanoic acid, (2*S*-*cis*)-2-[1,2,3,4,6,11-hexahydro-2,5,12-tri-hydroxy-7-methoxy-6,11-dioxo-4-[[2,3,6-trideoxy-3-[(trifluoro-acetyl)amino]-α-L-*lyxo*-hexopyranosyl]oxy]-2-naphtha-cenyl]-2-oxoethyl ester; Valstar



[56124-62-0] $C_{34}H_{36}F_3NO_{13}$ (723.65).

Preparation—US Pat 4,035,566 (1977).

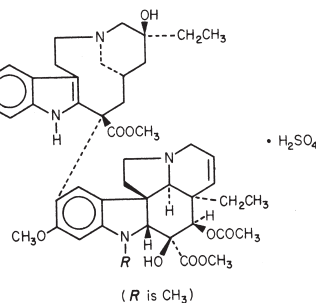
Description—Orange or orange-red powder; highly lipophilic.

Solubility—Soluble in methylene chloride, ethanol, methanol or acetone; relatively insoluble in water.

Comments—indicated intravesically for the treatment of BCG-refractory carcinoma *in situ* (CIS) of the urinary bladder in patients who are not candidates for immediate cystectomy because of unacceptable morbidity or mortality. Principal toxicity is local bladder irritation, which occurs during or shortly after instillation in most patients receiving the drug and usually resolves within 1 to 7 days. The most common local bladder symptoms reported are urinary frequency, urinary urgency, and dysuria, which occur in 61%, 57%, and 56% of patients, respectively. Bladder spasm, hematuria, and bladder pain have been reported in 31%, 29%, and 28% of patients, respectively. It must not be administered intravenously.

VINBLASTINE SULFATE

Vincaleukoblastine, sulfate (1:1) (salt); Velban



(*R* is CH_3)

[143-67-9] $C_{46}H_{58}N_4O_9.H_2SO_4$ (909.06).

Preparation—By extracting the leaves, bark, or stems of *Vinca rosea* with aqueous or aqueous-alcoholic sulfuric acid, isolating the alkaloid from the extract by the usual precipitation and solvent techniques and purifying by chromatography on aluminum oxide. Conversion to the (1:1) sulfate may be effected by dissolution of the alkaloid in an equimolar quantity of dilute H_2SO_4 and either evaporating to dryness or precipitating with a suitable organic solvent. US Pat 3,097,137.

Description—White to slightly yellow, amorphous or crystalline powder; odorless; hygroscopic.

Solubility—Freely soluble in water.

Comments—Interferes with the assembly of the microtubules, by combining with tubulin; the result is mitotic arrest in metaphase. However, there is also evidence that vinblastine exerts its antineoplastic effect by interfering with glutamate and aspartate metabolism. The antineoplastic spectrum and toxicity are much different than for vincristine, which also interacts with tubulin. It is approved for use in *advanced Hodgkin's disease, lymphocytic* and *histiocytic lymphoma, mycosis fungoides, testicular cancer,* and *Kaposi's sarcoma.* This drug is a component of first-choice combinations for the treatment of *testicular carcinoma, Hodgkin's disease,* and *bladder cancer.* It is an alternative drug for *choriocarcinoma, squamous cell carcinoma* of the head and neck, *renal-cell carcinoma, neuroblastoma, breast tumors, cervical carcinoma, Kaposi's sarcoma, melanoma,* and *mycosis fungoides.* It also has been used to treat lymphosarcoma, lymphocytic lymphoma, reticulum-cell sarcoma, and Letterer-Siwe's disease. This drug is subject to pleiotropic drug resistance.

Nausea, vomiting, headache, and paresthesias occur within 4 to 6 hr and last from 2 to 10 hr. Severe bronchospasm may occur, especially if mitomycin has been given. Diarrhea, constipation, adynamic ileus, anorexia, and stomatitis also may occur and are premonitory of neurotoxic effects, such as severe headache, malaise, mental depression, paresthesias, and loss of deep tendon reflexes. Neurotoxicity occurs in 5% to 20% of cases, more frequently at higher doses. CNS damage occasionally is permanent when excessive doses have been used. Blindness and death have been reported. Alopecia occurs in approximately 30 to 60% of users, but it generally is reversible. Mild bone-marrow depression with leukopenia occurs in a high percentage of patients and may require discontinuation of the drug. The thrombocytes are less affected, unless other thrombocytogenic drugs also are being given or recently have been given. Anemia is rare. The blood-cell count must be determined weekly. The drug is toxic locally, and extravasation should be avoided. It may cause phlebitis at the site of injection. Inappropriate secretion of ADH may occur. It is teratogenic in animals, and probably should not be used during the first trimester of pregnancy.

In plasma it is approximately 75% protein bound. It manifests three-compartment kinetics, the second phase having a half-life of 1 to 1.5 hr and an elimination half-life of 18 to 40 hr. It is metabolized largely by the liver and doses should be reduced by 50% in patients who have impaired liver function.

VINCRISTINE SULFATE

Vincaleukoblastine, 22-oxo-, sulfate (1:1) (salt); Oncovin; Vincasar PFS

Leurocristine sulfate (1:1) (salt) [2068-78-2] $C_{46}H_{56}N_4O_{10}.H_2SO_4$ (923.04).

The structure is the same as for *Vinblastine Sulfate,* except that *R* is CHO, an aldehyde.

Preparation—With suitable modifications in the chromatographic part of the process, vincristine sulfate may be prepared as described above for *Vinblastine Sulfate.* US Pat 3,205,220.

Description—White to slightly yellow, amorphous or crystalline powder: odorless; hygroscopic.

Solubility—Freely soluble in water.

Comments—Combines with the protein tubulin and prevents assembly of microtubules, thus disrupting various cellular processes, including spindle formation and mitosis. Synthesis of RNA and proteins also is suppressed. It is approved for use in *Hodgkin's lymphomas, rhabdomyocsarcoma, neuroblastoma,* and *Wilms' tumor.* The alkaloid is the second most widely used of the antineoplastic drugs. It is especially useful in the treatment of hematological malignancies. It is a component in 27 first-choice combinations for the treatment of *acute lymphocytic leukemia,* the *acute phase of chronic myelocytic leukemia, Hodgkin's disease, non-Hodgkin's lymphoma, Burkitt's lymphoma, diffuse histiocytic lymphoma, follicular lymphoma, cervical carcinoma, oat-cell bronchogenic carcinoma, Wilms' tumor, medulloblastoma, soft-tissue sarcomas, Ewing's sarcoma,* and *embryonal rhabdomyosarcoma.* It is an alternative drug for treatment of *breast carcinoma, cervical carcinoma, testicular carcinoma, glioblastoma, neuroblastoma,* and *chronic lymphocytic leukemia.* Some authorities prefer to use this drug only to induce remissions and not for maintenance, because chronic use often results in neurotoxicity. Cross resistance to other drugs occurs by means of pleiotropic drug resistance.

It differs from most other antineoplastics in that bone-marrow depression frequently does not occur; this is one reason why vincristine is used in combinations. However, leukopenia can occur, and WBC counts should be made before each dose. Treatment usually is limited by the neurotoxic effects. Adverse effects usually begin with nausea, vomiting, constipation, abdominal cramps, and weight loss; these effects readily are reversible. Severe bronchospasm may occur, especially if mitomycin has been given. The drug also may cause slowly reversible reactions, such as alopecia and peripheral neuropathy, Serious neuropathic effects may occur; they include loss of deep tendon reflexes, neuritic pain, numbness of extremities, headache, ataxia, and visual defects; paresis or paralysis and atrophy of certain extensor muscles may occur late; paralysis of cranial nerves 2, 3, 6, and 7 may occur. Neuropathies may persist for several months. Severe hypertension, agitation, or mental depression also may occur transiently. The drug is toxic locally, and extravasation should be avoided. It is best given into the tubing of a running intravenous solution.

It is cleared rapidly from the blood. It manifests three-compartment kinetics, with half-lives of 0.08, 2.3, and 85 hr. Seventy percent is secreted into the bile. In obstructive jaundice or impaired liver function the toxicity is greater, and the dose should be reduced by 50%. Approximately 12% is excreted in urine. It does not penetrate into the brain, hence it cannot be used for CNS leukemias. Caution must be taken never to administer this agent intrathecally as it will result in death of the patient.

VINORELBINE

Didehydrodeoxynorvincaleukoblastine; Navelbine

$C_{45}H_{54}N_4O_8.2C_4H_6O_6$

Preparation—White to yellow or light brown amorphous powder

Description—Large dimeric asymmetric compound composed of a dihydroindole nucleus (vindoline), which is the major alkaloid present in the periwinkle (*Catharanthus roseus* [Apocynaceae]), and an indole nucleus (catharanthine), which is present in low concentrations in the plant.

Solubility—aqueous solubility of the drug exceeds 1000 mg/mL in distilled water; pH of approximately 3.5.

Comments—Vinorelbine is a semisynthetic vinca alkaloid whose mechanism of action is identical to that of vinblastine and vincristine (ie, inhibits cell mitosis in the M phase through inhibition of tubulin polymerization) resulting in inhibition of microtubule assembly and cellular metaphase arrest. Indicated for the treatment of unresectable, advanced non-small cell lung cancer (NSCLC) as a single agent or for Stage III or IV NSCLC in combination with cisplatin for first-line treatment. Also active for metastatic breast cancer, Hodgkin's disease, and advanced ovarian cancer. Myelosuppression with neutropenia is the dose-limiting toxicity, but nausea and vomiting, transient elevations in liver function tests, mild to moderate peripheral neuropathy (paresthesias, loss of deep tendon reflexes, myalgias) and SIADH are also reported. Dosage must be adjusted for hepatic insufficiency. Caution must be used to avoid extravasation as it is a vesicant.

Extensively metabolized in the liver by the cytochrome P-450 (CYP3A) isoenzymes to two metabolites, vinorelbine *N*-oxide and deacetylvinorelbine. Deacetylvinorelbine, the primary metabolite, has been shown to possess antitumor activity similar to the parent drug. Concurrent administration of drugs that effect CYP3A isoenzyme may effect the metabolism of this agent and cause increased toxicities. A steady-state volume of distribution of 25.4–40.1 L/kg has been reported and mean terminal elimination half-life of 27.7–43.6 hours and a mean plasma clearance of 0.97–1.26 L/hour per kg have been reported.

CHAPTER 87

Immunoactive Drugs

Daniele K Gelone, PharmD

The immune system is a highly orchestrated specialized series of responses the immune system is quite complex. Several types of cells are involved. These are cells, the ancestral line of which has derived from bone marrow stem cells. Some of the descendants of the stem cells migrate to sites elsewhere in the body, where they become small lymphocytes. There are two general types of lymphocytes involved in the immune responses: the B cells and the T cells. The B lymphocytes get the designation B from the fact that in birds they derive from stem-cell clones in the bursa of Fabricus; in man, the location of analogous clones may be in the intestinal mucosal Peyer's patches. The T cells get their designation from the fact that they are derived from stem cells cloned in the thymus gland. Undifferentiated lymphocytes take up residence in lymph tissue in the spleen, tonsils, intestines, and other sites.

B and T cells respond to antigen by cellular transformation, proliferation, and differentiation. Proliferation increases the population of immunocompetent cells and differentiation creates cells with various roles to play in the immune response. Both B and T cells differentiate into what broadly may be termed effector cells and memory cells. The memory cells revert to an inactive state (G_0) but respond to later immune challenge by accelerated proliferation, differentiation, and activity. During their residence in the bursa equivalent, the future effector B cells become programmed to respond to an antigen by transformation into plasma cells, which produce antibodies (immunoglobulins I_A, I_D, I_E, I_G, and I_M), the role of which is to combine with circulating antigens. The immunity conferred by B cells is known as humoral immunity.

Hypersensitivity mediated through the humoral immune system is called immediate hypersensitivity, because the response is rapid. T cells become programmed in the thymus to respond in various ways to antigen that has become fixed to cell surfaces or engulfed by macrophages. The cytotoxic T cell (effector cell, *killer* cell), with the aid of complement, attacks and lyses those cells to which the offending antigen is attached. There are different cytotoxic T cells for different antigens. There are also helper T cells, which promote B-cell activity, and suppressor T cells, which restrain both the cytotoxic T cells and the B cells. Helper and suppressor B cells also exist. T-cell-mediated immunity is known as cell-mediated immunity. This is the immune response involved in graft rejection, autoimmunity, and delayed hypersensitivity.

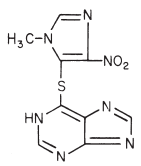
The priming of lymphocytes in response to antigen is known as the primary response. The final effector response is known as the secondary, or efferent, response.

There are other bone-marrow, stem-cell-derived cells, such as macrophages and K cells that participate in the immune response. In the primary response, the macrophages phagocytose antigens, process them, and present the processed antigen to helper T lymphocytes, which initiate the recruitment of other lymphocytes. Thus the macrophages are an integral part of the afferent limb of the primary response. They also appear to be involved in the efferent response; they fix and alter antigen prior to its recognition by the T cells.

IMMUNOACTIVE AGENTS—An immunoactive drug is one that can attenuate the expression of at least one type of immune response. The numerous cell types involved in the immune system afford an equal number of places of immunosuppressive drugs to intervene. It is conceivable that a T cell responsive to one antigen may be affected more than is another T cell specific to another antigen, or that suppressor T cells might be affected more than cytoxic or helper T cells.

AZATHIOPRINE

1*H*-Purine, 6-[(1-methyl-4-nitro-1*H*-imidazol-5-yl)thiol]-, Imuran



6-[(1-Methyl-4-nitroimidazol-5-yl)thio]purine [446-86-6] $C_9H_7N_7O_2S$ (277.26).

Preparation—-*N*,*N*'-Dimethyloxaldiamide is reacted with phosphorus pentachloride to give 5-chloro-1-methylimidazole. This is nitrated, and the resulting 5-chloro-1-methyl-4-nitroimidazole condensed with purine-6-thiol (mercaptopurine) in an appropriate dehydrohalogenating environment. US Pat 3,056,785.

Description—Yellow, matted powder that is odorless and has a slightly bitter taste; light sensitive, nonhygroscopic, and stable to reasonable temperatures; decomposes at approximately 245°.

Solubility—Insoluble in water; slightly soluble in alcohol or chloroform; soluble in dilute solutions of alkali hydroxides (unstable); sparingly soluble in dilute mineral acids.

Comments—Approved for prevention of renal transplant rejection. Azathioprine (AZA) is an imidazole derivative of the antimetabolite 6-mercaptopurine, which was developed in the 1950s. It is a pro-drug of 6-mercaptopurine (6-MP) and classified as an antimetabolite agent. It has been utilized by solid organ transplant clinicians for nearly 30 years. It was also commonly used in the treatment of a variety of autoimmune diseases like rheumatoid arthritis and certain malignancies, such as leukemia. After the introduction of cyclosporine, the role of AZA was consigned to that of an adjunctive agent. Although it had significantly impacted medical practice, resulting in the awarding of the Nobel prize, it has now been largely replaced at most transplant centers with newer more effective and better tolerated immunoactive agents (eg, mycophenolate mofetil or sirolimus).

AZA is rapidly converted in the liver and RBCs into 6-MP, which is then metabolized to an inactive metabolite, 6-thiouric acid. The active metabolite (6-MP) is incorporated into the cellular DNA inhibiting purine nucleotide synthesis and interfering with the synthesis and metabolism RNA. This effectively inhibits gene replication and

resultant T cell activation. It suppresses T lymphocyte and monocyte (hence macrophage) production more than B lymphocyte production. AZA works in the afferent and not the efferent immune phase and hence does not suppress ongoing graft rejection.

After oral administration, AZA is rapidly and incompletely absorbed. It is distributed quickly and widely throughout all body fluids. The bioavailability of AZA is ~15% with ~40% detected as 6-MP. Despite having relatively short plasma half-lives (~50 and 75 minutes, respectively), the affect on purine inhibition and subsequent T activation is significant and persists much longer than either AZA or 6-MP. Clinical experience has indicated that once daily dosing is adequate as dosing regimens greater than twice daily administration have failed to improve therapeutic results. Clinicians have often employed a milligram-per-milligram conversion between the oral and intravenous doses for the sake of simplicity. However, given the bioavailability, some recommend reducing the intravenous dose to one half the oral dose. Acute toxicity is seen more frequently after intravenous administration, particularly with long courses of therapy, and is most likely caused by greater bioavailability. Full doses may be appropriate in patients' whose complete blood count is normal.

The parent compound and its metabolites are excreted primarily in the urine; however, dosage adjustments are not recommended in renal failure as the kinetics of the active compounds are unaltered. Dosage adjustments may be necessary in patients experiencing oliguria or tubular necrosis immediately status post cadaveric renal transplant.

Myelosuppression, manifested as leukopenia, megaloblastic anemia, or thrombocytopenia, is the major dose-limiting adverse event associated with azathioprine occurring in ~11% of patients. It appears approximately 2 weeks post initiation of the agent. Dosage adjustments should be based according to complete blood counts, white blood cells >3500/mm^3, and platelets. Nausea, vomiting, and diarrhea are frequent and may occur acutely. Occasionally, hepatotoxicity may occur and is reflected by abnormal liver function tests, including elevated bilirubin or transaminases, but damage seems slight and seems to disappear during the course of treatment. However, in the presence of liver dysfunction the drug should be withheld. Other toxicity or intercurrent infection occurs in approximately one-third of patients under immunosuppressive treatment with the drug.

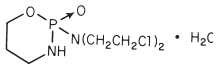
In antiarthritic doses, infections are not increased, and other adverse effects are less frequent and less severe. Pancreatitis, alopecia, arthralgia, skin rashes, serum sickness, stomatitis, esophagitis, steatorrhea, retinopathy, peritoneal hemorrhage, and pulmonary edema also may occur in a small percentage of cases. Although the incidence is rare, an increase in reticulum cell sarcoma and lymphoma has been noted in transplant patients receiving azathioprine. The incidence of adverse effects is less when azathioprine is used in combination regimens, which allows clinicians to reduce doses of the agents. All immunosuppressants increase the risk of infections as well as certain types of cancer, including post-transplant lymphoproliferative disease.

It should be noted that a clinically significant drug-drug interaction exists between allupurinol and aziothioprine. Allupurinol, a xanthine-oxidase inhibitor, impairs the degradation of 6-MP resulting in significantly increased plasma concentrations of 6-MP. If not appropriately recognized and managed, concomitant use of these agents may result in a life-threatening pancytopenia. Thus, azathioprine therapy is considered a contraindication to allopurinol use. If necessary, allopurinol should be used with extreme caution and requires dose reductions of 60% to 80% to azathioprine, followed by more frequent monitoring of complete blood counts. Mycophenolate mofetil is preferred as an alternate to azathioprine as it does not interact with allopurinol.

Therapeutic drug monitoring of azathiorpine or 6-MP is not performed. In organ transplantation doses are based on milligram per kilogram basis. Most protocols employ initial doses ranging from 1mg/kg to 3mg/kg of body weight administered as a single daily dose. Doses are typically adjusted thereafter according to complete blood counts. Doses should reduced or discontinued in the face of hepatotoxicity or cytopenia

CYCLOPHOSPHAMIDE

2*H*-1,3,2-Oxazaphosphorin-2-amine, *N,N*-bis(2-chloroethyl)-tetrahydro-, 2-oxide, monohydrate; Cytoxan; Neosar



[6055-19-2] $C_7H_{15}Cl_2N_2O_2P.H_2O$ (279.10); anhydrous [50-18-0] (261.09).

Caution: Great care should be taken to prevent inhaling its particles and exposing the skin to it.

Preparation—3-Amino-1-propanol is condensed with *N,N*-bis(2-chloroethyl)phosphoramidic dichloride [$(ClCH_2CH_2CH_2)_2N–POCl_2$] in dioxane solution under the catalytic influence of triethylamine. The condensation is double, involving both the hydroxyl and the amino groups, thus effecting the cyclization.

Description—White, crystalline powder; liquefies on loss of its water of crystallization.

Solubility—1 g in approximately 25 mL water; soluble in alcohol.

Comments—An alkylating agent. Unlike other β-chloroethylamino alkylators, it does not cyclize readily to the active ethyleneimonium form until activated by hepatic enzymes. The liver is protected by the further metabolism of activated metabolites to inactive end products. Thus, the substance is stable in the GI tract, tolerated well, and effective by the oral and parenteral routes; it does not cause local vesication, necrosis, phlebitis, or even pain.

Cyclophosphamide is approved for Stage III and IV, malignant lymphomas, multiple myeloma, leukemias, mycosis fungoides, neuroblastoma, retinoblastoma, nephritic syndrome, and carcinoma of the breast. Its use in solid organ transplantation has been limited to rare instances. In prior years, it was employed as an alternative in patients experiencing leukopenia or hepatotoxicity with azathioprine use. In more recent years, it has been relegated to rare use in solid organ transplantation recipients undergoing rejection episodes characterized as severe, refractory, or extended episodes that are resistant to conventional/standard therapies.

It has been shown to be of value in the treatment of rheumatoid arthritis, Wegner's granulomatosis, hemophilia A with factor VIII destruction, idiopathic thrombocytopenic purpura (alone or in combination), erythroid aplasia, childhood nephrotic syndrome, pemphigus and vulgaris, dermatomyositis, or systemic lupus erythematosus. The long-term toxicities of cyclophosphamide should be considered if the drug is to be used as other than a cancer chemotherapeutic agent.

Cyclophosphamide is one of the most potent immunosuppressive agents, inhibiting both humoral and cell-mediated immunity. It is a prodrug. The drug is metabolized by the hepatic microsomal system to alkylating metabolites, adolphosphamide and 4-hydroxycyclophosphamide, that, in turn, are converted to phosphoramide mustard and acrolein, which are thought to be responsible for its cytotoxic effects.

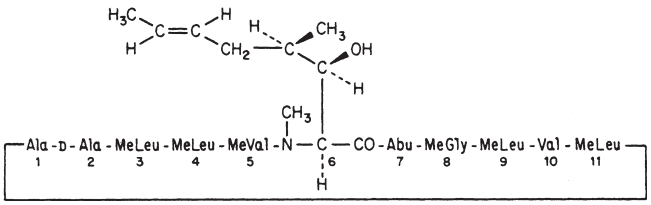
After oral administration, cyclophosphamide is well absorbed yielding >75% bioavailabilty. Cyclophosphamide and its metabolites are distributed throughout the body. It is distributed to the tissues with a volume of distribution greater than the total body water. It is undergoes extensive metabolism in the liver through the cytochrome p450 mixed function oxidase enzymes with up to ~30% of the drug excreted unchanged in the urine. High doses rapidly induce the metabolism of the drug.

Approximately 25% of the drug is protein bound. The half-life of cyclophosphamide following oral and intravenous administration range from ~1 to 6.8 hours and ~4 to 16 hours, respectively. Renal or hepatic dysfunction does not require dosage alterations. However, dosage adjustments may be necessary in patients undergoing hemodialysis as ~72% of cyclophophamide is removed after 6-hour hemodialysis treatment.

Cyclophosphamide causes dose dependent bone marrow suppression. Leukopenia is the inevitable side effect and is used as an index of dosage. Clinicians should monitor white blood counts (avoidance of WBC <3500/mm^3) with expected nadir typically occurring within 2 weeks after therapy initiation. Dosages should be adjusted to achieve WBC between 4000 and 6000/mm^3. Anemia and thrombocytopenia may occur, although less frequently than leukopenia. Alopecia occurs in approximately 50% of patients receiving maximal prolonged treatment. Other side effects include sterile hemorrhagic cystitis in 20% of those receiving treatment, anorexia, nausea and vomiting (regardless of route of administration), anaphylactoid reactions, fever, hemolytic-uremic reaction, pulmonary infiltrates and fibrosis, mucosal ulcerations, dizziness, occasional, hypoprothrombinemia, nail ridging, cutaneous pigmentation, water intoxication, aspermia in males (3–6 months or longer in onset), anovulation in 30% to 50% of females, and occasional hepatic dysfunction. Bladder telangiectasis and abnormal urinary cytology occur; in long-term use, bladder fibrosis and transitional cell carcinoma occasionally occur. 2-Mercaptoethanesulfonate (Mesna) protects the bladder from this acrolein metabolite. The blood count should be monitored closely during induction and at least weekly thereafter. Cyclophosphamide is relatively platelet-sparing; cyclophosphamide is carcinogenic. All immunosuppressants increase the risk of infections as well as certain types of cancer, including post-transplant lymphoproliferative disease.

CYCLOSPORINE

Cyclosporine; Sandimmune, Gengraf, Neoral



[59865-13-3] $C_{62}H_{111}N_{11}O_{12}$ (1202.63).

Preparation—US Pat 4,117,118 (1978).

Description—A fungal metabolite first isolated from cultures of *Trichoderma polysporum* and *Cylindrocarpon ilucidivum*. White, prismatic needles from acetone melting about 150°. $[\alpha]^{23}_{D}$ -244° (c = 0.6, chloroform); -189° (c = 0.5, methanol).

Solubility—Insoluble in water or alcohol.

Comments—Suppresses helper T lymphocytes without significantly affecting suppressor T or B lymphocytes. Thus, it is a selective immunosuppressive drug without the cytotoxicity characteristic of most other immunosuppressive drugs. Because it works only in the primary (afferent) immune phase, it must be administered before exposure to the attacking antigen. It has a modest effect to suppress some humoral immunity.

Cyclosporine is a nonpolar, cyclic polypeptide antibiotic consisting of 11 amino acids of fungal origin. The unique cyclic structure of the drug is responsible for its immunosuppressive effects. It gained widespread clinical use in the early 1980s and significantly improved 1-yr graft survival rates, which in turn revolutionized transplant clinical practice and ushered in the modern era of selective immunosuppressive therapy. For most centers, kidney transplant 1-yr graft survival rates improved from 50% to 90% the world over; however, longer-term graft survival rates of that period were not impacted to the same degree with the initiation of CSA. Over the past two decades, CSA has become a mainstay of therapy at many transplant centers today. It is usually employed in combination with other immunoactive agents allowing clinicians the opportunity to reduce doses and minimize side effects associated with each agent. Typically cyclosporine is used in triple combination maintenance regimens, which includes steroids and an additional immunosuppressive agent with distinct mechanism of action.

It is a very effective immunosuppressive and is approved for organ transplant rejection, prevention of cardiac, kidney, or liver transplant rejection, rheumatoid arthritis, and severe recalcitrant psoriasis. It is less successful in pancreatic, lung, or bone-marrow transplantation. It has also been employed in graft-versus-host disease and its prevention.

Cyclosporine is a calcineurin phosphatase inhibitor, which inhibits T cell activation and proliferation, including production of interleukins from CD4 cells while sparing CD8 cells, B cells, macrophages, and granulocytes. The exact mechanism of immunosuppressive action of cyclosporine is not fully understood but appears to mainly involve inhibition of lymphocytic proliferation and function.

Following oral administration, cyclosporine is incompletely and variably absorbed. It exhibits considerable inter- and intra-individual variation, bioavailability ranging from 2% to 89%, depending on numerous variables including organ transplant type, individual patient, post-transplantation time, bile flow (micellar absorption of the drug involving bile), GI state (eg, decreased with diarrhea), and the formulation administered. Several oral preparations (Sandimmune, Neoral) are commercially available and corresponding bioavailability varies with each. Following oral administration with Sandimmune cyclosporine, oral bioavailabilty ranges from 10% to 90%, with overall absorption of ~30%. Oral absorption of Sandimmune is highly dependent on bile, which results in enhanced variability among patients experiencing diarrhea, diabetic gastroparesis, biliary diversion, or malabsorption. Currently, the Neoral formulation of cyclosporine has now largely replaced Sandimmune in clinical practice. Neoral imparts a much improved bioavailability ranging from 30% to 45%, less dependence on bile for absorption, more consistent oral absorption and less variable pharmacokinetic profile. However, some patients may still be maintained on the Sandimmune formulation. It should be noted that the oil-based Sandimmune formulation is not bioequivalent to the microemulsion Neoral formulation or its AB-rated generic equivalents.

Plasma levels peak in approximately 3.5 hr. In plasma, approximately 90% is protein bound, ~58% bound to red blood cells and ~33% bound primarily to lipoproteins. The pharmacokinetics are multicompartmental. The volume of distribution is 1 to 13 (average, 4) L/kg; it is concentration-dependent. Nearly all the drug is metabolized by cytochrome P-450 III in the liver and gut; 94% of the metabolites are excreted into the bile, and 6% are eliminated into the urine. The pharmacokinetic inter-/intra-patient variabilities exhibited by the CSA formulations may also be caused by inherent polymorphisms expressed by metabolic enzymes (cyp3A4) and or p-glycoprotein countertransport proteins. In infants and children, the volume of distribution and clearance are greater than in adults. Thus, pediatric and African-American patients may require increased dosages. Additionally, elderly patients or those experiencing liver dysfunction may require longer intervals between dosage administration. The elimination half-life is 10 to 27 hr; there is a circadian periodicity to the elimination rate, the rate being faster in the morning.

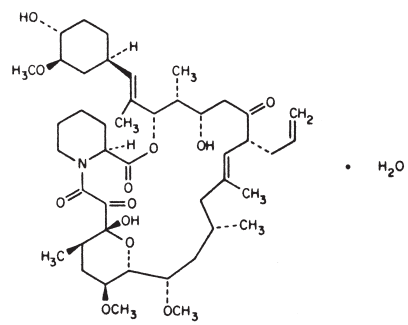
Nephrotoxicity is a common, serious adverse effect, which may be related to renal vasoconstrictive or tubular toxicity associated with the agent. Cyclosporine causes both acute and chronic renal insufficiency. Concomitant use with other potentially nephrotoxic agents, such as nonsteroidal anti-inflammatory drugs (NSAIDs), aminoglycosides, trimethoprim, or sulfamethoxozole may increase patients susceptibility to nephrotoxicity. Other adverse effects include hypertension, hyperlipidemia, glucose intolerance, bruising, nausea, vomiting, hepatotoxicity, electrolyte imbalances manifested as hypomagnesemia, hyperuricemia or hypokalemia, headaches, or diarrhea. Neurotoxicity manifests as parasthesias, tremors, convulsions, or encephalopathy. Hemolytic-uremic syndrome with microangiopathic anemia and thrombocytopenia has been reported with CSA use and requires discontinuation of the agent. Several unique side effects of CSA include gingival hyperplasia, acne, hirsutism, increased appetite, and pancreatitis. Leukopenia, anemia, and thromboembolism occur rarely. All immunosuppressants increase the risk of infections as well as certain types of cancer, including post-transplant lymphoproliferative disease. It is teratogenic.

It should also be noted that CSA is subject to many clinically significant drug-drug interactions secondary to inhibition, induction, or competitive metabolism through the cytochrome p450 3A4 isozyme system. Therefore, the addition of any new agent should be screened for drug interactions (decreased or increased metabolism; potentiation of side effects) potential prior to implementation. Decreased cyclosporine plasma concentrations have occurred with concomitant phenobarbital, phenytoin, carbamazepine, rifampin, naficillin, Saint John's Wort, or rifabutin use. Increased cyclosporine plasma concentrations have occurred with concomitant amiodarone, fluconazole, itraconazole, ketoconazole, diltiazem, nicardipine, verapimil, erythromycin, cimetidine, clarithromycin, danazol, grapefruit juice, miconazole, metoclopramide, or bromocriptine.

Dosage guidelines vary according to disease, organ transplant type, time post-transplant, concomitant immunosuppression, and transplant center. Initial oral dosages may range from 3 to 15mg/kg/day given as divided dose every 12 hours. The intravenous dose is approximately 1/3 the oral dose. Thereafter, dosages are adjusted to achieve specific goal trough levels. Goal trough concentrations vary according to disease, concomitant immunosuppression, organ transplant type, time post-transplant, transplant center, and assay type. Therapeutic drug monitoring is routinely performed. Whole blood assay therapeutic range is 100 to 400 mcg/L. Plasma assay therapeutic range 50 to 200 mcg/L.

TACROLIMUS HYDRATE

Prograf, FK506



[109581-93-3] $C_{44}H_{69}NO_{12}.H_2O$ (822.05).

Preparation—Obtained from *Streptomyces tsukubaensis*.

Description—Colorless prisms that melt about 128°.

Solubility—Soluble in methanol, ethanol, acetone, ethyl acetate, chloroform, or ether; sparingly soluble in hexane or ligroin; practically insoluble in water.

Comments—Tacrolimus is approved for prophylaxis and treatment of kidney and liver transplant rejection. It has also been useful in the prevention of rejection in heart and lung transplantation. It is a macrolide lactone antibiotic compound, which is structurally related to sirolimus. First approved for use in the liver transplant population, it has since gained in popularity and is used in the majority (>50%) of centers. Tacrolimus, a calcineurin phosphatase inhibitor, shares a similar mechanism of action to that of CSA. However, it binds specifically to its own cytoplasmic immunophilin, FK-binding protein, thereby forming a complex that inhibits calcium-sensitive phosphatase calcineurin. It inhibits T-cell activation and, as such, broadly suppresses the immune system. Based on in vitro concentrations, it is purported to be significantly more potent (10–100 times greater) than cyclosporine.

Tacrolimus is available as both intravenous and oral preparations. Absorption from the gut is variable and erratic, with approximately 20% to 25% bioavailability from 1- or 5-mg capsules, and peak blood concentrations were achieved 1.5 to 3.5 hr after ingestion. Unlike cyclosporine, its absorption is independent of bile secretion. Tacrolimus is widely distributed throughout the blood. It is highly protein bound with a terminal half-life for elimination of 11.7 hr in liver transplant patients; ~19 hours in renal transplant patients. Like CSA, tacrolimus is metabolized through the liver and gut (cytochrome p450 3A4 isoenzyme system) and is subject to similar clinically significant drug-drug interactions (see above). It is primarily excreted in bile with minimal renal elimination. It is also subject to inter-/intra-patient pharmacokinetic variability, which may be caused by polymorphisms expressed by metabolic enzymes (cyp3A4) and or p-glycoprotein countertransport proteins. As with CSA, the addition of any new agent should be screened for drug interactions (decreased or increased metabolism; potentiation of side effects) potential prior to implementation.

The most common side effects are headache, fever, tremor, hypertension, abdominal pain, diarrhea, nausea, renal dysfunction, and insomnia. Overall, the incidence of adverse reactions was comparable with cyclosporine-based immunosuppressive therapy. However, alopecia, glucose intolerance and neurotoxicity seem to occur more frequently with tacrolimus.

Dosage guidelines vary according to disease, organ transplant type, time post-transplant, concomitant immunosuppression, and transplant center. Initial oral dosage may range from 0.1 to 0.3 mg/kg per day administered as a divided dose every 12 hours. The intravenous dose may range from 0.05 to 0.10 mg/kg/day as a continuous infusion. Some centers may recommend lower initial doses. Thereafter, dosages are adjusted to achieve specific goal trough levels. Goal trough concentrations vary according to disease, concomitant immunosuppression, organ transplant type, time post-transplant, transplant center, and assay type. Therapeutic drug monitoring is routinely performed. Whole blood assay therapeutic range is 5 to 20 mcg/L. Plasma assay therapeutic range is 0.1 to 0.5 mcg/L.

LYMPHOCYTE IMMUNE ANTI-THYMOCYTE GLOBULIN (EQUINE)

Atgam

A preparation of equine immunoglobulin containing antibodies (primarily IgG) prepared from the hyperimmune serum of horses immunized with human thymus lymphocytes.

Description—Transparent to slightly opalescent (pink) aqueous solution of the protein.

Comments—Historically, Atgam, one of the first commercially available polyclonal antibody agents, has played an important role in transplantation. Antithymocyte globulin equine (ATG [equine]) (Atgam) is used for the treatment of acute rejection in renal allograft recipients. It has also been used to prevent renal, cardiac, and lung transplant rejection. The globulin also has been reported to be of value in the treatment of T-cell leukemias, graft-versus-host disease, and selected cases of aplastic anemia. Typically it is used as an adjunctive to other immunosuppressive therapy. Polyclonal agents are usually administrated in combination with other immunosuppressive agents as induction or sequential therapy or in the treatment of acute rejection. Induction or sequential therapy is used to induce acceptance of the newly transplanted organ or provide an increased overall immunosuppressive effect for a short period of time when acute rejection is most likely, typically the first 3 months post-transplantation. The term *sequential therapy* is used as most induction or sequential therapy agents, such as Atgam or Thymoglobulin, are administered for short courses (up to 14 days immediately post-transplant dependent on the agent used) while providing prolonged levels of immunosuppression secondary to exceptionally long half-lives and effect. The agents used in combination with sequential or induction agents are deemed maintenance agents, such as cyclosporine, mycophenolate mofetil, and corticosteroids, as patients are required to take these agents for the lifetime of the graft. Although polyclonal agents have been highly effective, they are also costly and potent immunosuppressive agents, and not without considerable long-term effects. Therefore, over the past decade, clinicians have tried to optimize results through judicious use of these agents in patient populations with the greatest need and greatest potential for gain. Currently, most transplant protocols utilize polyclonal antibody preparations in high immunologic risk patients. Patients characterized as high immunologic risk may include patients with elevated pre-transplant panel reactive antibodies, African-American recipients, re-transplants, and cases of delayed graft function.

Atgam has now been largely replaced by its successor, Thymoglobulin, at most transplant centers as clinical trial data has proven it superior in both the treatment and prevention of rejection.

Atgam attacks T lymphocytes but not B lymphocytes. Efficacy is enhanced, and adverse effects are attenuated when the globulin is used in combination with other immunosuppressive agents. After administration of the antithymocyte agent, profound depletion of peripheral blood lymphocytes ensues and is mediated by several pathways including cells coated with antibodies undergo complement-mediated cell lysis of lymphocytes, clearance by the reticuloendothelial system or T lymphocyte proliferation may also be affected. Additionally, its immunosuppressive effect continues long after therapy discontinuation. This is demonstrated by the blunted proliferative response of lymphocytes that return to circulation and continued suppression of the CD4 subset, which may be effected for several years.

Atgam is administered intravenously in a dose of 10 to 20 mg/kg/day for a course of 7 to 14 days. However, most centers use shorter courses of therapy for induction regimens. Atgam exhibits an extended half-life ranging from 3 to 9 days. But, large inter-patient variations have been reported. The first dose is administered over a 6-hour infusion; subsequent doses may be administered over shorter infusion times (4 hours). Anaphylactic reactions and allergic reactions are possible, and prophylactic regimens are commonly employed. Prior to use, a skin test for sensitivity to horse serum is advisable. Patients are premedicated with acetaminophen, diphenhydramine, and methylprednisolone 1 hour prior to administration to ameliorate side effects.

Frequent adverse effects include chills, fever, urticaria, pruritus, generalized rashes, leukopenia, diarrhea, arthralgias, headache, and thrombocytopenia. Dosage adjustments may be necessary in the face of leukopenia or thrombocytopenia. Complete blood counts should be monitoring daily while on therapy. Less frequently experienced adverse effects are stomatitis, hypotension, chest pain, back pain, night sweats, pain at the injection site, and peripheral thrombophlebitis. Rarely there may be tachycardia, myalgias, pulmonary edema, serum sickness, anaphylaxis, malignancies, laryngospasm, local and systemic infections, and activation of herpes simplex infections. All immunosuppressants increase the risk of infections as well certain cancers, including post-transplant lymphoproliferative disease. It is important to ensure that patients receive appropriate antiviral prophylaxis while receiving Atgam or any other potent immunosuppressive regime.

LYMPHOCYTE IMMUNE ANTI-THYMOCYTE GLOBULIN (RABBIT)

Thymoglobulin

A preparation of rabbit immunoglobulin containing antibodies (primarily IgG) prepared from the hyperimmune serum of rabbit immunized with human thymus lymphocytes.

Thymoglobulin, a polyclonal anti-thymocyte globulin, is derived by inoculating rabbits with human thymocytes, purifying the resulting solution from unwanted materials, yielding a solution specific for lymphocytes. Approved in 1999, it is the second commercially available polyclonal antibody preparation available on the market. Since its introduction, it has become the preferred polyclonal agent used to treat and prevent rejection in solid organ transplant recipients. It has also been useful in treating graft-versus-host disease, steroid-resistant rejection, and aplastic anemia. Thymoglobulin is used in clinical practice in the same manner as Atgam; as either an induction or sequential therapy (see above for full description) or as treament for rejection. It has, however, replaced Atgam secondary to superior results including: improved rates of graft survival, less severe rejection, fewer rejection episodes, greater reversed rejection episodes, and fewer recurrent rejection episodes.

Thymoglobulin exerts its immunosuppressive action similarly to Atgam (see above). After its administration, a profound decrease in circulating lymphocytes occurs. The usual dose of thymoglobulin is 1.5 to

2.5mg/kg per day administered intravenously (first dose over 6-hour continuous infusion, subsequent doses over 4-hour continuous infusion) for a duration of 5 to 14 days. However, many centers may use modified protocols with lower doses or alternate day dosing schedules. Again, shorter courses of therapy are commonly used for induction regimens. It has a half-life of ~30 days; inter-patient variation exists. As with Atgam and OKT3, premedication regimens (acetaminophen, diphenhydramine, and methylprednisolone) should be administered 1 hour prior to Thymoglobulin administration to offset known side effects. Allergies are possible, however, skin tests are not necessary prior to Thymoglobulin use. However, patients possible allergy to rabbits should be ascertained prior to administration.

Thymoglobulin has similar side effect profile to Atgam. These include leukopenia (occurs more frequently with thymoglobulin), fever, chills, nausea, diarrhea, headaches, and arthralgias. Dosage adjustments may be necessary in the face of leukopenia or thrombocytopenia. Complete blood counts should be monitored daily while on therapy. All immunosuppressants increase the risk of infections as well certain cancers, including post-transplant lymphoproliferative disease. It is important to ensure that patients receive appropriate antiviral prophylaxis while receiving Thymoglobulin or any other potent immunosuppressive regime.

MUROMONAB-CD3

Orthoclone OKT3

A murine monoclonal antibody (anti-CD3), $IgG_{2\alpha}$, of two chains having molecular weights of approximately 50,000 and 25,000.

Preparation—Mouse myeloma is fused into lymphocytes from immunized animals producing a hybridoma, which then secretes antigen-specific antibodies to the T3 antigen of T lymphocytes.

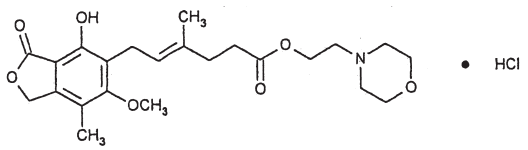
Comments—OKT3, or muromonab-CD3, approved in the mid-1980s, was the first monoclonal antibody preparation approved for therapeutic use in humans. Muromonab-CD3 is a murine IG2 monoclonal antibody that targets the ε chain of CD3. Initially it was commonly used to treat rejection and eventually to prevent it. OKT3 has been proven useful in both the prevention and treatment of rejection. In renal graft rejections, the success rate has been reported to be as much as 94%. Despite that, it has now been relegated to a secondary role as newer polyclonal antibody agents are preferable first-line options, given their similar efficacy and reduced toxicity profiles. Currently, OKT3 is reserved to treat severe rejection episodes or steroid resistant rejection episodes. When employed, it is used in combination with triple-drug immunosuppressive maintenance regimen.

OKT3 is a potent immunoactive agent with several pathways thought responsible for its effect. Anti-CD3 blocks cell signals that induce proliferation of cytotoxic lymphocytes and also causes the removal of T lymphocytes from the circulation, returning only after several days after administration. The mechanisms involved include T cell opsonization and their clearance by mononuclear phagocytic cells, complement mediated cell lysis, modulation of TCR-CD3 complex off the T cell surface, and steric hindrance. During therapy, CD3 positive cells are depleted while other T-cells (CD2, CD4, and CD8) reappear. T cells containing CD3 and other surface markers reappear ~2 days after discontinuation of therapy. It has a half-life of ~18 hours. However, short-term treatment with OKT3 or polyclonal antibody preparations has been associated with persistent immunosuppressive effects. It is administered intravenously as a bolus (over 1 minute) and various regimens exist. A typical regimen used is 5mg/day for 10 to 14 days. However, doses as low a 2 mg/day have proven effective as induction therapy.

OKT3 has many significant adverse drug reactions. The most dangerous of which is "cytokine release syndrome," which is characterized by flu-like symptoms, high fever, chills, arthralgias, headache, chest pain, tacchycardia, wheezing, nausea, and diarrhea. Some patients may experience more severe reactions including hypotension, rapidly developing pulmonary edema (dyspnea may be seen clinically), seizures, encephalopathy, aseptic meningitis or renal insufficiency. Cytokine release syndrome results from muromonab-CD3-activated T cells and monocytes releasing IL-1, IL6, and tumor necrosis factor. Adverse reactions occur most frequently following the initial dosage administration or upon dose increases. Most adverse effects persist only during the first 2 days of treatment. Rarely occurring side effects include anaphylaxis and coagulopathies such as thrombocytopenia or graft thrombosis. The severity of these reactions may be blunted with the use of premedications including methylprednisolone, acetaminophen, or diphenhydramine. Premedications are administered 1 hour prior to the administration of muromonab-CD3. Additionally, ensure that patients are within 3% of his/her dry body weight as another preventive measure. All immunosuppressants increase the risk of infections as well as certain types of cancer, including post-transplant lymphoproliferative disease. It has been implicated with higher rates of post-transplant lymphoproliferative disease when used in combination with triple-drug regimens or in patients receiving cumulative doses totaling >75mg of OKT3 (administered over greater than a 2-week period). Therefore, doses exceeding these specific parameters are not recommended. However, many clinicians conclude it is not specifically due to this specific agent but rather to the overall net immunosuppressive effect. Various opportunistic infections have occurred, herpes simplex and cytomegalovirus infections being the most common. Therefore, it is important to ensure that patients receive appropriate antiviral prophylaxis while receiving OKT3 or any other potent immunosuppressive regime.

MYCOPHENOLATE MOFETIL

4-Hexenoic acid, (*E*)-6-(1,3-dihydro-4-hydroxy-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl)-4-methyl-, 2-(4-morpholinyl)ethyl ester (and hydrochloride); CellCept (base); CellCept IV (hydrochloride)



(Base) [115007-34-6] $C_{23}H_{31}NO_7$ (433.49). (HCl) [116680-01-4] $C_{23}H_{31}NO_7$.HCl (469.96).

Preparation—*J Am Chem Soc*, 1986; 108:806.

Description—(Base) White to off-white crystalline powder. Apparent Log P (pH 7.4 buffer) is 238. pK_a 5.6 (morpholino group) and 8.5 (phenolic OH).

Solubility—(Base) In water 43 μg/mL at pH 7.4; 4.27 mg/mL at pH 3.6; in DMSO 50 mg/mL. Freely soluble in acetone; soluble in methanol and sparingly soluble in ethanol. (HCl) 65.8 mg/mL in 5% dextrose.

Comments—Approved for prophylaxis of organ rejection in renal, cardiac, and liver transplant patients. It has also been used to treat a wide-variety of autoimmune diseases, diffuse proliferative nephritis, prevention of lung or pancreas transplant rejection, psoriasis, and refractory uveitis. Mycophenolic acid, the active metabolite of mycophenolate mofetil, was originally discovered in 1896. Mycophenolate mofetil was developed as an alternative to azathioprine for mainitenance immunoactive agent, specifically designed to improve potency and selectivity for immune tissue throughout the body. The morpholinoethyl ester derivative of MPA, mycophenolate mofetil, was pursued because of its improved bioavailability. Safety and efficacy of the agent were proven in three pivotal trials. Clinically, mycophenolate mofetil (used as part of triple-drug regimens) has resulted in significantly improved acute rejection rates, morbidity, and mortality. Hence, it has successfully replaced AZA in the large majority of transplant programs. It is also thought to have improved chronic rejection rates as well. Generally, it is used in triple-drug combination regimens with cyclosporine or tacrolimus or sirolimus and steroids. However, it has also been useful in the development of novel transplant immunoactive regimens including steroid-sparing regimens and treatment for acute rejection (in addition to other therapy).

On metabolism to its active metabolite MPA, it inhibits *de novo* guanine–purine biosynthesis and thereby suppresses lymphocyte production. It is absorbed rapidly and completely from the GI tract and undergoes virtually complete metabolism of MPA, which itself may be metabolized further to an inactive glucuronide. MPA is 97% bound to albumin in the blood. Coingestion of food decreased blood levels by 40%. Oral bioavailability, based on MPA blood levels, is approximately 94%. More than 94% appears in the urine, the majority of which is the MPA glucuronide (MPAG). However, enterohepatic recirculation of the inactive metabolite, MPAG may occur. Concomitant agents such as cyclosporine (results in lower serum [MPA]), antibiotics, bile acid sequestrants, or other disease states may alter this process. Patients experiencing renal dysfunction are susceptible to accumulation of MPA. This is thought to be due to the reconversion through beta-glucuronidation of MPAG to MPA. The half-life of MPA in the blood is approximately 17.9 hr. Both the parent compound (~99%) and MPA (~82%) are

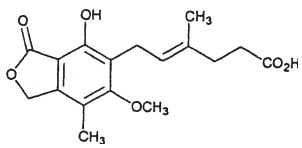
highly protein bound to albumin. Use caution when administering mycophenolate mofetil in patients experiencing uremia, hyperbilirubinemia, hypoalbuminemia, or those receiving other highly protein bound agents.

Mycophenolate mofetil (MMF) is available as both an intravenous and oral preparations. The majority of transplant recipients are well enough immediately post-transplant to receive the oral formulation. Typical oral dosage is 1g administered orally twice a day. Doses may vary (500 mg up to 1.5 g administered orally twice a day) dependent on concomitant immunosuppresion, organ transplant type, or immunologic risk. Doses greater than 3g/day have been associated with higher rates of side effects, particularly GI disturbances. Therapeutic drug monitoring is not the standard of care at most centers; however, MPA levels may be performed for cause.

Mycophenolate mofetil is well tolerated. The most commonly occurring side effects are GI intolerances; diarrhea (~30%), constipation, nausea, dyspepsia, and vomiting. Other common adverse reactions include leukopenia, anemia, thrombocytopenia, or leukocytosis. Dosage adjustments may be necessary with hematologic and GI side effects (change schedule to QID). Dosage reductions, in face of GI intolerances, are associated with increased risks of acute rejection. Thus, every attempt should be made to maintain patients on full-dose therapy. All immunosuppressants increase the risk of infections as well as certain types of cancer, including post-transplant lymphoproliferative disease.

MYCOPHENOLIC ACID

4-Hexenoic acid, (*E*)-6-(1,3-dihydro-4-hydroxy-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl)-4-methyl-, Myfortic



[24280-93-1] $C_{17}H_{20}O_6$ (329.34).

Preparation—*J Am Chem Soc* 1986; 108:806. Total synthesis, *Tetrahedron*, 2003; 59:1989–1994.

Description—Produced by *Penicillium brevi-compactum* and related organisms. Needles from water melting about 141°.

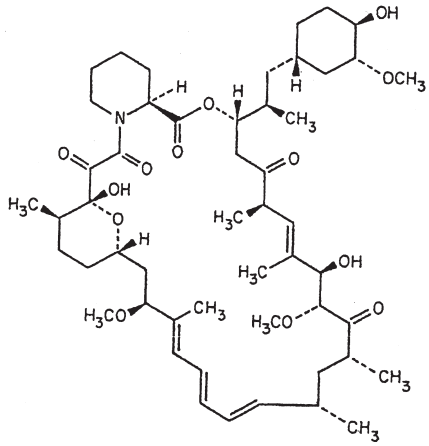
Solubility—Practically insoluble in water; freely soluble in alcohol; moderately soluble in ether or chloroform; sparingly soluble in hydrocarbon solvents.

Comments—Introduced onto the market in 2004, Myfortic is the enteric-coated formulation designed to deliver the active component, mycophenolic acid. It is the second product commercially available. Myfortic was designed to overcome the GI adverse events associated with its predecessor, MMF. Additionally, they sought to improve clinical effectiveness by enhancing adherence to full-dose regimens, as GI intolerances (previous experience with MMF) led to dose reductions or discontinuations, which increased risk of rejection. Clinical trials have proven Myfortic equally safe and effective to MMF. Both agents have comparable side effect profiles (see above). The most commonly occurring side effects were diarrhea and leukopenia. Despite its enteric coating, it did not correlate clinically to improved GI tolerability. Considering the data available to date, Myfortic does not impart any clinical advantage over mycophenolate mofetil.

Typically dosage is 720 mg twice daily with or without food. Compared with MMF 1000 mg twice daily, the Myfortic regimen provides equimolar amounts of MPA. Myfortic therapy should be initiated within 24 hours post-transplant in de novo transplant recipients. Dose adjustments are not necessary in the elderly or in patients with delayed graft function. Patients with severe chronic renal insufficiency (glomerular filtration rate of <10 mL/min), however, should be monitored for signs of MPA toxicities. A pharmacokinetic analysis demonstrated that mycophenolate sodium achieved higher serum MPA concentrations compared with MMF equal doses. This did not result in improved efficacy, but rather suggests that relative to overall exposure, tolerability may be improved. Additionally, it may allow patients to achieve higher therapeutic MPA concentrations. Following mycophenolic acid administration, mean absolute bioavailability of MPA is 71%; peak plasma concentration is achieved in 1.5 to 2 hours.

SIROLIMUS

Rapamycin; Rapamune



[53123-88-9] $C_{51}H_{79}NO_{13}$ (914.17).

Preparation—Produced by *Streptomyces hygroscopicus*. *J Antibiot*, 1975; 28:721 and US Pat 5,100,899 (1992).

Description—White to off-white powder melting at 181°.

Solubility: Insoluble in water; freely soluble in benzyl alcohol, chloroform, acetone and acetonitrile. Soluble in DMSO.

Comments—Sirolimus, or rapamycin, is a new immunoactive agent approved in 1999 for use in kidney transplantation. It is a macrocyclic triene antibiotic derived from *Streptomyces hygroscopicus* from soil samples collected on Easter Island (Rapa Nui) in 1968. Originally pursued for its potential as an antifungal agent, sirolimus' immunosuppressive activities were later recognized and studied following the discovery of tacrolimus' immunosuppressive prowess. It is a macrolide antibiotic, which is structurally similar to tacrolimus. But sirolimus demonstrates a novel mechanism of action and distinct side effect profile. Like the calineurin phosphostase inhibitors, sirolimus is also an immunophilin binding agent. Sirolimus engages immunophilin forming the rapamycin-FK binding protein (FKBP) complex. Unlike the calcineurin inhibitors, rapamycin-FKBP complexes do not inhibit calcinuerin phosphatase or cytokine transcription but rather binds a kinase enzyme, the mammalian target of rapamycin (mTOR). mTOR inhibition prevents cytokine mediated cell proliferation between phase G1 and S and results in T- and B- cell inhibition. Since its introduction, it has provided clinicians with another effective alternative maintenance agent. Additionally, it has been instrumental in the development of novel immunosuppressive regimens, including steroid sparing protocols and calcineurin inhibitor sparing regimens. Sirolimus is available as an oral solution or in tablets. Following oral administration, it is poorly absorbed. Bioavailability is reported at ~15%. The half-life is between ~57 and 62 hours but has been reported to be reduced in the pediatric population. Like, CSA and tacrolimus, sirolimus is subject to variable pharmacokinetics. Sirolimus' distribution is relatively similar to tacrolimus, approximately 95% is bound to red blood cells with 3% in plasma. Up to 40% in the plasma fraction are associated with lipoproteins, and the remaining amount (60%) is free unbound drug. Sirolimus is very lipophilic and has a large volume of distribution. It is metabolized through the liver and gut (p450 3A4) into multiple metabolites. Additionally, like CSA and tacrolimus, it is also susceptible to drug interactions mediated by the cytochrome p450 3A4 isoenzyme system as well as p-glycoprotein. It is eliminated largely in feces (~90%) with minimal excretion in the urine (2%).

It should also be noted that sirolimus is subject to many clinically significant drug-drug interactions secondary to inhibition, induction, or competitive metabolism through the cytochrome p450 3A4 isozyme system. Therefore, the addition of any new agent should be screened for drug interactions (decreased or increased metabolism; potentiation of side effects) potential prior to implementation. Increased sirolimus levels have been reported with concomitant fluconazole, itraconazole, ketoconazole, clotrimazole, diltiazem, nicardipine, verapimil, erythromycin, cimetidine, clarithromycin, danazol, grapefruit juice, miconazole, metoclopramide or bromocriptine. Decreased sirolimus levels have been reported with phenobarbital, phenytoin, carbamazepine, rifampin, or rifabutin use. Additionally, concomitant cyclosporine use increases overall sirolimus exposure (AUC increased by 230%). Upon 4-hour separation between the two agents, the magnitude of the effect was greatly diminished (AUC sirolimus increased by 80%). Thus, clinicians have targeted lower cy-

closporine trough concentrations and/or lowered doses. The aforementioned interaction does not occur with concomitant tacrolimus therapy. The magnitude of some the interactions can be severe; ketoconazole increase sirolimus levels by 990%; rifampin reduces sirolimus concentrations by ~90%. Therefore, these combinations should be avoided.

Dosage guidelines vary according to disease, organ transplant type, time post-transplant, concomitant immunosuppression, and transplant center. Initial loading dosages are typical and range from 6 to 15 mg administered orally once per day; maintenance oral doses range from 2 to 5 mg administered orally once per day. Thereafter, dosages are adjusted to achieve specific goal trough levels. Target trough concentrations vary according to disease, concomitant immunosuppression, organ transplant type, time post-transplant, transplant center, and assay type. Therapeutic drug monitoring is routinely performed. Whole blood assay therapeutic range is 3–36 ng/mL.

Sirolimus is has several unique and dose-dependent adverse events, the most notable being hyperlipidemia, manifested as hypertriglyceridemia or hypercholesterolemia. This side effect is more severe when sirolimus is used in combination with cyclosporine. Thus, it is imperative to appropriately recognize and treat it with non-pharmacologic measures and 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (HMG-CoA reductase inhibitors). Patients who receive both sirolimus and an HMG CoA reductase inhibitor are more susceptible to myopathy or rhabdomyolysis as both are substrates of the p450 system. Additionally, although sirolimus does not cause nephrotoxicity alone, it does, however, potentiate cyclosporine-induced nephrotoxicity when they are coadministered. Other side effects include bone marrow suppression such as leukopenia, anemia, or thrombocytopenia; liver dysfunction; GI intolerance such as nausea, vomiting, dyspepsia and diarrhea; delayed wound healing (particularly with high doses); electrolyte disturbances; skin ulcers; lymphocytes. All of the above side effects are dose dependent.

DACLIZUMAB

Humanized anti-TAC monoclonal antibody comprised of four subunits, two heavy chains and two light chains; Zenapax

MATURE HUMANIZED HEAVY CHAIN

H	QVQLVQSGAE	VKKPGSSVKV	SCKASGYTFT	SYRMHWVRQA
	PGQGLEWIGY	INPSTGYTEY	NQKFKDKATI	TADESTNTAY
	MELSSLRSED	TAVYYCARGG	GVFDYWGQGT	LVTVSSASTK
	GPSVFPLAPS	SKSTSGGTAA	LGCLVKDYFP	EPVTVSWNSG
	ALTSGVHTFP	AVLQSSGLYS	LSSVVTVPSS	SLGTQTYICN
	VNHKPSNTKV	DKKVEPKSCD	KTHTCPPCPA	PELLGGPSVF
	LFPPKPKDTL	MISRTPEVTC	VVVDVSHEDP	EVKFNWYVDG
	VEVHNAKTKP	REEQYNSTYR	VVSVLTVLHQ	DWLNGKEYKC
	KVSNKALPAP	IEKTISKAKG	QPREPQVYTL	PPSRDELTKN
	QVSLTCLVKG	FYPSDIAVEW	ESNGQPENNY	KTTPPVLDSD
	GSFFLYSKLT	VDKSRWQQGN	VFSCSVMHEA	LHNHYTQKSL
	SLSPGK-OH			

MATURE HUMANIZED LIGHT CHAIN

H	DIQMTQSPST	LSASVGDRVT	ITCSASSSIS	YMHWYQQKPG
	KAPKLLIYTT	SNLASGVPAR	FSGSGSGTEF	TLTISSLQPD
	DFATYYCHQR	STYPLTFGQG	TKVEVKRTVA	APSVFIFPPS
	DEQLKSGTAS	VVCLLNNFYP	REAKVQWKVD	NALQSGNSQE
	SVTEQDSKDS	TYSLSSTLTL	SKADYEKHKV	YACEVTHQGL
	SSPVTKSFNR	GEC-OH		

LOCATION OF DISULFIDE BRIDGES

Type	Location		Description
bridge	Cys-22	-Cys-96	disulfide bridge
bridge	Cys-143	-Cys-199	disulfide bridge
bridge	Cys-219	-Cys-213	disulfide bridge
bridge	Cys-225	-Cys-225	disulfide bridge
bridge	Cys-228	-Cys-228	disulfide bridge
bridge	Cys-260	-Cys-320	disulfide bridge
bridge	Cys-366	-Cys-424	disulfide bridge
bridge	Cys-22	-Cys-96	disulfide bridge
bridge	Cys-143	-Cys-199	disulfide bridge
bridge	Cys-219	-Cys-213	disulfide bridge
bridge	Cys-260	-Cys-320	disulfide bridge
bridge	Cys-366	-Cys-424	disulfide bridge
bridge	Cys-23	-Cys-87	disulfide bridge
bridge	Cys-133	-Cys-193	disulfide bridge
bridge	Cys-23	-Cys-87	disulfide bridge
bridge	Cys-133	-Cys-193	disulfide bridge

[152923-56-3] Dacliximab [$C_{6394}H_{9888}N_{1696}O_{2012}S_{44}$ (protein moiety) MW ca 144 to kDa, as predicted from DNA sequencing.

Preparation—US Pat 5,530,101 (1996).

Description—A composite of 90% human and 10% murine antibody sequences. The human elements are from human IgG1 and the Eu myeloma antibody. Murine sequences are from the complimentarity-determining regions of a murine anti-TAC subunit.

Solubility—The product, as the concentrate, contains 25 mg in 5 mL of pH 6.9 buffer.

Daclizumab, an IL-2 receptor antagonist, is one of the newest monoclonal antibody preparations available on the market. It is a monoclonal antibody composed of human and murine antibody sequences. It contains primarily human components (90%) with smaller proportion being murine (10%) in nature. Currently, IL-2 receptor antagonists are used primarily as induction agents in immunosuppressive protocols. Compared with polyclonal antibody induction therapy, IL-2 receptor antagonists did not provide adequate rejection prophylaxis among high immunologic risk renal transplant recipients when used in combination with triple-drug maintenance immunosuppression regimens. Consequently, they are no longer favored in that population and have been relegated to use among lower risk patients. Those regimens have been proven safe and effective in adult and pediatric patients in reducing acute rejection. Additionally, they have been increasingly used in novel immunosuppressive regimens such as calcineurin-free or sparing regimens and steroid-free or withdrawal regimens.

IL-2 receptor antibodies specifically bind to the alpha-subunit of the interleukin-2 receptor (CD-25) located on the surface of activated T lymphocytes. It interferes with IL-2 driven proliferation and differentiation. This usually results in diminished T cell responses that yields prolonged immunosuppressive action (at least 6 weeks). Daclizumab has an exceptionally long half-life; ranging from 11 to 38 days.

The above mechanisms may explain the prolonged immunosuppressive action demonstrated by the IL-2 receptor antagonists.

Daclizumab is administered intravenously over 15 minutes. The recommended dose is 1mg/kg/day within 24 hours of surgery followed by equal doses administered every 14 days for up to five doses. This dosing regime is possible because of its extended half-life. Many centers may use alternate protocols requiring fewer doses.

Daclizumab has a relatively mild side effect profile. Unlike OKT3 or polyclonal antibody agents, it is not associated with first dose effects or cytokine release syndrome. In clinical trials, it has demonstrated side effects similar to those reported among patients receiving placebo; including infection and malignancy. Hypersensitivity may occur. No significant drug interactions are reported for daclizumab.

BASILIXIMAB

Immunoglobulin G1, anti-(human interleukin 2 receptor) (human-mouse monoclonal CHI621 γ1-chain), dusulfide with human-mouse monoclonal CHI621 light chain, dimer; Simulect

[179045-86-4] Immunosuppressant monoclonal antibody.

Preparation—A glycoprotein produced by recombinant DNA technology and obtained from fermentation media of an established mouse myeloma cell line. EP 449,769 (1991).

Description—Approximate MW 144 kDa.

Solubility—Soluble in water.

Basiliximab is an anti-CD25 monoclonal antibody preparation. Like daclizumab, it is considered an IL2 receptor antagonist. It is a chimeric antibody composed of 75% human and 25% murine components. Therefore, basiliximab does not have the same affinity for the IL-2 receptor when compared to daclizumab. Compared to older monoclonal antibodies such as OKT3, daclizumab and basiliximab demonstrate low immunogenic potential as well as improved side-effect profiles. Clinical applications of basiliximab are similar to that of daclizumab (see above). It also demonstrates the same mechanism of action as described for daclizumab (see above).

It is administered intravenously as a single 20-mg dose on the day of transplant surgery and on the 4th day post-transplantation. Unlike OKT3 or polyclonal antibody agents, it is not associated with first dose effects or cytokine release syndrome. Basiliximab is well tolerated. In clinical trials, it has demonstrated side effects similar to those reported among patients receiving placebo, including infection and malignancy. Hypersensitivity may occur. No significant drug interactions are reported for basilximab.

CHAPTER 88

Parasiticides

Steven P Gelone, PharmD

Parasitic infections are now a worldwide problem. Increased travel, use of immunosuppressants, and the spread of AIDS has led to a greater prevalence of parasitic infections (*Med Lett Drugs Ther* April 2002). Consequently, the subject is an important part of pharmacology. In its broadest aspects, it includes the problem of eradication of all organisms that live within or upon man. However, the discussion in this chapter is limited to the anthelmintics and those agents that are applied directly to the skin of the human host in the treatment of pediculosis and scabies.

ANTI-INFECTIVES

The term *anthelmintic* frequently is restricted to drugs acting locally to expel parasites from the GI tract. However, there are several types of worms that penetrate other tissues; drugs that act on these parasitic infections are also known as anthelmintics. Furthermore, drugs that kill worms are referred to commonly as vermicides; those that affect the worm in such a manner that peristaltic activity or catharsis expels it from the intestinal tract are referred to as vermifuges. This arbitrary division serves no useful purpose because many anthelmintics manifest both actions, according to the dose employed. Therefore, the anthelmintics are defined more properly as drugs used to combat any type of helminthiasis.

The worm parasites of man belong to two phyla: *Nemathelminthes* (roundworms) and *Platyhelminthes* (flat worms).

The roundworms include the hookworm, roundworm, whipworm, pinworm, *Strongyloides stercoralis, Trichinella spiralis,* and *Wuchereria bancrofti.*

There are two common varieties of hookworm: *Necator americanus,* the American variety, and *Ancylostoma duodenale,* the European variety. They are cylindrical worms, 1 to 2 cm long, with two pairs of hooks near the mouth. They attach themselves to the mucosa of the duodenum and derive their nourishment by sucking blood from the surrounding blood vessels.

The common roundworm, *Ascaris lumbricoides,* is the most prevalent of human helminths. It may be 7 to 23 cm in length, 3 to 6 mm in diameter, grayish to reddish in color, and inhabits the upper part of the small intestine; therefore, it is vomited up occasionally.

The whipworm, *Trichuris trichiura,* is approximately 5 cm long and resembles a whip. It inhabits the cecum principally, but is found also in the lower part of the ileum and the appendix.

The pinworm or threadworm, *Enterobius vermicularis,* is 1.5 to 3 mm long. It inhabits the small intestine, cecum, and colon.

S stercoralis is only approximately 2 mm long. It inhabits the duodenum chiefly, but may be found in the stomach, biliary passages, pancreatic ducts, and various parts of the intestinal tract.

Infection with *T spiralis* causes trichinosis, a condition that results from eating incompletely cooked pork infested with the larvae of the worm. When such meat is eaten, the cysts dissolve, the parasites mature, and a new crop of larvae develops that penetrate the intestinal mucosa and eventually lodge in the muscles.

The most important filarial worm is *W bancrofti,* which is transmitted by the bite of the mosquito. Symptoms result from the blocking of the lymphatic ducts with the adult worms.

The flatworms are of two types: segmented (cestodes) and nonsegmented (trematodes). The cestodes include the tapeworms, and the trematodes include the flukes.

Four common varieties of parasitic tapeworms are found in man; *Taenia saginata* (beef tapeworm), *Taenia solium* (pork tapeworm), *Diphyllobothrium latum* (fish tapeworm), and *Hymenolepis nana* (dwarf tapeworm). Except for the dwarf tapeworm, they are from 2 to 10 m in length and may contain 3000 to 4000 segments, each segment being capable of producing hundreds of eggs. The dwarf tapeworm is only 6 to 12 mm in length, but it consists of 150 to 200 segments. The larval stage of all tapeworms is spent in the muscles of the intermediate host, and human infection occurs through eating imperfectly cooked meat and fish.

Three varieties of blood fluke inhabit the blood stream of man, causing schistosomiasis: *S haematobium, S mansoni, S mekongi,* and *S japonicum.* These parasites cause epigastric distress, abdominal pain, anorexia, diarrhea with blood and mucus in the stools, enlarged and tender liver, pyrexia, and ascites. The intermediate host is either a freshwater snail or a freshwater mollusk. Transmission is by way of contaminated water.

Parasitic worms are harmful to the human host for several reasons. They deprive the host of food, injure organs or obstruct ducts, may elaborate substances toxic to the host, and may provide a portal of entry for other organisms. It is desirable, therefore, to eradicate the parasites as soon as they have been discovered. Nevertheless, the need for treatment must be weighed carefully against the toxicity of the drug; the mere presence of a parasite does not necessarily demand that it must be treated.

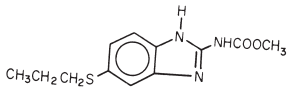
Proper choice of the anthelmintic is important, as most drugs are more effective against some species than others, and virtually all antiparasitic drugs induce some adverse effects. The drug selected should offer the best combination of effectiveness and relative safety. There is an excellent review (*Med Lett Drugs Ther* April 2002) of the choice of drugs for parasitic infections.

Many of the newer drugs require little or no change in the patient's normal routine. When the patient has a tapeworm infestation, a thorough examination of the stools produced by the second purgation is necessary. Unless the head of the worm has been expelled and identified, the worm regenerates. Usually

three specimens of stools are examined 1 week after administration of the anthelmintic. If ova or parasites are still present, the treatment should be repeated. All drugs that are poisonous to the worms are also poisonous to the patient. Therefore, the recommended methods of treatment for each drug should be followed carefully and the patient watched closely for the appearance of any untoward drug effects.

ALBENDAZOLE

Carbamic acid, [5-(propylthio)-1*H*-benzimidazol-2yl-], methyl ester; Albenza



[54965-21-8] $C_{12}H_{15}N_3O_2S$ (265.34).

Preparation—Etherification of 4-mercaptoacetanilide with *n*-propyl bromide yields 2-nitro-4-(propylthio)acetanilide, which is hydrolyzed to the amine, reduced to the diamine with stannous chloride, then converted to the benzimidazole structure with *S*-methylthiourea, and finally acylated at the 2-amino group with methyl choloformate. *J Med Chem* 1971;14:580. US Pat 3,915,986 (1975).

Description—Colorless crystals melting about 209° (decompn).

Solubility—Insoluble in water; soluble in dimethyl sulfoxide (DMSO), acetic acid, strong acids, or bases; can be regenerated from these solutions by neutralization if not heated or kept for too long a time.

Comments—A synthetic, benzimidazole-derivative anthelmintic that is used for the treatment of parenchymal neurocysticercosis resulting from active lesions produced by the larval form of *T solium* (pork tapeworm) and the treatment of cystic hydatid disease of the liver, lung, and peritoneum, produced by the larval form of the dog tapeworm (*Echinococcus granulosus*).

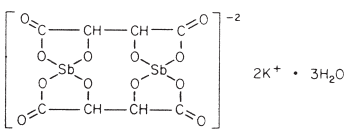
The precise mechanism of action is not clear; however, it appears to exert its primary anhelmintic effice by binding to the free β-tubulin in parasite cells, thereby producing a selective inhibition of parasite micotubule polymerization, and inhibition of micotubule-dependent glucose uptake. Inhibition of parasite β-tubulin occurs at lower concentrations of albendazole than those that are needed to inhibit human microtubule polymerization.

When employed in the treatment of neurocysticercosis, corticosteroids are often administered in conjunction with albendazole to reduce the frequency and severity of adverse nervous system effects. When employed for the treatment of cystic hydatid disease, it is most often used perioperatively to reduce the risk of intraoperative dissemination of daughter cysts.

Albendazole is administered orally with food. Bioavailability is increased by the presence of fat. For example, in the presence of 40 g of fat, the plasma concentrations of albendazole are approximately 5 times that observed in fasting patients. It is contraindicated during pregnancy because of potential risk to the fetus. In addition, liver function tests are recommended prior to each course of treatment and at 2-week intervals during treatment. Should clinically important increases in liver function test results be observed, its use should be discontinued.

ANTIMONY POTASSIUM TARTRATE

Antimonate(2-), bis[μ-[2,3-dihydroxybutanedioato(4-)-*O*^{1}, *O*^{2}, *O*^{3}, *O*^{4}]]-di-,dipotossium, trihydrate, stereoisomer



Tartar Emetic [28300-74-5] $C_8H_4K_2Sb_2O_{12}.3H_2O$ (667.85); anhydrous [11071-15-1] (613.81).

Preparation—By dissolving a mixture of 10 parts of potassium bitartrate with 8 parts of antimony trioxide [Sb_2O_3] in 75 parts of boiling water, filtering the solution while hot and allowing it to crystallize.

Description—Colorless, odorless, transparent crystals or a white powder; the crystals effloresce on exposure to air; solutions are acid to litmus.

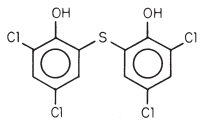
Solubility—1 g dissolves in 12 mL water, approximately 15 mL glycerin or approximately 3 mL boiling water; insoluble in alcohol.

Incompatibilities—*Mineral acids,* when added to aqueous solutions of antimony potassium tartrate, precipitate basic salts of antimony, with possibly some potassium bitartrate. *Alkali hydroxides* and *carbonates* of sufficient concentration precipitate antimony trioxide. Precipitation is retarded by citrates, tartrates, glycerin, or sugar. Many metallic salts form insoluble tartrates. Addition of *alcohol* to an aqueous solution may cause precipitation. An insoluble tannate is formed with *tannic acid.*

Comments—Formerly used for infections caused by *Schistosoma japonicum.* It is also an *emetic,* chiefly by virtue of its irritant action on the GI mucosa. Subemetic doses produce an expectorant action owing to reflex stimulation of the salivary and bronchial glands. Toxic effects induced by antimony potassium tartrate frequently include painful local inflammation, coughing, and vomiting when intravenous injection is rapid, muscle and joint stiffness, and bradycardia. Occasional adverse effects include colic, diarrhea, rash, pruritus, and myocardial damage. Rarely, liver damage, hemolytic anemia, renal damage, shock, and sudden death are encountered.

BITHIONOL

Phenol, 2,2′-Thiobis(4,6-dichloro-,



[97-18-7] $C_{12}H_6Cl_4O_2S$ (356.05).

Preparation—By reaction of 2,4-dichlorophenol and sulfur chloride.

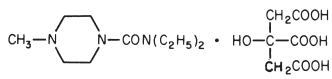
Description—White or off-white, crystalline powder; melts about 188°.

Solubility—Practically insoluble in water; freely soluble in alcohol or ether; soluble in solutions of alkali hydroxides.

Comments—The drug of choice for infections caused by *Fasciola hepatica* (sheep liver fluke) and, alternative drug for those caused by *Paragonimus westermani* (lung fluke). Untoward reactions are frequent and include photosensitivity skin reactions, vomiting, diarrhea, abdominal pain, and urticaria. Available from the Parasitic Disease Drug Service, CDC, Atlanta, GA 30333.

DIETHYLCARBAMAZINE CITRATE

1-Piperazinecarboxamide, *N,N*-diethyl-4-methyl-, 2-hydroxy-1,2,3-propanetricarboxylate; Hetrazan



N,N-Diethyl-4-methyl-1piperazinecarboxamide citrate (1:1) [1642-54-2] $C_{10}H_{21}N_3O.C_6H_8O_7$ (391.42).

Preparation—By acylating piperazine with diethylcarbamoyl chloride, and then methylating at the N^4-position by treatment with formaldehyde and formic acid. Treatment of the purified base with an equimolar portion of citric acid yields the official citrate.

Description—White, crystalline powder; odorless, or has a slight odor; slightly hygroscopic; melts between 134° and 139°.

Solubility—Very soluble in water; sparingly soluble in alcohol; practically insoluble in acetone, chloroform, or ether.

Comments—The drug of choice for treating filariasis infections (*W bancrofti, Brugia malayi, Mansonella ozzardi, Loa loa,* and *tropical eosinophilia*). In adequate dosage it clears the blood rapidly of the microfilariae and appears to be curative. The drug should be administered with special caution in Loa loa, because it can provoke an encephalopathy. Antihistamines or corticosteroids may be needed to control the allergic reactions caused by the disintegration of microfilariae.

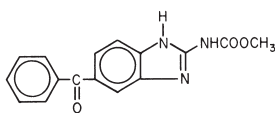
Untoward reactions are frequent but not serious; they include severe allergic or febrile reactions, owing to the filarial infection, and GI disturbances. Rarely, encephalopathy and loss of vision are encountered.

Note—Available only from the manufacturer.

EMETINE HYDROCHLORIDE—page 1310.

MEBENDAZOLE

Carbamic acid, (5-benzoyl-1*H*-benzimidazol-2-yl)-, methyl ester; Vermox



Methyl 5-benzoyl-2-benzimidazolecarbamate [31431-39-7] $C_{16}H_{13}N_3O_3$ (295.30).

Preparation—Synthesis of mebendazole and related anthelmintic benzimidazolecarbamates is described in German Pat 2,029,637 (corresponding to US Pat 3,657,267). See *CA* 74:100047s, 1971.

Description—White to slightly yellow powder; melts about 290°.

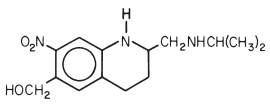
Solubility—Practically insoluble in water, alcohol, ether, or chloroform.

Comments—The anthelmintic of choice in hookworm (*Ancylostoma duodenale* and *Necator americanus*), pinworm (*Enterobius vermicularis*), roundworm (*Ascaris lumbricoides*), whipworm (*T trichiura*), and guinea worm (*Dracunculus medinensis*); in filariasis (*Mansonella perstans*); and as an alternative drug for *Visceral Larva Migrans.* It also is used as an adjunct to steroids for the treatment of trichinosis (*T spiralis*). It blocks the glucose uptake by susceptible helminths, thereby depleting glycogen stored within the parasite. The glycogen depletion results in a decreased formation of adenosine triphosphate (ATP); the latter is required for survival and reproduction of the helminth. Side effects are usually mild and transient; abdominal pain and diarrhea have occurred in cases of massive infection and expulsion of worms. Leukopenia is rare but has been reported. The drug is contraindicated in pregnancy and in persons who have shown hypersensitivity to it.

METRONIDAZOLE—page 1669.

OXAMNIQUINE

6-Quinolinemethanol, 1,2,3,4-tetrahydro-2-[[(1-methylethyl)amino]methyl]-7-nitro-, Vansil



[21738-42-1] $C_{14}H_{21}N_3O_3$ (279.34).

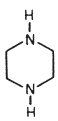
Preparation—From 6-(methoxymethyl)quinaldinic acid to form the acyl chloride, which with diethylamine yields the amide. Reduction of the amide with lithium aluminum hydride and Raney nickel produces the diethylaminomethyl derivative. Nitration of the latter compound in the 7-position followed by demethylation of the 6-position yields oxamniquine (US Pat 3,821,228).

Description—A light, orange, crystalline powder melting about 151°.

Solubility—Soluble in 3300 in water; soluble in acetone, chloroform, or methanol.

Comments—An alternate drug for infection caused by *Schistosoma mansoni,* including the acute and the chronic phase with hepatosplenic involvement. It significantly reduces the egg load of *S mansoni.* Contraindicated in pregnancy. Adverse effects observed include occasional headache, fever, dizziness, somnolence, nausea, diarrhea, rash, insomnia, and electrocardiogram (ECG) changes. Convulsions and neuropsychiatric disturbances also have been observed, but are rare.

PIPERAZINE



[110-85-0] $C_4H_{10}N_2$ (86.14).

Preparation—By catalytic deamination of diethylenetriamine and of ethylenediamine. US Pat 2,267,686.

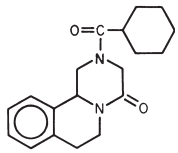
Description—White to slightly off-white lumps or flakes having an ammoniacal odor; melts between 109° and 113°; boils between 145° and 146°; in water it crystallizes with $6H_2O$ in colorless crystals called *piperazine hydrate,* melting at 44° and boiling between 125° and 130°. Soluble in water or alcohol; insoluble in ether. Incompatible with salts of heavy metals, alkaloidal salts or with acetanilid, phenacetin, or nitrites.

Comments—*Piperazine and several of its salts—the adipate, calcium edetate, citrate, phosphate,* and *tartrate*—have been used as anthelmintics for treatment of roundworm and pinworm infections. When administered orally, therapeutic doses have little or no pharmacological effects on the host. Adverse effects are transient, usually mild and disappear when the drug is discontinued. Occasionally, patients may complain of nausea, vomiting, mild diarrhea, abdominal cramps, headache, and dizziness.

More serious adverse effects such as seizures and respiratory depression are rare and occur after large doses. Piperazine should be used with caution in patients who have severe malnutrition oranemia. It is contraindicated in patients who have impaired renal or hepatic function or seizure disorders and in those patients who are hypersensitive to piperazine. Although piperazine has been used, without adverse effects, in pregnant women, its safe use in pregnancy has not been established clearly.

PRAZIQUANTEL

4*H*-Pyrazino[2,1-*a*]isoquinolin-4-one, 2-(cyclohexylcarbonyl)-1,2,3,6,7,11b-hexahydro-, Biltricide



[55268-74-1] $C_{19}H_{24}N_2O_2$ (312.41).

Preparation—Aminomethyltetrahydroisoquinoline, cyclohexane carbonyl chloride, acetonitrile, and aqueous hydrochloric acid are refluxed in the presence of pyridine to first form the cyclohexanecarbamoylmethyl derivative that cyclizes to form the product (US Pat 4,001,411).

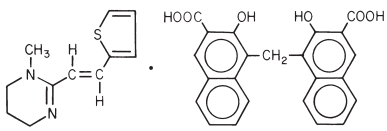
Description—A hygroscopic solid with a bitter taste, melting about 137°.

Solubility—Freely soluble in chloroform; soluble in ethanol; very slightly soluble in water.

Comments—The drug of choice for infections caused by *S japonicum, S mekongi, S haematobium,* and *S mansoni.* It is also an investigational drug of choice for tapeworm infestations and numerous fluke infections. It increases the permeability of the worm's cell membrane to calcium ions; this causes massive contraction and paralysis of its musculature and disintegration of its tegumental layer. Adverse effects include sedation, abdominal discomfort, fever, sweating, nausea, eosinophilia, headache, and dizziness.

PYRANTEL PAMOATE

(*E*)-1,4,5,6-tetrahydro-1-methyl-2-[2-(2-thienyl)ethenyl]-, compd with 4,4′-methylenebis[3-hydroxy-2-naphthalenecarboxylic acid] (1:1); Antiminth



[22204-24-6] $C_{11}H_{14}N_2S.C_{23}H_{16}O_6$ (594.68).

Preparation—Thiophene is converted to 2-thiophenecarboxaldehyde (I) via a Vilsmeier-Haack reaction. *N*-Methyl-1,3-propanediamine is condensed with acetonitrile to yield 1,4,5,6-tetrahydro- 1,2-dimethylpyrimidine, which is then coupled with I in the presence of methyl formate to yield pyrantel (base). The pyrantel is isolated as the tartrate and metathesized with a soluble alkali-metal pamoate.

Description—Yellow to tan powder that is tasteless and free of characteristic odor; decomposes slowly in light; nonhygroscopic in air under ordinary conditions; relatively stable in heat; melts with decomposition between 247° and 261°.

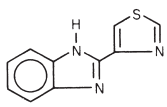
Solubility—Insoluble in water; very slightly soluble in alcohol.

Comments—One of the anthelmintics of choice in the treatment of *ascariasis* (common roundworm infection) and *enterobiasis* (pinworm) infection. It is also an investigational drug for the treatment of hookworm, moniliformis, and trichostrongylus infections. Side effects occur only occasionally and are relatively mild; GI disturbances, headache, dizziness, rash, and fever have been reported.

QUINACRINE HYDROCHLORIDE—page 1667.
SURAMIN SODIUM—see RPS-19, page 1326.

THIABENDAZOLE

1*H*-Benzimidazole, 2-(4-thiazolyl)-, Mintezol; Thibenzole



2-(4-Thiazolyl)benzimidazole [148-79-8] $C_{10}H_7N_3S$ (201.25).

Preparation—Ethyl pyruvate is brominated, and the resulting 2-bromo ester is reacted with thioformamide whereby cyclization occurs with formation of ethyl 4-thiazolecarboxylate. This ester is saponified

and condensed with *o*-phenylenediamine to introduce the benzimidazole moiety. US Pat 3,017,415.

Description—White to practically white, odorless or practically odorless, tasteless powder; stable in light and nonhygroscopic; melts between 296° and 303°; pK_a 4.7.

Solubility—Practically insoluble in water; slightly soluble in acetone or alcohol; very slightly soluble in chloroform or ether.

Comments—The anthelmintic of choice in *S stercoralis,* cutaneous larva migrans (creeping eruption), *Angiostrongylus costaricensis.* It also is recommended as an alternate drug in the treatment of *Capillaris philippensis, D medinensis* (guinea worm) infections, and visceral larva migrans. No special diet or purgation is needed with this drug. Side effects usually include nausea, vomiting, vertigo, headache, and weakness. Leukopenia, crystalluria, rash, disturbance of color vision and hallucinations also have been reported. In rare instances, shock, tinnitus and Stevens–Johnson syndrome have been observed. Because from one third to one half of patients usually are incapacitated for several hours after receiving the drug, it should be given on days when the patient does not have to go to school or work. Patients on the drug should be cautioned not to engage in activities requiring mental alertness.

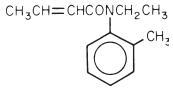
PEDICULICIDES AND SCABICIDES

Pediculicides are compounds effective in the treatment of pediculosis. Pediculosis in man is caused by three species of sucking lice known as *Pediculus humanus* variety *capitis* (the head louse), *P humanus* variety *corporis* (the body louse) and *Phthirius pubis* (the crab louse). These parasitic, wingless insects thrive where personal hygiene is neglected. The eggs (nits) of the body louse are attached to the fibers of clothing while those of the other two species are attached to hairs by a chitin-like cement. Cutting the hair short or shaving the area is helpful in destroying the eggs. The period of development from egg to adult is approximately 2 to 4 weeks. To be effective completely, an antipedicular agent must kill both parasites and eggs. Should the latter fail to be destroyed, repeated applications of the agent may be necessary to destroy the newly hatched lice.

Scabicides are compounds that are effective against *Sarcoptes scabiei,* the animal parasite that causes scabies in man. The parasite, a mite, thrives where personal hygiene is neglected. After copulation takes place on the surface of the skin, the female mite excavates a sinuous inward-sloping burrow in the corneous layer of the skin. The eggs are laid in the burrow and, after hatching, the larvae and nymphs may exit. For this infestation to be eradicated, an antiscabious agent must kill both parasites and eggs. If the eggs are not destroyed, repeated applications of the antiscabious agent may be necessary. The life cycle from egg to adult parasite is from 8 to 15 days. Sulfur ointment has been a time-honored scabicide. Except for alternate use in scabies (*S scabies*), it now has been replaced by more effective agents. Because many agents possess both antipedicular and anti-scabious properties, the pediculicides and scabicides are listed together.

CROTAMITON

2-Butenamide, *N*-ethyl-*N*-(2-methylphenyl)-, Eurax



N-Ethyl-*o*-crotonotoluidide [483-63-6] $C_{13}H_{17}NO$ (203.28).

Preparation—By condensation of a crotonyl halide, ester, salt, or a derivative thereof with *N*-ethyl-*o*-toluidine.

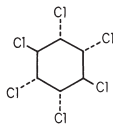
Description—Colorless to slightly yellowish oil; faint aminelike odor.

Solubility—Practically insoluble in water; miscible with alcohol.

Comments—A scabicidal and antipruritic agent, effective in eradicating scabies infestations and useful for symptomatic treatment of pruritic skin. Allergic sensitivity or primary irritation reactions may occur in some patients. It should not be applied to acutely inflamed skin, raw, weeping surfaces, or in the eyes or mouth. In scabies, it is recommended that crotamiton be thoroughly massaged into the skin of the entire body, from the chin down; a second application 24 hours later is advised to assure complete eradication of mites. A cleansing bath should be taken 48 hours after the last application. In pruritus the cream is massaged gently into affected areas until absorbed; repeated as needed.

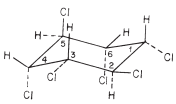
LINDANE

Cyclohexane, (1α,2α,3β,4α,5α,6β)-1,2,3,4,5,6-hexachloro-, Gamma Benzene Hexachloride; Gammexane; BHC; 666;



γ-1,2,3,4,5,6-Hexachlorocyclohexane [58-89-9] $C_6H_6Cl_6$ (290.83).

Gamma benzene hexachloride, as this compound was formerly officially called, is one of the nine theoretical stereoisomeric forms of 1,2,3,4,5,6-hexachlorocyclohexane. It has been shown to have the conformation



and, in terms of equatorial-axial notation, becomes *1e,2e,3e,4a,5a,6a*-hexachlorocyclohexane.

Preparation—By the chlorination of benzene in the presence of light. The reaction product is a mixture of stereoisomers containing from 10% to 15% of the insecticidally active gamma isomer that may be separated by solvent extraction processes.

Description—White, crystalline powder; slight, musty odor.

Solubility—Practically insoluble in water; slightly soluble in ethylene glycol; 1 g in 20 mL dehydrated alcohol, 3.5 mL chloroform or 40 mL ether.

Comments—Widely used as an *ectoparasiticide* and *ovicide.* It is an alternative drug for the treatment of *Sarcoptes scabiei* (scabies), *P capitis* (head lice) and *P pubis* (crab lice). As a *scabicide,* it is employed in a 1% concentration in a vanishing cream or lotion. The mixture is applied in a thin layer over the entire cutaneous surface from the neck down. One ounce usually is sufficient for an adult. Leave it on for at least 12 hr; remove it by thorough washing. One application is usually curative; retreatment is indicated only if living mites can be demonstrated. The shampoo is used for the treatment of *P pubis* and *capitis.* Approximately 1 oz (for short hair) and 2 oz (for long hair) is worked thoroughly into the hair and allowed to remain in place for 4 min; small quantities of water are added then until a lather forms; the hair is rinsed thoroughly, toweled briskly and any nits removed with nit comb or tweezers.

Adverse effects include occasional eczematous skin rash and conjunctivitis; rarely, convulsions and aplastic anemia have been observed.

MALATHION—page 1732.

PRECIPITATED SULFUR

Precipitated Sulphur; Lac Sulfuris; Milk of Sulfur

Sulfur [7704-34-9] S (32.06).

Preparation—To a slurry of 1 part of lime and 10 parts of water, 2 parts of sublimed sulfur are added, thoroughly mixed and the mixture boiled with frequent agitation until all of the sulfur is dissolved:

$$12S + 3Ca(OH)_2 \rightarrow 2CaS_5 + CaS_2O_3 + 3H_2O$$

After cooling, the clear liquid is decanted through a filter, and a slight excess of HCl, calculated from the quantity of lime used, is added to the filtrate. The acid decomposes the calcium pentasulfide and the thiosulfate with the precipitation of sulfur:

$$2CaS_5 + CaS_2O_3 + 6HCl \rightarrow 3CaCl_2 + 12S + 3H_2O$$

Description—Very fine, pale yellow, amorphous or microcrystalline powder; odorless and tasteless.

Solubility—Practically insoluble in water; very slightly soluble in alcohol; slightly soluble in olive oil. Distinguished from other forms of sulfur by more rapid solubility in carbon disulfide: on shaking 1 g of precipitated sulfur with 5 mL carbon disulfide, it should dissolve quickly except for a small amount of insoluble matter usually present.

Incompatibilities—Sufficiently hydrophobic that it sometimes causes trouble in lotions, where it tends to float on the surface. Among substances that have been shown to promote the wetting of sulfur, and thus aid its dispersion, are triethanolamine oleate and benzoin tincture. Trituration of the sulfur with a few drops of alcohol, glycerin, or a dilute solution of a wetting agent is also of some service.

Comments—An active parasiticide; a 10% sulfur paste or ointment is used as an alternative treatment for *S scabiei* (mites). Sulfur also is actively keratolytic and, in the form of full-strength ointment or in combination with other keratolytic agents such as salicylic acid, it is used in the treatment of skin disorders such as *psoriasis, seborrhea, eczema-dermatitis* and *lupus erythematosus.* The percentage of sulfur in an ointment should be reduced in the event that a patient's skin shows intolerance. Prolonged use of sulfur may result in a characteristic dermatitis venenata.

PYRETHRINS WITH PIPERONYL BUTOXIDE

RID; A-200 Pyrinate

Preparation—Pyrethrins are the insecticidal extracts of the pyrethrum flower and are usually synthesized from pyrethrolone [(*Z*)(+)-4-hydroxy-3-methyl-2-(2,4-pentadienyl)-2-cyclopentene-1-one, $C_{11}H_{14}O$] and chrysanthemic acid [2,2-dimethyl-3-(2-methyl-1 propenyl)cyclo-propanecarboxylic acid, $C_{10}H_{17}O_2$] to yield a mixture ofpyrethrins I and II. Piperonyl butoxide, [5-[[2-(2-butoxyethoxy)ethoxy]methyl]-6-propyl-1,3-benzodioxazole, $C_{19}H_{30}O_5$] has a synergistic effect on pyrethrins and rotenone, another floral insecticide.

Comments—This combination (pyrethrins 0.3%, piperonyl butoxide 3.0%) is an alternative treatment for *P humanis, P capitis,* and *P pubis.* It is contraindicated in individuals sensitive to the ingredients or ragweed, harmful if swallowed or inhaled, and may be irritating to the eyes and mucous membranes. Discontinue use and notify a physician if irritation or skin rash occurs. Usually it is applied topically only once and after 5 to 7 days later if needed to kill hatching progeny.

CHAPTER 89

Immunizing Agents and Allergenic Extracts

Steven P Gelone, PharmD

Immunizing agents and allergenic extracts are two of the main groups of drugs that are classified as *biologics* by the Food and Drug Administration (FDA). The properties of these agents are sufficiently unique that they are under the control of a separate division of the FDA; ie, the *Center for Biologics Evaluation and Research* (CBER) rather than the *Center for Drug Evaluation and Research* (CDER). This is perhaps one of the things that has confused many laymen and professionals alike into thinking that biologicals are not drugs. To the contrary, they were the first group of drugs to fall under Federal Control and were originally defined in the Public Health Service Act of 1902. More importantly, the biologics as a group and, more specifically the active immunizing agents, have likely prevented more morbidity and mortality than all other drugs combined. *Vaccina vaccine* must be considered the most effective drug to date since it has totally eradicated smallpox from our world. A similar success for the *poliomyelitis virus vaccines* appears imminent.

Characteristics of Biologics

Biologics (Table 89-1) are drugs in every sense of the word but they have unique characteristics that are helpful to review before considering the specific groups and individual agents. To be sure, none of the characteristics listed below is completely unique to biologics but, considered together, they describe what make these drugs special when compared to what are called *conventional drugs* for the purpose of this discussion.

1. Biologics are *natural products*. Virtually all of the drugs in this group are derived from once living organisms including man, higher animals, plants, and microorganisms. Although there may ultimately be a few exceptions to this rule, even the so-called *synthetic proteins* today are produced in living systems.
2. Biologics are relatively *crude products* by contemporary pharmaceutical standards. Most of these products contain cells, tissues, or even entire organisms. Even the relatively *pure* products that contain no biological structural elements are often mixtures of chemicals with varying degrees of activity.
3. The active constituents of biologics are *macromolecules,* proteins and/or, less commonly, polysaccharides. This is a particularly important consideration with respect to formulation, administration, and pharmacokinetics.
4. Most biologics are *standardized by bioassay*. The doses of very few of these products can be expressed in the conventional units of mass of active constituent but rather are usually expressed in units of biological activity that are characteristic to the individual agent.
5. Biologics are *immunogenic*. Conventional drugs with low molecular weights can induce immune responses by acting as haptens, but this is a relatively uncommon occurrence with most drugs. Biologics virtually always contain complete immunogens (proteins and polysaccharides) that are highly immunogenic by themselves. Even the increasingly common *human* or *humanized proteins* are rarely completely identical to their natural analogs and are usually more immunogenic than conventional drugs. There is nothing more central to understanding biologics than knowledge of the principles of immunology.
6. Biologics have some very *unique hazards*. Adverse toxic, idiosyncratic and, as noted above, allergic reactions can occur with biologics as with other drugs. But some biologics consist of living microorganisms that actually infect the patient and, on occasion, may even be transmitted to others. Some biologics carry a significant risk of microbial contamination because of their source. Certainly any product containing cells carries some risk of carrying an unknown biological contaminant. Those vaccines that are used for mass immunization have a very unique ability to alter the epidemiological patterns of disease that may have both advantages and disadvantages within a community.

IMMUNIZING AGENTS

Immunizing agents are among the oldest of modern drugs and can be dated to the beginning of immunology in 1798 when Edward Jenner introduced his vaccine for smallpox. The active immunizing agents are also, from virtually all perspectives, the most successful and powerful drugs yet developed. First, their main action is to *prevent* rather than to treat disease; most of the commonly used agents are highly effective and several have been singularly successful as noted earlier. Second, in spite of a number of real and potential hazards, they have generally proven to be remarkably *safe* in actual practice. Finally, and very importantly, active immunizing agents are generally available at a relatively *low cost*.

Passive immunizing agents date to the early part of the 20th century following the discovery of antibodies. Various antitoxins derived from animals held an important place in therapy prior to the development of antibiotics but these products, in contrast to the vaccines, had a number of problems with respect to both efficacy and safety and for a number of years their utility was quite limited. Presently, antibody preparations are rapidly gaining prominence in therapeutics largely because of the following developments: availability of human immune globulins; development of intravenous dosage forms; monoclonal antibody (MAb) technology; and the ability to prepare humanized MAbs.

Immunity

Immunity in the broadest sense may be defined simply as inborn or acquired resistance to disease and necessarily involves all of what may collectively be called the *host defenses* (Fig 89-1). It is common practice to restrict immunity and related terms to specific defenses and use *resistance* to denote those that are nonspecific. This is not fixed, however, and one will see the

Table 89-1. Biologicals[a]

Active Immunizing Agents (Vaccines)
Allergenic Extracts
Biological Response Modifiers (Cytokines)
Blood and Blood Derivatives
Cellular Therapies
Diagnostic Products
In vitro antibodies and antigens
***In vivo* diagnostic skin test antigens**
Enzymes and Venoms
Passive Immunizing Agents (Antibody Products)

[a] Products considered in this chapter are indicated in bold type. Consult *Establishments and Products Licensed under Section 351 of the Public Health Services Act* at the FDA Web site [http://www.fda.gov] for a complete list of currently licensed biologics.

terms used in a variety of different contexts. What is most important to understand is that much of the terminology of immunology is context-based, and the observer must be careful in trying to apply rigid definitions.

Immunizing agents are broadly classified on the basis of the type of immunity that they induce and knowing the properties of the different types of immunity is fundamental to the understanding of immunizing agents and their applications. *Active immunity* is a form of acquired immunity that develops in an individual in response to an immunogen. This may be naturally acquired by exposure to an infectious disease or artificially acquired by receiving active immunizing agents *(vaccines).* The term *vaccination* is used as a synonym for active immunization. There is a lag time of several days after first exposure to an immunogen and protective levels of immunity are typically not achieved for 1 to 2 weeks. Because of the phenomenon of *immunologic memory*, second and subsequent exposures to the same immunogen usually result in faster and stronger responses. However, it is important to recognize that immunologic memory is not infinite and will wane in the absence of periodic *booster doses* of the immunogen.

Passive immunity involves the transfer of the effectors of immunity, usually the specialized molecules called immunoglobulins or antibodies, from an immune individual to another. This occurs naturally by the active transport across the placental barrier of IgG antibodies from mother to fetus and, to a lesser extent, by the transfer of sIgA antibodies in the mother's milk. Passive immunizing agents include those derived from humans (*homologous*) or other higher animals (*heterologous*). The onset of passive immunity is much quicker, but the duration is much shorter because there is no active immune response to the immunogen and thus no memory. Immunoglobulins, especially if derived from foreign sources, are highly immunogenic proteins and may elicit an active immune response that is the basis for *serum sickness* and other allergic reactions.

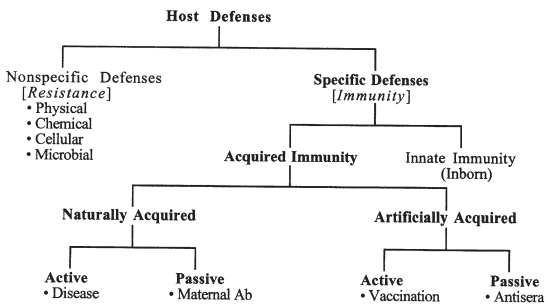


Figure 89-1. The host defenses.

ACTIVE IMMUNIZING AGENTS

Active immunizing agents are immunogenic drugs that are usually administered to a patient prior to their being exposed to a disease with the intention of providing long-term, even permanent, protection against the disease. Often there is the secondary goal of preventing the patient from serving as a reservoir and thereby transmitter of the disease. Active immunization can conceivably and, perhaps, one day will be used for a variety of conditions ranging from cancer to drug abuse. But all of the currently available active immunizing agents (Tables 89-2–89-5) are employed in the control of infectious disease and the discussion of these agents is restricted to this perspective.

Types of Products

Vaccine may be defined as pharmaceutical suspension or solution of an immunogenic substance or compound(s) that is intended to induce active immunity. In the past it was common to limit the term to products that contained whole microorganisms, but today the term may be applied to all active immunizing agents and the process of active immunization is called *vaccination.*

The majority of vaccines still consist of entire microorganisms that may be either *inactivated* (killed) or *live attenuated*. Attenuated refers to strains of organisms that have a reduced disease-causing capacity but that retain the major immunogenic characteristics of the so-called *wild* strains that circulate in the community. It can be seen that viruses comprise most of the live attenuated vaccines while most of the bacterial vaccines contain killed bacteria or their components. It is important to understand that the live vaccines contain less immunogen than the killed and must actually cause an infection and replicate within the patient in order to induce a protective immune response. In evaluating a vaccine, the first two things that should be looked at are (1) the identity of the immunogen(s), ie, the disease(s) protected against, and (2) whether the product contains live or inactivated immunogen.

Toxoids are protein toxins that have been modified (eg, by treatment with formalin) to reduce the toxicity without significantly altering the immunogenicity. Two of the oldest and best known active immunizing agents are diphtheria toxoid and tetanus toxoid that protect against the bacteria exotoxins elaborated by *Corynebacterium diphtheriae* and *Clostridium tetani,* respectively.

Better methods of producing and purifying macromolecules in recent years have led to significant advances in the production of vaccines containing more highly purified compounds that represent important *virulence factors* of the microorganisms. The antiphagocytic capsular polysaccharides of *Hemophilus influenzae* type b, *Streptococcus pneumoniae*, and *Neisseria meningitidis* have been used to prepare effective vaccines against these important bacterial pathogens. The hepatitis B virus vaccine is the first to be produced by recombinant technology and contains a synthetic protein that has immunogenic epitopes of the hepatitis B surface antigen. Several acellular pertussis vaccines have been licensed and are expected ultimately to replace the killed whole cell vaccine of *Bordetella pertussis*.

The products described above are formulated as aqueous suspensions or lyophilized powders for reconstitution. In some cases the antigen has been *adsorbed* on an *adjuvant* (eg, alum or aluminum hydroxide) that enhance the immune response, probably by delaying absorption and prolonging the period of immunogenic stimulation. The diphtheria and tetanus toxoids and pertussis vaccine (DTP) are adsorbed in the vast majority of the products in which they occur, and this is so noted on the label; products containing no adjuvants are commonly referred to as *fluid* preparations.

Table 89-2. Bacterial Vaccines[a]

VACCINE	DISTRIBUTOR	ADMINISTRATION[b]
Live Attenuated Vaccines		
Bacillus Calmette Guérin (BCG) Vaccine		PC
Mycobax	Aventis Pasteur	
Tice BCG	Organon Technika	Intravesical
Typhoid Vaccine, Live, Oral		
Vivotif Berna	Berna Products	Oral
Inactivated Vaccines		
Anthrax VaccineAdsorbed	BioPort Corporation	SC
Cholera Vaccine	Wyeth	ID, SC, IM
Hemophilus Influenza Type B		
Conjugate Vaccines		IM
ActHIB (Tetanus toxoid conjugate)	Aventis Pasteur	
HibTITER (Diphtheria CRM_{197} conjugate)	Wyeth	
PedvaxHIB (Meningococcal Protein Conjugate)	Merck	
Lyme Disease Vaccine *LYMErix*	Merck	
Meningococcal Polysaccharide Vaccine, Groups A, C, Y, and W-135		SC or Jet
Menomune-A/C/Y/W-135	Aventis Pasteur	
Pertussis Vaccine, Adsorbed	Michigan Biologic Products Inst	IM
Pneumococcal Conjugate Vaccine, 7-Valent *Prevnar*	Wyeth	
Pneumococcal Vaccine, 23-Valent		SC or IM
Pneumovax-23	Merck	
Pnu-Imune-23	Wyeth	
Tetanus Toxoid, Adsorbed	Aventis Pasteur	
Massachusettes Public Health Biologic Lab	IM or Jet	
Te Anatoxal Berna	Berna Products	
Typhoid Vi Capsular Polysaccharide Vaccine		IM
Typhim Vi	Aventis Pasteur	
Typhoid Vaccines, Inactivated	Wyeth	SC
Typhoid Vaccine, live-oral	Berna Biothech, Ltd.	

[a] The terms *live* and *inactivated* (*Killed*) are omitted from some of the names in this table but will appear in the official name of the product on the label.
[b] Routes of administration include intradermal (ID), intramuscular (IM), percutaneous (PC), subcutaneous (SC) and Jet injector.

Table 89-3. Combined Bacterial Vaccines[a]

VACCINE	DISTRIBUTOR
Diphtheria and Tetanus Toxoids and Whole-Cell Pertussis Vaccine (DTwP)	Aventis Pasteur
Tri-Immunol	Wyeth–Lederle
Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine (DTaP)	
AcelImune	Wyeth–Lederle
Infanrix	GSK
Tripedia	Aventis Pasteur
Diphtheria and Tetanus Toxoids, Adsorbed, for Pediatric Use (DT)	Biocine Sclavo
Aventis Pasteur	
Wyeth	
Diphtheria and Tetanus Toxoids, Adsorbed, for Adult Use (Td)	Biocine Sclavo
Aventis Pasteur	
Massachussettes Public Health Biologic Lab	
HIB Conjugate Vaccine and Hepatitis B Virus Vaccine	
Comvax	Merck

[a] The term *inactivated* (*Killed*) is omitted from some of the names in this table but will appear in the official name of the product on the label. All products in this table are administered by the intramuscular route except for the Mixed Respiratory Vaccine that is administered subcutaneously. Hepatitis B is a virus not a bacterial vaccine.

Table 89-4. Live Attenuated Virus Vaccines[a]

VACCINE	DISTRIBUTOR	ADMINISTRATION[b]
Influenza Virus Vaccine		
FluMist	MedImmune	IN
Measles Virus Vaccine		
Attenuvax	Merck	SC or Jet
Mumps Virus Vaccine		
Mumpsvax	Merck	SC or Jet
Poliovirus Vaccine, Oral Trivalent		
Poliovax	Aventis Pasteur	
Rubella Virus Vaccine		
Meruvax II	Merck	SC or Jet
Smallpox Vaccine		
Dryvax	Wyeth/DoD	PC
Varicella Virus Vaccine		
Varivax	Merck	SC
Yellow Fever Virus Vaccine[c]		
YF-Vax	Aventis Pasteur	SC
Combination Vaccines		
MMR Virus Vaccines		
M-M-R II	Merck	SC or Jet
Measles and Rubella Virus Vaccines		
M-R Vax II	Merck	SC or Jet

[a] The term *live* is omitted from the names in this table but will appear in the official name of the product on the label.
[b] Routes of administration include percutaneous (PC), subcutaneous (SC), intranasal (IN) and Jet injector.
[c] Distribution is limited to designated Yellow Fever Vaccination Centers authorized by state health departments to issue yellow fever certificates of vaccination.

Table 89-5. Inactivated Virus Vaccines[a]

VACCINE	DISTRIBUTOR	ADMINISTRATION[b]
Hepatitis A Vaccine		
Havrix	GSK	IM or Jet
Vaqta	Merck	
Hepatitis B Vaccine		
Engerix-B	GSK	IM
Recombivax-HB	Merck	
Hepatitis A and Hepatitis B combination vaccine		
Twinrix	GSK	IM
Influenza Virus Vaccines, Trivalent Types A & B		IM or Jet
Fluvirin (Purified surface antigen)	Evans Vaccines	
Fluzone (Subvirion or whole-virion)	Aventis Pasteur	
Japanese Encephalitis Vaccine		
JE-Vax	Aventis Pasteur	SC
Poliovirus Vaccine, Inactivated		
Ipol	Aventis Pasteur	SC
Rabies Virus Vaccine	Bioport	IM
Imovax Rabies (Human diploid cell)	Aventis Pasteur	IM or ID
RabAvert (Purified chicken embryo cell)	Chiron Behring GmbH and Co	IM

[a] The term *inactivated* (*Killed*) is omitted from some of the names in this table but will appear in the official name of the product on the label.
[b] Routes of administration include intradermal (ID), intramuscular (IM), subcutaneous (SC) and Jet injector.

A *simple vaccine* is one that protects against a single disease whereas a *combined vaccine* is, as the name implies, a combination product that protects against two or more diseases (cp, Tables 89-3 and 89-4). This should not be confused with the *valency* of a vaccine that refers to the number of strains of an organism causing a single disease.

Virtually all of the information described above is found in the official name of the product (Tables 89-2–89-5). This name provides a guide to most of the important information that one needs to know about any vaccine.

Storage, Handling, and Administration

It is common practice to assume that when a vaccine is administered that the patient is immunized and generally no measures are taken to confirm this (eg, serological confirmation of antibody formation). The validity of this assumption depends in large measure upon the vaccine being properly stored, handled, and administered. Anyone administering vaccines, and this is increasingly including the pharmacist, should be familiar with the *General Recommendations on Immunization* published by CDC.[3]

The immunogens in vaccines are susceptible to alteration or inactivation by heat, freezing, and extremes of pH and care should be taken to store and reconstitute the products within the labeled limits. Most vaccines should be stored at refrigerator temperatures (2–8 °C) but a few are frozen (eg, varicella vaccine) and some for *field use* may not require refrigeration. Unless designed to do so, vaccines should never be mixed with each other or with other drugs.

The route of administration can have a profound effect on the quantity and quality of the immune response. The majority of vaccines are still administered by a parenteral route (Tables 89-2–89-5). Adjuvant products and killed bacterial vaccines are usually administered by intramuscular injection; subcutaneous injection usually provides an immune response but often results in a painful sterile cyst at the injection site. Live virus vaccines are usually administered by subcutaneous injection. A few vaccines are administered by intradermal injection (eg, typhoid, some rabies vaccines) and multiple puncture techniques (eg, BCG, vaccinia). Jet injectors may be used with some products to expedite the vaccination of large numbers of people. Vaccines should never be administered intravascularly since this is both less effective and results in more adverse reactions.

The quantity of immunogen in a vaccine is determined by a bioassay and expressed in units that are nearly always unique to that immunogen; a notable exception is those vaccines that contain purified microbial components that are expressed in mcg. Parenteral vaccines are typically administered in volumes of 0.1 to 1 mL with 0.5 mL being the most common. It should be noted that the products from different manufacturers do not always contain completely identical immunogens and some may have different dosage regimens (cp, *Hemophilus influenzae* type b vaccines). When multiple vaccines are available, the best practice is to complete an immunization series with the same vaccine. However, in those cases where this is not possible, it is generally better to use a different vaccine than to not vaccinate.

A distinction needs to be made between the multiple doses in a *primary immunization series* and *booster* doses of a vaccine. Primary immunization series are designed to assure that most if not all of those vaccinated will elicit a positive immune response. For example, if the efficacy of a single dose of a vaccine is 80%, a primary series of 3 doses would be expected to immunize most of the vaccinees. Primary series are especially important in pediatric immunizations since very young children may fail to respond because of underdeveloped immune systems ($<$ 2 years of age) and/or interference by maternal antibodies ($<$ 6 months of age).

A true *booster* dose of a vaccine is intended to enhance immunity in an immunized individual. In this respect, it is important to recognize that immunologic memory is not infinite in duration in spite of the apparent *life long immunity* imparted by either vaccination or having a disease. Immunity may be boosted following primary immunization by exposure to the natural disease, exposure to cross-reacting antigens or nonspecific activation during another immune response by the so-called *bystander effect*. The first of these is probably most important, and it follows that any mass immunization program that reduces the prevalence of a disease also reduces the opportunity for *natural boosters*. Most of the mass immunization procedures have not been in effect long enough to completely evaluate if this is a problem, but it's clear from the experience with diphtheria immunization that immunity can wane with age in the absence of booster doses of vaccine.

Efficacy

The effectiveness of a vaccine can be measured in several ways. Serological responses, such as the appearance of *neutralizing antibody* in the serum, are most easily measured and are often used as an indication of immunity. However, in many diseases cell-mediated immunity or local mucosal immunity are more

important; these are not reflected by serum antibody titers and are generally more difficult to evaluate. The degree of clinical protection afforded a vaccinated population against a disease is a better measure of product efficacy but, even when high, does not assure immunity in an individual patient. Both measures of efficacy will be found in product literature, and the pharmacist should be aware of the limitations of each.

Generally speaking, live vaccines provide better immunity than killed, and the *natural route* of administration is even better (eg, mucosal administration versus parenteral). Experience with the poliovirus vaccines[4] illustrate this well. The inactivated poliovirus vaccines provide an excellent antibody response that protects well against systemic disease but produce little local immunity in the gut that is necessary to prevent infection and transmission of the wild virus. The live, oral poliovirus vaccines provide excellent antibody and cell-mediated immunity both systemically and locally in the gut. The live intransal influenza virus vaccine licensed in 2000 reflects this trend in vaccine development.

It is impractical and probably even unwise to try to develop a vaccine for every infectious disease. Most of the common acute infectious diseases are not serious enough to warrant the expense or risks of vaccination even if it may be effective. The emphasis until recently has been to develop vaccines for those diseases that cannot be adequately controlled by other means (eg, virus, toxigenic bacteria) and/or are serious enough to merit the investment, especially when viewed from the perspective of public health. Some of the newer vaccines have been directed against bacterial diseases that have classically been managed with anti-infective therapy. The impetus for this direction has been twofold: recognition that anti-infectives agents do not provide complete control for infectious diseases and advances in molecular science that have permitted development of microbial component vaccines.

Just as live vaccines are more effective than killed, those vaccines that are directed against specific virulence factors of the pathogen are often better than those containing the entire killed organism. This principle applies to diphtheria and tetanus toxoids, which have been used very effectively for more than 50 years as well as newer vaccines for pertussis (cp, whole cell versus acellular vaccines) and typhoid (cp, killed whole cell versus live attenuated versus toxoid).

The capsular polysaccharide vaccines are an important advance in the microbial component vaccines and also illustrate the effect of age and several other factors on efficacy. The original *Hemophilus influenzae* type b vaccines were poorly effective in children under 2 years of age, as are the unconjugated pneumococcal and meningococcal vaccines (Table 89-2). Among several explanations for this is the fact that polysaccharides often induce a *thymic-independent* immune response (Chapter 60) that results in atypical antibody production (primarily IgM) and little or no memory, especially in the very young. Conjugation of the polysaccharides to protein carriers have resulted in *Hemophilus influenzae* type b vaccines that are very effective in young children and a conjugated pneumococcal vaccine was released in February, 2000.

Most vaccines are administered with the goal of inducing immunity and protecting the individual patient. Vaccines for communicable disease are often employed with the important objective of public health to break the transmission of the disease and thereby protect the unvaccinated. This protection of the unvaccinated by the vaccinated is called *herd immunity* and represents one of the finest achievement of health science.

The principle of herd immunity is simple. If the immunity acquired by an individual can prevent colonization by the pathogen as well as protection against disease, the chain of transmission of the disease within the community can be broken. The level of immunization required to completely stop transmission and eliminate the disease from a community is directly related to the *communicability* of the disease; diseases with high communicability rates like measles require much higher levels of immunization to provide effective herd immunity. Effective herd immunity against a disease is the result of a concerted public health effort (eg, mass active immunization campaigns) with which all health professionals should cooperate. It is also important to remember that there is no herd immunity established against a noncommunicable disease such as tetanus; in such cases it is essential for each individual to be immunized.

The poliomyelitis vaccines described above are an excellent example of how the effectiveness of herd immunity can vary with product formulation. Rubella (German measles) is an example of where the major goal of the mass immunization effort is the establishment of herd immunity. This is a relatively mild disease in both children and adults but can be devastating if contracted in fetal life. And because rubella is not nearly as communicable as measles, a significant proportion (~15%) of women of child-bearing age remain susceptible to the disease in the absence of any preventative measures. These susceptible women and thereby their unborn children are protected from rubella by the herd immunity resulting from the vaccination of normal children, the major reservoir of the disease.

Perhaps the greatest benefit of herd immunity is the potential to *eradicate* certain diseases through mass active immunization. Candidate diseases for eradication must meet the following criteria: be communicable and susceptible to herd immunity; have one, or at most a few, antigenically stable strains; man must be the only natural reservoir of infection; and there must be an effective vaccine and delivery system for a mass immunization program. Diseases like influenza with its propensity for antigenic change and rabies with many animal reservoirs are poor candidates for eradication. On the other hand, the World Health Organization (WHO) declared smallpox eradicated in 1980 and the goal has been established to eradicate poliomyelitis virus by the year 2010; there has not been a case of wild virus poliomyelitis in the Americas since 1991. Measles, mumps, and rubella also have been identified as targets for eradication.[5]

The history of measles immunization[5] provides great insight for anyone interested in a study of the problems encountered in the development of an effective vaccine and vaccination procedures. Several problems were encountered with the original killed vaccine including the occurrence of atypical disease in some patients that was likely due to immune complex disease. One of the early live vaccines was poorly attenuated and often administered concurrently with immune globulin that may have interfered with the immune response. The live vaccines were originally given at or before 1 year of age, and there appeared to be vaccine failures due to the underdeveloped immune system and/or interference from maternal antibodies. The immunization programs originally appeared to be very successful for there were dramatic decreases in the incidence of measles, but after a time there were many reports of measles outbreaks in older children and young adults who had been previously vaccinated. It will probably never been certain how much each of the factors of the high communicability of measles, declining immunity in the absence of natural disease, inadequate vaccine design, and poorly designed immunization procedures has contributed to the overall problem of controlling measles.

Indications and Uses

The indications and recommendations for the use of vaccines arise from several sources. The FDA approves the indications for each licensed product on the basis of safety and efficacy as with other drugs. The Advisory Committee on Immunization Practices (ACIP) of the US Public Health Service (PHS) makes recommendations for both *mass* and *selective immunization programs* that impact public health. The consolidated recommendations of the ACIP, American Academy of Pediatrics (AAP), and American Academy of Family Practice (AAFP) are published in *Morbidity and Mortality Weekly Report* and can be

accessed at the CDC Web site (http://www.cdc.gov/nip/default.htm). All 50 states have school immunization laws, many also covering day-care centers, which require all or most of the pediatric immunizations listed in Table 89-6; detailed information on these laws may be obtained from state health departments, but exemptions are usually permitted for medical and religious reasons.

A convenient way to classify active immunization procedures is as follows: routine pediatric immunizations (with an adolescent follow-up evaluation); routine adult immunizations; routine geriatric immunizations; and selective immunizations.

ROUTINE PEDIATRIC IMMUNIZATIONS—The ACIP currently recommends that all normal children be immunized against 8 infectious diseases and for hepatitus A in areas of high incidence (Table 89-6). Pediatric immunization remains one of the most important public health measures in this country, and every pharmacist should be able to discuss these diseases, vaccines, and immunization procedures with patients.

Simultaneous immunization for diphtheria, tetanus, and pertussis (DTP) has been routine in the US since the late 1940s and has resulted in dramatic reductions in the incidence of all of these diseases. Diphtheria was a common childhood disease, and there were more than 200,000 cases in 1921 with 10,000 deaths; currently there only a few annual cases of respiratory diphtheria reported, and these are nearly always in adults. Tetanus is now mainly a disease of older adults in this country, and several dozen cases are reported each year. There are perhaps a million annual cases in the world with a case-fatality rate of 20% to 50%, and more than half of these are neonatal tetanus associated with an infected umbilicus; maternal immunization and sanitary deliveries effectively control neonatal tetanus.

Pertussis (whooping cough) was a major cause of childhood mortality during the first half of the 20th century when typically there were more than 200,000 cases a year in the US with 5000 to 10,000 deaths. The disease is mainly a problem in the very young with 50% to 70% of the deaths occurring in those under 1 year of age, which is the main reason for starting DTP administrations at 2 months of age; immunization for pertussis is not recommended after 6 years of age. The incidence of pertussis was reduced to less than 2000 cases in 1980 but has gradually increased to more than 7000 cases in recent years. There has, over the years, been controversy over the safety of pertussis vaccines, but there is absolutely no question that the benefits far outweigh the risks. Health professionals need to be aware of the dangers of apathy due to the low prevalence of disease and exaggerated concerns about the hazards of immunization. It is absolutely essential to maintain the currently high immunization rates for DTP (about 90%) or these diseases will emerge again.

Hemophilus influenzae type b (Hib) was the leading cause of invasive bacterial disease (eg, meningitis) among children until pediatric immunization was introduced in 1988. The importance of the conjugated vaccines was described above, and it is hoped that similarly effective vaccines can be developed for pneumococcal and meningococcal infections. It should be kept in mind that common noninvasive *Hemophilus influenzae* infections (eg, otitis media) are generally caused by nontypable strains, and Hib vaccine does not protect against these infections.

In 1952, shortly before the advent of polio immunization, there were 57,000 cases (about 40% paralytic) and 3,100 deaths in the US. The *Salk* inactivated vaccine was introduced in 1954 and the *Sabin* live vaccine in 1961; there has been no poliomyelitis in the Americas in recent years except for vaccine-associated disease and a few importation cases. The use of the live oral vaccine has always been controversial because of the vaccine-associated disease that occurs in small numbers of vaccinees and susceptible contacts. Because of the progress toward the global eradication of polio, the ACIP changed its recommendation from the use of OPV to IPV only (Table 89-6).

Measles, mumps, and rubella (German measles) are three important virus diseases that potentially can be eradicated by mass active immunization. The first measles vaccine was licensed in 1963, and individual vaccines for the others were available shortly thereafter. The combined vaccine (MMR) was licensed in 1971 and has been recommended for routine immunizations since 1977. In the time since the individual vaccines appeared the incidence of measles, mumps, and rubella has declined more than 99%. Some of the problems with measles vaccination were mentioned earlier, and the recent emphasis has been on assuring that all children receive a second dose of MMR. In spite of much publicity, there are still many misconceptions about these diseases. An estimated 2 million children around the world die each year from measles, and many others have permanent neurological sequelae that may not be recognized as a consequence of the disease (eg, hearing and/or sight loss). Although generally not as serious, neurological problems also may occur with mumps, but many worry more about sterility that rarely occurs. Congenital rubella syndrome has virtually disappeared in this country because of the vaccination. The way to continue to control all of these diseases is by continued compliance with the immunization program.

Hepatitis B infection is a major worldwide health problem with many facets including acute and chronic disease, liver failure and cirrhosis, hepatic carcinoma, and chronic carriers. Disease in newborns is usually asymptomatic, but more than 50% of those infected will become chronic carriers. Neonates born to mothers who are positive for the hepatitis B surface antigen (HBsAg) should be immunized immediately both with the vaccine and hepatitis B immune globulin. The first hepatitis B vaccine was prepared from plasma-derived HBsAg and licensed in 1981. Recombinant proteins reflecting the immunogenicity of HBsAg are used in the current vaccines that have been recommended for the universal immunization of infants since 1991. Vaccination provides a high level of protection against both hepatitis B and hepatitis D, which requires the hepatitis B coat to become infectious, but it is too early to evaluate the complete impact of the immunization program on the epidemiology of the disease.

Varicella (*chickenpox*) is a highly communicable disease that is generally benign but sometimes may be accompanied by serious complications (eg, bacterial superinfection, encephalitis); the disease is more serious in adults and particularly in the immunodeficient where it can cause devastating disease. After this primary infection the varicella-zoster virus lies dormant in sensory nerve roots and may, in 10% to 20% of those who had chickenpox, be reactivated to cause Herpes zoster (*shingles*). The varicella vaccine was licensed in 1995 and appears to be very effective in protecting against chickenpox but it is much too early to completely evaluate the impact of the immunization program on the epidemiology of varicella-zoster.

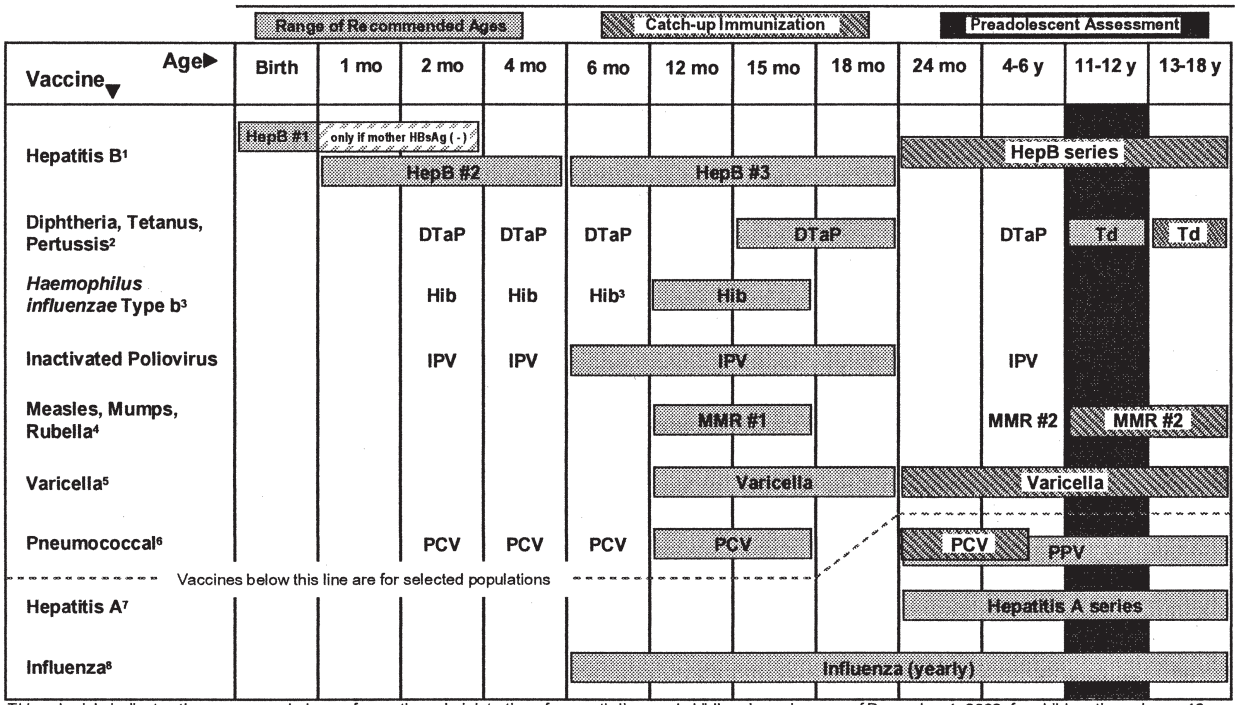
Rotaviruses are the major cause of severe dehydrating diarrhea in infants and children in both developed and other nations. There are approximately 40 to 50 deaths each year in this country and significant costs associated with treating rotavirus diarrhea. Immunization was expected to reduce these costs substantially, but the vaccine was withdrawn from the market due to reported cases of bowel obstruction.

Hepatitus A vaccination is recommended by ACIP for children residing in communities with annual infection rates of 20 cases per 100,000 or higher. Routine immunization is suggested where the rate is 10–20 cases per 100,000.

IMMUNIZATION OF ADOLESCENTS—Vaccination programs in the US have focused upon infants and children but many adolescents (age 11–21) experience vaccine-preventable diseases because the vaccine was not available when they were younger, failure to comply with the ACIP recommendations, or the presence of chronic diseases, which makes them candidates for certain selective immunization. Additionally, adolescence is a time of new infectious risks for many because of travel, experimentation with drugs, sexual activity, and starting work or a hobby. The ACIP, AAP, AAFP, and AMA now recommend a routine visit to health-care providers at age 11 to 12 years, which emphasizes the screening for immunization deficiencies and administration of indicated vaccines.[6]

Table 89-6. Routine Pediatric Immunization

Recommended Childhood and Adolescent Immunization Schedule — United States, January – June 2004



This schedule indicates the recommended ages for routine administration of currently licensed childhood vaccines, as of December 1, 2003, for children through age 18 years. Any dose not given at the recommended age should be given at any subsequent visit when indicated and feasible. ▨ Indicates age groups that warrant special effort to administer those vaccines not previously given. Additional vaccines may be licensed and recommended during the year. Licensed combination vaccines may be used whenever any components of the combination are indicated and the vaccine's other components are not contraindicated. Providers should consult the manufacturers' package inserts for detailed recommendations. Clinically significant adverse events that follow immunization should be reported to the Vaccine Adverse Event Reporting System (VAERS). Guidance about how to obtain and complete a VAERS form can be found on the Internet: http://www.vaers.org/ or by calling 1-800-822-7967.

1. Hepatitis B (HepB) vaccine. All infants should receive the first dose of hepatitis B vaccine soon after birth and before hospital discharge; the first dose may also be given by age 2 months if the infant's mother is hepatitis B surface antigen (HBsAg) negative. Only monovalent HepB can be used for the birth dose. Monovalent or combination vaccine containing HepB may be used to complete the series. Four doses of vaccine may be administered when a birth dose is given. The second dose should be given at least 4 weeks after the first dose, except for combination vaccines which cannot be administered before age 6 weeks. The third dose should be given at least 16 weeks after the first dose and at least 8 weeks after the second dose. The last dose in the vaccination series (third or fourth dose) should not be administered before age 24 weeks.

Infants born to HBsAg-positive mothers should receive HepB and 0.5 mL of Hepatitis B Immune Globulin (HBIG) within 12 hours of birth at separate sites. The second dose is recommended at age 1 to 2 months. The last dose in the immunization series should not be administered before age 24 weeks. These infants should be tested for HBsAg and antibody to HBsAg (anti-HBs) at age 9 to 15 months.

Infants born to mothers whose HBsAg status is unknown should receive the first dose of the HepB series within 12 hours of birth. Maternal blood should be drawn as soon as possible to determine the mother's HBsAg status; if the HBsAg test is positive, the infant should receive HBIG as soon as possible (no later than age 1 week). The second dose is recommended at age 1 to 2 months. The last dose in the immunization series should not be administered before age 24 weeks.

2. Diphtheria and tetanus toxoids and acellular pertussis (DTaP) vaccine. The fourth dose of DTaP may be administered as early as age 12 months, provided 6 months have elapsed since the third dose and the child is unlikely to return at age 15 to 18 months. The final dose in the series should be given at age ≥4 years. **Tetanus and diphtheria toxoids (Td)** is recommended at age 11 to 12 years if at least 5 years have elapsed since the last dose of tetanus and diphtheria toxoid-containing vaccine. Subsequent routine Td boosters are recommended every 10 years.

3. *Haemophilus influenzae* type b (Hib) conjugate vaccine. Three Hib conjugate vaccines are licensed for infant use. If PRP-OMP (PedvaxHIB or ComVax [Merck]) is administered at ages 2 and 4 months, a dose at age 6 months is not required. DTaP/Hib combination products should not be used for primary immunization in infants at ages 2, 4 or 6 months but can be used as boosters following any Hib vaccine. The final dose in the series should be given at age ≥12 months.

4. Measles, mumps, and rubella vaccine (MMR). The second dose of MMR is recommended routinely at age 4 to 6 years but may be administered during any visit, provided at least 4 weeks have elapsed since the first dose and both doses are administered beginning at or after age 12 months. Those who have not previously received the second dose should complete the schedule by the 11- to 12-year-old visit.

5. Varicella vaccine. Varicella vaccine is recommended at any visit at or after age 12 months for susceptible children (i.e., those who lack a reliable history of chickenpox). Susceptible persons age ≥13 years should receive 2 doses, given at least 4 weeks apart.

6. Pneumococcal vaccine. The heptavalent **pneumococcal conjugate vaccine (PCV)** is recommended for all children age 2 to 23 months. It is also recommended for certain children age 24 to 59 months. The final dose in the series should be given at age ≥12 months. **Pneumococcal polysaccharide vaccine (PPV)** is recommended in addition to PCV for certain high-risk groups. See *MMWR* 2000;49(RR-9):1-38.

7. Hepatitis A vaccine. Hepatitis A vaccine is recommended for children and adolescents in selected states and regions and for certain high-risk groups; consult your local public health authority. Children and adolescents in these states, regions, and high-risk groups who have not been immunized against hepatitis A can begin the hepatitis A immunization series during any visit. The 2 doses in the series should be administered at least 6 months apart. See *MMWR* 1999;48(RR-12):1-37.

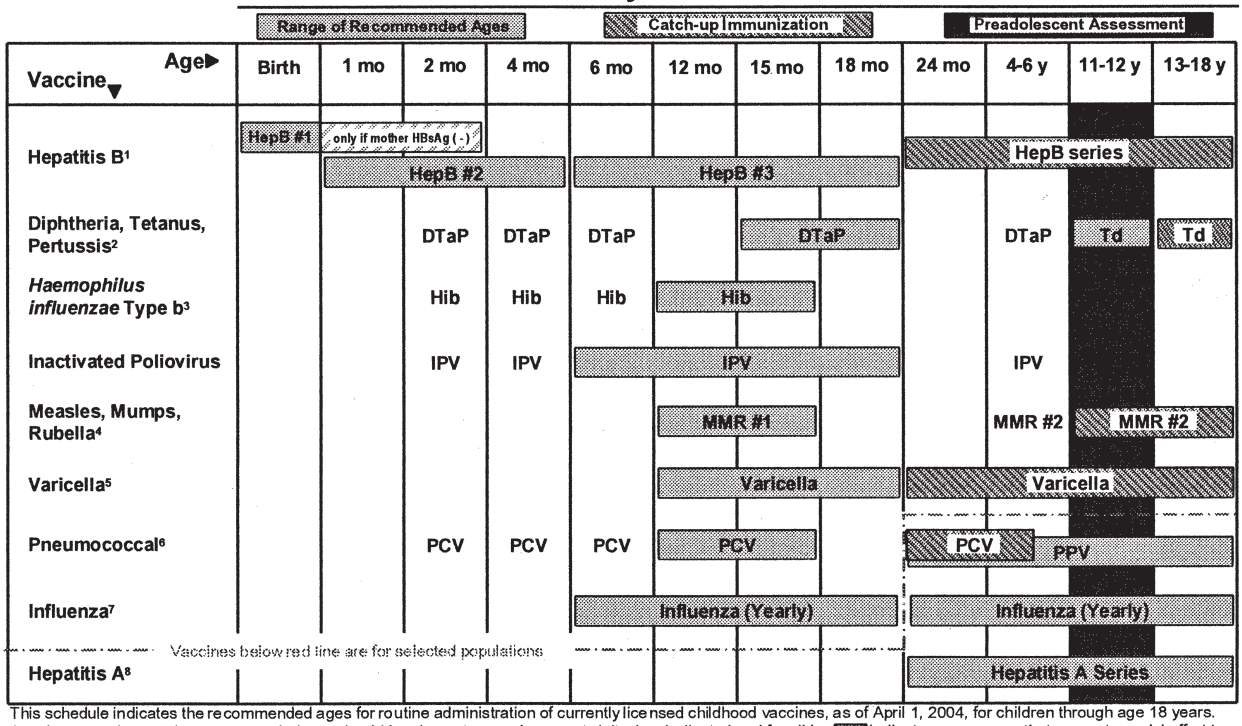
8. Influenza vaccine. Influenza vaccine is recommended annually for children age ≥6 months with certain risk factors (including but not limited to children with asthma, cardiac disease, sickle cell disease, human immunodeficiency virus infection, and diabetes; and household members of persons in high-risk groups [see *MMWR* 2003;52(RR-8):1-36]) and can be administered to all others wishing to obtain immunity. In addition, healthy children age 6 to 23 months are encouraged to receive influenza vaccine if feasible, because children in this age group are at substantially increased risk of influenza-related hospitalizations. For healthy persons age 5 to 49 years, the intranasally administered live-attenuated influenza vaccine (LAIV) is an acceptable alternative to the intramuscular trivalent inactivated influenza vaccine (TIV). See *MMWR* 2003;52(RR-13):1-8. Children receiving TIV should be administered a dosage appropriate for their age (0.25 mL if age 6 to 35 months or 0.5 mL if age ≥3 years). Children age ≤8 years who are receiving influenza vaccine for the first time should receive 2 doses (separated by at least 4 weeks for TIV and at least 6 weeks for LAIV).

For additional information about vaccines, including precautions and contraindications for immunization and vaccine shortages, please visit the National Immunization Program Web site at www.cdc.gov/nip/ or call the National Immunization Information Hotline at 800-232-2522 (English) or 800-232-0233 (Spanish).

Approved by the Advisory Committee on Immunization Practices (www.cdc.gov/nip/acip), the American Academy of Pediatrics (www.aap.org), and the American Academy of Family Physicians (www.aafp.org).

Table 89-6. *(continued)*

Recommended Childhood and Adolescent Immunization Schedule United States July–December 2004



This schedule indicates the recommended ages for routine administration of currently licensed childhood vaccines, as of April 1, 2004, for children through age 18 years. Any dose not given at the recommended age should be given at any subsequent visit when indicated and feasible. ▨ Indicates age groups that warrant special effort to administer those vaccines not previously given. Additional vaccines may be licensed and recommended during the year. Licensed combination vaccines may be used whenever any components of the combination are indicated and the vaccine's other components are not contraindicated. Providers should consult the manufacturers' package inserts for detailed recommendations. Clinically significant adverse events that follow immunization should be reported to the Vaccine Adverse Event Reporting System (VAERS). Guidance about how to obtain and complete a VAERS form can be found on the Internet: www.vaers.org or by calling 800-822-7967.

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Infants born to HBsAg-positive mothers should receive HepB and 0.5 mL of Hepatitis B Immune Globulin (HBIG) within 12 hours of birth at separate sites. The second dose is recommended at age 1–2 months. The last dose in the immunization series should not be administered before age 24 weeks. These infants should be tested for HBsAg and antibody to HBsAg (anti-HBs) at age 9–15 months.

Infants born to mothers whose HBsAg status is unknown should receive the first dose of the HepB series within 12 hours of birth. Maternal blood should be drawn as soon as possible to determine the mother's HBsAg status; if the HBsAg test is positive, the infant should receive HBIG as soon as possible (no later than age 1 week). The second dose is recommended at age 1–2 months. The last dose in the immunization series should not be administered before age 24 weeks.

2. Diphtheria and tetanus toxoids and acellular pertussis (DTaP) vaccine. The fourth dose of DTaP may be administered as early as age 12 months, provided 6 months have elapsed since the third dose and the child is unlikely to return at age 15–18 months. The final dose in the series should be given at age ≥4 years. **Tetanus and diphtheria toxoids (Td)** is recommended at age 11–12 years if at least 5 years have elapsed since the last dose of tetanus and diphtheria toxoid-containing vaccine. Subsequent routine Td boosters are recommended every 10 years.

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4. Measles, mumps, and rubella vaccine (MMR). The second dose of MMR is recommended routinely at age 4–6 years but may be administered during any visit, provided at least 4 weeks have elapsed since the first dose and both doses are administered beginning at or after age 12 months. Those who have not previously received the second dose should complete the schedule by the visit at age 11–12 years.

5. Varicella vaccine. Varicella vaccine is recommended at any visit at or after age 12 months for susceptible children (i.e., those who lack a reliable history of chickenpox). Susceptible persons age ≥13 years should receive 2 doses, given at least 4 weeks apart.

6. Pneumococcal vaccine. The heptavalent **pneumococcal conjugate vaccine (PCV)** is recommended for all children age 2–23 months. It is also recommended for certain children age 24–59 months. The final dose in the series should be given at age >12 months. **Pneumococcal polysaccharide vaccine (PPV)** is recommended in addition to PCV for certain high-risk groups. See *MMWR* 2000;49(RR-9):1-35.

7. Influenza vaccine. Influenza vaccine is recommended annually for children aged ≥6 months with certain risk factors (including but not limited to asthma, cardiac disease, sickle cell disease, HIV, and diabetes), healthcare workers, and other persons (including household members) in close contact with persons in groups at high risk (see *MMWR* 2004;53;[RR-6]:1-40) and can be administered to all others wishing to obtain immunity. In addition, healthy children aged 6–23 months and close contacts of healthy children aged 0–23 months are recommended to receive influenza vaccine, because children in this age group are at substantially increased risk for influenza-related hospitalizations. For healthy persons aged 5–49 years, the intranasally administered live, attenuated influenza vaccine (LAIV) is an acceptable alternative to the intramuscular trivalent inactivated influenza vaccine (TIV). See *MMWR* 2004;53;[RR-6]:1-40. Children receiving TIV should be administered a dosage appropriate for their age (0.25 mL if 6–35 months or 0.5 mL if ≥3 years). Children aged ≤8 years who are receiving influenza vaccine for the first time should receive 2 doses (separated by at least 4 weeks for TIV and at least 6 weeks for LAIV).

8. Hepatitis A vaccine. Hepatitis A vaccine is recommended for children and adolescents in selected states and regions and for certain high-risk groups; consult your local public health authority. Children and adolescents in these states, regions, and high-risk groups who have not been immunized against hepatitis A can begin the hepatitis A immunization series during any visit. The 2 doses in the series should be administered at least 6 months apart. See *MMWR* 1999;48(RR-12):1-37.

For additional information about vaccines, including precautions and contraindications for immunization and vaccine shortages, please visit the National Immunization Program Web site at www.cdc.gov/nip/ or call the National Immunization Information Hotline at 800-232-2522 (English) or 800-232-0233 (Spanish).

Approved by the Advisory Committee on Immunization Practices (www.cdc.gov/nip/acip), the American Academy of Pediatrics (www.aap.org), and the American Academy of Family Physicians (www.aafp.org).

Most persons in this country infected with hepatitis B virus acquired their infection as an adolescent or young adult; the virus is transmitted primarily through sexual contact, intravenous drug use, household contacts, or occupational exposure. Since the routine immunization of infants began in 1991, a number of individuals currently in the 11- to 12-year old group needs to be immunized.

Nearly half of the cases of measles in recent years have been in individuals over age 10 and this shift in the epidemiological pattern is felt to be due largely to the failure of primary immunization. Those adolescents who have not received two doses of MMR beginning at or after 12 months of age should be properly immunized at this time.

Booster doses of adult diphtheria and tetanus toxoids (Td) are recommended every 10 years, but there has never been a strategy implemented for effecting this recommendation. The adolescent office visit is a convenient time to administer the first Td booster.

Varicella immunization became routine in 1995 and many adolescents remain susceptible. Varicella vaccines should be given at the adolescent visit to any patient who has not been immunized or has no reliable history of chickenpox.

The adolescent office visit also should be used to identify individuals who are at risk for other vaccine-preventable disease and selective immunization should be conducted as indicated. It is estimated that more than 8 million children and adolescents are candidates for annual influenza immunization but few are ever vaccinated. This includes patients with chronic pulmonary disease (eg, asthma, cystic fibrosis) or cardiovascular disease; residing in chronic-care facilities and having a chronic medical condition; having required regular medical follow-up or hospitalization during the preceding year because of chronic metabolic disease (eg, diabetes), renal disease, hemoglobulinopathy, or immunosuppression; or receiving long-term aspirin therapy and at a risk of developing Reye's syndrome after influenza infection (up to 18 years of age).

It is estimated that 340,000 persons from 2 to 18 years of age have chronic illnesses that increase the risk of pneumococcal disease and should be vaccinated with the 23-valent vaccine. This includes those with anatomic or functional asplenia including sickle cell disease, nephrotic syndrome, cerebrospinal fluid leaks, or conditions associated with immunosuppression.

Hepatitis A virus infections occur in about 140,000 persons a year in the US and the highest rates of disease are in those 5 to 14 years of age. Hepatitis A vaccine should be administered to adolescents who plan to travel of work in areas where the disease is prevalent; human immune globulin may be used for short term prophylaxis when protection is needed faster than the vaccine can provide. Vaccination may be considered for adolescents who reside in communities that experience periodic outbreaks of hepatitis A. Adolescents should definitely be vaccinated if they have chronic liver disease, are receiving clotting factors, use illegal drugs of any kind or are males who have sex with males.

There are other selective immunizations that may be occasionally indicated in adolescents and many of these are described under adult immunizations.

IMMUNIZATION OF ADULTS UNDER AGE 65—The first thing to consider about the immune state of an adult patient is whether or not they have completed the recommended pediatric immunizations. Pertussis vaccine is not recommended for adults but the other nine vaccines are commonly indicated under different circumstances if there is not evidence of immunity; ie, reliable history of having the disease or positive serological test. When a patient is found to be susceptible to any of these nine diseases, their history should be reviewed vis-a-vis the recommendations for the appropriate vaccine(s) to determine if vaccination is indicated. Three circumstances where it is particularly important that the pediatric immunizations are up-to-date are the following:

1. Women of child-bearing age who may become pregnant since the immunity (ie, IgG) that they transfer to the fetus depends on their immune status.
2. Individuals with chronic diseases since they may be more susceptible to the disease or its adverse effects.
3. Individuals who travel internationally since some of these diseases remain prevalent in other parts of the world.

The only routine immunization that is recommended for all normal adults between the ages of 18 and 65 years is a booster dose of adult diphtheria and tetanus toxoid every 10 years. Unfortunately there is no strategy for accomplishing this, and many, if not most, adults in this country do not comply with this recommendation and may not even be aware of it. For some, this booster is received in the emergency room at the time of traumatic injury and may consist only of tetanus toxoid; in cases of contaminated wounds the tetanus booster should be administered if more than 5 years has elapsed since the last dose.

Annual influenza immunization is recommended for those at high-risk of influenza complications (described above) as well as those capable of nosocomial transmission of influenza to high-risk patients; ie, pharmacists, physicians, nurses, and others who provide in-patient, out-patient, and home health-care services as well as nonprofessional caregivers. Annual vaccination is also wise for those who provide essential community services, and individuals in institutional settings such as schools, to minimize disruption of activities during outbreaks. However, it should be noted that the current inactivated influenza vaccines are probably better at preventing the complications of influenza than of preventing the disease and its transmission. It is anticipated that the live, intranasal vaccine will provide both better protection and have a stronger impact on the epidemiologic patterns of the disease.

The bacterial capsular polysaccharide vaccines should be considered for individuals with anatomic or functional asplenia as well as those with any major immunosuppression (eg, HIV infection, organ transplant, some cancers). Pneumococcal vaccine should be administered to other high-risk individuals including those with cardiovascular or pulmonary disease, chronic hepatic or renal disorders, and diabetes mellitis. Meningococcal vaccine is recommended for some travelers and some closed populations where outbreaks may occur.

International travel is very common today for business, travel, and hobby, and all travelers should review the current recommendations of CDC[7] well in advance of any trip. Most travelers to developed areas of the world need only to have their routine immunizations up-to-date. The only disease for which an *International Certificate of Vaccination* may still be required is yellow fever. Travelers to underdeveloped countries or the back country of developed countries may find other vaccines recommended; hepatitis A vaccine is most likely but cholera, plague, and typhoid vaccines may occasionally be suggested.

Hepatitis B immunization is essential for health-care workers with exposure to human blood and tissues, and there are a number of other vaccinations that are recommended for those in high-risk occupations. Laboratory and field workers exposed to *Yersinia pestis* or wild rodents and fleas should receive plague vaccine. Military recruits will receive adenovirus, hepatitis A, and meningococcal vaccines and sometimes others.

The majority of vaccines are administered prior to exposure to the infectious organism but in diseases with long incubation periods postexposure active immunization, with or without concurrent passive immunization, may be effective. Postexposure active immunization is routinely used to prevent rabies in individuals exposed through the bites of infected animals while the usual pre-exposure immunization is recommended only for those who have occupational exposure. Both hepatitis A and hepatitis B have sufficiently long incubation periods to warrant postexposure vaccination when needed.

BCG vaccine is one of the most widely used worldwide but is very rarely recommended in this country. It appears to be effective in preventing serious miliary and meningeal tuberculosis, but its efficacy in preventing common pulmonary tuberculosis is questionable. It is recommended only in extremely high-risk individuals where other controls are impractical. It

should be mentioned that BCG vaccine is commonly used to treat bladder cancer by direct instillation into the bladder. This is sometimes called nonspecific immunotherapy, but the precise mechanism is unknown; the vaccine does promote a local inflammatory response that may be responsible for the anti-tumor effects.

IMMUNIZATION OF ADULTS AGE 65 AND OVER— Older age is often thought of as being synonymous with declining immunity, although there is little objective evidence to indicate that most older persons suffer from major immunodeficiency. There is an increasing incidence and severity of chronic diseases that often increase the risk and complications of a number of infectious diseases. The elderly may respond poorer to some vaccines, but this does not appear to be a general problem. Although applicable throughout life, an important principle in preparing for old age is to effect immunization while still healthy whenever possible. The routine pediatric and selective immunizations described earlier are an important factor contributing to the increasing number of persons reaching old age. Evaluation of immune status and appropriate vaccination at age 65 is important to the quality of the later years.

Every individual should continue to receive adult diphtheria and tetanus toxoid boosters every 10 years and, if this has not been done, it is important to update these vaccinations at age 65. Unfortunately many older Americans are susceptible to these diseases as reflected in the epidemiological pattern of tetanus.

All individuals age 65 and over should receive annual influenza immunization and a single dose of pneumococcal vaccine. Those who received pneumococcal vaccine prior to age 65 should receive a booster dose if it has been 5 or more years since the first dose. Those at highest risk of fatal pneumococcal disease (eg, asplenia) also should receive a booster dose at 5 years after the initial dose.

Pharmacists and other health professionals should encourage individuals of all ages to receive appropriate immunization. Although the immunization rates for children in this country are generally good, the immunization rates for both healthy and chronically ill adults of all ages are relatively poor.

Adverse Reactions

The vaccines that are routinely used today are generally very safe as well as highly effective. There are, as with any drugs, risks of vaccination that range from common, minor, and inconvenient to rare, serious, and life-threatening. There are also some misconceptions on the part of both lay persons and professionals that may unnecessarily prevent or delay vaccination. As with most drugs, the acute hazards are much better understood than the chronic, and there are some potential risks associated with vaccines that should always be kept in mind. Pharmacists and others who administer vaccines will find the CDC publication on the risks of vaccination[8] helpful.

The most common adverse effects of vaccines are mild toxic and/or allergic reactions although, as with most adverse drug reactions, the mechanism usually remains unconfirmed. Both of these tend to be more common with the inactivated products than with live vaccines since they usually contain more antigen and require booster doses. It is not surprising, for example, that products containing whole, killed, gram-negative bacteria such as the cholera, plague, and killed typhoid vaccines frequently cause minor inflammation at the site of injection as well as mild systemic febrile responses. Reactions such as this occurring shortly after injection, and especially after the first dose, are almost certainly direct toxic reactions.

That vaccines may cause allergic reactions is also quite predictable considering their immunogenic character. This is an uncommon problem with the live virus vaccines that are administered locally and/or boosted less frequently. The too-frequent administration of tetanus toxoid, which was formerly very commonly done in emergency rooms, is associated with local and systemic immune complex reactions. These Arthus-type skin reactions or any of the systemic symptoms of serum sickness are expected to occur within several hours of administration, especially following booster vaccination with an inactivated product.

IgE-mediated or anaphylactic sensitivity is more cause for concern and may take the form of urticaria (hives), angioedema, wheezing or even life-threatening shock. These reactions usually occur soon (0–60 minutes) after administration and, if due to the vaccine antigen, will generally occur after a booster dose. Reactions to components of the production medium (eg, eggs), antibiotics (eg, neomycin) or preservatives (eg, thimerosol) are very rare today but are likely to occur on the first dose in previously sensitized persons who are strongly allergic. Anaphylactic sensitivity to a vaccine or component is generally a contraindication to vaccination but there are some protocols for immunizing sensitive individuals.[3]

Inactivated vaccines pose very little infectious hazard if they are manufactured properly. That accidents may happen is best illustrated by the so-called *Cutter incident* in 1955 when improperly inactivated polio virus in IPV caused disease in a number of vaccinees.

Live vaccines are unique among pharmaceutical products in that infection of the patient receiving the product is intentional. There are several obvious as well as some subtle hazards associated with these products.

Live vaccines generally are contraindicated in pregnancy but the risk, at least with the current vaccines, is largely theoretical and occasionally the benefits merit vaccinating a pregnant woman who is at serious risk of disease. Rubella has, of course, been of particular concern and there is some evidence that the vaccine virus may be transmitted to the fetus; there have been many pregnant women inadvertently immunized with rubella vaccine but never a confirmed case of vaccine-associated congenital rubella. The medicolegal aspects of vaccinating a pregnant woman also must be considered, particularly in light of the relatively high incidence of miscarriages and birth defects during usual pregnancies.

Severely immunocompromised individuals can be safely administered inactivated vaccines, although the immune response may be poor, but should generally not receive live vaccines that have the potential to cause serious disease in such individuals. Serious immunosuppression can result from congenital immunodeficiency, HIV infection, malignancy (eg, leukemia, lymphoma, generalized malignancy), chemotherapy, and/or immunosuppressive therapy. The decisions in this area can be difficult, and there may or may not be data available to guide the clinician. For example, immunization of HIV-positive patients with MMR has caused no problems to date, and it is generally recommended that it be given to asymptomatic patients and considered even for those with symptoms. The immunosuppressive effects of corticosteroids are poorly defined but most steroid therapy is *not* a contraindication for live vaccines including the following: short-term therapy of less than 2 weeks; low to moderate dose therapy including physiologic maintenance doses (replacement therapy); long-term alternate day therapy; and topically or locally administered steroids including aerosols and intra-articular injections. The best practice is, whenever possible, to vaccinate prior to the immunosuppression.

Live vaccines also may pose a threat to the unvaccinated contacts of recent vaccinees. Poliovirus may be transmitted and cause disease especially in household contacts; vaccinees living with immunosuppressed individuals should only receive IPV. Varicella vaccine may cause chickenpox or shingle-type rashes in immunosuppressed individuals (eg, leukemia patients), and they may transmit the virus to susceptible contacts. Although vaccinees may shed measles, mumps, and rubella viruses after vaccination, there is no evidence of transmission of the viruses following MMR.

In addition to the real risks of vaccines, there are several potential problems that merit mention. Mass active immunization changes the epidemiological pattern of a disease and can

have several consequences. What were formerly childhood diseases may in the unvaccinated be deferred until later in life where some are more serious; this has been the concern of some with mumps immunization particularly if the immunity is not as long as desired. On a longer term, the absence of a disease from a community for generations may result in a population even more susceptible than it was prior to immunization; apathy in immunization coupled with reintroduction of the disease could prove devastating to a community.

The viruses for vaccines are much like other drugs in the fact that much more is understood about their acute adverse effects than the chronic. The possibility of the virus causing an inapparent chronic or integrated infection as well as the potential for such things as oncogenesis and tetratogenesis cannot be completely ignored. The requirement that viruses be grown in living cells also increases the risk for inadvertent contamination with unknown organisms. These esoteric concerns are far outweighed by the benefits of vaccination, but their existence emphasizes two important points: first, active immunization should not be considered for trivial conditions and second, continuous diligence and study is required of all immunizing agents and procedures.

Contraindications

The contraindications given above are associated with adverse reactions to vaccination while those described below are generally related to achieving a poor immune response.

Active immunization should generally not be conducted in infants under 1 or 2 years of age unless there is a special risk and/or an effective procedure has been established. Maternal antibodies can persist for 6 or more months in a neonate, and it takes several years for the immune system to develop completely; infants usually respond poorly to any immunizing agent relative to older individuals, and there may be a risk of vaccine-induced illness if live vaccines are administered too early. Those pediatric immunizations recommended before 1 year of age all require completion of a primary series of doses to assure effectiveness. When other vaccines must be given early, revaccination at a later age is virtually always indicated.

Serious febrile illness is a contraindication to active immunization, especially with live virus vaccines, but there can be much confusion about this. Most acute febrile illnesses are caused by viruses that induce interferon and can interfere with virus replication and the response to the vaccine. The administration of any vaccine to a seriously ill individual can confound the evaluation of the illness and/or any reaction to the product. These factors must be weighed against the urgency for the vaccination. All vaccines can be administered to individuals with minor illnesses such as common diarrhea and mild upper respiratory disease with or without fever. These conditions are so common in children that failure to do so may seriously interfere with the vaccination program.

Live vaccines are contraindicated for varying periods after administration of immunoglobulin containing preparations because specific antibodies can interfere with the immune response; this is usually not a problem with killed vaccines that contain sufficient immunogen to overcome any inhibition. The products that can interfere with immunization include all human immune globulin preparations, whole blood, and several blood components (eg, packed RBCs, plasma/platelet products).

The effect of immune globulin on virus vaccines varies considerably with the vaccine. For example, OPV and yellow fever vaccines can be administered without regard to immune globulin administration. It has generally been recommended to wait 6 weeks to 3 months before administering most live vaccines such as MMR. But this interval is not sufficient for measles vaccine when high doses of intravenous immune globulin are administered and vaccination may have to be delayed for up to 11 months.[5] As always, the recommended intervals have to be viewed with respect to the urgency of vaccination in the individual case.

National Childhood Vaccine Injury Act

The National Childhood Vaccine Injury Act (NVICA) became effective March 21, 1988 and has two main objectives: (1) to avoid future crises that may interrupt the National Immunization Program and (2) to provide financial compensation for patients who suffer vaccine-related injuries. The act requires that the providers of vaccinations keep certain permanent records of covered vaccinations as well as to report on certain adverse events. A surcharge is placed on the price of covered vaccines to fund the program, and compensation is paid to persons who suffer specified injuries from receiving these drugs. The covered vaccines currently include all of the routine pediatric immunizations (Table 89-6). The details of the record-keeping and reporting requirements as well as the current list of covered vaccines may be found at the CDC Web site.

Immunization Records

Proper documentation of immunizations is important from several respects. It helps ensure that those in need of vaccination receive it without the need for serologic testing and helps prevent overvaccinating, which increases the risks of hypersensitivity reactions. A comprehensive vaccination record should include not just the history of vaccinations but also ancillary information such as documentation of having had a disease or serologic testing for immunity. The NVICA specifies the records to be maintained by the provider.[2]

Official immunization cards have been adopted by every state to facilitate the assessment of immunization status by schools and child-care centers. A permanent immunization record card should be established for each newborn infant and maintained by the parents. Some states are developing computerized immunization record systems, and there is even consideration of a national immunization registry.

PASSIVE IMMUNIZING AGENTS

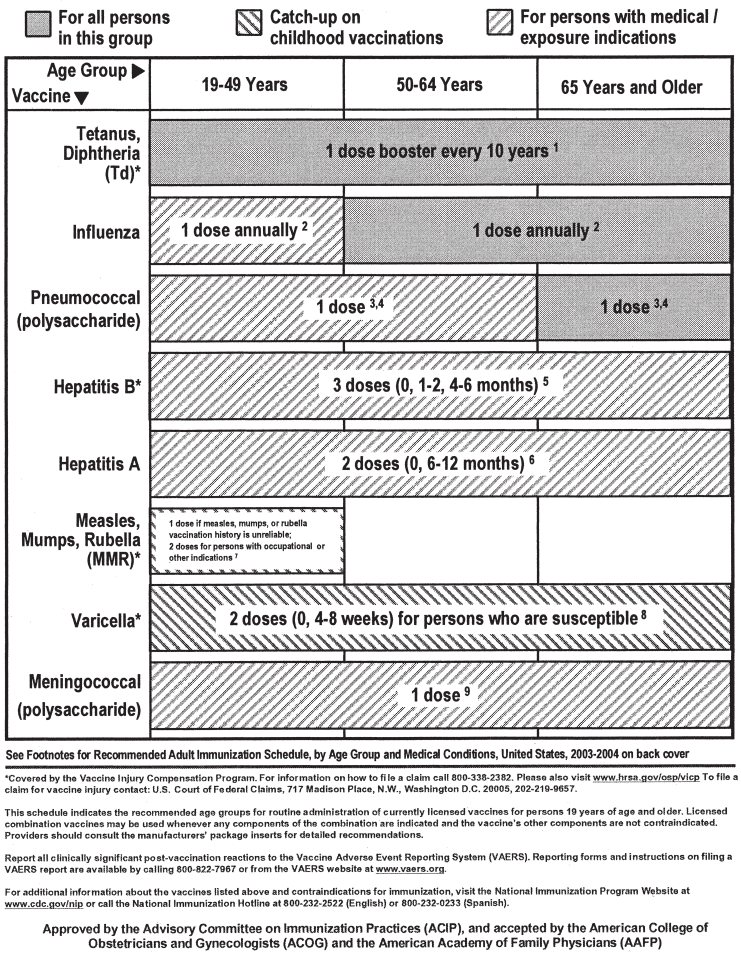
Passive immunization in the broadest sense involves the administration of any specific immune effector, antibody or effector T cell. In practice it has been restricted to the use of antibodies since effector T cells are limited in number, difficult to harvest, and, perhaps most importantly, MHC-restricted and not usually effective when transferred from one individual to another. There have, however, been recent attempts to harvest the T cells of the individual patient, expand their number *in vitro* with colony-stimulating factors, and reintroduce the cells into the patient. The currently employed passive immunizing agents are all derived from immunoglobulins, and the majority of these consist mainly of IgG isotypes (see Chapter 60).

Human serum was used as early as 1907 for the prevention of measles and later for mumps and pertussis. Animal-derived antitoxins were used extensively prior to World War II to treat diphtheria, tetanus, scarlet fever, and other diseases with mixed results. Intramuscular human immune globulin (IGIM) became available after the war and was first used to treat a form of agammaglobulinemia (Bruton's disease) in 1952. Intravenous human immune globulin (IGIV) was developed over the 1980s and represents a major advance in passive immunizing agents. The first MAbs (digoxin immune Fab and muromonab CD3) were licensed in 1986, but only as the 20th century closes is this technology beginning to have a major impact on clinical medicine.

The antibody-containing products available in the US as of January 2000 are listed in Tables 89-7–89-9. Depending on how one defines passive immunization, it can be correctly argued that not all of these are passive immunizing agents. The emphasis at this point will be on those products that are used to

Table 89-7. Routine Adult Vaccine Recommendations

Recommended Adult Immunization Schedule, United States, 2003-2004 by Age Group



See Footnotes for Recommended Adult Immunization Schedule, by Age Group and Medical Conditions, United States, 2003-2004 on back cover

*Covered by the Vaccine Injury Compensation Program. For information on how to file a claim call 800-338-2382. Please also visit www.hrsa.gov/osp/vicp To file a claim for vaccine injury contact: U.S. Court of Federal Claims, 717 Madison Place, N.W., Washington D.C. 20005, 202-219-9657.

This schedule indicates the recommended age groups for routine administration of currently licensed vaccines for persons 19 years of age and older. Licensed combination vaccines may be used whenever any components of the combination are indicated and the vaccine's other components are not contraindicated. Providers should consult the manufacturers' package inserts for detailed recommendations.

Report all clinically significant post-vaccination reactions to the Vaccine Adverse Event Reporting System (VAERS). Reporting forms and instructions on filing a VAERS report are available by calling 800-822-7967 or from the VAERS website at www.vaers.org.

For additional information about the vaccines listed above and contraindications for immunization, visit the National Immunization Program Website at www.cdc.gov/nip or call the National Immunization Hotline at 800-232-2522 (English) or 800-232-0233 (Spanish).

Approved by the Advisory Committee on Immunization Practices (ACIP), and accepted by the American College of Obstetricians and Gynecologists (ACOG) and the American Academy of Family Physicians (AAFP)

impart passive immunity for infectious and toxic diseases, but, as will be seen, the difference between these and the other antibody products is not always clear. All of the products are listed in the tables to assist the reader in making comparisons, but some of the products are described in greater detail in other chapters under their respective therapeutic categories.

Types of Products

When considering immunoglobulin-containing products, it is useful to think in terms of three dichotomies: human or animal, intramuscular or intravenous, polyclonal or monoclonal.

Human immune globulin products are derived from pooled plasma obtained from 1000 or more donors. The antibody content of all of these products is primarily IgG (90–98% depending on the product), and the four isotypes are generally within the range of their natural distribution: IgG_1 (60–70%), IgG_2 (23–29%), IgG_3 (4–8%) and IgG_4 (2–6%). The other isotypes are largely removed since they usually contribute little to the activity of the products and may give rise to adverse reactions. The composition of the products is very similar for both the so-called *normal* immune globulin preparations (IGIM, IGIV) as well as the specific or *hyperimmune* globulin products (eg, hepatitis B immune globulin). The former are standardized by assaying for several common antibodies (eg, measles, diphtheria, poliovirus, and often others), while the specific immune globulins also are assayed for the labeled antibody; the latter products are obtained from the pooled plasma of individuals having high titers of the labeled antibody such as recent vaccinees.

Heterologous antibody products (Table 89-8) must have their source displayed on the label, and this is nearly always equine. The horse was chosen because it has a large blood volume and is rarely used as a food animal in this country, which lessens the chance for sensitization. MAbs are often derived from sheep (ovine) or mice (murine). There is little functional difference between human and animal antibodies, but there is sufficient structural difference that allergy is a major problem with heterologous sera. *Serum sickness* is a systemic immune complex disease that occurs 5 to 14 days after administration of foreign antibodies; this active immune response also serves to clear the antibodies and heterologous products thus have a shorter duration of action than the homologous. Subsequent administration of a heterologous serum will result in an even faster and stronger reaction and may even be accompanied by IgE-mediated anaphylactic reactions. It is apparent that heterologous products are severely limited and has been a major factor in delaying the development of products containing MAbs; there are technical difficulties in producing human MAbs by hybridoma technology (Chapter 60). Technological advances in preparing *chimeric* (human-animal) and *humanized* MAbs has led to a number of products at the end of the millennium, and many more can be expected early in the 21st century.

Table 89-7. *(continued)*

Recommended Adult Immunization Schedule, United States, 2003-2004 by Medical Conditions

For all persons in this group | Catch-up on childhood vaccinations | For persons with medical / exposure indications | Contraindicated

Medical Conditions ▼ / Vaccine ▶	Tetanus-Diphtheria (Td)*,[1]	Influenza[2]	Pneumococcal (polysaccharide)[3,4]	Hepatitis B*,[5]	Hepatitis A[6]	Measles, Mumps, Rubella (MMR)*,[7]	Varicella*,[8]
Pregnancy		A					
Diabetes, heart disease, chronic pulmonary disease, chronic liver disease, including chronic alcoholism		B	C		D		
Congenital Immunodeficiency, leukemia, lymphoma, generalized malignancy, therapy with alkylating agents, antimetabolites, radiation or large amounts of corticosteroids			E				F
Renal failure / end stage renal disease, recipients of hemodialysis or clotting factor concentrates			E	G			
Asplenia including elective splenectomy and terminal complement component deficiencies		H	E, I, J				
HIV infection			E, K			L	

See Special Notes for Medical Conditions below—also see Footnotes for Recommended Adult Immunization Schedule, by Age Group and Medical Conditions, United States, 2003-2004 on back cover

Special Notes for Medical Conditions

A. For women without chronic diseases/conditions, vaccinate if pregnancy will be at 2nd or 3rd trimester during influenza season. For women with chronic diseases/conditions, vaccinate at any time during the pregnancy.

B. Although chronic liver disease and alcoholism are not indicator conditions for influenza vaccination, give 1 dose annually if the patient is age 50 years or older, has other indications for influenza vaccine, or if the patient requests vaccination.

C. Asthma is an indicator condition for influenza but not for pneumococcal vaccination.

D. For all persons with chronic liver disease.

E. For persons < 65 years, revaccinate once after 5 years or more have elapsed since initial vaccination.

F. Persons with impaired humoral immunity but intact cellular immunity may be vaccinated. *MMWR* 1999; 48 (RR-06): 1-5.

G. Hemodialysis patients: Use special formulation of vaccine (40 ug/mL) or two 1.0 mL 20 ug doses given at one site. Vaccinate early in the course of renal disease. Assess antibody titers to hep B surface antigen (anti-HBs) levels annually. Administer additional doses if anti-HBs levels decline to <10 milliinternational units (mIU)/ mL.

H. There are no data specifically on risk of severe or complicated influenza infections among persons with asplenia. However, influenza is a risk factor for secondary bacterial infections that may cause severe disease in asplenics.

I. Administer meningococcal vaccine and consider Hib vaccine.

J. Elective splenectomy: vaccinate at least 2 weeks before surgery.

K. Vaccinate as close to diagnosis as possible when CD4 cell counts are highest.

L. Withhold MMR or other measles containing vaccines from HIV-infected persons with evidence of severe immunosuppression. *MMWR* 1998; 47 (RR-8):21-22; *MMWR* 2002; 51 (RR-02): 22-24.

Intramuscular human immune globulin (IGIM) is the prototype for the specific immune globulins that are administered by this route. A major limitation of these products is that, even with painful injections at several sites, the desired blood levels of IgG are not always attainable. Care must be taken not to inject these products intravascularly, for they contain immunoglobulin aggregates that can activate the complement system and cause serious anaphylactic reactions.

Intravenous human immune globulin (IGIV) is the prototype for the specific immune globulins that are administered by this route. Intravenous preparations are treated to prevent aggregation of the immunoglobulins, and there are virtually no limitations with respect to attainable blood levels. The first of these products marketed in the early 1980s were of questionable activity because of alteration of the Fc portion of the IgG molecules; ie, loss of the complement-activating and opsonizing activities required for antibacterial effects. The current products are evaluated for these *secondary* antibody activities. Later some of the products were associated with transmission of hepatitis C, but virus inactivation is now required in the manufacture of all immune globulins; the *P* in some of the product names represents *pasteurization* and *S/D* stands for surfactant/detergent, which are processes used to inactivate viruses.

IGIM and IGIV are polyclonal antibody preparations containing perhaps 10^7 different antibody specificities. These products are extremely broad spectrum when compared to MAbs but of relatively low activity for each specificity. MAbs are specific for essentially a single epitope (assuming no cross reactivity) and are highly concentrated when compared to the polyclonal products. This level of specificity is desirable when the drug is targeting a specific receptor in the body such as a tumor antigen (eg, rituximab), physiologically active molecule such as tumor necrosis factor (eg, infliximab), or drug (eg, digoxin immune Fab) but is likely a disadvantage when the goal is to neutralize an infectious organism. *Immunologic redundancy* with polyclonal antibodies specific for different epitopes, and of multiple isotypes, is probably more effective against pathogens. It also should be recalled that all of the epitopes in an MAb are highly concentrated and some of these may be foreign and cause allergic reactions; eg, idiotopes, allotypic markers (Gm, Km).

Immune Globulin Intramuscular

The IGIM products are aqueous solutions containing 15% to 18% protein of which more than 90% is IgG and each lot represents the pooled plasma of more than 1000 donors. They are standardized for antibody to measles, diphtheria, and poliovirus to assure reasonable uniformity of product but contain antibodies specific for numerous bacteria, viruses, and fungi.

The main indications of IGIM is for IgG-replacement therapy in disorders where there is a deficiency of IgG antibodies and for the passive prevention or modification of hepatitis A and measles in susceptible persons when given shortly after ex-

Table 89-8. Human Immune Globulins

IMMUNE GLOBULIN	DISTRIBUTOR
Immune Globulin Intramuscular (IGIM)	
BayGam	Bayer
Gammar-P.I.M.	Centeon LLC
Immune Globulin Intravenous (IGIV)	
Gammar-P.I.V.	Aventis Biologicals
Gamimune N	Bayer
Gammagard S/D	Hyland Immuno HealthCare
Iveegam	Immuno-Hyland
Polygam S/D	American Red Cross
Sandoglobulin	Novartis
Venoglobulin-I and *Venoglobulin-S*	Alpha Therapeutics
Anti-Infective Immune Globulins	
Cytomegalovirus Immune Globulin Intravenous	
CytoGam	MedImmune
Hepatitis B Immune Globulin	
BayHep B	Bayer
Nabi-HB	North American Biologicals.
Rabies Immune Globulin	
BayRab	Bayer
Imogam Rabies	Pasteur–Mérieux Connaught
Respiratory Syncytial Virus Immune Globulin, Intravenous	
RespiGam	Medimmune and Wyeth–Lederle
Tetanus Immune Globulin	
BayTet	Massachusetts Public Health Biologics Lab
Vaccinia Immune Globulin	Bayer Centers for Disease Control and Prevention
Varicella-Zoster Immune Globulin	Massachusetts Public Health Biologics Lab
Immunosuppressive Immune Globulins	
Rh_O (D) Immune Globulin	
BayRho-D	Bayer
Gamulin Rh and *Mini-Gamulin Rh*	Centeon LLC
Rh_OGAM and *MICRh_OGAM*	Ortho Diagnostics
Rh_O (D) Immune Globulin Intravenous	
WinRho SDF	North American

posure; passive immunization for measles is particularly important in household contacts less than 1 year of age since they are particularly prone to measles complications and have not yet been vaccinated. IGIM is not standardized for hepatitis B, and the specific immune globulin should be used in this case. IGIM can be used for the prevention of varicella in immunocompromised patients if varicella-zoster immune globulin is not available. It also has been used to prevent fetal damage in women who are exposed to rubella during the first trimester of pregnancy and who do not want a therapeutic abortion, but it is of questionable value for this purpose. The ACIP recommends immune globulin (IM or IV) administration to symptomatic HIV-positive and other severely immunocompromised patients who are exposed to measles, regardless of their immunization status.

Table 89-9. Heterologous Antisera

ANTISERUM	DISTRIBUTOR
Antitoxins	
Botulism Antitoxin Types A, B, and E (Equine)	CDC[a]
Botulism Antitoxin Monovalent Type E (Equine)	CDC[a]
Diphtheria Antitoxin (Equine)	CDC[a]
Antivenins	
Crotalidae Antivenin Polyvalent (Equine)	Wyeth–Ayerst
Micrurus fulvius Antivenin (Equine)	Wyeth–Ayerst
Latrodectus Mactans Antivenin (Equine)	Merck
Sculpturatus centruroides Antivenin (Caprine)	Arizona State University
Immunosuppressive	
Anti-thymocyte Globulin (Equine)	
ATGAM	Upjohn

[a] Centers for Disease Control and Prevention.

Immune globulins are probably effective in preventing or modifying infections by encapsulated bacteria and their complement-activating and opsonizing activities are most important in this respect. Antibody is more effective in preventing virus, fungal and other intracellular infections than in the resolution of established infection where cell-mediated immunity is much more important.

In treating immunodeficiency diseases the goal is to maintain IgG levels at about 200 mg/dL, which may require IGIM doses of 1mL/kg or more; lower doses are generally indicated for the other uses. Injection is preferably in the upper, outer quadrant of the gluteal region and doses of more than 10 mL should be divided and injected at several sites to reduce discomfort. The IgG titers peak within 2 to 5 days, and the serum half-life of IgG is usually about 20 to 25 days, but this can vary considerably.

There are few adverse reactions associated with IGIM except for local pain and tenderness at the injection site. Serious anaphylactic reactions occur occasionally and, as with all immune globulin products, are most often associated with selective IgA deficiency. This is the most common selective immunoglobulin deficiency, but the true incidence is not known and estimates range from 1:700 to 1:2,500.

IGIM is reported to be 80% to 95% effective in preventing hepatitis A depending upon the degree of exposure and time of treatment. It is probably much less effective in completely preventing the other virus diseases but is believed to lessen the in-

cidence of severe disease and complications. IGIM helps in controlling infections in antibody deficiency disorders, but serious immunodeficiency disease involves multiple problems that are not addressed by IGIM.

The fundamental properties of the specific immune globulins for hepatitis B, rabies, tetanus, vaccinia, and varicella-zoster are very similar to those of IGIM.

Immune Globulin Intravenous

The IGIV products are aqueous solutions or lyophilized powders that are reconstituted to provide 5% or 10% protein solutions except for Sandoglobulin, which is prepared as 3, 6, 9, or 12% solutions. The IgG content ranges from greater than 90% to 99% depending upon the specific product and is nearly all monomeric (>92% to 99%). Each lot represents the pooled plasma of from more than 1000 to 50,000 donors. Most of the powders can be stored at room temperature and the solutions at 2–8°, but there are some differences in the way that individual products are stored and reconstituted so that pharmacists should become familiar with the properties of the individual products used. Some of the products have less IgA and may be able to be used in some IgA-sensitive patients. There is much variation in the reported mean serum half-life (23–40 days) of the products, but this also varies considerably between patients. The individual products also vary in the approved labeled indications but, for most purposes, they are considered to be therapeutically equivalent and will be discussed as such below.

IGIV is especially useful in those conditions where rapid and/or high levels of antibody are desired and cannot be achieved with IGIM or in patients where IGIM is contraindicated because of such things as limited muscle mass or bleeding tendencies. The indications and uses of IGIV are somewhat paradoxical in that these products are employed both as anti-infectives and as immunosuppressive agents. Note however that the dose levels in the first case are similar to those for IGIM with the goal being to maintain baseline serum levels of IgG of at least 200 mg/dL; the dose levels of IGIV when used as an immunosuppressive generally exceed those that can be easily attained with IGIM. Several days is required for the serum levels of IgG to equilibrate since IgG is extensively redistributed to extravascular spaces.

IGIV is indicated for the treatment of primary immunodeficiency disease in much the same way as IGIM (see above). It also is indicated for the prevention of bacterial infections in patients with B cell chronic lymphocytic leukemia, the most common form of adult leukemia, and in children with AIDS. Doses in the range of 100 to 400 mg/kg every 3 to 4 weeks will usually maintain the IgG serum levels at the desired 200 mg/dL.

IGIV also is indicated for immune thrombocytopenia purpurea (ITP), Kawasaki disease, and bone marrow transplant patients. IGIV is presumably acting as an immunosuppressive in these conditions, but the reader should be aware that neither the detailed mechanisms of these diseases nor of IGIV are completely understood at this time.

Both the anti-infective and immunosuppressive activities of IGIV are important in bone marrow transplantation where it is effective in reducing the incidence and severity of both infections and *graft-versus-host disease*. Doses of 500 mg/kg are administered 7 and 2 days prior to transplantation, or at the beginning of conditioning therapy, and are continued weekly after transplantation for about 13 weeks.

In Kawasaki disease, IGIV plus aspirin therapy reduces the incidence of coronary artery abnormalities significantly more than aspirin therapy alone. Several different dosing schedules are used including a single dose of 2 g/kg within 10 days of onset of the disease or 400 mg/kg on four consecutive days.

The efficacy of IGIV in ITP depends on the age of the patient and form of the disease and, while often helpful in restoring platelet levels, is difficult to predict; acute childhood ITP probably responds best, but this is also the form with the highest rate of spontaneous remission. A wide variety of dosage regimens have been used to attain the goal of a platelet count of 30,000 to 50,000 cells/mm^3; one example is induction therapy of 400 to 2000 mg/kg for 1 to 7 consecutive days and, if required, maintenance therapy of 400 to 2000 mg/kg every 2 weeks.

The mechanism of the immunosuppressive activity of IGIV is not well understood but likely involves multiple mechanisms of varying importance depending upon the condition.[9] For example, ITP involves *antibody-dependent cell-mediated cytotoxicity* in which the antibody-coated platelets are lysed, primarily in the spleen, by effector cells such as macrophages that have Fc receptors for the autoantibodies. One theory is that antibodies in the IGIV, after forming immune complexes with their complementary antigens, compete for the Fc binding sites with the antibody-coated platelets; the efficacy of Rh_o(D) immune globulin intravenous in treating ITP in Rh-positive patients is notable in this respect. Another possibility is that the IGIV contains anti-idiotypic antibodies specific for the anti-platelet antibodies. It also may be speculated that immune complexes suppress the immune response by binding to Fc receptors and inhibiting B cell responsiveness, which appears to be a mechanism of feedback inhibition of antibody production. Note however that the mechanism of action of the immunosuppressive antibodies used in the management of allograft rejection (anti-thymocyte globulin, muromonab CD3 and daclizumab) is likely quite different than that of IGIV; these antibodies all inhibit specific receptors on lymphocytes and thereby suppress ongoing immune responses.

There are many off-label uses of IGIV, and an expert panel has reviewed and made recommendations on 53 of these.[10] The majority of the diseases are known or suspected to be immunologically mediated diseases (eg, autoimmune). Lassister's[11] evaluation of the studies of IGIV in the management of neonatal sepsis contains an excellent review of the factors to be considered in fetal and neonatal immunity.

The adverse reactions of IGIV tend to be mild and transient. Mild fever, chills, arthralgia, myalgia, and many other minor symptoms are most likely to occur when there are large time intervals (greater than 8 weeks) between treatment and a build up of what may be called the *antigen load*; the administered antibodies react with their complementary antigens that have accumulated since the last dose of IGIV and the immune complexes formed may cause the mild reactions until they are cleared. Such reactions can be controlled, in part, by using slower initial infusion rates. More serious anaphylactic reactions are rare and usually associated with IgA deficiency.

Cytomegalovirus immune globulin and respiratory syncytial virus immune globulin are both intravenous preparations that share the essential properties of IGIV except that their use is restricted to the conditions for which they are named.

Other Antibody Products

The heterologous antisera currently available are all, with the exception of anti-thymocyte globulin, used to treat intoxications by venomous animals or bacterial exotoxins. Each of these products have limited and specific indications that are well described in the product literature. Patients should always be skin-tested for anaphylactic sensitivity prior to receiving heterologous products; it is also notable that most of these products are administered by slow IV infusion since the onset of activity with IM administration is too slow to deal effectively with a serious intoxication. It is of interest to compare these products with digoxin immune Fab that is an immunoantidote derived from MAb technology. It too is a heterologous product, but it demonstrates the potential to develop humanized MAbs (or Fab fragments) for the safer and more effective management of intoxications of many types.

The MAb products marketed as of April 2004 are listed in Table 89-10. The six therapeutic categories represented by the

Table 89-10. Monoclonal Antibodies[a]

ANTIBODY	DISTRIBUTOR
Anticoagulant Antibodies	
Abciximab (Chimeric)*	
ReoPro	Lilly
Anti-Infective Antibodies	
Palivizumab (Humanized)	
Synagis	Medimmune and Ross Products
Antiinflammatory Antibodies	
Infliximab (Chimeric)	
Remicade	Centocor
Antineoplastic Antibodies	
Rituximab (Chimeric)	
Rituxan	IDEC and Genentech
Tratuzumab (Humanized)	
Herceptin	Genentech
Immunoantidote Antibodies	
Digoxin Immune Fab (Ovine)*	
Digibind	Glaxo–Wellcome
Digidote	Boehringer Mannheim
Immunosuppressive Antibodies	
Daclizumab (Chimeric)	
Zenapax	Hoffmann–LaRoche
Muromonab-CD3 (Murine)	
Orthoclone-OKT3	IDEC and Genentech

[a] Includes Fab fragments (*) derived from monoclonal antibodies but does not include the radioisotope-conjugated MAbs and fragments licensed for diagnostic purposes as of January 2000.

eight current products only partially reflect the potential of MAbs as therapeutic agents. Conceivably every known therapeutic class could ultimately be represented, possibly along with some that are currently unknown.

The MAb that is definitely a passive immunizing agent is palivizumab. This antibody is specific for an epitope in the F protein of the respiratory syncytial virus (RSV). The F protein on the surface of RSV is necessary for the virus to infect cells and, as expressed on the surface of the infected cells, is responsible for the cell fusion that results in syncytia. Palivizumab exhibits both *virus-neutralizing* and *fusion inhibitory activity*. It is indicated, as is RSV immune globulin intravenous (Table 89-7), for the prevention of serious lower respiratory tract disease caused by RSV in high-risk infants. This product may, more than any of the others, best reflect the future of passive immunization.

ALLERGENIC EXTRACTS

Allergenic extracts comprise a large group of products that are unique compared to other biologics and conventional pharmaceuticals. A specific license is required for their manufacture, and they are available mainly from specialty companies. In spite of nearly 90 years of clinical use for the diagnosis and treatment of allergy, allergenic extracts are relatively crude drugs by contemporary standards. Their composition is heterogeneous and ill-defined, their mechanism of action is understood poorly, and to date there are no totally reliable standards of potency. Allergenic extracts are administered (or dispensed) primarily in the allergist's office, and with few exceptions, these drugs do not enter conventional pharmaceutical distribution systems.

Common allergies are estimated to affect 10% to 30% of the population, and allergenic extracts, despite their shortcomings, are mainstays in the control of these diseases. Every pharmacist should have a fundamental understanding of allergenic extracts, and some clinical, institutional, and industrial specialists require expertise. In recent years allergy research has intensified, but an unfortunately small number of pharmaceutical scientists have entered the field.

Because of the complexity and large number of allergenic extracts, only the fundamental terminology, principles, properties, and types of products are included in this chapter. As noted earlier, the *diagnostic skin antigens* for infectious diseases are included in this discussion of allergenic extracts (*delayed hypersensitivity tests*) since they are most closely related to these products in both composition and use (Table 89-11).

ALLERGY

Allergy (*hypersensitivity*) may be defined as an *untoward immunological reaction* to an environmental immunogen called the *allergen*. The phenomenon is not a simple cause-effect rela-

Table 89-11. Mechanisms and Manifestations of Allergy[a]

	TYPE I[b]	TYPE II	TYPE III	TYPE IV
Names	IgE-Mediated Immediate Hypersensitivity	Cytotoxic	Immune Complex Arthus-type	Cell-Mediated Delayed Hypersensitivity Tuberculin-type
Immune Effectors	IgE	IgG	IgG, IgM	$CD4^+$ T Cells $CD8^+$ T Cells
Major cells involved in inflammation	Mast Cell Basophil	Macrophage (Antibody-dependent cell-mediated cytotoxicity) or, less commonly,	Neutrophil	Macrophage
Mediators	Histamine			
Leukotrienes	Complement-mediated lysis	Lysozomal enzymes	Cytokines	
Onset in sensitized individual	0–30 minutes	Immediate (but symptoms inapparent)	2–24 hours	6–24 hours
Manifestations	Allergic rhinitis			
Allergic asthma				
Atopic dermatitis				
Gastroenteropathy	Hemolytic anemia			
	Neutropenia			
	Thrombocytoenia	Vasculitis		
Serum Sickness				
Glomerulonephritis				
Arthus-type rash				
	Allergic contact dermatitis			
	Hypersensitivity pneumonitis			

[a] Based upon the classification of Coombs and Gell.[12]
[b] The characteristics of *late phase reactions* are not represented in this table.

tionship, however, for exposure to an allergen results in disease only in a small portion of the population. The occurrence of allergic disease is determined by the characteristics of the individual as well as those of the allergen and the conditions of exposure. Disease occurs only in those previously sensitized by exposure to the allergen and the ability to become sensitized is, at least sometimes, genetically determined (see *Atopy*). Sensitization also may vary with the age of the individual, nature of the allergen, route and degree of exposure and many other factors.

The immunological processes involved in allergy result in inflammation and tissue damage but otherwise do not differ fundamentally from those seen in the normal immune response (Chapter 60). The classification system of Coombs and Gell (Table 89-1) that considers four basic mechanisms of immunologically mediated disease remains a very useful frame of reference for allergic disease

Most of the common allergies are *IgE-mediated* and allergenic extracts are most useful in the diagnosis (*immediate sensitivity tests*), and to a lesser extent immunotherapy, of these conditions. *Cytotoxic allergy* and *immune complex disease* are more prominent in autoimmune and alloimmune diseases (Chapter 60) and are not as important in the present context. Many environmental allergens, including the well-known poison ivy, produce allergic contact dermatitis and this cell-mediated immunity is the basis for *delayed hypersensitivity tests*.

Atopy

Atopy is the inherited tendency to develop IgE-mediated allergy to common inhaled and ingested allergens. The atopic diseases include the common *allergic rhinitis* (hay fever) and *allergic asthma*, *atopic dermatitis*, and, less commonly, *allergic gastroenteropathy*. Allergenic extracts are most useful in the management of the first two conditions.

The etiology of atopy is poorly understood. The atopic individual frequently has a family history of allergy and typically is allergic to multiple allergens. Serum IgE usually is elevated, and eosinophilia is usually present in the blood and tissues. The shock tissues are hyperresponsive, and this may involve autonomic imbalance such as a β-adrenergic deficit (or cholinergic excess) in the case of asthma. The nature of the allergen and the route of exposure via mucous membranes undoubtedly play important roles.

The IgE-mediated conditions *urticaria-angioedema* and *anaphylaxis* are nonatopic diseases in that there is no genetic predisposition, and the shock tissues not hyperirritible. The allergens are most often ingested or injected, and the most common offenders are foods and drugs. Sensitivity testing and immunotherapy are of limited value in these nonatopic conditions with the notable exception of *Hymenoptera (stinging insect) sensitivity*.

The manifestations of both atopic and nonatopic IgE-mediated disease are what are often considered to be the *typically allergic symptoms.* It is important for the pharmacist to understand that allergy can be manifest by other symptoms and, especially, that rhinitis, asthma, urticaria, and anaphylaxis can result by nonimmunological mechanisms.

Allergens

Allergens are the inciting agents of allergy. It is common to speak of substances such as pollens, danders, dusts, etc, as allergens when, in fact, the true allergens are found in the individual compounds within these substances. As in other immunological reactions, the specificity resides in small fragments within the molecules called *epitopes*.

The chemical identity of most allergens is unknown, but the tools of molecular biology are being employed for both the elucidation of structure and synthesis of recombinant allergens. When isolated, individual allergens are named by the system of the International Union of Immunological Societies.[13] The first three letters of the genus are followed by the first letter of the species and then a Roman numeral; eg, *Amb a I* is antigen E of short ragweed (*Ambrosia artemisifiolia*). Baldo has reviewed the structural characteristics of both environmental and drug allergens.[14]

Most known allergens are proteins or glycoproteins and do not appear to differ much from other immunogens except perhaps being somewhat smaller (mol wt 10,000-70,000). Most allergenic substances contain multiple allergens that vary in their allergenic potency, ie, *major* and *minor* allergens. Allergens from related sources often are similar chemically and *cross-allergenicity* is common between biologically related substances. The number and diversity of potential allergens in the environment is great, which provides a major complication in the control of allergy.

A variety of low-molecular-weight chemicals may serve as allergenic *haptens* (partial immunogens) and induce allergy after combining covalently with a suitable protein carrier. While this is an important process in drug allergy, most common environmental allergens appear to be complete immunogens. A notable exception is the case of common allergic contact dermatitis caused by a variety of plants, drugs, clothing additives, and other substances. The plants most responsible for contact dermatitis in North America belong to the *Anacardiaceae* family, primarily the genus *Toxicodendron* (Rhus), and include poison ivy, oak, and sumac. The allergenic components of these plants, called urushiols, are found in the oleoresin fraction and are derivatives of pentadecylcatechol or heptadecylcatechol. Many plants of the *Compositae* family, which includes the ragweeds, also cause contact dermatitis, and the allergens have been identified as sesquiterpenoid lactones.

The chemical differences between the common atopic and contactant allergens are of significance in the preparation of allergenic extracts. The plant oleoresins containing the contactants usually are removed during the defatting process and are not present in the aqueous allergenic extracts. The ether-soluble fraction, on the other hand, can be used for the preparation of patch-testing materials.

Diagnosis of Allergy

The diagnosis of an allergic disease requires first the determination of allergic etiology and second the identification of the specific allergen(s). Understanding the fundamental principles in the diagnosis of allergy is important to pharmacists, particularly in the community setting, where they are called upon for the initial evaluation of reactions to both drugs and environmental substances. In such cases important decisions must be made whether to refer the patient to a physician or emergency facility, recommend OTC therapy or to take another course of action.

Physical diagnosis, while important, is not sufficient to establish allergic etiology since the symptoms of allergic diseases can result from other causes. Important in this respect are the *intrinsic* (nonallergic) diseases of asthma, rhinitis, and urticaria that should be distinguished from the *extrinsic* (allergic) diseases. This distinction between allergy and intrinsic diseases is not always clear, and some clinical conditions likely involve both. It is important, however, since a number of drug idiosyncrasies are associated with intrinsic disease and may be mistaken for allergy.

A *detailed history* is perhaps the most important step both in determining whether the condition is an allergy as well as suggesting possible allergens. This should include consideration of the patient's symptoms in relation to familial, seasonal, home environment, occupational, medication, and related personal factors.

Clinical laboratory tests are assuming greater importance in the diagnosis of allergy. Diagnostic testing services are available to measure total serum IgE and immunogen-specific IgE for many allergens. These tests can be used in conjunction with

sensitivity tests and in those with dermographia, very young patients or others where skin testing may be unreliable. Determination of IgG, IgA, and IgM may be helpful in differentiating various autoimmune, infectious, or other diseases that may mimic allergies. These and related tests also may be used to monitor immunotherapy.

Sensitivity testing with allergenic extracts is still the principal method of determining specific allergic etiology. Sensitivity testing has been used since the early part of the century for the diagnosis of allergy. A variety of different test methods may be employed, but all involve the administration of a small amount of allergen to the patient who is observed for reactions suggestive of allergy. While simple in principle, both the administration and interpretation of sensitivity tests require a great deal of expertise and should be conducted only by qualified individuals. Also, since sensitivity testing is a costly, discomforting, and time-consuming procedure, it is impractical to test the patient for all possible allergens. A detailed history provides the main basis for selection of the specific tests to be performed.

Immediate Sensitivity Tests

These tests, as the name implies, are used to detect IgE-mediated allergy, and there are two general types of test procedures.

CUTANEOUS TESTS—These are the simplest of the immediate sensitivity tests and somewhat safer than intradermal tests. The back as well as the arms can be used for testing that enables 50 or more allergens to be evaluated in a single office visit. Cutaneous tests also are less sensitive, which some feel is an advantage that provides better correlation with clinical allergy. Allergists often employ a cutaneous test for preliminary screening followed by intradermal tests for more complete evaluation of the allergens to which the patient is sensitive. The skin is abraded with a sharp needle (*prick test*) or scarifier (*scratch test*) either before or after application of a drop of a relatively concentrated (1:00 to 1:10 *w*/*v*) allergenic extract. The test sites, grading of reactions, and precautions are similar to those described for the intradermal tests.

INTRADERMAL TESTS—These are the most sensitive of the immediate sensitivity tests and are accomplished by injecting relatively dilute (1:1000 to 1:100 *w*/*v*) allergenic extracts directly into the skin on the volar surface of the lower or upper arm. The back should not be used because of the difficulty in dealing with systemic reactions. Multiple extracts can be tested at one time using sites 2 to 3 inches apart and marked with an appropriate code. The tests are inspected after 15 minutes or again at 30 minutes if the characteristic wheal and flare reactions are not developed fully. The tests are graded from 0 to 4+ depending upon the size of the wheal. Generalized allergic reactions are relatively uncommon, but a rubber tourniquet and epinephrine (1:1000) should always be available when these tests are performed.

Histamine controls are used to eliminate false-negative reactions by confirming the wheal/flare reaction of the skin and quality of the technique. Diluent controls are used to detect the rare individual with *dermographia* that gives positive tests to the skin trauma. Although a single concentration of allergenic extract often is used for testing, more information can be obtained by a *threshold dilution titration* using a 10-fold dilution series.

Other types of immediate sensitivity tests using allergenic extracts such as *provocation tests* and *passive transfer tests* are employed less commonly and are described in standard references on allergy.

EFFECT OF DRUGS ON SENSITIVITY TESTS—Antihistamines (H_1-antagonists) and other drugs with antihistaminic activity such as the tricyclic antidepressants suppress the immediate skin-test reactions. Long-acting agents may suppress the reaction for as long as 6 weeks. H_2-antagonists do not suppress the immediate skin-test reactions alone but may act synergistically with the H_1-antagonists. Oral and parenteral β_2-adrenergic agonists have been reported to decrease the allergen induced wheal, and potent topical corticosteroids may suppress skin reactivity locally. Inhaled β_2-adrenergic agonists, methylxanthines, and cromolyn do not interfere with skin testing. Oral corticosteroids and nonsteroidal anti-inflammatory agents have little effect on immediate skin tests. It is recommended that tricyclic antidepressants, chlorpromazine, and hydroxyzine be discontinued for at least 5 days before testing, and that the short-acting antihistamines be discontinued for at least 24 hours. Beta-blocking agents can increase the immediate skin test reaction significantly and patients on these drugs may be less responsive to the beta-agonists needed to treat a systemic reaction to an allergenic extract. The optimal time for skin testing is when the patient has recently taken no drugs that may potentially interfere, and in all cases it is important to administer a positive control (ie, histamine).

Treatment of Allergy

The types, causes, and contributing factors of allergy are numerous. Therapy is thus complex and variable but can be divided into three main types.

Environmental controls are designed to eliminate or at least minimize exposure to the allergen.[15] The avoidance of an allergen is relatively simple and effective in some instances but most allergens cannot be eliminated totally from the environment. However, minimizing exposure to the allergen always enhances the effectiveness of other therapeutic measures and should always be accomplished as much as possible.

Symptomatic drug therapy is required in the control of most common allergies. The many drugs used for this purpose include the antihistamines and leukotriene antagonists, corticosteroids, and sympathomimetics.

Specific *immunotherapy* may be employed for certain allergies as described below.

Immunotherapy

The immunotherapy of allergy is accomplished by administration of gradually increasing doses of allergen over a period of months or years with the anticipation of the patient developing increasing tolerance to the allergen. This is called commonly *desensitization* or *hyposensitization,* but these terms tend to imply unconfirmed mechanisms and may be confused with other clinical procedures. For example, different *desensitization* procedures have been used in drug allergy (eg, penicillin, sulfonilamide, insulin, etc) but these are short-term procedures that likely involve different mechanisms.

Immunotherapy was first used for hay fever in England in 1911 and is still used nearly exclusively in the treatment of IgE-mediated allergy. There have been many attempts to desensitize against the cell-mediated *Rhus* contact dermatitis (poison ivy and oak), but they have met with little success and the products marketed for this purpose remain controversial.

The precise mechanism of immunotherapy remains unknown, but a variety of both humoral and cellular immunological changes have been observed over the course of allergen administration.[16] Clinical improvement in some patients correlates well with the level of IgG *blocking antibodies* that, as suggested by the name, may bind the allergen and prevent its interaction with the mast cell-bound IgE. This is undoubtedly too simple an explanation, and it appears that the parenteral exposure to allergen (most disease involves mucosal exposure) alters the factors that regulate the production of allergen specific IgE.

The efficacy of immunotherapy is difficult to judge. There have been many controlled clinical trials, but most of these have considered allergic rhinitis and asthma caused by common aeroallergens (eg, ragweed pollens, common grass, and tree pollens). Immunotherapy commonly is recommended and is considered to be effective for these conditions when properly employed. The treatment of hay fever and asthma due to other aeroallergens (eg, molds) is based mainly upon experience with the common allergens but is common and likely effective in

skilled hands. Hymenoptera insect venom therapy is highly effective and recommended for any patient who has experienced systemic anaphylaxis following a sting. Immunotherapy is not recommended for food allergies that are best treated by elimination diets or for dander allergies except in rare instances where avoidance is impossible (eg, veterinarians).

The variety of regimens and techniques used in the immunotherapy of allergy are described in standard reference works on allergy. The optimum duration of therapy is uncertain but usually continues until the patient is symptom-free for at least 1 year. The average course of therapy may require 3 to 5 years. Success often is relative but some patients remain free of symptoms for extended periods. In others there is sufficient reduction of symptoms that symptomatic therapy alone can be employed but some patients require resumption of immunotherapy.

Immunotherapy is not without risk.[17] Most patients develop some swelling and redness at the injection site, but reactions that persist for more than 24 hours are a signal to proceed cautiously. Particularly uncomfortable local reactions may be treated with oral antihistamines and cold compresses. The possibility of serious generalized allergic reactions always is present. Patients should remain in the physician's office for at least 20 minutes after each course of immunotherapy or longer if they are in one of the following high-risk groups: unstable asthma, seasonal exacerbation, high degree of hypersensitivity, receiving beta-blockers or *rush immunotherapy* (ie, more rapid dose escalation than with conventional therapy). During pregnancy there is no evidence of major adverse effects of allergenic extracts on the fetus, but uterine contractions may occur as part of a generalized allergic reaction. It generally is recommended that immunotherapy not be started during pregnancy and that slight reduction of the maintenance dose be considered for those who become pregnant during therapy.

It should be remembered that the most successful therapy of allergy is achieved by avoidance of the allergen(s) and that all other forms of therapy are essentially adjunctive. Immunotherapy should not be continued indefinitely in the absence of clinical improvement. Treatment failures may result from improper selection of allergens, development of new sensitivities, improper use of environmental controls, and various problems associated with the allergenic extracts that are discussed in the next section.

ALLERGENIC EXTRACTS

Allergenic extracts are concentrated solutions or suspensions of allergens used for the diagnosis and treatment of allergic diseases. Most are injectable products administered in the physician's office, and for many years they were prepared by the individual users. Commercial extracts gradually replaced extemporaneous preparation as a number of small specialty companies began marketing allergenic extracts several decades ago. More recently, many of the familiar names in allergy products have merged into the larger pharmaceutical companies, and today several of the manufacturers of allergenic extracts are multinational corporations. There are more than 900 different diagnostic allergenic extracts and about 600 therapeutic extracts currently licensed by the FDA. Because of the great number of allergenic extracts on the market only the general characteristics of the products are described here. Additional information on these and related products may be obtained from the licensed manufacturers listed in Table 89-12.

Handling

Allergenic extracts usually are designated as being *aqueous* or *glycerinated* products. Normal saline or similar isotonic electrolyte solution is the diluent for the former while the latter contain 50% glycerin in the diluent. The preparations normally are buffered to pH 8 and contain phenol (0.4%) as a preservative. The preparation of allergenic extracts is described in earlier editions of this book and more detailed information on their production is available from the manufacturers and FDA.

Table 89-12. Licensed Manufacturers of Allergenic Extracts[a]

ALK Laboratories, Inc.
Allergologisk Laboratorium A/S
ALO Laboratories, Inc.
Allergy Laboratories, Inc.
Allermed Laboratories, Inc.
Antigen Laboratories, Inc.
Center Laboratories, Inc[b]
Greer Laboratories, Inc
Hollister-Steir Labs[b]
Nelco Laboratories, Inc

[a] *Establishments and Products Licensed under Section 351 of the Public Health Services Act,* available at the FDA Web site [http://www.fda.gov].
[b] Aqueous and alum precipitated extracts.

The most common measures of allergenic potency are by *weight/volume* (*w/v*) and the *protein nitrogen unit* (PNU) (Table 89-13). Weight/volume is the weight of allergenic substance extracted per volume of extracting fluid. For example, a 1:50 extract is prepared by extracting 1 g of substance with 50 mL of solvent and decimal dilutions of this extract provide 1:500, 1:5000, etc concentrations. One protein nitrogen unit represents 0.01 mcg of total protein nitrogen in the product.

A typical allergenic substance contains multiple allergenic molecules and epitopes of varying potency, and there is significant chemical and biological variation with different lots of the substance. Neither the *w/v* concentration nor the PNU are directly related to allergenic potency nor can the two units be reliably compared with each other. One must understand well this variation that occurs between the lots of the same product and between similar products produced by different manufacturers in order to safely and effectively employ allergenic extracts in the clinic.

The FDA has licensed *standardized allergenic extracts* (Tables 89-14–89-18) since 1983 that are bioassayed against FDA reference standards. The potency of these products are expressed in terms of *allergy units* (AU) or *bioequivalent allergy units* (BAL). The potency between lots is definitely more consistent than with conventional extracts, but variation may still occur and the same general principles of use still apply.

The absence of a completely reliable method of standardization along with the extreme variation between patients dictates that the appropriate dosage for immunotherapy must be determined clinically. The initial dilution of extract, starting dose, and progression of dosage is determined by a skilled clinician on the basis of the patient's history and sensitivity tests. Some things to keep in mind are that dilute extracts tend to lose activity more rapidly and that care must be exercised when changing to a new lot since it may be significantly more potent.

Table 89-13. Units of Potency for Allergenic Extracts

UNIT	DESCRIPTION
Weight/Volume (*w/v*)	Allergenic substance (g) per volume (mL) of extracting fluid
Protein Nitrogen Unit (PNU)	1 mg protein N 5 100,000 PNU
Allergy Unit (AU)	Bioassay compared to reference standard
Bioequivalent Allergy Unit (BAU)	Bioassay compared to reference standard

Table 89-14. Pollen Extracts

Trees		
Acacia	Elderberry	Orange
Alder, grey	Elm, American	Osage orange
Almond	Eucalyptus	Palo verde
Apple	Fir	Peach
Apricot	Hackberry	Pear
Arbor vitae	Hazelnut	Pecan
Ash	Hemlock	Pepper tree
Aspen	Hickory	Pine
Bayberry	Hop-hornbeam	Plum
Beech	Ironwood	Poplar
Birch, spring	Juniper	Privet
Birch, white	Locust	Redwood
Bottle brush	Maple	Russian olive
Box elder	Melaleuca	Spruce
Carob tree	Mesquite	Sweet gum
Cedar	Mock orange	Sycamore
Cherry	Mulberry	Tamarack
Chestnut	Oak, white	Tree of heaven
Cottonwood	Olive	Walnut
Cypress		Willow
Grasses		
Bahia	Corn	**Redtop**[a]
Barley		
Beach	**Fescue, meadow**[a]	**Rye grass, perennial**[a]
Bent	Grama	Salt
Bermuda grass[a]	Johnson	Sorghum
Bluegrass, Kentucky[a]	Koeler's	Sudan
Brome	Oats	
Orchard grass[a]	**Sweet vernal grass**[a]	
Bunch	Quack	**Timothy grass**[a]
Canarygrass		Velvetgrass
		Wheat
Weeds and garden plants		
Alfalfa	Fireweed	Poppy
Amaranth	Gladiolus	Povertyweed
Aster	Goldenrod	Quailbush
Balsam root		
Bassia	Greasewood	
Hemp	**Ragweed, giant**[a]	
Beach bur		
Broomweed	Honeysuckle	
Hops		
	Ragweed, short[a]	
Burrow brush		
Careless weed	Iodine Bush	
Jerusalem oak	**Ragweed, western**[a]	
Castor bean	Kochia	Rose
Chamise	Lamb's quarters	Russian thistle
Clover	Lily	Sagebrush
Cocklebur	Marigold	Saltbrush
Coreopsis	Marshelder	Scale
Cosmos	Mexican tea	Scotch broom
Daffodil	Mugworta	Sea blight
Dahlia	Mustard	Sheep sorrel
Daisy	Nettle	Snapdragon
Dandelion	Pickleweed	Sugar beet
Dock	Pigweed	Sunflower
Dog fennel	Plantain, English	Western waterhemp
		Winter fat
		Wormseed
		Wormwood

[a] Standardized extract for which FDA reference standard is available. The FDA discontinued licensing of the 8 nonstandardized grass extracts July 1998.

Scratch test extracts are glycerinated products supplied in 1 to 5 mL dropper vials. They are relatively concentrated solutions, usually in strengths of 1:5 to 1:20 depending on the allergen. *Intradermal test extracts* are aqueous solutions supplied in 1 to 5 mL multiple dose vials and are more dilute (1:500 to 1:5000). *Therapeutic extracts* are supplied in multiple-dose vials in a variety of sizes (5–100 mL) and dilutions (1:10 to 1:100). Since these extracts are diluted before use, most companies provide a variety of dilution vials that contain a volume of diluent that facilitates preparation of 10-fold dilutions. *Adjuvant extracts* of several types have been used for many years but only alum-adsorbed extracts are available

Table 89-15. Dust Extracts

House dusts		
House	Mattress	Upholstery
Dust mites		
D farniae[a]	**D pteronyssinus**[a]	**Mite mix**[a]
Other dusts[b]		
Cedar and red cedar	Cotton gin	Oak
Grain, elevator	Padauk	Wood dusts

[a] Standardized extract for which FDA reference standard is available.
[b] See also Table 89-16.

commercially (Table 89-12). *Autogenous extracts* sometimes are prepared from allergenic substances collected from the individual patient's environment. Standard and custom diagnostic and therapeutic sets and mixtures also are available as are a variety of auxiliary supplies used in allergy practice.

Prescriptions for therapeutic allergenic extracts may contain up to a dozen or more allergens, although many clinicians prefer to use multiple extracts if more than 4 to 5 allergens are to be included. These prescriptions are labeled according to clinician preference on the basis of the total allergen content or the concentration of the greatest single allergen present. The prescriptions are usually prepared in the allergist's office or obtained through the manufacturers' prescription service. A few pharmacists offer this specialized service.

It is vitally important that allergenic extracts be handled and stored properly. They tend to show reduced potency within a matter of weeks or months after their preparation, but there have been few detailed studies on the stability of these products. Both high temperatures and freezing usually have deleterious effects, and the latter may cause agglomeration of adjuvant extracts. Some extracts contain proteolytic enzymes that may contribute to decomposition of the allergens. Both glycerinated and lyophilized products are more stable than aqueous extracts. Very dilute extracts tend to lose potency by adsorption to the surfaces of containers and syringes and thus usually are prepared close to the time use. All allergenic extracts should be refrigerated at 2° to 8° and freezing should be avoided. Care must be exercised in changing to new lots or different dilutions of extracts because of possible variations in potency. It generally is recommended that quantities of extract sufficient to last the patient for 1 year be prepared to avoid frequent changes in extracts.

Role of the Pharmacist

Few pharmacists are called on today to prepare allergenic extracts or to dispense prescriptions for these products. Some pharmacies, particularly in hospitals, may stock allergenic extracts and related supplies for allergists. Actually, the training of a pharmacist is suited uniquely to many of the services required in the allergy clinic, and it is unfortunate that more pharmacists have not become involved in this area.[18]

Table 89-16. Fungal Extracts

Alternaria	Fusarium	Phoma
Aspergillus	Gelasinospora	Pullularia
Botrytis	Geotrichum	Rhizopus
Candida	Gliocladium	Rhodotorula
Cephalosporium	Helminthosporum	Rusts
Cephalothecium	Hormodendrum	Saccharomyces
Chaetomium	Microsporium	Smuts
Cladosporium	Mucor	Spondylocladium
Cryptococcus	Mycogone	Stemphylium
Curvularia	Nigraspora	Trichoderma
Epicoccum	Paecilomyces	Trichophyton
Epidermophyton	Penicillium	Verticillium

Table 89-17. Miscellaneous Inhalant Extracts

Mammalian epidermals		
Camel	Dog	Horse
Cat hair[a]	Gerbil	Mohair
Cat pelt[a]	Goat	Monkey
Chinchilla	Guinea pig	Mouse
Cow	Hamster	Rabbit
Deer	Hog	Wool (sheep)
Feathers		
Canary	Duck	Pigeon
Chicken	Goose	Turkey
	Parakeet	
Miscellaneous inhalants		
Acacia	Hemp fiber	Lycopodium
Algae	Henna	Orris root
Castor bean	Flaxseed	Pyrethrum
Cotton linters	Guar gum	Silk, raw
Cottonseed	Jute	Sisal
Derris root	Karaya gum	Tobacco leaf
Fern spores	Kapok	Tragacanth
Grain dusts	Leather	Wood dusts

[a] Standardized extract for which FDA reference standard is available.

In a few institutions allergenic extracts are provided by the pharmacist on a prescription order. Some patients require only a single extract, but even in these cases appropriate dilutions must be prepared. More frequently, patients are allergic to multiple allergens, and complex extract mixtures are required. The basic techniques and facilities required for this service are essentially the same as those used in a typical IV-additive program, but the pharmacist should have some additional training and experience in handling allergenic extracts.[18]

In addition to assuming responsibility for the preparation and control of allergenic extracts, the pharmacist also may provide a variety of patient-oriented services in the allergy clinic.[19] These services include obtaining patient histories, performing allergy testing procedures, and patient consultation. Common allergic diseases are found in up to 30% of the population, and patients with these ailments obtain a variety of drugs and medical supplies from community pharmacies. Thus, there are many opportunities for pharmacists to be of service to the allergy patient in traditional practice sites as well as the allergy clinic. To accomplish this effectively, pharmacists must have a fundamental understanding of allergy and the products used in the control of allergic diseases.

PRODUCTS

This section contains a summary of the principal allergenic extracts available today. It is impractical to provide an individual monograph for each product, and they have been grouped according to the type of allergenic substance (eg, pollens or dusts). This type of classification is used in the manufacturers' literature and also has merit when considering both the product characteristics and clinical allergy. These are described briefly for each group with emphasis on the following: clinical significance of the allergen group, most-common offenders of the group, and general usefulness and limitations of the extracts.

The lists of allergenic extracts are not intended to be comprehensive but rather to illustrate the scope of the problem in each case. Only one name, usually the common one, is given for each extract, while in practice a number of both common and scientific names may be used. Similarly, individual extracts usually are derived from a single species of plant, animal, or microorganism, but only the genus is given in the list; however, extracts of most of the common allergenic species are commercially available. Extracts containing allergens from more than one source are designated as mixtures and, while many are commercially available, only a few are

Table 89-18. Insect Extracts[a]

Stinging Insect-Whole Body		
Ant, black	Ant, carpenter	Ant, fire
Ant, red	Ant mix (black/red)	
Stinging Insect-Venom Protein		
Honey bee[a]	**Wasp[a]**	**White-faced hornet[a]**
Yellow hornet[a]	**Yellow jacket[a]**	**Mixed vespid[a]**
Inhalant Allergy to Insects		
Aphid	Deerfly	**Mites, dust[a]**
Black fly	Fruit fly	Mosquito
Butterfly	Honey bee, whole body	Moth
Caddis fly	Horse fly	Mushroom fly
Cicada/locust	House fly	Screwworm fly
Cricket	Leafhopper	Sow bugs
Cockroach	May fly	Spider
Daphnia	Mexican bean weevil	Water flea

[a] Standardized extracts. The potency of insect venom extract is expressed in mg.

listed. Not all manufacturers produce all of the extracts, and it should be recognized that different companies may employ significantly different source materials and processes in preparing products of the same name. The products from different manufacturers cannot be considered to be equivalent in all respects.

Most of the products listed are provided as diagnostic extracts for both scratch and intradermal testing, but therapeutic extracts may or may not be routinely available. Similarly, the availability of both lyophilized and adjuvant products is limited. Many of the extracts also are available in diagnostic test sets. These are not listed but include various regional, pollen, food, mold, pediatric, titration, and other test sets. Manufacturing services for custom therapeutic mixtures and autogenous extracts are also available. The individual manufacturers should be contacted for more specific information on their products and services.

Pollen Extracts

Pollens (Table 89-14) are the most common group of atopic allergens and, in fact, hay fever is sometimes called *pollinosis*. Pollens are produced only by seed-bearing plants and not by algae, fungi, mosses, or ferns. Not all pollens are of equal clinical significance for there is variation in both allergenicity and degree of exposure. Allergy usually results from *anemophilous* (wind-borne) rather than *entomophilous* (insect-borne) pollens. Conifers such as the pines are copious pollen producers but the pollens, with few exceptions, are less allergenic than others.

Pollen allergy is largely a problem of temperate climates. In Arctic and alpine regions where summers are short, plants generally reproduce vegetatively (asexually), and most subarctic plants are conifers. In the tropics there tends to be a proliferation of species with a small number of individual plants so that the degree of exposure to a specific pollen is minimized. Anemophilous plants also tend to be less common in regions of extremely high humidity.

Seasonal and geographical variation is more pronounced with pollen allergy than other types. Pollen seasons vary with both the plant and locale, but the following generalizations can be made: trees from late winter to spring, grasses from spring to early summer, and weeds from late summer to fall. Pollen allergy is a significant problem in most parts of North America, but the allergens vary somewhat with the region and are determined best by consulting one of the published guides. Perhaps 100 of the approximately 300 pollens represented in commercial extracts are fairly common offenders.

Allergenic extracts prepared from some of the common pollens (eg, ragweed, several grasses, and trees) have been among the most widely studied. Controlled studies generally have shown these products to be reliable for both diagnosis and therapy when properly prepared and employed. Many of the products listed have not been studied extensively, but their reliability often is assumed based on extrapolation of the data on the common pollens.

Dust Extracts

House dust is the most common atopic allergen, and the dust mite (*Dermatophagoides* spp) is by far the most important allergenic constituent. Although house dust may contain a wide variety of other allergens that may be important in individual cases, the dust mite is definitely the number one offender.

The dust mite appears to be distributed virtually universally and usually is found in furnishings stuffed with vegetable fibers (eg, cotton) used by humans. In contrast to the cockroach, another important arthropod allergen, dust mites are not associated with poor hygiene.

House-dust sensitivity differs from pollen allergy in several respects and is suspected particularly when the patient's history includes one or more of the following factors: perennial symptoms that worsen when the patient remains indoors, increased nocturnal symptoms, increased symptoms when performing household chores, and increased symptoms associated with turning on heating or air conditioning systems.

House dust is a ubiquitous allergen, and its total elimination is virtually impossible; however, it is important that the patient maintain as dust-free an environment as possible, particularly in the bedroom. Instructions for the preparation of dust-free rooms and products to minimize the circulation of dust and kill mites are available.

The reliability of sensitivity testing for the diagnosis of house dust allergy has improved greatly with the introduction of standardized dust mite extracts (Table 89-15). These products are also effective for immunotherapy, however, it is still important to employ stringent environmental controls in the management of house dust allergy.[15]

Relatively little information is available on other dust extracts. These are generally less-common allergens, and many are associated with occupational allergies. Some of these are implicated as a cause of extrinsic allergic alveolitis described under *Fungal Extracts*.

Fungal Extracts

The fungi are a large group of organisms that may be involved in many types of diseases, including intoxications, infections and allergy (Table 89-16). Most fungi are saprophytes and compared to bacteria are relatively uncommon causes of infec-

tious disease. Mycotoxins are of great concern in several areas of health including as possible contaminants of allergenic extracts. A number of fungi have been implicated increasingly as important causes of several types of allergic disease.

Molds are one of the major causes of atopic allergy. Allergic asthma and rhinitis, as well as various cutaneous reactions, can be precipitated by inhalation of mold spores or mycelial fragments in sensitive individuals. Fungi are ubiquitous and may be found in the home on textiles, leather goods, upholstered furniture, food, and plants. Damp, warm places such as basements and closets tend to favor mold growth, which is often encountered as common *mildew*, which most often is *Aspergillus* or *Penicillium* spp. Fungal allergy resulting from indoor exposure tends to be perennial; that from outdoor exposure shows more distinctive seasonal and geographical patterns but these are less pronounced than in pollen allergy. Fungal allergy is generally more difficult to evaluate because of taxonomic confusion, biologic complexity, and less predictable seasonal and geographical patterns than with pollens.

Sensitivity testing for fungal allergens appears to be generally reliable. It also is useful at times to identify the specific fungi in the patient's environment and fungal identification services are available. Therapy should include efforts to create a mold-free environment, but this is difficult to accomplish completely. Several studies indicate that immunotherapy may be of value for some patients. One problem is that the allergenic extracts are prepared variously from mycelium, medium, or both, and too little is known about the fungal allergens to know the most-appropriate method of preparation.

Fungi, along with a variety of organic dusts, have been found to be important causes of another respiratory allergy, *extrinsic allergic alveolitis* (hypersensitivity pneumonitis). Many names related to either the allergen or affected individuals have been applied to this condition; eg, farmer's lung, mushroom-workers disease, wood-dust asthma, etc. The disease shows no relationship to atopy but usually can be related to recent high-level exposures to the offending inhalant.

Extrinsic allergic alveolitis results primarily from a cell-mediated reaction to allergens in the lung but may involve some immune complex disease in the early stages. Diagnosis is based mainly on a detailed personal history. Both cell-mediated and immune complex allergy may provide cutaneous reactions on allergen challenge, but they differ in time-course and appearance from the immediate skin test reactions. The products listed in Table 89-16 are not useful in the diagnosis of extrinsic allergic alveolitis and effective therapy depends mainly on avoidance of the allergen.

Miscellaneous Inhalant Extracts

Atopic allergies may be caused by a variety of inhalant allergens other than pollens, dusts, and molds. The epidermals from domestic animals (cat, dog, horse) are the best-known, but the variety of inhalant allergens is remarkable. Exposure of an average individual to some of the substances listed below might appear unlikely, but this is not necessarily the case. Probably few people recognize that camel hair may be found in imported textiles and rugs, that the plant gums acacia, karaya, and tragacanth are present in hundreds of food, cosmetic, and drug products, and that pyrethrum is an active constituent of many household insecticides. Many of these substances are also ingestant (see *Food Extracts*) and contactant (see *Patch-Testing Materials*) as well as inhalant allergens.

Sensitivity testing with many of the extracts listed in Table 89-17 is fairly common but based largely on experience with common aeroallergen extracts. Little information is available on the use of most of these products for immunotherapy. Several cat allergens have been characterized and standardized extracts are available. Avoidance of the allergen remains the preferred method of control and usually can be achieved, although at times only with great effort.

Insect Allergy

Insect allergy is a term rather loosely applied to describe allergy from both insects and arthropods such as spiders and mites. Allergy may result from inhalation of body emanations but most often occurs following a sting or bite.

Allergy to stinging insects of the order *Hymenoptera* is of greatest clinical significance and has been studied most widely. The honeybee is the most common offender, but the bumblebee, wasp, hornet, and yellow jacket also may cause reactions. Hymenoptera sensitivity is estimated to result in 40 deaths annually in this country and the incidence of serious allergy is estimated at 1 to 10:100,000. Allergy with few exceptions involves IgE-mediated reactions and may be manifest as urticaria, angioedema, asthma, or systemic anaphylaxis. Death usually results from cardiovascular collapse and/or respiratory failure and typically occurs within 1 hour following the sting.

Serious reactions may occur in individuals without a history of sensitization, but they are more common in those who have previously exhibited a systemic reaction following a sting. It is of the utmost importance that sensitive individuals be aware of their problem and understand preventive measures and emergency procedures. *Emergency kits* are available for the treatment of *Hymenoptera* sensitivity in the field. These and the services that can be rendered by the community pharmacist are discussed by Sadik.[20]

Diagnosis of insect allergy usually is self-evident, but problems may arise in identifying the insect. Cross-sensitivity among *Hymenoptera* is common but by no means absolute, and species-specific allergens are important.

Sensitivity testing and immunotherapy commonly are recommended and employed for allergy to the stinging insects. The venom extracts (Table 89-18) have been shown to be highly effective when properly employed. These products are standardized somewhat differently than the other standardized extracts. The venoms are assayed for several known components (ie, hyaluronidase, antigen 5, phospholipase A), as well as total protein nitrogen. The quantity and potency of the products are expressed in mcg rather than allergy units.

Fire-ant allergy is being reported with increasing frequency. The fire ant has now spread over 13 southern states and is particularly a problem along the Gulf coast. It is a member of the *Hymenoptera* and causes similar allergic reactions,but its allergens appear to differ considerably from those of other stinging insects. Skin-testing with whole-body extracts appears to be reliable for the determination of sensitivity and reports on immunotherapy are encouraging.

Allergic reactions have been attributed to many biting insects including the mosquito, chigger, flea, louse, bedbug, kissing bug, and many flies. The majority of the reactions have been localized, with both the immediate- and delayed-types reported. The pathogenesis of most of these sensitivities remains to be verified, but since many appear to be cell-mediated reactions, it is not surprising that the limited information on sensitivity testing and immunotherapy is contradictory.

Allergic rhinitis and asthma can develop after inhalation of scales, hairs, or other emanations of various insects. This is analogous to the allergy seen with common inhalants but most often is seen in individuals who by reason of occupation or hobby are exposed to large numbers of insects. The cockroach has been increasingly implicated as an important cause of allergic asthma especially in central city areas. The caddis fly, mayfly, and aphid occur in large numbers in some locales and have been implicated frequently. Allergenic extracts for a number of these have proven to be effective for skin-test diagnosis and may be of value for immunotherapy (Table 89-18).

Food Extracts

Various food products are the most common ingestant allergens. Food allergy may seem simple but, in fact, is an extremely complex clinical entity. One problem stems from the tendency of many to attribute virtually any GI disturbance of unknown etiology to *food allergy*. GI disturbance may arise from many causes, including enzyme deficiencies (lactose intolerance), intoxications, infections, and others. Also, food allergy may and often is manifest outside the GI tract. The indiscriminate use of the term *food allergy* is to be condemned strongly.

Food allergens (Table 89-19) may cause atopic (asthma, rhinitis, gastroenteropathy) and nonatopic (urticaria-angioedema, anaphylaxis) symptoms, but both are IgE-mediated. Food allergy is usually not life-threatening, but some individuals may suffer serious exacerbation of asthma or, on rare occasions, systemic anaphylaxis. Strongly allergic individuals must be trained on how to deal with serious reactions and some should carry emergency kits with epinephrine to deal with inadvertent exposures.

Relatively few foods are responsible for the majority of reactions (peanuts, milk, nuts, fish, shellfish, eggs, and soy are the most common offenders) but many others may cause food allergy.[21] Food allergy may occur at any age but is probably most common in childhood and may be related to an underdeveloped GI system. Patients commonly appear to *outgrow* some food allergy (eg, cow's milk), but this is probably not the case with most foods.

Only a few food allergens have been characterized, but it is possible that many are not present in fresh foods but are the products of food processing or digestion. The diagnosis of food allergy depends heavily upon a detailed history along with the use of carefully designed elimination and challenge test diets. Skin testing is useful in the hands of experienced clinicians but requires some modified techniques.[21]

The therapy of food allergy is often even more difficult than the diagnosis. Elimination of the offending food(s) is about the only effective therapy, but it is often difficult to design a nutritious and palatable diet when multiple and/or common allergens are involved (eg, milk, eggs, peanuts). Immunotherapy is very difficult to assess for reasons noted above and therapeutic food extracts are not generally recommended.

It is notable that, of all of the allergies to environmental substances, food allergy is the most similar to that of drug allergy.[22] Ingestants (ie, foods and drugs) and injectants (ie, drugs and *Hymenoptera* stings) are the major cause of the nonatopic, IgE-mediated urticaria(hives), angioedema and anaphylaxis.

Table 89-19. Food Extracts[a]

Meat		
Beef	Goat	Rabbit
Chicken	Goose	Turkey
Deer	Lamb	
Duck	Pork	
Dairy		
Casein	Egg, whole	Milk, cow
	Egg, white	Milk, goat
	Egg, yolk	
Fish		
Bass	Halibut	Sardine
Bluefish	Herring	Scallop
Carp	Lobster	Shrimp
Clam	Mackerel	Smelt
Codfish	Oyster	Swordfish
Crab	Pike	Trout
Flounder	Red Snapper	Tuna
Haddock	Salmon	Whitefish
Nuts		
Almond	Chestnut	Peanut
Brazil	Coconut	Pecan
Cashew	English Walnut	Pistachio
	Filbert	
Grains		
Barley	Corn	Rye
Buckwheat	Oat	Wheat
	Rice	
Fruits		
Apple	Cranberry	Peach
Apricot	Date	Pear
Avocado	Fig	Pineapple
Banana	Grape	Plum
Blackberry	Grapefruit	Raspberry
Blueberry	Honeydew	Strawberry
Carrot	Lemon	Tangerine
Cantaloupe	Lime	Watermelon
Cherry	Orange	
Vegetables		
Artichoke	Celery	Pea
Asparagus	Cucumber	Potatoes
Beans	Eggplant	Pumpkin
Beet	Green Pepper	Radish
Broccoli	Lentil	Rhubarb
Brussell Sprouts	Lettuce	Spinach
Cabbage	Mushroom	Squash
Carrot	Olives	Tomato
Cauliflower	Onion	Turnip
Spices		
Allspice	Garlic	Peppermint
Bay Leaf	Licorice	Poppy Seed
Caraway Seed	Mustard Seed	Sage
Cinnamon	Nutmeg	Sesame
Clove	Oregano	Spearmint
Dill	Paprika	Thyme
Ginger	Pepper, Black	Vanilla

[a] This is not a comprehensive list and the absence of a food does not imply that it is never allergenic.

Veterinary Allergenic Products

Veterinary allergy is an emerging field, and pharmacists involved in animal health can expect increasing activity in this area. The general principles of immunology and allergy noted earlier apply for the most part to animals as well. Veterinary biologics are controlled by the US Department of Agriculture (USDA) as described earlier. Greer Laboratories markets a line of veterinary allergenic extracts and supplies. Most of the currently available products are marketed primarily for dogs.

It is estimated that as many as 20% of the dogs in the US have allergies. *Flea allergic dermatitis* is the most common canine allergy, and its control requires the complete eradication of fleas from the environment. Immunotherapy is rarely successful.

Atopy is the second most common allergic condition in dogs and, as in humans, is associated with inhaled pollens, molds, house dust, and other aeroallergens. *Canine allergic inhalant dermatitis* is a common form of atopy and is manifest by pruritus (scratching, foot licking, face rubbing) and sometimes sneezing, rhinitis, and conjunctivitis. Immunotherapy is often successful in the management of atopy.

Food allergy and *contact dermatitis* are also common in dogs; immunotherapy is of no value in the treatment of these conditions. It is apparent that the problems of canine allergy are quite analogous to those of human allergy.

DELAYED HYPERSENSITIVITY TESTS

Delayed hypersensitivity tests are used to detect the presence or absence of cell-mediated allergy and, as their name indicates, the time-course of a positive reaction varies considerably from those of the immediate hypersensitivity tests discussed above. Cell-mediated responses begin in a sensitized individual as early as 5 to 6 hours after exposure to the immunogen, and a maximum response is usually observed within 96 hours.

Table 89-20. Patch-Testing Allergens

American College of Dermatology Standard-Tray Allergens[a]	
Balsam of Peru	Imidazolidinyl urea
Benzocaine	Lanolin alcohol
Black rubber mix	Mercaptobenzothiazole
p-tert-Butylphenolformaldehyde	Mercapto mix
Carba mix	Neomycin sulfate
Cinnamic aldehyde	Nickel sulfate anhydrous
Colophony	*p*-Phenylenediamine
Epoxy resin	Potassium dichromate
Ethylenediamine dihydrochloride	Quaternium-15
Formaldehyde	Thiuram mix
Commercial Patch Test Products	
Standard-Tray Allergens (in reclosable syringes)	Hermal Laboratories
T.R.U.E. Test[b]	GSK

[a] For a description of the individual standard-tray allergens, consult Marks and DeLeo.[3]
[b] *T.R.U.E.* stands for *thin-layer rapid use epicutaneous test* and consists of two unit dose patches, each with 12 allergens, for administration to the upper back.

There are two main types of clinically useful delayed hypersensitivity tests: the *patch test* used to evaluate allergic contact dermatitis (Table 89-20) and diagnostic skin antigens used to evaluate several infectious diseases and the status of cell-mediated immunity (Table 89-21).

Patch-Testing

Contact dermatitis is a term that has been used in two main ways: first, to describe any rash resulting from a substance touching the skin and second, as a synonym for *allergic contact dermatitis*. The latter is used in present context and refers to eczematous lesions resulting from cell-mediated hypersensitivity reactions analogous to tuberculin sensitivity.

Table 89-21. Diagnostic Skin Antigens

VACCINE	DISTRIBUTOR
Candida albicans Skin Test Antigen	
Candin	ALK
Coccidioidin	
BioCox (Coccidioidin Mycelial Derivative)	Iatric
Spherulin (Coccidioidin Spherule Derivative)	ALK
Histoplasmin	
Generic (Mycelial Derivative)	Pfizer
Histolyn-CYL (Controlled Yeast Lysate)	ALK
Multiple Skin-Test Antigen Device	
Multitest CMI	Aventis Pasteur
Mumps Skin Test Antigen	
MSTA	Aventis Pasteur
Tetanus Toxoid Fluid	Aventis Pasteur
Wyeth	
Trichophyton	
Dermatophytin	Bayer
Tuberculin, Old (OT), Multiple Puncture Device	
Mono-Vac Test (OT)	Aventis Pasteur
Tuberculin, Tine Test OT	Wyeth
Tuberculin, Purified Protein Derivative (PPD) Multiple Puncture Device	
Aplitest	Pfizer
Sclavo Test-PPD	Biocine Sclavo
Tuberculin, Tine Test PPD	Wyeth
Tuberculin, Purified Protein Derivative (PPD) Intradermal Solution	
Aplisol	Pfizer
Tubersol Diagnostic Antigen	Aventis Pasteur

Similar clinical manifestations may occur by other mechanisms: primary irritant dermatitis, from direct chemical irritation; photocontact (phototoxic) dermatitis, which requires light to generate the irritant; and photoallergic dermatitis, which requires light to generate the allergen. These are not necessarily independent, for a number of contact allergens also may be irritants, but allergic reactions generally occur with lower concentrations of the offending agent. A variety of other conditions also must be differentiated from contact dermatitis (eg, atopic dermatitis, dermatomycoses), and virtually any disease of the skin may result in increased response to both contact irritants and allergens.

The best known and most common contact dermatitis in North American is *rhus dermatitis* (poison ivy, poison oak, and poison sumac[23]), but the scope of the problem is much greater than this. It is estimated that at least 35 million Americans are affected by contact dermatitis with the incidence and causes varying in different populations. The overall socioeconomic impact is great for it is a leading cause of industrial illness. The 20 American Academy of Dermatology standard-tray allergens (Table 89-20) are among the most common causes of allergic contact dermatitis and illustrate some of the complexity of the problem. Particularly notable are the drugs and drug additives that laymen may not recognize as constituents of drug products. The pharmacist can assist the sensitive patient with both drug product selection and avoidance.

The diagnosis of contact dermatitis depends mainly on a detailed history and complete physical examination. The area of the body affected is suggestive of the contactant and other factors (eg, light, dermatophytes). The patch test is presently the only practical way to demonstrate contact sensitivity and is used for the following purposes: to verify clinically diagnosed contact sensitivity; to determine the specific allergens including those that may not have been clinically suspected; as a predictive test to determine what the patient can safely tolerate; and to exclude contact dermatitis in puzzling clinical situations.

Patch testing usually involves application of the test substance to a piece of cloth or soft paper placed on the outer arm or upper back, covered with an impermeable substance and taped in place. After 24 to 48 hours, the patch is removed and the test site examined for presence of the characteristic rash. Patients receiving anti-inflammatory steroids or immunosuppressive therapy and those with other significant deficiency of cell-mediated immunity may be expected to have a reduced skin-test response. The monograph of Marks and DeLeo[24] is an excellent introduction to patch testing and includes a description of each of the allergens included in the American Academy of Dermatology standard tray.

The therapy of contact dermatitis involves, most importantly, avoidance of the contactant. Cool compresses and topical steroids are the mainstays of therapy, but systemic steroids may be employed for serious cases. Other topical medications should be avoided since they may contain irritants or sensitizers.

There have been a number of attempts at both oral and parenteral immunotherapy for poison ivy and several reports of success over the years; however, both forms of therapy have the potential of precipitating serious reactions in highly sensitive individuals and immunotherapy is not generally applicable in the management of contact dermatitis. Avoidance of the allergen is definitely the preferred and generally effective method of control.

Diagnostic Skin Test Antigens

Dermal reactivity in the form of delayed hypersensitivity develops in the course of many infectious diseases. Much study over the years has shown that this dermal sensitivity not only indicates that the patient is or has been infected with the microorganism in question, but also reflects the patency of cell-mediated immunity. Delayed hypersensitivity testing is of major

value in the management of tuberculosis and is of some utility for the evaluation of several systemic mycoses (coccidiomycoses, histoplasmosis). These and other skin test antigens (Table 89-21) also are used to evaluate the status of cell-mediated immunity.

Tuberculin testing is an important procedure in the management of tuberculosis in this country. High-risk populations are screened to identify those who may be infected and benefit from chemoprophylaxis as well as those who have clinical disease and require therapy. Two forms of tuberculin products (Table 89-21) are available: old tuberculin (OT) and purified protein derivative (PPD). Both of these are available in multiple puncture devices (*tine test*) for transcutaneous administration; these products can be stored at room temperature and are particularly useful for the rapid mass screening of large groups. PPD solutions for intradermal administration (*Mantoux test*) are more sensitive, must be refrigerated and are used for definitive tuberculin testing of individuals.

Tuberculin tests are read 48 to 96 hours after administration and a positive reaction consists of induration of 2 mm or greater in diameter, or the presence of any vesiculation at the site of application. A positive test indicates only that the individual is hypersensitive to tuberculin, which implies past or present infection with *Mycobacterium tuberculosis*. A positive tuberculin test is an indication for additional diagnostic testing (eg, chest x-ray) to determine if prophylactic or therapeutic measures are required.

The other skin test antigens listed in Table 89-21 are very similar to the tuberculin test in principle and application. They have not, however, proven to be as useful in the evaluation of infection for a number of reasons including the problem of frequent cross-reactivity with immunogens from other organisms giving rise to false positive reactions.

A number of drugs can interfere with delayed hypersensitivity tests. Dermal reactivity may be depressed in patients taking corticosteroids or other immunosuppressive agents as well as those recently vaccinated with live virus vaccines (eg, measles, mumps, rubella, and polio viruses). Tuberculin testing can be administered simultaneously with these vaccines, but otherwise it should be deferred until 4 to 6 after vaccination. Persons immunized with BCG vaccine often convert to tuberculin positive and the interpretation of the test results is more complicated in these patients.

Delayed hypersensitivity may be suppressed in patients with a variety of conditions including acquired and congenital immune deficiencies, autoimmune disease, infections (bacterial, fungal, mycobacterial, virus), malignancy, malnutrition, and others. The absence of a dermal reactivity in a patient who has been sensitized to the immunogen in question is called *anergy*.

The usual method for assessing the competence of cell-mediated immunity is to employ a battery of 4 to 6 common immunogens referred to as an *anergy-test panel*. The panel is selected with the expectation that the patient will show a positive delayed hypersensitivity response to at least 2 to 4 immunogens if not anergic. This testing is of little value in evaluating primary immune deficiency during the first year of life since a failure to react may simply represent lack of exposure to the immunogens.

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CHAPTER 90

Anti-Infectives

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The distinction between the terms *antibiotic* and *antimicrobial agent* has little meaning today. The term antibiotic traditionally refers to a substance produced by a microorganism. However, most agents are produced by chemical synthesis, or various moieties are attached to the basic core structure of an antibiotic after microbial fermentation.

The pathogenic microorganisms that can invade the human body and cause disease include a number of bacteria, viruses, fungi, and parasites. The major pharmacological approaches to treat these infections will be covered under the following headings: antiseptics and disinfectants, systemic antimicrobials, antimycobacterials, antifungals, and antivirals. Only the major antimicrobial drugs will be discussed in each section of this chapter to emphasize the general characteristics of specific drug families and their major subclasses. Common features will be summarized, and unique uses or problems will be highlighted for important drugs within each class.

ANTISEPTICS, DISINFECTANTS AND SPERMICIDES

The terms *antiseptic* and *disinfectant* refer to an agent that kills microbes upon contact. Drugs in this category are not taken internally and are not used to treat disease. These agents are used to prevent infection by destroying microorganisms on foreign surfaces and skin. Antiseptics are applied to living tissues and inhibit microorganism growth but this degerming action is only temporary. Presurgical scrubs reduce the normal and pathogenic flora on the skin if used appropriately, but bacterial multiplication resumes in minutes to hours.

The agents in this class are very diverse groups of chemicals and have a variety of mechanisms of action that include: highly reactive oxidizing and alkylating agents (ie, general protoplasmic poisons); protein denaturing agents that damage microbial cell walls or cytoplasmic membranes; lower surface tension; inhibit essential enzymes; and other examples of nonselective actions. The effectiveness of antiseptics and disinfectants is influenced by concentration, temperature, and time of exposure.

Many of these agents are poorly effective in the presence of serum or other organic media, or else they are excessively damaging to the tissues. Tissue damage, of course, is not of concern when such agents are employed for the disinfection of inanimate objects; on the other hand, corrosiveness, staining, and other effects then become important considerations. The best and most effective antiseptics are iodine and chlorhexidine in combination with alcohol.

Notable problems of commonly used preparations are listed in each monograph. Cationic detergents are very poor antiseptics or disinfectants due to their inactivation by soap and organic tissue components. It commonly is believed that antiseptics are nonselective and that they have a continuous spectrum of activity. Although this is essentially true, certain significant absolute exceptions exist, and the relative susceptibilities of the numerous microorganisms must be considered in antiseptic use. For example, hexachlorophene is effective primarily against gram-positive organisms, and cationic antiseptics are not effective against sporulating organisms. Certain bacteria are even capable of growing in 70% ethanol.

No really satisfactory classification of antiseptics exists. The most widely used scheme is the chemical classification. Nevertheless, the drugs listed below are not arranged according to chemical type. However, it will be noted that the major chemical categories represented are oxidizing agents (including the halogens and halogen-releasing compounds), phenols and related compounds, compounds of heavy metals (especially of mercury), surface-active agents (especially the cationic detergents) and scattered representatives from the alcohols and glycols, aldehydes, and acids. Locally effective antibiotics are discussed with the antibiotics.

It should be kept in mind that systemic antimicrobial drugs are often superior to topical ones. This is because topical agents usually do not penetrate into infected sites as well as systemic agents do. Nevertheless, topical drugs are often efficacious, simply by limiting surface infections so that tissue defenses can clean up below without continual reinfection from superficial foci. Furthermore, some superficial disorders do not seem to respond to safe systemic agents, or, if they do, there may be cogent reasons for withholding systemic drugs, for example, to avoid sensitizing the patient or creating resistant microorganisms. Therefore, there is still an important place for topical antiseptics. However, topical antiseptics can damage tissue defenses, so that sometimes they may exacerbate lesions. Such occasions are not always predictable, and they evidently depend in part on the condition of the patient and the activity of the immunological response to infection. A summary of the activities of antiseptics is shown in Table 90-1.

ACETIC ACID, DILUTED—page 1083.
ACRISORCIN—see RPS-17, page 1226.

ALCOHOL

For the full monograph, see RPS-20, page 1038.

Comments—An *antiseptic* with the following susceptibilities: gram–positive and gram–negative bacteria, highly susceptible; spores, resistant; lipophilic viruses, susceptible; hydrophilic viruses, variable; and fungi, no data.

ALUMINUM ACETATE TOPICAL SOLUTION—page 1282.
BACITRACIN—page 1653.

BENZALKONIUM CHLORIDE

Ammonium, alkyldimethyl(phenylmethyl)-, chloride;
Zephiran Chloride

Alkylbenzyldimethylammonium chloride [8001-54-5]; a mixture of alkylbenzyldimethylammonium chlorides of the general formula

Table 90-1. Activities of Antiseptics

CHEMICAL	CLASS/AGENTS GM+	GM−	ACTIVITY	BACTERIA SPORES	VIRUSES LIPOPHILIC	FUNGI HYDROPHILIC	USE
Alcohols							
Ethanol	HS	HS	R	S	V	—	Antiseptic
Isopropanol							
Aldehydes	S	HS	S	S	MS	S	Disinfectant
Formaldehyde							
Glutaraldehyde							
Chlorhexidine gluconate	HS	MS	R	V	R	—	Antiseptic
Chlorine sodium hypochlorite	HS	HS	S	S	S	MS	Disinfectant, irrigant
Hexachlorophene	S	R	R	R	R	R	Soap, shampoo
Iodine	HS	HS	S	S	R	S	Antiseptic
Povidone-iodine							
Phenols	HS	HS	R	R	R	—	Disinfectant
Oxidizing agents	HS	HS	S	V	V	S	Disinfectant, irrigant
Hydrogen peroxide							
Quaternary Ammonium (Benzalkonium chloride Cetylpyridinium chloride Benzethonium chloride)	HS	HS	R	S	R	—	Disinfectant

Key: HS = highly susceptible, MS = moderately susceptible, S = susceptible, R = resistant, V = variable, —no data.

$[C_6H_5CH_2N(CH_3)_2R]Cl$, in which R represents a mixture of alkyls, including all or some of the group beginning with n-C_8H_{17} and extending through higher homologs, with n-$C_{12}H_{25}$, n-$C_{14}H_{29}$ and n-$C_{16}H_{33}$ comprising the major portion. On the anhydrous basis, the content of n-$C_{12}H_{25}$ homolog is not less than 40%, and the content of the n-$C_{14}H_{29}$ homolog is not less than 20%, of the total alkylbenzyldimethylammonium chloride content. The amounts of the n-$C_{12}H_{25}$ and n-$C_{14}H_{29}$ homolog components comprise together not less than 70% of the total alkylbenzyldimethylammonium chloride content.

Preparation—By treating a solution of *N*-alkyl-*N*-methylbenzylamine in a suitable organic solvent with methyl chloride, the solvent being so chosen that the quaternary compound precipitates as it is formed.

Description—White or yellowish white, thick gel or gelatinous pieces; aromatic odor and a very bitter taste; solutions are alkaline to litmus and foam strongly when shaken.

Solubility—Very soluble in water and alcohol; 1 g of the anhydrous form dissolves in approximately 6 mL benzene and in approximately 100 mL ether.

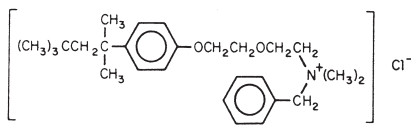
Incompatibilities—Like other cationic surface-active agents, benzalkonium chloride is incompatible with *soap* and other *anionic agents*. The large organic ions of the two agents are oppositely charged and, in sufficient concentration, can precipitate from solution. *Nitric acid* and *nitrates* cause precipitation.

Comments—A *bacteriostatic* in low and bactericidal in high concentrations. Gram–positive bacteria are more sensitive than gram–negative bacteria. The antiseptic has a slow action. It requires 7 min for the bacterial count on the skin to be decreased by a mere 50%, while only 36 sec is required by 70% ethanol; to effect a 90% reduction, 25 min is required for this compared to 2 min for the 70% ethanol.

It is used for application to skin and mucous membranes. It is used widely in OTC ophthalmic solutions and as applications to contact lenses. It also is used for the sterilization of inanimate articles, such as surgical instruments. Its solutions have low surface tension and possess detergent and emulsifying actions. It has relatively low systemic toxicity. It does not destroy bacterial spores, it is ineffective against some viruses, it is inactivated by soap and other anionic surface–active agents, and when applied to the skin, it has a tendency to form a film under which bacteria remain viable. Organic matter from tissue inactivates the drug, so that it has limited efficacy in the disinfection of wounds. The drug can cause irritation and damage the epidermis, and it also can cause allergies.

BENZETHONIUM CHLORIDE

Benzenemethanaminium,*N*,*N*-dimethyl-*N*-[2-[2[4-(1,1,3,3-tetramethylbutyl)phenoxy]ethoxy]ethyl]-, chloride



Benzyldimethyl[2-[2-[*p*-(1,1,3,3-tetramethylbutyl)phenoxy]-ethoxy]ethyl]ammonium chloride. [121-54-0] $C_{27}H_{42}ClNO_2$ (448.09).

Preparation—From *p*-diisobutylphenol with dichlorodiethyl ether, dimethylamine and benzyl chloride.

Description—White crystals; mild odor; very bitter taste; melts at approximately 160°; aqueous solution (1%) slightly alkaline, and foams strongly when shaken.

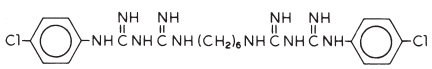
Solubility—1 g in 0.6 mL water, 0.6 mL alcohol, 1 mL chloroform or 6000 mL ether.

Comments—A *disinfectant* with the following susceptibilities: gram–positive and gram–negative bacteria, highly susceptible; spores, resistant; lipophilic viruses, susceptible; hydrophilic viruses, resistant; and fungi, no data.

BENZOIC ACID—see RPS-19, page 1327.
BENZYL ALCOHOL—see RPS-19, page 1151.
BORIC ACID—page 1083.
BUTYLPARABEN—see RPS-18, page 1170.

CHLORHEXIDINE GLUCONATE

D-Gluconic acid, compd with *N*,*N*″-bis(4-chlorophenyl)-3,12-diimino-2,4,11,13-tetraazatetradecanediimidamide (2:1); Hibiclens, Hibistat



1,1′-Hexamethylenebis[5-(*p*-chlorophenyl)biguanide] di-D-gluconate [18472-51-0] $C_{22}H_{30}Cl_2N_{10}\cdot 2C_6H_{12}O_7$ (897.77).

Preparation—Chlorhexidine base may be prepared by refluxing a mixture of hexamethylenebis [dicyandiamide], [NCNHC(:NH)-NH-$(CH_2)_3]_2$, and *p*-chloroaniline hydrochloride in 2-ethoxyethanol at 130° to 140° for 2 hours (Rose, Swain. *CA* 1956; 50: 1082h). The digluconate, diacetate, and dihydrochloride salts may be obtained by neutralizing the base with the respective acids.

Description—Colorless to pale-yellow solution. Usually available in 5% or 20% aqueous solution. pH (5% aqueous solution) 5.5 to 7.

Solubility—Very soluble in water; 1 g in 5 mL alcohol or 3 mL acetone.

Comments—*Bactericidal* to both gram-positive and gram-negative bacteria, although it is not as potent against the latter. It disrupts the plasma membrane of the bacterial cell, and cellular contents are lost.

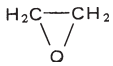
In a 4% aqueous solution as a surgical scrub, it decreases the cutaneous bacterial population more than either hexachlorophene or povidone-iodine. It is slightly less effective than povidone-iodine if the skin is contaminated with certain *gram-negative bacteria*. A 1% aqueous solution has erratic antiseptic effects, but a 0.5% solution in 95% ethanol is more effective than a 4% aqueous solution. Chlorhexidine solutions leave a residue on the skin that gives a persistent antibacterial effect lasting 1 or 2 days. Its actions are not affected by blood, pus, or soaps.

It is used for the preoperative preparation of both surgeon and patient, for the treatment of superficial skin infections, burns, acne vulgaris, the irrigation of wounds,and surgical infections. It can be used in the hospital nursery to bathe neonates for prophylaxis against staphylococcal and streptococcal infections.

It is absorbed negligibly from the skin and mucous membranes; it has low systemic toxicity. However, serious injury may occur when it enters open wounds of the eye,and deafness may occur if it enters the middle ear through a perforated eardrum. A few cases of sensitization have been reported.

ETHYLENE OXIDE

Oxirane



Ethylene oxide [75-21-8] C_2H_4O (44.05).

Preparation—Ethylene is catalytically oxidized with air at high temperature.

Description—Colorless, flammable gas; liquid at less than 12°.

Solubility—Soluble in water, alcohol, or ether.

Comments—An *alkylating agent* that has a very broad germicidal spectrum, including spores and viruses. Since it is reactive at room temperature, it may be used for the disinfection and sterilization of heat-labile objects, such as certain catheters and endoscopes in the hospital. Because it is applied as a gas, it is advantageous for the sterilization of objects that would be harmed by immersion in aqueous or other media.

Inhalation of the gas causes nausea, vomiting, and neurologic disorders, and severe exposures can cause death. Consequently, sterilization must be done only in appropriate chambers or rooms. Chemical burns can result from the wearing of ethylene oxide-sterilized clothing, shoes, or gloves that have been aired inadequately after sterilization; thrombophlebitis or hemolysis can result from the use of catheters, and tracheitis from endotracheal tubes that have retained a residue of the gas. Polyvinyl tubing and bags are especially dangerous because of the formation of chlorohydrin. Therefore, after exposure, these items should be aired for 5 days at room temperature or 8 hr at 120°. The gas also is used as a fumigant.

The gas is highly explosive at concentrations above 3%, so that it needs to be mixed with CO_2 or fluorocarbons before use.

The gas kills vegetative bacteria very rapidly, but desiccated microorganisms and spores are killed only slowly, so that a 3-hr exposure at 30° is advised. The optimal humidity for action is 30% to 40%.

ETHYLPARABEN—see RPS-18, page 1171.

FORMALDEHYDE

Comments—A *disinfectant* with the following susceptibilities: gram-positive bacteria, susceptible; gram-negative bacteria, highly susceptible; spores, susceptible; lipophilic viruses, susceptible; hydrophilic viruses, moderately susceptible; and fungi, susceptible.

GLUTARAL

Pentanedial; Glutaraldehyde; Glutaric Dialdehyde; Cidex

$OCH(CH_2)_3CHO$ [111-30-8] $C_5H_8O_2$ (100.12).

Preparation—The 1:1 Diels-Alder adduct of acrolein and a vinyl alkyl ether is hydrolyzed, forming glutaral and an alkanol.

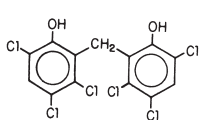
Description—Colorless liquid; pungent odor; boils about 188° with decomposition; stable in light; oxidizes in air; polymerizes on heating. *Glutaral Concentrate* is a 50% (*w*/*w*) solution in water.

Solubility—Soluble in water and in alcohol.

Comments—A *disinfectant* with the following susceptibilities: gram-positive bacteria, susceptible; gram-negative bacteria, highly susceptible; spores, susceptible; lipophilic viruses, susceptible; hydrophilic viruses, moderately susceptible; and fungi, susceptible.

HEXACHLOROPHENE

Phenol, 2,2′-methylenebis[3,4,6-trichloro-, G-11; AT-7;



[70-30-4] $C_{13}H_6Cl_6O_2$ (406.91).

Preparation—By the Baeyer condensation reaction involving two molecules of 2,4,5-trichlorophenol, and one molecule of formaldehyde. Sulfuric acid is employed as the dehydrant.

Description—White to light tan, crystalline powder; odorless or only slightly phenolic odor; melting range 161° to 167°; incompatible with benzalkonium chloride; pK_a 5.7.

Solubility—Insoluble in water; freely soluble in acetone, alcohol and ether; soluble in chloroform and dilute solutions of fixed alkali hydroxides.

Comments—An effective *bacteriostatic antiseptic* against gram-positive bacteria but it has low activity against gram-negative organisms. On the skin the bacterial population initially will decrease by only 30% to 50% but within 1 hr the decrease will exceed 90%. When washes are repeated 2 or more times a day, the decrease will reach 95% to 99% in 3 or 4 days from a persisting residuum of the drug in the skin. This reservoir can be removed by ethanol, isopropyl alcohol and soap and water washes or other detergents. The drug is effective whether applied as a tincture, detergent emulsion or soap; the tincture is the most effective and a 0.23% tincture foam has been reported to be more effective than a 3% soap. In soaps, one hydroxyl group is neutralized, which moderately decreases activity.

Preparations containing this are used widely as antiseptic scrubs by physicians, dentists, food handlers and others. The incidence and severity of pyogenic skin infections are reduced by routine use.

In infants, it can cause myelinopathy and spongiform encephalomalacia following topical application; for this reason, it is no longer used in hospital nurseries to bathe infants. Avoid contact with eyes and do not use on burns or mucous membranes. By the oral route it can cause nausea, vomiting and abdominal cramps with associated water and electrolyte derangements. Topically, the drug can cause dermatitis and sensitization. It is teratogenic.

HYDROGEN PEROXIDE SOLUTION

Hydrogen Dioxide

[7722-84-1] H_2O_2 (34.01).

Preparation—Hydrogen peroxide: by many methods, one of the most important ones involving electrolysis of sulfuric acid in a solution containing sulfate, whereby persulfate is formed, which is hydrolyzed to hydrogen peroxide. Solutions containing as much as 90% H_2O_2 in each 100 mL.

Description—Clear liquid; colorless; odorless or having an odor resembling that of ozone; usually deteriorates on standing or on protracted agitation; decomposes rapidly when in contact with many oxidizing or reducing substances; when rapidly heated, it may decompose suddenly.

Comments—A *germicide* active by virtue of the release of nascent oxygen; it is short acting because the release occurs rapidly. It is the substance released by activated neutrophils, and it is an effective *microbicide* when applied in close contact with most microorganisms. However, the ubiquitous enzyme catalase often destroys it before it reaches organisms in wounds. Effervescence helps cleanse wounds mechanically.

IODINE

Iodine

[7553-56-2] I (126.90).

Preparation—From the iodide in the ashes of seaweed by chlorination, from the iodate in chile saltpeter by reduction with sulfite ion, or from the iodide in oil well brines by oxidation with chlorine or nitrite ion.

Description—Heavy, grayish black plates or granules, a metallic luster; characteristic odor; specific gravity approximately 4.9; melts at approximately 114° but volatilizes even at room temperature.

Solubility—1 g in 3000 mL water, 13 mL alcohol, 80 mL glycerin; freely soluble in chloroform, carbon tetrachloride, ether, and glacial acetic acid; soluble in solutions of iodides by the formation of I_3^-.

Incompatibilities—Oxidizes *hypophosphites, sulfites*, the lower valence forms of some *metals* and *other reducing agents*, the iodine being reduced to an iodide. *Thiosulfates* (hyposulfites) also react with free iodine. It reacts with *fixed oils* to form addition compounds, and with *volatile oils* to form various derivatives. The reaction with *turpentine oil* is violent. An explosive iodide of nitrogen may be formed with *ammonia water* or *ammoniated mercury*. *Alkali hydroxides* and *carbonates* react with iodine to form iodides and iodates. Many *alkaloids* are precipitated from aqueous solutions of their salts. In *alcoholic solution* iodine slowly forms hydrogen iodide if alkali iodide is absent.

Comments—One of the best all-around *antiseptics*. It is active against bacteria, fungi, spores, yeasts, protozoa and viruses. Although it is available in high concentration in various complexes (with iodide ion, poloxamer, povidone, etc, called iodophores) or tinctures, its solubility in water is only 0.033% (1:3,000). The advantage of iodophores or concentrates is that they provide a reservoir (called available iodine) from which to replenish iodine that is depleted in combining with microbial components and organic materials resulting in a sustained action. Iodine can complex loosely with amino and heterocyclic groups in tissues constituents that serve as repository iodine. Ethanol and other organic solvents in tinctures act superadditively with free iodine.

Most bacteria are killed within 10 sec by a 1% solution, 1 min by 1:20,000 (0.05%) and 10 min by 1:500,000 (0.0002%). A 0.15% solution may kill wet bacterial spores, amebic cysts, and enteric viruses in about 15 min, but dry spores may require hours, even with 1:3000. On the skin, a 1% tincture will kill 90% of the bacteria in 90 sec.

Its tinctures and solutions are used widely by the lay public for the *disinfection of cuts and abrasions*. The 2% solution is the best-available OTC preparation for this purpose because it lacks the irritancy of tinctures and hypertonicity of the strong solution. Solutions are effective even in strengths as low as 0.1%, which is sometimes used for *wound irrigation*. The tincture is the best preparation for *presurgical preparation of the intact skin*. It may be used to purify drinking water. However, *Giardia* is less sensitive than bacteria and amebae and requires higher concentrations and longer incubations.

It has a high therapeutic index among antiseptics. Tinctures sting and also cause local damage. The strong tincture, especially, can cause burns, even on intact skin; it was this toxicity that gave iodine a bad reputation.

ISOPROPYL ALCOHOL

2-Propanol

$CH_3CH(OH)CH_3$ [67-63-0] C_3H_8O (60.10).

Preparation—Most of the isopropyl alcohol prepared commercially is obtained by treating propylene with H_2SO_4 followed by hydrolysis. The olefin is obtained in the cracking of petroleum.

Some of the alcohol also is obtained by the reduction of acetone through high-pressure hydrogenation.

Description—Transparent, colorless, mobile, volatile liquid; characteristic odor; slightly bitter taste; specific gravity 0.783 to 0.787; distilling range 81° to 83°; refractive index 1.376 to 1.378 at 20°.

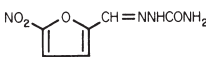
Solubility—Miscible with water, alcohol, ether, and chloroform.

Comments—For the *disinfection* of hypodermic syringes and needles and, as the rubbing alcohol, a skin antiseptic. It is superior to ethyl alcohol in regard to its *antiseptic* properties. All concentrations greater than 70% are effective skin disinfectants. It does promote bleeding at an injection site, which may make reading of allergic tests difficult. It cannot be relied on to destroy the spores of organisms such as *Clostridium tetani*, *Clostridium welchii*, or *Bacillus anthracis*. It has a greater effect than ethanol to dry and irritate the skin. It is not potable and should not be given by mouth. It is recognized as a rubefacient, although it is used more widely as an antiseptic.

METHYLENE BLUE—page 1348.
METHYLPARABEN—see RPS-18, page 1172.

NITROFURAZONE

Hydrazinecarboxamide, 2-[(5-nitro-2-furanyl)methylene]-, Furacin; Amifur



5-Nitro-2-furaldehyde semicarbazone [59-87-0] $C_6H_6N_4O_4$ (198.14).

Preparation—By condensing 5-nitro-2-furaldehyde with semicarbazide hydrochloride in the presence of sodium acetate.

Description—Odorless, lemon-yellow, crystalline powder; nearly tasteless, but develops a bitter aftertaste; darkens slowly on exposure to light; melts at approximately 236° with decomposition; pH (saturated solution) 5 to 7.5.

Solubility—1 g in 4200 mL water, 590 mL alcohol, 350 mL propylene glycol, and polyethylene glycol mixtures as much as 1%; practically insoluble in chloroform and ether.

Comments—A *local antibacterial* agent with a broad spectrum of activity.

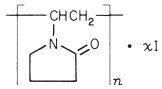
Most bacteria of surface infections of the skin or mucosal surfaces are sensitive to the drug. It is applied topically in the treatment of mixed, superficial infections of the skin. It finds use, especially, in the treatment of 2nd- and 3rd-degree burns and in skin grafting in which there are complications from bacterial infections that are refractory to the usual drugs of choice but in which bacterial sensitivity to the drug is demonstrable. It has not yet been shown to be useful in the treatment of minor burns, wounds, or cutaneous ulcers that are infected. It retains its antibacterial activity in blood, serum, and pus; phagocytosis is not inhibited, and nitrofurazone does not interfere with healing. However, it is a slowly acting drug, and at least 24 hr are required for it to take effect properly. Therefore, no treatment should be less than 2 or 3 days in duration.

Approximately 1% of patients become sensitized to the drug, sometimes within 5 days of initiation of treatment. The systemic toxicity is low.

PHENOL—page 1087.
PHENYLETHYL ALCOHOL—page 1066.
PHENYLMERCURIC ACETATE—see RPS-18, page 1172.
PHENYLMERCURIC NITRATE—page 1059.
PINE TAR—page 1286.
POLYMYXIN B SULFATE—page 1654.
POTASSIUM PERMANGANATE—see RPS-19, page 1270.

POVIDONE-IODINE

2-Pyrrolidinone, 1-ethenyl-, homopolymer, compd with iodine



1-Vinyl-2-pyrrolidinone polymer compd with iodine [25655-41-8]; contains 9–12% of available iodine.

Preparation—Povidone having an average molecular weight of 40,000 is heated with elemental iodine in the presence of a little water whereby a small amount of the iodine enters into loose organic union with the polymer to form a compound which contains approximately 10% of available iodine.

Description—Yellowish-brown, amorphous powder; slight, characteristic odor; aqueous solution is acid to litmus.

Solubility—Soluble in water or alcohol; practically insoluble in chloroform, carbon tetrachloride, ether, solvent hexane or acetone.

Comments—Kills both gram-positive and gram-negative bacteria, fungi, viruses, protozoa, and yeasts. The povidone component increases the solubility of iodine and provides a slow-release form of iodine. The affinity of povidone for iodine is greater than that of iodide, so that the concentration of free iodine is less than 1 ppm. Consequently the immediate bactericidal action of povidone-iodine is only moderate compared to that of iodine solutions. Although it takes 6 to 8 hr for the skin bacterial population to return to normal, which is longer than with iodine solutions, the effective duration of action for surgical purposes is only about 1 hr.

It is claimed that it stings less than iodine preparations. This is not true; it is iodine tincture that stings, and tinctures of this drug also sting. Iodine solutions are more effective in wound irrigation. It stains the skin and clothing less than iodine solutions and is also less of an irritant under occlusive dressings.

Its antiseptic preparations are indicated clinically for the prevention and treatment of surface infections as well as to degerm the skin prior to injection and hyperalimentation procedures; for seborrhea; for disinfection of wounds, burns, lacerations, and abrasions; for preoperative and postoperative scrubbing and washing of hospital operating-room personnel and for preoperative skin preparation of patients. It has no clear advantage over iodine solutions or tinctures.

PROPYLENE OXIDE—see RPS-18, page 1173.
PROPYLPARABEN—see RPS-18, page 1173.
PYRITHIONE ZINC—see RPS-18, page 1173.
SALICYLIC ACID—page 1288.

SELENIUM SULFIDE

Selenium Disulfide, Selsun; Exsel; Selsun Blue

Selenium sulfide (SeS_2) [7488-56-4] SeS_2 (143.08); contains 52.0 to 55.5% of selenium.

Preparation—Among other ways, by adding an aqueous solution of selenious acid to an aqueous solution containing a stoichiometric excess of hydrogen sulfide.

Description—Reddish brown to bright-orange powder; not more than a faint odor.

Solubility—Practically insoluble in water or organic solvents.

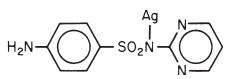
Comments—An *antibacterial, antifungal,* and *mildly keratolytic* agent used in the local treatment of seborrheic dermatitis of the scalp. It is effective in the treatment of tinea versicolor. It is also useful in the management of acne vulgaris and juvenilis and atopic eczema, but it has not been approved for these uses. Some authorities attribute its antiseborrheic efficacy to cytostatic actions. It induces inflammation of the mucous membranes and exposed tissues, so that care should be exercised in the application of the compound. It also causes *rebound* oiliness of the scalp. It should not be allowed to get into the eyes.

Occasionally, it causes loss of hair. Although it has considerably lower toxicity than selenites and some other selenium compounds and is available OTC, care nevertheless should be taken to keep preparations away from the mouth.

SILVER NITRATE—page 1287.
MILD SILVER PROTEIN—see RPS-18, page 1173.

SILVER SULFADIAZINE

Benzenesulfonamide, 4-amino-*N*-2-pyrimidinyl-, monosilver (1+) salt; Silvadene; SSD



N^1-2-Pyrimidinylsulfanilamide monosilver(1+) salt [22199-08-2] $C_{10}H_9AgN_4O_2S$ (357.13).

Description—A white powder.
Solubility—Practically insoluble in water.
Comments—Combines in one compound the *antibacterial* properties of silver ion and sulfadiazine; it is especially effective against *Ps aeruginosa*. It is indicated for topical use as an adjunct for prevention and treatment of wound sepsis in patients with second-and third-degree burns. It can penetrate the eschar. Although some sulfadiazine is absorbed, it is rarely sufficient to cause crystalluria. However, bacterial resistance to sulfonamides can occur. The drug does not cause pain at the site of application. Hypersensitivity may occur. Silver inactivates proteolytic enzymes used for debridement.

SODIUM BENZOATE—see RPS-19, page 1271.

SODIUM HYPOCHLORITE SOLUTION

Antiformin, Dakin's Solution, Hyclorite

An aqueous solution containing 4.0 to 6.0% *w*/*w* of sodium hypochlorite [7681-52-9] NaClO (74.44).
Preparation—By electrolysis of a solution of sodium chloride in a cell permitting reaction of chlorine with sodium hydroxide; an equivalent quantity of sodium chloride is produced simultaneously.
Description—Clear, pale greenish yellow liquid; slight odor of chlorine; affected by light.
Comments—A *disinfectant* and *irrigant* with the following susceptibilities: gram-positive and gram-negative bacteria, highly susceptible; spores, susceptible; lipophilic and hydrophilic viruses, susceptible; and fungi, moderately susceptible.

SYSTEMIC ANTIBACTERIAL DRUGS

Systemic antibacterial agents can be bactericidal (kill microbes) or bacteriostatic (growth inhibition) but also rely on host defenses to aid in eliminating bacterial pathogens. A given agent may be bactericidal under some conditions but be only bacteriostatic at other times, depending on the concentration of drug and type of bacteria. For a neutropenic patient a bactericidal agent would be necessary to maximize the potential for successful treatment.

The antibacterial agents can be classified into specific classes as well as divided into five major groups according to their primary mechanism of action or cellular biochemical pathway that is inhibited. The antibiotics and systemic antibacterial agents will be grouped into the following categories: inhibition of bacterial cell wall synthesis (penicillins, cephalosporins, carbapenems, and vancomycin), damage to cytoplasmic membrane (polymixins), modification of synthesis or metabolism of nucleic acids (quinolones, rifampin and nitrofurantoin), inhibition of protein synthesis (aminoglycosides, tetracyclines, chloramphenicol, erythromycin, and clindamycin) and folate-inhibitors or modification of energy metabolism (sulfonamides and trimethoprim).

Factors to consider when selecting systemic antimicrobial agents for therapy in patients should include identification of likely or specific microorganism, antimicrobial susceptibility, bactericidal versus bacteriostatic, and host status (ie, allergy history, age, pharmacokinetic factors, renal and hepatic function, pregnancy status, genetic or metabolic abnormalities, anatomical site of infection and host defenses, especially neutrophil function). The systemic antibacterial drugs will be described according to their major chemical families because similarities of antibiotics within each class are extensive. The major differences of unique members within each subclass will be emphasized.

Sulfonamides

The sulfonamides and trimethoprim act by inhibiting folic acid synthesis that most bacteria must synthesize whereas humans can rely on dietary sources. Sulfonamides were the first antimicrobial agents, but their clinical use has been greatly restricted as a result of the development of resistant bacteria, their significant side effects, and the availability of other drugs. The sulfonamides are no longer the preferred drugs for treatment of urinary tract infections (UTIs) but are still effective for some infections. Some examples include the treatment of initial, uncomplicated UTIs, nocardiosis, and topical treatment of burn areas. The trimethoprim-sulfamethoxazole combination has many therapeutic applications that expand the usefulness of sulfonamides to treat some urinary, respiratory and GI infections, pneumocystis, toxoplasmosis, and prevention of bacterial peritonitis (Table 90-2).

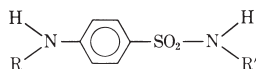
Table 90-2. Sulfonamides

DRUG	COMMENTS
Sulfisoxazole	Highly soluble, short half-life
Sulfmethoxazole	Highly soluble, intermed. half-life
Sulfadiazine	Best tissue levels, intermed. half-life
Sulfathalidine	Not absorbed orally, used only for ulcerative colitis
Sulfacetamide	Only used topically, ophthalmic

HISTORY—The compound *p*-aminobenzenesulfonamide, now known as *sulfanilamide*, was first synthesized in 1908, but it was many years before its therapeutic value was discovered. In 1932 a German firm prepared a red dye, 4-(4′-sulfamylphenylazo)-m-phenylenediamine or, p′-sulfamylchrysoidine, and in 1935 Domagk reported remarkable curative effects of this compound and named it *Prontosil*.

In the same year, a group of French investigators found that the antibacterial property of the drug resided in the *p*-aminobenzenesulfonamide portion of the molecule. In 1937 Ewins and Phillips of England synthesized sulfapyridine, which was the first sulfonamide used with great success in combating pneumonia. Then followed sulfathiazole, sulfadiazine, and a large number of other sulfonamides.

All the official, and generally all the therapeutically useful, antimicrobial sulfonamides are characterized by the structure.



ANTIMICROBIAL PROPERTIES—The sulfonamides originally possessed a wide antimicrobial spectrum that included all gram-positive cocci, except enterococcus, all gram-positive bacilli, nearly all *Enterobacteriaceae* and gram-negative cocci, *H influenzae, Bordetella pertussis, Pasteurella,* some *Pseudomonas, Chlamydia* (psittacosis, *Trachoma, Lymphogranuloma venereum*), *Actinomycetes, Nocardia,* and some *Toxoplasma* and malaria. However, resistance to the drugs has limited the spectrum greatly.

In most circumstances, these agents exert only a bacteriostatic action, and ultimate elimination of the invading microorganisms depends upon the cellular and humoral defense mechanisms of the host. However, bactericidal concentrations of these agents sometimes are attained in the urinary and intestinal tracts, where the concentration of drug may be quite high.

The mechanism of the antimicrobial action of the sulfonamides has been analyzed extensively. The sulfonamides compete with *p*-aminobenzoic acid and prevent its normal cellular use, particularly its incorporation into folic acid (pteroylglutamic acid, PGA). Thus, sulfonamide-sensitive organisms are primarily those that synthesize their own folic acid. Organisms able to use preformed folic or tetrahydrofolic acid or the tetrahydrofolate-dependent pyrimidines and thymidine are not affected by these agents generally. This mechanism is of importance as an example of the general concepts of biological antagonism and antimetabolites. The efficacy of sulfonamides generally is enhanced when the drugs are used in combination with trimethoprim that inhibits conversion of dihydrofolate to tetrahydrofolic acid and thence to folinic acid.

Microorganisms initially sensitive to the sulfonamides may become resistant to these drugs. The clinical importance of such

acquired bacterial resistance is attested by the fact that the majority of the strains of *N gonorrhoeae* now isolated from patients with gonococcal urethritis are resistant to these agents, whereas the sulfonamides were once the agents of choice against such organisms. *Enterobacteriaceae*, especially, have become resistant.

Certain combinations of the sulfonamides with various antibiotics minimize the development of bacterial resistance and achieve chemotherapeutic results not attainable with either agent alone. Specific examples of valid combinations of the sulfonamides with other chemotherapeutic agents are indicated below.

ABSORPTION, DISTRIBUTION, AND EXCRETION— Sulfonamides in which the para-amino group is free are absorbed readily into the blood stream, mostly via the small intestine. Although only a small amount may remain unabsorbed, the local concentration in the bowel may be high enough to exert a prominent antibacterial action on some of the bowel flora. Absorption from the skin and vagina is erratic. Once into the bloodstream, sulfonamides bind to serum albumin to varying degrees, ranging from less than 10% to more than 90%, depending on the particular drug. Protein binding limits penetrance into the tissues, and glomerular filtration is a determinant of the rate of excretion.

Concentrations in tissue fluids usually range from about 50% to 80% of those in the plasma. Highly polar sulfonamides do not penetrate tissues well, but they are excreted rapidly.

Thus, sulfisoxazole is mainly extracellular in distribution and is of limited usefulness in systemic infections; because it is filtered rapidly in the renal glomerulus and resorbed poorly by the renal tubules (being lipid-insoluble), high concentrations are reached in the urine, which makes it effective in the treatment of UTIs. Nevertheless, when the UTI is extraluminal, more widely distributed sulfonamides, such as sulfadiazine, may be more effective.

Sulfonamides are acetylated in the liver to an extent of 30% to 85% depending on the sulfonamide and the patient. The fraction of the acetylate conjugate in the urine varies accordingly. Crystallization of sulfonamide, conjugate, or both may occur in the urine, depending on the solubility properties of each form of the drug at the pH of the urine and on the volume of urine. In general, both parent and acetylated sulfonamides are more soluble in alkaline than acid urine.

TOXICITY— Untoward effects during therapy with sulfonamides represent the major limitation to their clinical use. The most frequently observed side effects are crystalluria and related renal damage, hematuria being noted in approximately 2% of patients receiving sulfadiazine or other pyrimidine congeners. GI side effects include nausea, vomiting, abdominal pain, diarrhea, anorexia, stomatitis and rare pancreatitis. Of the neurologic effects, headache, vertigo, and insomnia are the most frequent, but tinnitus, psychic depression, ataxia, hallucinations, peripheral and optic neuritis, acute myopia, and convulsions occasionally occur. This incidence is less when adjuvant alkali and fluid therapy is instituted or when sulfonamide mixtures or the more soluble congeners are employed.

Hypersensitivity reactions, such as drug fever, dermatitis, hepatitis, polyarteritis nodosa, lupoid syndrome, pulmonary eosinophilia, and rare myocarditis, occur in about 2% of patients receiving most present-day sulfonamides. The incidence of hypersensitivity reactions is higher in patients receiving sulfapyridine. Agranulocytosis, aplastic anemia, leucopenia, and thrombocytopenia have been noted during sulfonamide therapy, but the incidence is low when sulfadiazine and the other newer congeners are employed.

Hemolytic anemia may occur; persons whose erythrocytes are deficient in glucose 6-phosphate dehydrogenase (G6PD) are especially susceptible. Sulfonamide-induced hepatocellular jaundice is now rare. Long-acting sulfonamides that may cause exudative erythema multiforme (Stevens-Johnson syndrome) are no longer available in the US.

CNS effects are observed infrequently during current sulfonamide therapy, and cyanosis, acid-base disturbances, and other miscellaneous toxic effects, formerly common during therapy with sulfanilamide, sulfathiazole, or sulfapyridine, are observed only rarely during the administration of sulfadiazine.

Sulfonamides displace bilirubin from plasma proteins and hence can cause kernicterus in the newborn. It is not recommended that sulfonamides be administered to infants younger than 2 mo. Consequently, sulfonamides should be avoided in pregnant women near term and in newborn or premature infants. Some sulfonamides have been shown to be teratogenic in rats. If at all possible, then, sulfonamides should be avoided in pregnancy.

Because the sulfonamides may cause serious untoward effects, they should be administered only when bacteriological diagnosis indicates that these agents can be expected to be superior to drugs of other classes. Constant medical surveillance, preferably daily, is necessary, and periodic blood counts and urinalysis are mandatory.

COMMENTS— Sulfonamide therapy alone has a minor place in the chemotherapy of infectious diseases. Major advantages of sulfonamides are their low cost and ease of administration; major disadvantages are their untoward effects and limited efficacy. The combination, trimethoprim-sulfamethoxazole is the treatment of choice for infections caused by *Shigella, Nocardia, Ps maltophila, Ps cepacia, Yersinia enterocolitica, Aeromonas hydrophila* and *Pneumocystis carinii*. Sulfonamides share alternate-drug status with other drugs in the treatment of infections caused by *H influenzae* (if not life-threatening), *Mycobacterium fortuitum*, *Chlamydia trachomatis*, lymphogranuloma venereum, and meningococcal meningitis.

Sulfonamides sometimes are combined with penicillin or erythromycin in the treatment of otitis media and may be combined with pyrimethamine in toxoplasmosis. Many strains of meningococcus are more sensitive to sulfonamides, but the occurrence of resistant strains has made penicillin G the drug of first choice. They are of use in some UTIs caused by *E coli, Salmonella, Shigella, Staphylococcus, Klebsiella-Enterobacter, Pr mirabilis,* and *Pr vulgaris*.

Sulfonamides are given with pyrimethamine to treat toxoplasmosis in immunosuppressed patients. In regions in which there is a problem of resistance of malarial parasites to the usual antimalarials, sulfonamides may be given in combination with trimethoprim, quinine, pyrimethamine, or other antimalarials. The beneficial effect of sulfasalazine in ulcerative colitis is understood poorly.

TYPES AND CHOICE OF PREPARATIONS— The antimicrobial spectrum of all sulfonamides is essentially the same. However, on the basis of solubility and degree of absorption from the GI tract, the sulfonamides can be divided into two broad classes, namely, those employed for systemic chemotherapy and those intended only for intestinal chemotherapy.

Oral administration of the sulfonamides is preferred. However, when medication cannot be taken by mouth, the soluble sodium or diolamine salts may be given parenterally. Topical chemotherapy rarely is effective, except in the most superficial infections, and may be dangerous because of sensitization. A possible exception is topical use of sulfacetamide sodium in trachoma and inclusion conjunctivitis, for which both topical and systemic treatments are used. A summary of the sulfonamides is presented in Table 90-2.

MIXTURES— Sulfonamide mixtures are designed to minimize the incidence of crystalluria and related renal injury associated with systemic use of sulfonamides. Since the solubility of a particular sulfonamide is not influenced by the presence of others in the same solution, a higher total concentration of sulfonamide can be attained in the urine without precipitation after administration of a mixture than is possible if a single sulfonamide is given.

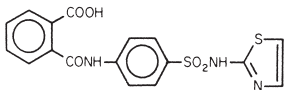
There is no clinical necessity for less soluble triple sulfonamides because preparations that are more water-soluble are available.

INCOMPATIBILITIES—The sodium derivatives are soluble in water, invariably imparting to the solution a marked alkalinity. Hence, such solutions are incompatible with all acidic substances and with precipitable amines.

Local anesthetics related to para-aminobenzoic acid antagonize the action of the sulfonamides. Ethyl aminobenzoate, procaine, isocaine, butacaine, and tetracaine are related in this way.

PHTHALYLSUFATHIAZOLE

Benzoic acid, 2-[[[4-[(2-thiazolylamino)sulfonyl]phenyl]-amino]-carbonyl]-, Sulfathaladine



[85-73-4] $C_{17}H_{13}N_3O_5S_2$ (403.43).

Preparation—US Pat 2,324,015 (1943).

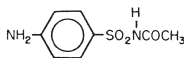
Description—Foams about 244° to 250° then melts about 272° to 277° dec.

Solubility—Slightly soluble in alcohol, very slightly soluble in ether, very soluble in fixed bases and acids, practically insoluble in water.

Comments—A sulfonamide which is not absorbed orally and is used only for ulcerative colitis.

SULFACETAMIDE

Acetamid, N^1-sulfanilyl-; ing of Sultrin, Trysul



[144-80-9] $C_8H_{10}N_2O_3S$ (214.24).

Preparation—By reacting sulfanilamide with acetic anhydride, followed by controlled alkaline hydrolysis to remove the N^1-acetyl group and subsequent acidification to a pH of approximately 4.

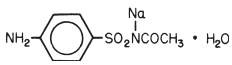
Description—White, crystalline powder; melts about 183°; pK_a 1.78.

Solubility—1 g in approximately 140 mL water; soluble in alcohol; insoluble in ether.

Comments—Employed topically in combination with sulfabenzamide and sulfathiazole for the treatment of vaginitis caused by *Gardnerella (Hemophilus) vaginalis*.

SULFACETAMIDE SODIUM

Acetamide, N-(4-aminophenyl)sulfonyl-, monosodium salt, monohydrate; Soluble Sulfacetamide



N-Sulfanilylacetamide monosodium salt monohydrate [6209-17-2] $C_8H_9N_2NaO_3S{\cdot}H_2O$ (254.24); *anhydrous* [127-56-0] (236.22).

Preparation—By reacting sulfanilamide with acetic anhydride, followed by controlled alkaline hydrolysis to remove the N^1-acetyl group and subsequent acidification to a pH of approximately 4 to form sulfacetamide which is dissolved in the required quantity of NaOH solution and the solution is evaporated to dryness or precipitated with alcohol.

Description—White, crystalline powder; odorless; bitter taste; pH (1 in 20 solution) between 8 and 9.5.

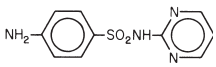
Solubility—1 g in 2.5 mL water; sparingly soluble in alcohol; practically insoluble in benzene, chloroform, or ether.

Comments—Its *antibacterial* spectrum is similar to that of the other sulfonamides, but it is less potent, owing to poor penetration into both tissues and bacteria. Employed in high concentration by local application, it is of benefit in various ophthalmologic infections, especially those caused by pyogenic cocci, gonococcus, *E coli,* and Koch-Weeks' bacillus.

Trachoma also may respond well sometimes. Since the drug is nonirritating even in high concentration, it can be employed in sufficient concentration to achieve penetration of the ocular tissues.

SULFADIAZINE

Benzenesulfonamide, 4-amino-*N*-(2-pyrimidinyl)-,



N^1-2-Pyrimidinylsulfanilamide [68-35-9] $C_{10}H_{10}N_4O_2S$ (250.27).

Preparation—By combining *p*-acetamidobenzenesulfonyl chloride with 2-aminopyrimidine in the presence of a mild alkaline agent, then splitting off the acetyl group by hydrolyzing with acid or alkali.

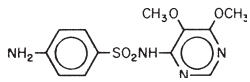
Description—White or slightly yellow powder; odorless or nearly so; stable in air, but slowly darkens on exposure to light; melts between 251° and 254°.

Solubility—1 g in approximately 13,000 mL water; sparingly soluble in alcohol and acetone; 1 g in approximately 620 mL human serum at 37; freely soluble in dilute mineral acids, solutions of potassium and sodium hydroxides or ammonia TS.

Comments—The therapeutic uses have been described in the general statement. Sulfadiazine is bound to plasma proteins to the extent of 40% to 50%, and concentrations of the drug in the CSF vary from 50% to 80% of those in the plasma; this is a good tissue concentration, as antibacterial agents go. Thus, it is the sulfonamide of choice for CNS infections susceptible to sulfonamides and for which superior agents are not available; nocardiosis is an example, as is antibiotic-resistant meningococcal meningitis. It readily enters cells, and the volume of distribution is slightly greater than total body water. The tissue-penetrating properties have proven to be of importance in combating UTIs, so that in some such infections it may be superior to the more soluble sulfonamides.

SULFADOXINE

Sulfanilamide, N^1-(5,6-Dimethoxy-4-pyrimidinyl)-, Fanasil, Fanzil



[2447-57-6] $C_{12}H_{14}N_4O_4S$ (310.34).

Preparation—By the general method for N^1-substituted sulfanilamides using 4-amino-5,6-dimethoxypyrimidine for the condensation with the sulfonyl chloride.

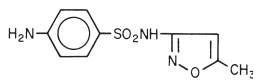
Description—White, to creamy white, crystalline powder; melts about 192°.

Solubility—Very slightly soluble in water; slightly soluble in alcohol.

Comments—Has antimicrobial activity similar to that of *Sulfadiazine*. Its principal use, however, is in the prophylaxis or suppression of malaria caused by chloroquine-resistant *P falciparum*. It is used only in combination with pyrimethamine, in a fixed-dose formulation.

SULFAMETHOXAZOLE

Benzenesulfonamide, 4-amino-*N*-(5-methyl-3-isoxazolyl)-, Gantanol



N^1-(5-Methyl-3-isoxazolyl)sulfanilamide [723-46-6] $C_{10}H_{11}N_3O_3S$ (253.28).

Preparation—By the general method for N^1-substituted sulfanilamides using 3-amino-5-methylisoxazole as the coupling amine. The latter may be prepared by heating ethyl 5-methylisoxazole-3-carbamate with aqueous sodium hydroxide. US Pat 2,888,455.

Description—White to off-white, crystalline powder; practically odorless; stable in air; melts about 172°.

Solubility—1 g in 3400 mL water, 50 mL alcohol, 1000 mL chloroform, or 1000 mL ether.

Comments—Chemically, closely related to *Sulfisoxazole*; has high aqueous solubility and low tissue penetrance, with the volume of distribution being considerably less than the extracellular space. It is bound to plasma proteins to the extent of about 68%. Thus, it is best suited to treatment of UTIs caused by susceptible organisms. It is the sulfonamide most used around the world in combination with trimethoprim or pyrimethamine for the treatment of various systemic infections.

SULFAMETHOXAZOLE AND TRIMETHOPRIM

Co-Trimoxazole, TMP-SMZ, Bactrim, Septra

Comments—Sulfamethoxazole and trimethoprim inhibit sequential steps in the formation of tetrahydrofolic acid. Thus, the inhibition is magnified by the independent actions at two consecutive metabolic steps, and bacteriostasis may be altered to that of bactericidal. The incidence of resistance is low but has been increasing with widespread use of the drug. The double blockade also widens the antibacterial spectrum from that of either agent alone.

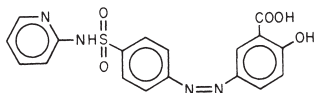
The predominant use is in the treatment of UTIs, especially recurrent, chronic, or complicated infections not considered controllable by single drugs. With these limitations of use, the rate of development of

resistant strains in a community can be retarded. UTIs caused by *E coli, Klebsiella-Enterobacter,* and *Proteus* spp are the ones mostly treated. The combination provides the treatment or prophylaxis of choice for pneumonitis caused by *Pneumocystis carinii* and enterocolitis caused by *Isospora* in immunocompromised patients. However, tissue distribution of sulfamethoxazole is poor, and the pharmacokinetics of the mixture is not optimal for treatment of systemic infections. Trimethoprim enters the CSF and tissues more readily than does sulfamethoxazole, so that the ratio is less than 20:1 at these sites.

In the presence of the sulfonamide, trimethoprim is bound poorly by plasma proteins, so that it filters rapidly into the urine, and less than 40% is metabolized. Consequently, the urine concentration may be 100 times that in plasma, whereas the sulfamethoxazole concentration may be only 3 times higher, thus departing from the supposedly optimal 20:1 ratio. The half-life of trimethoprim is about 9 hr. Impairment of renal function increases the half-life of each drug, the greater effect being on that of sulfamethoxazole.

SULFASALAZINE

Benzoic acid, 2-hydroxy-5-[[4-[(2-pyridinylamino)sulfonyl]-phenyl]azo]-, Salicylazosulfapyridine; Azulfidine



[599-79-1] $C_{18}H_{14}N_4O_5S$ (398.39).

Preparation—N^1-2-Pyridylsulfanilamide is diazotized and coupled with salicylic acid.

Description—Light brownish yellow to bright yellow, fine powder; practically tasteless and odorless; melts about 255° with decomposition.

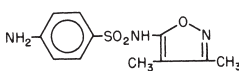
Solubility—1 g in >10,000 mL water, 2900 mL alcohol, >10,000 mL chloroform, or >10,000 mL ether.

Comments—Poorly absorbed from the small intestine, so that the major portion of drug passes into the colon where bacterial enzymes release both 5-aminosalicylic acid and sulfapyridine from the drug. It has a suppressive effect on *ulcerative colitis*, that is not defined precisely. The local antibacterial effect of sulfapyridine in decreasing anaerobic bacteria may not be significant due to systemic absorption. The 5-aminosalicylate inhibits arachidonic acid cascade, both cyclooxygenase and lipoxygenase pathways. Most important may be the inhibition of leukotriene B_4 production by PMNs.

Since some sulfapyridine is absorbed from the colon, this drug has the toxic potential of *Sulfapyridine*.

SULFISOXAZOLE

Benzenesulfonamide, 4-amino-*N*-(3,4-dimethyl-5-isoxazolyl)-, Gantrisin



N^1-(3,4-Dimethyl-5-isoxazolyl)sulfanilamide [127-69-5] $C_{11}H_{13}N_3O_3S$ (267.30).

Preparation—By the general method for N^1-substituted sulfanilamides using 3,4-dimethyl-5-aminoisoxazole for the condensation with the sulfonyl chloride.

Description—White to slightly yellowish crystalline powder; odorless; melts about 199°.

Solubility—1 g in approximately 6700 mL water; soluble in diluted hydrochloric acid.

Comments—The *antibacterial* properties and therapeutic uses resemble those of sulfadiazine. However, it does not penetrate cells and pass barriers as well as most sulfonamides. Consequently, it is not always effective against systemic infections that are sensitive to other sulfonamides. UTIs caused by sulfonamide-susceptible bacteria respond favorably. However, in genitourinary tract infections in which penetration into the involved tissues is required, it may not be as effective as sulfadiazine. It is secreted into prostatic fluid, but it is not known whether it is secreted into other genitourinary fluids. The extent of protein binding in plasma is 86%. It is metabolized primarily by acetylation and oxidation in the liver. Both it and the conjugate are excreted rapidly by the kidney and reach high concentrations in the urine. The half-life is about 6 hr. Since both the free and acetylated forms are highly soluble, even in acidic urine, adjuvant alkali therapy is not necessary and fluids need not be forced. The incidence of renal toxicity is lower than that caused by sulfadiazine or sulfonamide mixtures. With this exception, untoward effects during its therapy are similar to those caused by other sulfonamides (see the general statement).

Antibiotics

Antibiotic substances are technically chemical compounds produced by living cells and that inhibit, in very low concentrations, the growth of microorganisms although the term has come to refer to all systemic drugs used to treat bacterial infections. Although antibiotics have been isolated from tissues of higher plants and animals, the term generally has come to refer to inhibitory substances of microbial origin.

The historical development of the field of antibiotics began with the discovery by Chain, Florey, and associates at Oxford University who discovered the favorable therapeutic and pharmacological properties of extracts of cultures of the mold *Penicillium notatum*, found to produce penicillin by Fleming in 1929. The introduction of various acids, amines, or amides into the medium in which the mold is developing leads to the production of biosynthetic penicillins. Dozens of biosynthetic penicillins have been prepared in this manner in an attempt to obtain compounds superior to penicillin G with respect to various physical, microbiological, or pharmacological properties. In 1958 methods were devised for preparing the penicillin nucleus, thus making it possible to biosynthesize penicillins that could not be formed in a more normal medium. The resulting compounds were often more acid-stable, more penicillinase-resistant, or had a wider antibacterial spectrum.

The wide use of antibiotics in animal nutrition and disease has resulted in the sensitization of a relatively large number of the susceptible people, many of whom have serious reactions upon contact with these drugs. Such agricultural use also contributes to the pool of antibiotic-resistant bacteria in a community.

In this chapter penicillin is considered in detail because it is the historical prototype. It was the first antibiotic to be produced commercially and still assumes a position of major importance in this field.

DETECTION AND ISOLATION OF ANTIBIOTIC-PRODUCING ORGANISMS

The detection of productive organisms is based on the ability of cultures of the candidate organism to inhibit certain concomitantly cultured test bacteria under controlled conditions in vitro. A number of different test organisms are used, because no one organism is representative of the antibiotic susceptibilities or organisms in general. Thus, the use of a certain strain of *S aureus* as the test organism will detect all antibiotics inhibitory to that organism, but the antibiotic may or may not also be effective against *E coli*, for example, or even against various other strains of *S aureus*. To ensure securing a valid antibacterial spectrum, a number of species and types of strains must be used in the testing.

Antibiotic-producing organisms can be obtained by testing pure cultures of organisms available in culture collections or isolated from natural sources, and "screening," or selection through suitable techniques from the vast heterogeneous mixed population of the soil or other natural habitations of microorganisms. In the first case, the practice consists simply of adding to broth or agar cultures, seeded with the test organism, suitable quantities or culture filtrates of the cultures being examined, incubating and inspecting for inhibition of the test organism. The screening method involves plating out in serial dilution an aqueous extract of soil or other natural substrate using a medium, usually agar, previously seeded with the test organism. During incubation the various organisms of the soil population develop, and those forming antibiotic substances are distinguished by a clear zone or halo around the colony, indicative of inhibition of the test organism which, in the region beyond the clear zone, grows abundantly in the form of a marked turbidity throughout the agar.

Many modifications of this principle are employed. Thus, the use of different media, pH, temperature, and substrates will expose, for screening, different types of soil organisms. These conditions must be compatible with the growth of the particular test organism employed. Theoretically, the best chance for detecting the largest possible number of antagonists lies in the preincubation of the agar cultures containing the soil dilutions, but without the test bacteria. This is followed by a secondary incubation after the test organism is applied to the plate by streaking or spraying. In this manner slow-growing soil organisms are given the opportunity to develop and manifest antibiotic-producing ability.

Once detected, the antagonist is isolated in pure culture and identified, and the optimal conditions for production of the antibiotic substance produced by it are investigated. The composition of the medium is important. Different organic and inorganic nitrogenous substances are tested, with and without various carbohydrates, minerals, heavy metals, etc.

Once a favorable medium is established, other known strains of the antagonist, obtained either from stock-culture collections or isolated from nature, are compared for the character and amount of the antibiotic produced, and the highest yielding strain selected for further work. The antibacterial spectrum is obtained, ie, the relative effectiveness of the antibiotic in inhibiting the growth of a large variety of gram-positive and gram-negative bacteria, rickettsiae, viruses, and fungi, especially those that are pathogenic. This indicates those infections in which it may be useful chemotherapeutically.

Several concentrates or isolates of the antibiotic, not necessarily pure, then are examined for toxicity in mice. Only low-toxicity preparations and, in particular, those in which toxicity is inversely proportional to the antibacterial potency are of interest. Toxicity and pharmacological data are obtained in animals and, if favorable, in clinical trials on human beings. If the clinical trials show the antibiotic to be a promising therapeutic agent, attention is turned to large-scale manufacture. Chemical studies of the structure of the pure compound will indicate the feasibility of chemical synthesis. Generally, antibiotics are complex substances whose synthesis may be extremely difficult, or at least uneconomical, compared with microbiologic production. This is the case now with most of the successful antibiotics, such as penicillin, streptomycin or chlortetracycline.

The gradual increase in numbers of strains of microorganisms resistant to antibiotics, especially the staphylococci, and the numbers of individuals developing sensitivity to them make it extremely desirable that screening programs for the isolation and development of new agents be continued.

PRODUCTION

The development and operation of the large-scale commercial production of antibiotic substances may be exemplified by a description of the manufacture of penicillin. In general, the approach and methods employed are typical. Two types of processes for the microbiological production of antibiotics are:

The surface process, in which the antibiotic-producing organism grows in the form of a pad on the surface of a liquid medium in trays or bottles, or on the surface of a finely divided moist solid substrate such as wood shavings or wheat bran.

The submerged process, in which the organism develops in a liquid medium, maintained continuously under mechanical agitation and aeration, so that the organism develops uniformly and homogeneously in the form of a suspension of single cells, or small aggregates or colonies, throughout all portions of the culture liquid.

The penicillin is excreted into the culture fluid. The molds used industrially today are derived from *Penicillium chrysogenum*.

In the submerged process, growth is accelerated greatly and the handling of large quantities greatly facilitated. It is considerably more efficient than the surface processes, and hence is the only feasible method for large-scale commercial production. Stationary, closed tanks, known as fermenters, of 5000- to 30,000-gal capacity, are used in penicillin manufacture. Most of these are equipped with vertical single-shaft propeller or turbine-type agitators and with a mechanical means of comminuting and distributing sterile air, introduced for maximum dispersal effect in the region of the agitator. The tanks have a detachable manhole on the top, sight glasses, and outlets to valve-closed sampling lines and accessory feed chambers, enabling inoculation by hand if necessary, particularly in small seed tanks, and the addition whenever necessary of other (sterile) materials, such as antifoam agents, during the fermentation. All outlets from the tank are exposed continuously to flowing steam to minimize chances of contamination. The culture medium is sterilized by high-pressure steam and subsequently cooled. Temperature control during growth of the mold is maintained automatically at 23° to 25°. The compressed air, which is introduced into the fermenters, is sterilized by filtration through steam-sterilized cartridges of suitable size and filled, for example, with glass wool.

Inoculum for large tanks is obtained by building up the amount of growth successively through a series of seed tanks, from tank to tank, and transferring under air pressure through sterile pipe lines. Generally, this massive inoculum amounts to 5% to 10% of the main batch and, consequently, seed tanks are approximately 1/10 the volume of the next larger tank. The first and smallest seed tank is inoculated with a laboratory-prepared culture, consisting either of spores or of a small flask of submerged growth obtained on a laboratory-, rotary-, or reciprocal-type shaking machine.

The stock or master culture of the penicillin-producing mold is dry and cold-preserved in the form of spores. Continuous vegetative transfer of the mold on artificial media leads to loss of penicillin-producing power (physiological degeneration). Hence, the number of intermediate transfers between master culture and the final batch is kept at a minimum.

A Typical Production Medium	
Corn-steep liquor (solids)	2 to 5%
Crude lactose	2 to 3%
Calcium carbonate	0.5 to 1%

The culture medium used for commercial production of penicillin generally contains natural nitrogenous material, nitrate, α-aminoadipic acid, cottonseed meal, or corn-steep liquor, which is a by-product of the corn-milling industry, lactose, side-chain precursor, surface-active agent, and mineral salts (including sulfate). The penicillin potency is followed by assay every 3 to 6 hours and, at the time when the potency stops rising, the batch is harvested. Maximum activity generally is reached in 50 to 90 hours. Because of the instability of penicillin at ordinary temperatures, the batch is cooled to 5° and the mycelium filtered off by pressure filtration.

The penicillin is extracted and concentrated by charcoal adsorption or solvent extraction.

IMPROVEMENTS IN PRODUCTION—The greatest advancements in the production of penicillin have been the use of the submerged or tank method of production, the use of corn-steep liquor, and the progressive improvement in the penicillin-producing capacity of the mold.

The earliest widely used strain in tank production was *Penicillium notatum*, No 832, which yielded 50 to 60 units/mL. Later, a strain of *Penicillium chrysogenum*, No 1951B25, with maximum yields of 250 units/mL, was discovered. Spores of this organism, exposed to x-ray irradiation and tested from single spore isolates, led to selection of a mutant strain X1612 producing approximately 500 units/mL. Strain X1612 was subjected to ultraviolet irradiation and strain Q176, yielding penicillin potencies of more than double that of X1612, was obtained. This strain has been used widely in commercial production, but industry has even improved on it. Some variant strains produce several thousand units/mL. The improvement in strains suit-able for the surface production of penicillin followed a similar path although these were obtained by testing single spore isolates from parent cultures. A strain excellent

in submerged culture is not necessarily good for surface culture, and *vice versa*. Surface culture methods are no longer used for commercial production of any of the presently useful antibiotics.

A large number of different fungi are now known to produce penicillin. More than 20 different species of *Aspergillus* and *Penicillia* produce penicillin, as do the dermatophyte *Trichophyton mentagrophytes* and a thermophilic fungus, *Malbranchea pulchella*.

CONTROL

Federal control of antibiotics dates back to an amendment of the 1938 Food, Drug and Cosmetic Act (Section 507) under which the FDA was required to pretest all forms of penicillin and its preparations before releasing them for sale. This certification covered potency, demonstration of nontoxicity and moisture content (the presence of excess moisture makes penicillin less stable). When intended for parenteral use, it also was tested for freedom from pyrogens, for sterility, clarity, and pH of its solutions.

This amendment included the provision that when it was found by the Federal Security Administrator (now Secretary HHS) that the pretesting of penicillin or its preparations was no longer necessary to insure safety and efficacy of such drugs, they could be exempted from the pretesting requirement.

Under this provision of the Act the Federal Security Agency, FDA Division, finding that certain new, highly purified forms of penicillin no longer required pretesting, issued a notice in the *Federal Register* of April 13, 1949, exempting Crystalline Penicillin G Potassium and Crystalline Penicillin G Sodium from this provision.

In March 1947, the Congress of the US placed streptomycin under the certification system and in July 1949 included chlortetracycline, chloramphenicol, and bacitracin. Because these amendments include all derivatives as well, both dihydrostreptomycin and tetracycline, as well as pyrrolidinomethyl tetracycline and demeclocycline, were certifiable drugs.

In May 1963, the Drug Amendments passed by Congress in 1962 became effective and superseded all previous rulings. These now provide that all antibiotics used in humans are subject to certification. Furthermore, those certifiable prior to passage of these latest amendments, ie, chlortetracycline, bacitracin, streptomycin, penicillin, and chloramphenicol, also must be certified for veterinary use.

CLASSES AND AGENTS

Antibiotics are classified by various schemes, the two most important being according to mechanism of action and according to chemical relationship. The antibiotic monographs that follow will be arranged according to chemical relationships.

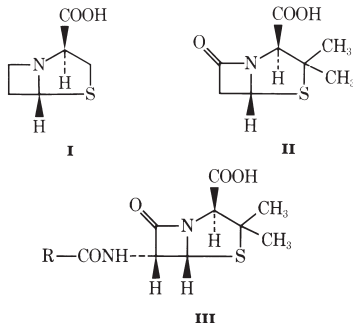
Beta-Lactam Antibiotics

PENICILLINS

HISTORY—During an inspection of some culture plates in the laboratory of St Mary's Hospital London, in 1928, Professor Alexander Fleming observed the lysis of staphylococcus organisms by a contaminating mold. Upon subculturing the mold he found in the broth a powerful, but nontoxic, antibacterial substance. He gave it the name "penicillin" from the organism *Penicillium notatum,* which caused the generation of the antibiotic.

CHEMISTRY—The name "penicillin" now designates a number of antibiotic substances produced by the growth of various *Penicillium* species or by other means. The better known natural penicillins are listed in Table 90-3. Penicillins F, G, and X were referred to formerly as I, II, and III, respectively.

The parent compound is (2*S*-*cis*)-4-thia-1-azabicyclo[3.2.0] hepatane-2-carboxylic acid (I). The 3,3-dimethyl-7-oxo derivative of I is known commonly by the trivial name penicillanic acid (II) and the penicillins are α-carboxamido derivatives of it (III):



Penicillins are named variously in the literature as derivatives of I, II, or III above. Nomenclature by I is purely systematic, whereas that by II or III is trivial. As derivatives of II, it is merely necessary to identify the specific α-carboxyamido group; as derivatives of III, only the R of the α-carboxamido group is identified.

The introduction of various acids, amines, or amides into the medium in which the mold is developing leads to the production of biosynthetic penicillins which differ only in R. Dozens of biosynthetic *penicillins* have been prepared in this manner in an attempt to obtain compounds superior to penicillin G with respect to various physical, microbiological, or pharmacological properties. In 1958 methods were devised for preparing the penicillin nucleus, thus making it possible to biosynthesize penicillins that could not be formed in a more normal medium. The resulting compounds were often more acid-stable, more penicillinase-resistant, or had a wider antibacterial spectrum.

Table 90-3. Penicillins

CLASS	COMMENTS
Natural Penicillins (best streptococcal and narrow spectrum)	
Penicillin G	Best narrow spectrum (streptococci), IV, IM
Penicillin V	Same spectrum as Pen G, oral only
Penicillinase-resistant Penicillins (antistaphylococcal)	
Cloxacillin	Oral
Dicloxacillin	Preferred oral
Methicillin	IV, interstitial nephritis may occur
Nafcillin	Preferred IV drug for Staph.
Oxacillin	Oral
Aminopenicillins (improved gram-neg, *H influenzae, Enterococcus, Shigella, Salmonella*)	
Amoxacillin	Good oral absorption,
Ampicillin	Preferred IV drug, incomplete oral absorp., diarrhea, rash
Bacampicillin	Oral prodrug converted to ampicillin
Extended-spectrum (antipseudomonal) penicillins	
Carbenicillin	IV, high sodium, oral prodrug available
Ticarcillin	IV, similar to carbenicillin but less sodium
Mezlocillin	IV, similar to piperacillin
Piperacillin	Preferred IV, best gram-neg. spectrum
Beta-Lactamase Combinations (expand spectrum to staph., beta-lactamase producers)	
Clavulanalate-Amoxacillin	Oral, more diarrhea than amoxacillin
Sulbactam-Ampicillin	IV, active vs. staph. and beta-lactamase-producing *H influenzae and Strep pneum*
Clavulanate-Ticarcillin	IV, active vs. more gram-neg. bacilli
Tazobactam-Piperacillin	IV, active vs. more gram-neg. bacilli

Much of the penicillin of commerce is pure crystalline G. It occurs in fermentation liquors together with variable amounts of K and F penicillins and smaller amounts of others, and is separated from the other penicillins during purification. Commercial practice suppresses, to a certain extent, the natural tendency of the mold to form penicillins other than the desired G by the incorporation of a precursor of G, namely phenylacetic acid, phenylacetamide, phenylethylamine, or other substance containing the phenylacetyl radical, which is built directly into the penicillin G molecule. Penicillin G has the additional advantage of being much easier to crystallize than K or F.

As seen in figures I, II, and III, penicillins are acids. The potassium salt predominates in use, with the sodium salt next. These salts are very soluble in water. The acid moiety can be used to combine penicillins with various bases, such as procaine or benzathine, to create insoluble salts, for repository use, or for the purpose of decreasing solubility so as to make the compound more resistant to gastric acid.

Penicillin in solution is very unstable at pH 5 or less and at 8 or more. Solutions of penicillin begin to deteriorate upon standing a few days, even in the cold. Certain penicillins are more resistant to acid hydrolysis and thus lend themselves better to oral administration.

CLASSIFICATION AND SPECTRUM—Penicillins formerly were classified according to pseudohistorical divisions, by "generation," similar to the classification of the cephalosporins. However, it is more useful to classify them according to a mixture of chemical and antimicrobial designations. The categories are *penicillin G, acid-stable penicillins, penicillinase-resistant penicillins, amino penicillins, extended-spectrum penicillins,* and *amdinopenicillins*. There is a great deal of overlap in the properties among the categories. For example, two of the penicillinase-resistant, all of the amino penicillins and one extended-spectrum penicillin are sufficiently acid-stable to be orally effective; amino penicillins, extended-spectrum penicillins, and amdinocillin are all resistant to certain β-lactamases (which often are called penicillinases indiscriminately) and variably resistant to Class II β-lactamases, to which the term, penicillinase, is becoming restricted. All penicillins are bacteriostatic at low and bactericidal at high concentrations. Their antimicrobial spectra differ according to the pattern of β-lactamase resistance, the ability to penetrate the outer membrane of gram-negative bacteria and selectivities for the various bacterial transpeptidases (penicillin binding proteins; PBPs).

Although penicillin G is destroyed largely by gastric acid, its low oral bioavailability can be compensated by increased dosage. Penicillin V is the only marketed member of the acid-stable class. These two drugs/classes have nearly identical antimicrobial spectra, except that sensitivities to penicillin-V are not high enough for a number of gram-negative infections to be treated by the oral route. The spectrum is *narrow* and mostly limited to gram-positive bacteria, gram-negative cocci, and a few miscellaneous bacteria. They are especially active against gram-positive bacteria, particularly *Strep pyogenes*, most *pneumococci, Cl tetani* and *perfringens, Coryn diphtheriae, B anthracis, Bacteroides, Eubacterium, Fusobacterium, Listeria monocytogenes, Peptococcus,* and *Peptostreptococcus*.

Although *Staph aureus* and *epidermidis* were originally mostly sensitive, they are now over 90% resistant in hospital populations and 50% in the community. *Strep viridans* is variably sensitive. *Strep faecalis* (enterococcus) is usually resistant. The gram-negative cocci, *N meningitidis* and *N gonorrhoeae*, are mostly sensitive, although resistance is increasing rapidly. Activity against the gram-negative bacilli is usually too low to be of clinical significance, but over 80% of strains of *E coli, Enterobacter*, most *Prot mirabilis* and some *Salmonella* and *Shigella* are sufficiently sensitive to respond in the urinary tract, where drug concentrations are high. Concentrations are also high in the bile, and these penicillins may be used to treat biliary tract infections caused by some enterobacteria and enterococci. These drugs are also active against *Actinomycetes, Leptospira, Providencia, Spirillum minus, Streptobacillus moniliformis,* and *Treponema pallidum*.

Resistance of gram-positive and a number of gram-negative bacteria to penicillins G and V results from the bacterial elaboration of so-called penicillinase. This kind of resistance was obviated by the development of penicillins, which penicillinase cannot destroy. The first member of the penicillinase-resistant class was *methicillin*, to which *cloxacillin, dicloxacillin, nafcillin,* and *oxacillin* were added. These drugs have approximately the same spectrum of activity as the former two drugs, except increased activity against most staphylococci (especially), enterococci, gonococci, and meningococci.

The *amino penicillins* include *ampicillin, amoxacillin, becampicillin, cyclicillin,* and *epicillin*. Each has an amino group adjacent to the carbonyl of the *N*-acyl substituent. Efficacy is increased against enterococcus, meningococcus, and several gram-negative bacilli, such as community-acquired *E coli, H influenzae, Pr mirabilis*, various *Salmonella* and *Shigella*. However, there is less activity against most gram-positive bacteria, *N gonorrhoeae, B anthracis, Bacteroides, Clostridium, Corynebacterium, Enterobacter, Eubacterium, Listeria, Peptococcus, Peptostreptococcus, Providencia, Streptobacillus, Actinomyces,* and *Treponema*; consequently, this group also has been called *shifted-spectrum penicillins*. There are important differences among the spectra of the various members, ampicillin having the broadest spectrum but amoxacillin being the only one to be effective against *Strep viridans*. Only ampicillin has clinically significant activity against *Salmonella* and *Shigella*.

The *extended-spectrum* (antipseudomonal) *penicillins* include *azlocillin, carbenicillin, indanylcarbenicillin, mezlocillin, piperacillin,* and *ticarcillin*. There is increased activity against *Acinetobacter, Citrobacter, E coli, Enterobacter, H influenzae, Klebsiella, Morganella morganii, Pr mirabilis* and *vulgaris, Providencia rettgeri* and *stuartii, Ps aeruginosa, Bacteroides, Clostridium, Eubacterium, Fusobacterium, Peptococcus, Peptostreptococcus,* and *Veillonella*. They are even less active than amino penicillins against most gram-positive bacteria, *Actinomycetes* and *Treponema*, and they are not used to treat infections by these pathogens. There are considerable differences among the members. Neither azlocillin nor mezlocillin is active against staphylococci; azlocillin is inactive against *Pseudomonas* or *Neisseria* and *carbenicillin* is inactive against *Eubacterium*. Only piperacillin is active against *Strep viridans* and azlocillin and mezlocillin against *Providencia stuartii*.

Amdinocillin is the only marketed member of the class by the same name. It has a very limited spectrum. No infections by gram-positive or anaerobic bacteria are treatable. Among the gram-negative bacteria only *Citrobacter, Enterobacter, E coli, Klebsiella, Salmonella, Serratia,* and *Shigella* are sensitive enough so that this drug is used alone to treat infections by them. In combination with other β-lactams, it may be used against *Prot mirabilis, Morganella morganii,* and *Providencia*.

RESISTANCE—The penicillin resistance of many gram-positive and gram-negative bacteria is owing to their elaboration of penicillin-destroying enzymes called *beta-lactamases*. They are produced by large numbers of bacteria and actinomycetes and convert penicillin into inactive *penicilloic acid* by liberation of a second carboxyl group. The enzymes from staphylococci, enterococci, meningococci, gonococci, and various other bacteria were the first-known beta-lactamases and were called *penicillinases*. Penicillinases are Group II beta-lactamases, acidic proteins which are resistant to mercuric ions. Although they are inducible, the capacity for induction is determined by a plasmid-located gene.

Resistance of bacteria to penicillin cannot be explained entirely on penicillinase production because many resistant organisms produce little or no penicillinase. Nonpenicillinase-mediated resistance is called *methicillin resistance*. It is caused by an alteration in the target transpeptidase (penicillin-binding protein I). With some bacteria, eg, *Staph aureus*, resistance develops very fast clinically, but some microorganisms, eg, *T pallidum*, never become resistant. Resistance by staphylococci currently is a major hospital problem.

More resistant bacteria dwell in hospital personnel than in the community at large, because such personnel are close to

patients under treatment. Acquired resistance is the result of the selection of natural penicillin-resistant strains that ordinarily are held in check by the sensitive parent strain. Resistant genes may be acquired by mutation, transduction by viruses, transformation, and conjugative transfer of resistant-gene-containing plasmids.

MECHANISM—Penicillin is known to interfere with the synthesis of peptidoglycans, which are part of the cell-wall material. Consequently, the growing protoplast cannot form a protective cell wall. Several wall enzymes are reversibly inhibited, the most important being a D, D-carboxypeptidase, which also functions as a transpeptidase. Conditions favoring rapid growth of bacteria are best for the inhibitory action of penicillin, owing to the fact that the cell must be producing cell wall-lysing enzymes during the time transpeptidases are inhibited in order for cell-wall lysis to occur. Under favorable conditions, penicillin exerts a direct bactericidal action, and successful penicillin therapy may be relatively independent of immunity mechanisms of the host.

POTENCY—The potency of penicillin is expressed in units/mg. *One International Unit is equivalent to the activity of 0.6 μg of pure crystalline sodium penicillin G* to which, by international conference, a potency of 1667 units/mg has been assigned. See Table 90-3. Because of the large doses now used, it is common to speak in terms of megaunits, ie, 1 megaunit equals 10^6 Units.

ASSAY—See *Biological Testing*.

COMMENTS—Although penicillin G is the original penicillin, it remains the drug of choice for the treatment of almost all infections caused by nonpenicillinase-producing, nonmethicillin-resistant gram-positive bacteria, the integrity of which depends upon cell walls. Thus, it is the drug of choice against infections by gram-positive, nonpenicillinase-producing cocci, such as *Staph aureus* or *epidermidis, Strep bovis*, Group B, *pyogenes, viridans, faecalis* (enterococcus; in combination with gentamycin, for serious infections, only) or *pneumoniae* (pneumococcus), *Peptococcus* or *Peptostreptococcus* and gram-positive bacilli, such as *B anthracis* or *Cl perfringens* or *tetani*. It is thus also the drug of choice against infections by nonpenicillinase-producing strains of the gram-negative coccus, *N meningitidis*, the gram-negative bacillus *Bacteroides fragilis* (especially oropharyngeal strains), *Fusobacterium, Leptotrichia buccalis, Pasteurella multicida, Spirillum minus,* or *Streptobacillus moniliformis*, the actinomycete, *Actinomyces israelii*, or the spirochete, *Leptospira* or *Treponema pallidum*.

It is an alternative drug to treat infections by *Coryn, diphtheriae, Vibrio vulnificus,* or *Borrelia burgdorferi*. Penicillin V shares with penicillin G first choice status in the treatment of lesser staphylococcal infections and streptococcal (pneumococcal) pneumonia.

Penicillinase-resistant penicillins are drugs of choice only for the treatment of infections by penicillinase-producing staphylococci. They also can be used as penicillinase inhibitors, to combine with penicillin G; however, clavulanate, sulbactam, and tazobactam are preempting that use.

An aminopenicillin is the drug of choice for the treatment of infections by *Strep* Group B (ampicillin; shares status with penicillin G), *Branhamella* catarrhalis (amoxacillin), *E coli* (ampicillin, combined with an aminoglycoside), *Prot mirabilis*, *Salmonella* (except *typhi*), *Eikenella corrodens* (with or without clavulanate or sulbactam), mild-to-moderate infections by *H influenzae* (with or without clavulanate or sulbactam), or *Listeria monocytogenes* (with or without gentamycin).

It is an alternate drug for the treatment of infections by penicillinase-producing *Staphylococcus* (with clavulanate), *Bordetella pertussis, E coli* (with clavulanate, sulbactam, or tazobactam), *Gardnerella vaginalis, H influenzae* (serious infections; initially in combination with chloramphenicol), *Kl pneumoniae* (with clavulanate or sulbactam), *Morganella morganii, Prot vulgaris* (with clavulanate or sulbactam), *Pasteurella multicida* (with clavulanate or sulbactam), *Salmonella typhi,* or *Shigella*.

An extended-spectrum (antipseudomonal) penicillin is the drug of choice only for the treatment of infections by sensitive *Ps aeruginosa*. It is an alternate drug for the treatment of infections by penicillinase-producing *Staphylococcus, Acinetobacter, Bacteroides fragilis* (gastrointestinal strains), *Enterobacter, Kl pneumoniae* (with clavulanate or sulbactam), *Morganella morganii* (with clavulanate or sulbactam), *Prot mirabilis* or *vulgaris* (with clavulanate or sulbactam), *Providencia rettgeri* or *stuartii* (with clavulanate or sulbactam), *Ps aeruginosa* (urinary tract infections), or *Serratia*.

A penicillin is employed sometimes in *combination* with other agents. The results of such therapy are often, but not invariably, superior to those obtainable with a penicillin alone. When it is administered with the tetracyclines, chloramphenicol, or the sulfonamides, antagonism may be noted if the microorganism is highly susceptible to a penicillin when it is administered alone. Nevertheless, it often is used in combination with chloramphenicol in the treatment of bacterial meningitis caused by *H influenzae*.

The number of bacteria and the quantity of pus appear to have only a minor influence upon the antibacterial action of penicillin, except when the organism produces an appropriate β-lactamase.

ADVERSE EFFECTS—Penicillin is practically nontoxic. However, hypersensitivity reactions occur in several percent of patients, depending on the type of preparation employed and the route of administration. The most-common manifestation of this allergic response is a skin rash. Nondermatological manifestations of allergy include serum sickness, angioedema, nephropathy, rare hemolytic anemia, Arthus reaction, rare pericarditis, enteropathy, hepatotoxicity, and anaphylaxis. Neutropenia, which occasionally results from high-dose therapy, does not appear to involve an immune process.

Side effects of oral administration of penicillins are nausea, vomiting, epigastric distress, diarrhea, and black "hairy" tongue.

Like other antibiotics, penicillin markedly can alter the normal bacterial flora of man. As a result, superimposed infection by a penicillin-resistant microorganism may develop during the course of treatment, and appropriate chemotherapy should be instituted as soon as possible. Overgrowth (suprainfection) even occurs in the bowel, because penicillin is secreted into the bile, which keeps the intestinal levels high. Coagulation disorders also may occur as the result of the suppression of enteric bacteria that synthesize vitamin K.

Very high concentrations of penicillin are neurotoxic, and nerve damage has resulted from intramuscular administration. Crystalline penicillin has an irritating effect when applied directly to the central nervous system. Symptoms after intrathecal administration include listlessness, headache, nausea, vomiting, respiratory difficulty, cyanosis, fall in blood pressure, thready pulse, muscular twitching, and convulsions. These are reduced or eliminated by lowering dosage.

With sodium and potassium salts, the effect of the cation load must be considered. Lastly, untoward effects sometimes result from the rapid bactericidal effects, because of the release of endotoxins and other bacterial cell components.

ABSORPTION, DISTRIBUTION, AND EXCRETION—Penicillin G in the form of its sodium or potassium salt is absorbed rapidly from subcutaneous and intramuscular sites. The intramuscular route is preferred. Penicillin G is given intravenously by continuous infusion only when it is imperative to maintain very high blood concentrations such as in the treatment of subacute *bacterial endocarditis*. The rate of absorption from intramuscular sites of injection may be slowed markedly by the use of repository (depot) preparations consisting of relatively insoluble salts of penicillin in a suitable vehicle. For example, therapeutic blood levels (for some purposes) persist 12 to 24 hours after a single 300,000-unit dose of *Procaine Penicillin in Aqueous Suspension*, 24 to 48 hours after *Procaine Penicillin in Oil,* and 1 wk or more after 1.2 million units of *Benzathine Penicillin G*. However, the slower the absorption, the lower the peak plasma level, and some uses are precluded.

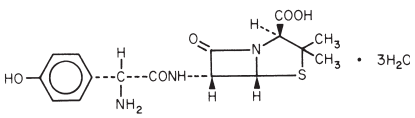
The absorption of penicillin G from the gastrointestinal tract is incomplete and irregular, but some acid-stable penicillins are absorbed well. To obtain the same blood concentrations as by the intramuscular route, 3 to 5 times the parenteral dose of penicillin G must be employed. Penicillin G should be ingested when the stomach is empty because penicillin binds to food substances. Although hydrochloric acid in the gastric juice destroys penicillin G, buffer agents have not proved to be necessary for successful oral medication, because the dose can be raised to compensate. Oral penicillin G therapy should never be relied upon alone in severe infections.

Penicillins are distributed in the extracellular water, but they penetrate cells poorly. Tissue concentrations are approximately ¼ the plasma concentration *at equilibrium*. Plasma levels fall so fast that there is not enough time for the build-up of high concentrations in many tissues. Diffusion of penicillins into CSF is minimal unless the meninges are inflamed. The preferred route of administration for treatment of bacterial meningitis is IV supplemented by IM injection. It usually is not recommended to use intrathecal administration of penicillins because of the irritative effect of even low doses of penicillin on the CNS. Local instillation may be used in various body cavities to supplement systemic administration.

Penicillins are secreted mostly into the urine, partly by glomerular filtration but mostly by tubular secretion (80%). Substances that interfere with renal tubular excretion of penicillin (see *Probenecid*) serve to enhance and prolong the effective blood levels of the antibiotic. Probenecid can block completely the renal tubular secretion of penicillin, which slows excretion; it also decreases removal from the CSF. Phenylbutazone also interferes with excretion to a degree comparable to probenecid; sulfinpyrazone, aspirin, indomethacin, and some sulfonamides also moderately interfere with the excretion of penicillin. The normal plasma half-time of penicillin G is approximately 45 minutes, but in persons over 65 years it is almost twice as long. In oliguria, it may be 7 to 10 hours. The penicillins are summarized in Table 90-3.

AMOXICILLIN

[2*S*-[2α,5α,6β(*S)]]-4-Thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid, 6-[[amino(4-hydroxyphenyl)acetyl]amino] 3,3-dimethyl-7-oxo-, trihydrate**



D(−)-α-Amino-*p*-hydroxybenzylpenicillin; [61336-70-7] $C_{16}H_{19}N_3O_5S \cdot 3H_2O$ (419.45); *anhydrous* [26787-78-0] (365.30).

Preparation—By acylation of 6-aminopenicillanic acid with D-(−)-2-(*p*-hydroxyphenyl)glycine.

Description—Fine, white to off-white, crystalline powder; bitter taste; high humidity and temperature over 37°adversely affect stability.

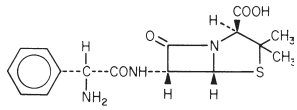
Solubility—1 g in 370 mL water or 2000 mL alcohol.

Comments—Amoxicillin, the *p*-hydroxy analog of ampicillin, has an antibacterial spectrum similar to that of *Ampicillin*, except that it is less active against *Streptococcus, N meningitidis, Clostridium, Salmonella,* and *Shigella*. Like ampicillin, it is destroyed by β-lactamases. However, it is more acid-stable than ampicillin, and absorption is not affected appreciably by food; it cannot be given parenterally. It is the drug of choice for infections caused by *Enterococcus faecalis* (enterococcus), *Branhamella catarrhalis,* or *Bacteroides fragilis* (mild to moderate infections). It is an alternate drug for infections by penicillinase-producing *Staphylococcus* (combined with clavulanate), *N gonorrhoeae* (with probenecid), *E coli* (with clavulanate), or *Pasteurella multicida* (with clavulanate). It cannot be given parenterally for severe infections. The toxicity is that of ampicillin, but there is less diarrhea and rash.

By the oral route, 75% to 90% is absorbed. In plasma, it is 17% protein-bound. The volume of distribution is 0.31 mL/g. From 50% to 72% is eliminated by renal tubular secretion. The half-life is about 1 hr when renal function is normal and 8 to 16 hr in renal failure.

AMPICILLIN

[2*S*-[2α,5α,6β(*S)]]-4-Thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid, 6-[(aminophenylacetyl)amino]-3,3-dimethyl-7-oxo-,**



[69-53-4] $C_{16}H_{19}N_3O_4S$ (349.40); *trihydrate* [7177-48-2] (403.45). Potency: 900 to 1050 μg of $C_{16}H_{19}N_3O_4S$/mg, calculated on the anhydrous basis.

Preparation—6-Aminopenicillanic acid is acylated with D-glycine. US Pat 2,985,648.

Description—White, crystalline powder; practically odorless; occurs as the trihydrate, which is stable at room temperature.

Solubility—1 g in approximately 90 mL water or 250 mL absolute alcohol; practically insoluble in ether or chloroform.

Comments—The *first aminopenicillin* (see the general statement). Its in vitro spectrum against gram-positive cocci is similar to but generally somewhat less effective than that of penicillin G, except that it is somewhat more effective against *Enterococcus faecalis* (enterococcus). It is ⅒ as effective against *Strep pyogenes*.

It is poorly effective against penicillinase-producing organisms. It is the drug of choice for treatment of infections due to sensitive strains of Strep Group B, *Enterococcus faecalis* (combined with gentamycin), *Listeria monocytogenes* (with or without gentamycin), *E coli* (with or without gentamycin) and *Prot mirabilis*, and *Salmonella* (not *typhi*). It is an alternative drug against *Kl pneumoniae* (with sulbactam), indole-positive *Proteus (M morganii, Pr vulgaris* and *Providencia rettgeri*; with sulbactam), *Salmonella typhi, Shigella, Gardnerella vaginalis, H influenzae* (serious infections; initially combined with chloramphenicol) or *Nocardia*. Some of these readily acquire resistance by elaboration of penicillinase, so it is given often in combination with sulbactam.

It causes allergic reactions typical of other penicillins. It is 5 times as allergenic as penicillin G. The incidence of rashes is about 7%, but most of these are not allergenic; they are especially prevalent in patients with infectious mononucleosis. Patients allergic to penicillin G are often also allergic to ampicillin. The drug also may cause nausea and vomiting, diarrhea, glossitis, and stomatitis. It is acid-resistant and is 30% to 50% absorbed by the oral route.

AMPICILLIN SODIUM

[2*S*-[2α,5α,6β(*S)]]-4-Thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid, 6-(aminophenylacetyl)amino]-3,3-dimethyl-7-oxo-, monosodium salt**

[69-52-3] $C_{16}H_{18}N_3NaO_4S$ (371.39). Potency: not less than 845 μg of ampicillin/mg, on the anhydrous basis.

Preparation—*Ampicillin* is dissolved in a suitable organic solvent and precipitated as the sodium salt by the addition of sodium acetate.

Description—White to off-white, crystalline powder; hygroscopic; pK_{a1} 2.66; pK_{a2} 7.24.

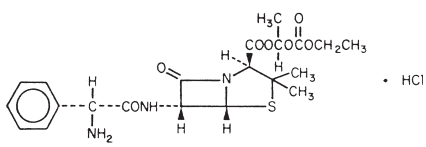
Solubility—Very soluble in water, isotonic NaCl or dextrose solutions.

Comments—Has the actions and uses of *Ampicillin*, and is the form in which ampicillin is employed for intramuscular and intravenous administration.

AZLOCILLIN SODIUM—see RPS-18, page 1187.

BACAMPICILLIN HYDROCHLORIDE

4-Thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid,[2*S*-[2α,5α,6β(*S)]]-,-6-[(aminophenylacetyl)amino]-3,3-dimethyl-7-oxo-, 1-[(ethoxycarbonyl)oxy]ethyl] ester, monohydrochloride,**



[37661-08-8]$C_{21}H_{27}N_4O_7S \cdot HCl$ (501.98).

Preparation—US Pat 3,939,270.

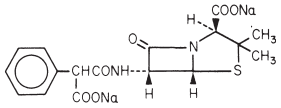
Description—White crystals; melts about 175°; pH (2% aqueous solution) 3 to 4.5.

Solubility—1 g in approximately 15 mL water, 7 mL alcohol or 10 mL chloroform.

Comments—An *aminopenicillin* with improved gram-negative activity against *H influenzae*, *Enterococcus*, *Shigella,* and *Salmonella*. It is an oral prodrug converted to *Ampicillin*.

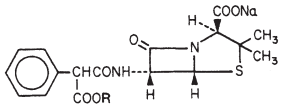
CARBENICILLIN DISODIUM

[2*S*-(2α,5α,6β)-4-Thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid, 6- [(carboxyphenylacetyl)amino]-3,3-dimethyl-7-oxo-, disodium salt; Geopen, Pyopen



(α-Carboxybenzyl)penicillin Disodium [4800-94-6] $C_{17}H_{16}N_2Na_2O_6S$ (422.36). Potency: the equivalent of not less than 770 μg of carbenicillin/mg, calculated on the anhydrous basis.

Preparation—One method consists of hydrolyzing esters of the type



(R = alkyl, aryl, or benzyl) with the aid of a suitable esterase, such as α-chymotrypsin or pancreatin, and extracting the acid and reacting it with aqueous $NaHCO_3$. *Chem Abstr* 1970; 72:41674a. The starting esters may be prepared by acylating 6-aminopenicillanic acid with monoesters of phenylmalonic acid. US Pats 3,282,926 and 3,492,291.

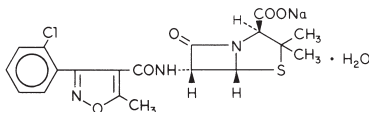
Description—White to off-white, crystalline powder; bitter taste; hygroscopic; odorless, pH (1% solution, *w/v*) 8.0. pK_{a1} 2.76; pK_{a2} 3.5.

Solubility—1 g in 1.2 mL water or 25 mL alcohol; practically insoluble in chloroform or ether.

Comments—An *extended-spectrum (antipseudomonal) penicillin*. It is given IV with high sodium. An oral prodrug (indanyl sodium) is available.

CLOXACILLIN SODIUM

[2*S*-(2α,5α,6β)]-4-Thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid, 6-[[[3-(2-chlorophenyl)-5-methyl-4-isoxazolyl]carbonyl]amino]-3,3-dimethyl-7-oxo-, monosodium salt, monohydrate; Cloxacillin Sodium Monohydrate, Tegopen, Cloxapen



[7081-44-9] $C_{19}H_{17}ClN_3NaO_5S{\cdot}H_2O$ (475.88); *anhydrous* [642-78-4] (457.86). Potency: the equivalent of not less than 825 μg of cloxacillin/mg.

Preparation—6-Aminopenicillanic acid is acylated with 3-(*o*-chlorophenyl)-5-methyl-4-isoxazolecarboxylic acid and the resulting cloxacillin is purified by recrystallization and converted to the sodium salt.

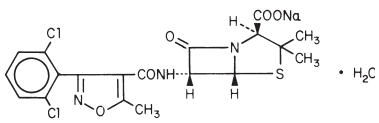
Description—White, odorless, crystalline powder having a bitter taste; stable in light and only slightly hygroscopic; decomposes about 173°; pH (1 in 100 solution) 7.5; pK_a (COOH) 2.7.

Solubility—Freely soluble in water; soluble in alcohol; slightly soluble in chloroform.

Comments—A *penicillinase-resistant penicillin (antistaphylococcal)* administered orally.

DICLOXACILLIN SODIUM

[2*S*-(2α,5α,6β)]-4-Thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid, 6-[[[3-(2,6-dichlorophenyl)-5-methyl-4-isoxazolyl]carbonyl]amino]-3,3-dimethyl-7-oxo-, monosodium salt, monohydrate; Dynapen, Pathocil, Dycill



[13412-64-1] $C_{19}H_{16}Cl_2N_3NaO_5S{\cdot}H_2O$ (510.32); *anhydrous* [343-55-5] (492.31). Potency: the equivalent of not less than 850 μg of dicloxacillin/mg.

Preparation—6-Aminopenicillanic acid is acylated with 3-(2,6-dichlorophenyl)-5-methyl-4-isoxazolecarboxylic acid and the resulting dicloxacillin (acid) is purified by recrystallization and converted to the sodium salt.

Description—White to off-white, crystalline powder; faint, characteristic odor; melts about 225° with decomposition; pK_a 2.67.

Solubility—Freely soluble in water; soluble in alcohol.

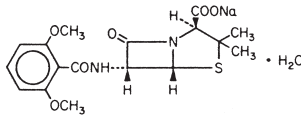
Comments—An oral *penicillinase-resistant penicillin* (see the general statement). As with all penicillinase-resistant penicillins, it is not as effective as penicillin G except against those organisms whose resistance depends on penicillinase production. Therefore, its use should be limited to the treatment of susceptible penicillinase-producing strains of *Staph aureus* or *epidermidis*.

The toxicity is the same as that of penicillins in general (see the general statement). Nausea and diarrhea sometimes occur, but they usually do not necessitate discontinuation of the drug. Rare hepatotoxicity has been observed. In persons with a low sodium tolerance, the sodium content must be taken into account.

By the oral route the amount absorbed is 37% to 50%. It is bound to plasma proteins to the extent of 90% to 97%, the highest among the penicillins. The volume of distribution is only 0.1 mL/g. Approximately 60% is excreted into the urine. Its half-life in plasma is 0.5 to 1.5 hr in normal patients but is 1 to 3 hr in renal insufficiency.

METHICILLIN SODIUM

4-Thia-l-azabicyclo[3.2.0]heptane-2-carboxylic acid, [2*S*-(2α,5α,6β)] 6-[(2,6-dimethoxybenzoyl)amino]-3,3-dimethyl-7-oxo-, monosodium salt, monohydrate



[7246-14-2]$C_{17}H_{19}N_2NaO_6S{\cdot}H_2O$ [132-92-3](anhydrous);[61-32-5](methicillin, acid) (420.41).

Preparation—Fermentation-produced 6-aminopenicillanic acid is condensed with 2,6-dimethoxybenzoyl chloride in a suitable organic solvent and the resulting methicillin is precipitated as the sodium salt by the addition of sodium acetate.

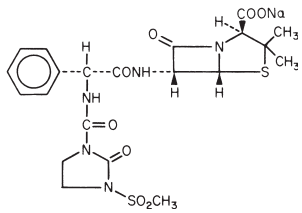
Description—Fine, white, crystalline powder; odorless, or a slight odor.

Solubility—Freely soluble in water; slightly soluble in chloroform; insoluble in other.

Comments—A *penicillinase-resistant penicillin (antistaphylococcal)*. It is given IV. Interstitial nephritis may occur.

MEZLOCILLIN SODIUM

[2*S*-[2α,5α,6β(*S)]]-4-Thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid, 3,3-dimethyl-6-[[[[[3-(methylsulfonyl)-2-oxo-1-imidazolidinyl] carbonyl]amino]phenylacetyl]amino]-7-oxo-, monosodium salt; Mezlin**



[51841-65-3] $C_{21}H_{24}NaN_5O_8S_2$ (561.56).

Preparation—Ger Pat 2,318,955.

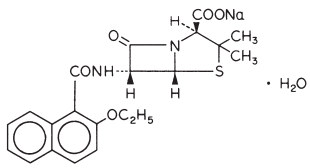
Description—Yellowish-white powder; pK_a 2.7.

Solubility—Very soluble in water; soluble in DMF or methanol; very slightly soluble in alcohol or acetone.

Comments—An *extended-spectrum (antipseudomonal) penicillin*. It is given IV and is similar to *Piperacillin*.

NAFCILLIN SODIUM

[2*S*-(2α,5α,6β)]-4-Thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid, 6-[[(2-ethoxy-1-naphthalenyl)carbonyl]amino]-3,3-dimethyl-7-oxo-, monosodium salt, monohydrate; Unipen, Nafcil, Nallpen



[7177-50-6] $C_{21}H_{21}N_2NaO_5S·H_2O$ (454.47); *anhydrous* [985-16-0] (436.46). Potency: equivalent to not less than 820 μg of nafcillin/mg.

Preparation—6-Aminopenicillanic acid is acylated by treatment with 2-ethoxy-1-naphthoyl chloride in an anhydrous organic solvent containing triethylamine. An aqueous extract of this product is admixed with a water-immiscible solvent and nafcillin is precipitated by the addition of sulfuric acid. Nafcillin sodium is precipitated by mixing ethanolic solutions of the acid and sodium ethylhexanoate. US Pat 3,157,639.

Description—White to yellowish white powder; not more than a slight characteristic odor.

Solubility—Freely soluble in water or chloroform; soluble in alcohol.

Comments—A *penicillinase-resistant penicillin*, the use of which is restricted to the treatment of infections caused by penicillinase-producing cocci (mostly staphylococci). After oral administration, serum levels are low and unpredictable, therefore the oral route is not recommended.

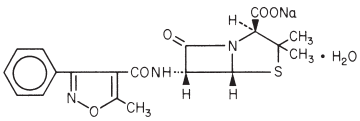
It is destroyed partly by gastric acid, and about 36% is absorbed from the gut, somewhat erratically. For serious infections, initial therapy should be by parenteral administration. About 90% is bound to protein in plasma. The volume of distribution is 0.26 to 0.44 mL/g. Only about 10% to 30% is eliminated unchanged in the urine. Nafcillin is excreted primarily by the liver with 60% of dose metabolized and 10% secreted unchanged in the bile. The half-life is 0.5 to 1 hr, except 1.2 to 1.5 hr in renal failure.

Untoward reactions are similar to those shown by other penicillins. It causes occasional nausea and diarrhea. It is irritating and may cause pain and an increase in serum transaminase activity after IM injection. Thrombophlebitis can occur with IV injection.

Cross-sensitivity between it and other penicillins may occur. It is preferred in adults because of the association of interstitial nephritis with methicillin. The sodium content must be considered when the drug is used in persons with a low sodium tolerance.

OXACILLIN SODIUM

[2*S*-(2α,5α,6β)]-4-Thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid, 3,3-dimethyl-6-[[(5-methyl-3-phenyl-4-isoxazolyl)carbonyl]-amino]-7-oxo-, monosodium salt, monohydrate; Bactocill, Prostaphlin



[7240-38-2] $C_{19}H_{18}N_3NaO_5S·H_2O$ (441.43); *anhydrous* [1173-88-2] (423.42). Potency: equivalent to 815 to 950 μg of oxacillin ($C_{19}H_{19}N_3O_5S$)/mg.

Preparation—Fermentation-produced 6-aminopenicillanic acid is condensed with 5-methyl-3-phenyl-4-isoxazolyl chloride in a suitable organic solvent and the resulting oxacillin is precipitated as the sodium salt by the addition of sodium acetate.

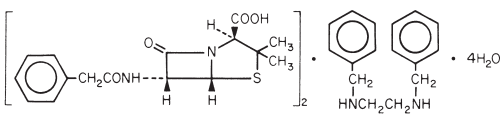
Description—Fine, white, crystalline powder; odorless or a slight odor.

Solubility—Freely soluble in water; slightly soluble in absolute alcohol, chloroform; insoluble in ether.

Comments—A *penicillinase-resistant penicillin* (*antistaphylococcal*) given orally.

PENICILLIN G BENZATHINE

[2*S*-(2α,5α,6β)]-4-Thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenylacetyl)amino]-, compd with *N,N′*-bis-(phenylmethyl)-1,2-ethanediamine (2:1), tetrahydrate; Bicillin, Permapen



[41372-02-5] $C_{16}H_{20}N_2·2C_{16}H_{18}N_2O_4S·4H_2O$ (981.19); *anhydrous* [1538-09-6] (909.13). Potency: 1090 to 1272 Penicillin Units/mg. One mg of Penicillin G Benzathine represents 1211 Penicillin G Units.

Preparation—Precipitates on mixing aqueous solutions containing *N,N*-dibenzylethylenediamine diacetate and sodium penicillin G in the required molar proportion.

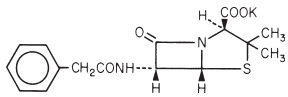
Description—White, odorless, crystalline powder; pH (saturated solution) 5 to 7.5.

Solubility—1 g in approximately 5000 mL water and approximately 65 mL alcohol.

Comments—Low water-solubility; hence, on IM injection, it is released slowly and yields prolonged blood levels of penicillin, generally for 1 to 4 wk. Its antibacterial activity is that of the penicillin G moiety (see the general statement), except that its long duration of action makes it especially suitable for *prophylaxis of rheumatic fever*. However, by the IM route the blood levels are quite low and are not suitable for most of the uses of the drug. For example, 1.2 million units will yield an average plasma level of only 0.15 unit/mL on the 1st day, and by the 14th day it will have fallen to 0.03 unit/mL. CSF concentrations are negligible. With concurrent probenecid the levels will be somewhat higher. Consequently, it is indicated only for the *prophylaxis* and *treatment* of *infections* caused by highly susceptible *group A streptococcus, syphilis* and *yaws*.

PENICILLIN G POTASSIUM

[2*S*-(2α,5α,6β)]-4-Thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenylacetyl)amino]-, monopotassium salt; Benzylpenicillin Potassium



[113-98-4] $C_{16}H_{17}KN_2O_4S$ (372.48). Penicillin G Potassium has a potency of not less than 1440 and not more than 1680 Penicillin G Units/mg.

Preparation—From 6-aminopenicillanic acid and phenylacetyl chloride in an inert organic solvent; the sodium salt is precipitated with sodium acetate.

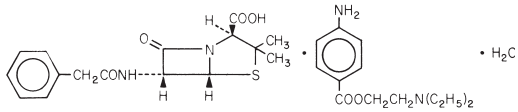
Description—Colorless or white crystals, or a white, crystalline powder; odorless or practically so; moderately hygroscopic; decomposed by prolonged exposure to temperatures of approximately 100°, moisture accelerating decomposition; not appreciably affected by air or light; solutions deteriorate at room temperature, but solutions stored lower than 15° remain stable for several days; rapidly inactivated by acids and alkalies, and also by oxidizing agents; pH (aqueous solution, 30 mg/mL) 5 and 7.5; pK_a (acid) 2.8.

Solubility—Very soluble in water, normal saline, or dextrose solutions; soluble in alcohol (but is inactivated by this solvent), glycerin or many other alcohols.

Comments—See the uses of penicillins in the general statement. The potassium salt has no advantage over the sodium salt except when high doses are used in patients on sodium restriction. The potassium salt also avoids the hypokalemic alkalosis that sometimes occurs during treatment with high doses of penicillins. The possibility of potassium intoxication from massive doses in oliguric patients should be kept in mind. The bioavailability by the oral route is 15% to 33%. In plasma 50% to 65% is protein-bound. The volume of distribution is 0.47 mL/g. Renal elimination is 60% to 90% of the total, the remainder being mostly biliary. The half-life is 0.5 to 0.7 hr, except 2.5 to 10 hr in renal failure or after probenecid.

PENICILLIN G PROCAINE

[2*S*-(2α,5α,6β)]-4-Thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenylacetyl)amino]-, compd with 2-(diethylamino)ethyl 4-aminobenzoate (1:1), monohydrate



[6130-64-9] $C_{16}H_{18}N_2O_4S·C_{13}H_{20}N_2O_2·H_2O$ (588.72); *anhydrous* [54-35-3] (570.70). Potency: 900 to 1050 Penicillin Units/mg. One mg represents 1009 Penicillin G units.

Preparation—An aqueous solution of sodium (or potassium) penicillin G undergoes metathesis with an equimolar quantity of procaine hydrochloride.

Description—White, fine crystals or a white, very fine, microcrystalline powder; odorless or practically so; not appreciably affected by air or light; pH (saturated solution) 7.5; rapidly inactivated by acids and by alkali hydroxides, also by oxidizing agents.

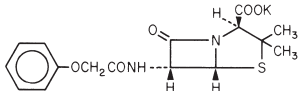
Solubility—1 g in 250 mL water, approximately 30 mL alcohol, or approximately 60 mL chloroform.

Comments—Upon IM injection it slowly releases the penicillin G and provides prolonged duration of effective blood levels. An IM dose of 300,000 units yields a peak plasma concentration of 1.5 units/mL at 1 to

3 hr, and the level is about 0.2 unit/mL at 24 hr and 0.05 unit/mL at 48 hr. Because of the relatively low peak blood levels, the drug is indicated only for *mild* to *moderately severe infections* by very susceptible organisms. For its uses and toxicity see the general statement. Allergies can occur due to the procaine component but other toxic effects of procaine are very rare. IV injection should never be used.

PENICILLIN V POTASSIUM

[2*S*-(2α,5α,6β)]-4-Thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid, 3,3-dimethyl-7-oxo-6-[(phenoxyacetyl)amino]-, monopotassium salt; Penicillin Potassium Phenoxymethyl



[132-98-9] $C_{16}H_{17}KN_2O_5S$ (388.48). Penicillin V Potassium has a potency of not less than 1380 and not more than 1610 Penicillin V units/mg.

Preparation—As for *Penicillin G*, using phenoxyacetyl chloride.

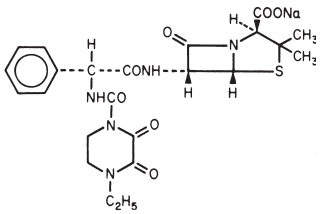
Description—White, odorless, crystalline powder; pH (aqueous solution, 30 mg/mL) 7.5; pK_a 2.73.

Solubility—Very soluble in water; 1 g in approximately 150 mL alcohol.

Comments—The antibacterial spectrum is essentially that of penicillin G against gram-positive bacteria, but this is less potent and effective against gram-negative bacteria. Consequently, it shares the same uses (see the general statement), except that in severe acute infections parenteral penicillin G is mandatory. It is inactivated less by gastric juice than is penicillin G.Penicillin V is the *preferred oral penicillin* for *less serious infections* because serum levels are 2 to 5 times higher than comparable doses of penicillin G and there is less individual variability in absorption. Like penicillin G, it may cause allergic reactions, and it frequently shows cross-sensitivity to the other penicillins. Its other toxicities are also those of penicillin G. The oral bioavailability is about 60% at best. It is 75% to 80% bound to plasma proteins. The volume of distribution is 0.73 mL/g, which is considerably larger than that of penicillin G. Only 20% to 40% is excreted unchanged in the urine. The half-life is about 0.5 to 1 hr.

PIPERACILLIN SODIUM

[2*S*-[2α,5α,6β(*S)]]-4-Thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid, 6-[[[[(4-ethyl-2,3-dioxo-1-piperazinyl)carbonyl]amino]-phenylacetyl]amino]-3,3-dimethyl-7-oxo-, monosodium salt; Pipracil**



[59703-84-3] $C_{23}H_{26}N_5NaO_7S$ (539.54). Potency: the equivalent of not less than 863 μg piperacillin/mg.

Preparation—US Pat 4,087,424.

Description—White crystals.

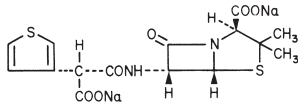
Solubility—1 g in approximately 1.5 mL water or methanol; 5 mL of ethyl alcohol.

Comments—An *extended-spectrum penicillin* with antibacterial activities characteristic of its class (see the general statement). It is the most active penicillin against *Ps aeruginosa*, with a potency nearly that of gentamicin. It is one of five drugs of choice for use against infections caused by *Ps aeruginosa*. It is more potent against *Klebsiella* and several other enteric bacilli than is carbenicillin or ticarcillin. It is an alternative drug for use against infections by *Acinetobacter, Bacteroides fragilis* (GI strains), *Enterobacter, E coli, Kl pneumoniae, Morganella morganii, Pr mirabilis* or *vulgaris, Providencia rettgeri* or *stuartii, Ps aeruginosa* (UTIs) or *Serratia*. It has a low efficacy against penicillinase- and other β-lactamase-producing bacteria. Resistance can develop rapidly to piperacillin during use, so that it should be administered only in combination with an aminoglycoside or penicillinase inhibitor (tazobactam) when used against *Ps aeruginosa* and other hard-to-suppress bacilli.

The oral bioavailability is too low and erratic to be of use. In plasma, 16% to 22% is protein-bound. The volume of distribution is about 0.18 to 0.30 mL/g. Renal excretion accounts for 60% to 80% of elimination. The half-life is 0.5 hr, except 0.6 to 1.2 hr in renal failure.

TICARCILLIN DISODIUM

[2*S*-[2α,5α,6β(*S)]]-4-Thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid, 6-[(carboxy-3-thienylacetyl)amino]-3,3-dimethyl-7-oxo-, disodium salt; Ticar**



[4697-14-7] $C_{15}H_{14}N_2Na_2O_6S_2$ (428.38). Potency: equivalent to not less than 800 μg of ticarcillin ($C_{15}H_{16}N_2O_6S_2$)/mg, calculated on the anhydrous basis.

Preparation—Belgian Pat 646,991. 2-(3-Thienyl)malonic acid, monobenzyl ester is converted to the acid chloride which is condensed with 6-aminopenicillanic acid, followed by hydrogenation to convert the ester to the free acid.

Description—White to pale-yellow powder; hygroscopic; unstable in acid medium; pK_a (acid form) 2.44, 3.64; acid solutions are unstable.

Solubility—1 g in 10 mL water or 66 mL ethanol; pH of a concentrated solution (>100 g/100 mL) approximately 7.0.

Comments—An *extended-spectrum penicillin* almost identical to *Carbenicillin* in its antibacterial spectrum and potency, except that it is twice as active against *Ps aeruginosa*. Resistance develops rapidly. With many infections, resistance is obviated by adding clavulanate. Also, for gram-negative infections, it is often combined with gentamicin or tobramycin to enhance activity and delay resistance.

The adverse effects are those of penicillins in general (see the general statement), and cross-sensitivity to penicillin occurs. Sodium overload and hypokalemia can occur, especially with high doses. In renal failure, high doses may inhibit platelet aggregation, and hemorrhagic phenomena may result.

It is not absorbed orally. In plasma, 55% to 65% is protein-bound. The volume of distribution is 0.22 mL/g. It is 86% eliminated by renal excretion. The half-life is 0.5 to 1 hr, except 15 hr in renal failure.

Beta-Lactamase Combinations

CLAVULINATE-AMOXICILLIN—A combination given orally. It has a broader spectrum of activity than amoxicillin (including anaerobic organisms) but causes more diarrhea than amoxicillin.

CLAVULANATE-TICARCILLIN—A combination given IV. It is active versus more gram-negative bacilli and anaerobes.

SULBACTAM-AMPICILLIN—A combination given IV. It is active versus *Staphylococcus* and beta-lactamase producing *H influenzae* and *Strep pneumoniae* and anaerobes.

TAZOBACTAM-PIPERACILLIN—A combination given IV. It is active versus more gram-negative bacilli and anaerobes.

CEPHALOSPORINS

The cephalosporins are a group of antibiotics closely related to the penicillins. The cephalosporanic acid moiety characteristic of cephalosporins is an analog of the penicillanic acid moiety characteristic of penicillins; cephalosporanic acid contains a dihydrometathiazine ring, while penicillanic acid contains a tetrahydrothiazole (thiazolidine) ring. Both have a beta-lactam ring. The 7-aminocephalosporanic acid derivatives are much more acid-stable than the corresponding 6-aminopenicillanic acid compounds. Cephamycins are cephalosporins that possess a 7-methoxy group that enhances beta-lactamase resistance. Cephamycins may induce beta-lactamase production.

The cephalosporins have a mechanism of action very similar to that of the penicillins, namely, they bind to one or more penicillin-binding proteins (PBPs) that are transpeptidases and inhibit the cross-linking of the peptidoglycan units in the bacterial cell wall. The intrinsic activity of a cephalosporin depends in part on resistance to beta-lactamases, affinity to PBPs and their ability to reach these targets that are extracellular for gram-positive bacteria and periplasmic for gram-negative bacteria. See Table 90-4.

Currently, the cephalosporins are classified into four generations based on their gram-negative spectrum and stability in

Table 90-4. Cephalosporins

CLASS	COMMENTS
First generation (Staph, some enteric gram-neg. bacilli)	
Cefadroxil	Oral, intermediate acting
Cefazolin	IM, IV, intermed. duration, less painful
Cephalexin	Oral, short acting
Cephalothin	IM, IV, short acting, weakest spectrum
Cephapirin	IM, IV, short acting
Cephradine	IM, IV, oral, short acting
Second generation (more active vs gram-neg, some active vs *H influenzae* & anaerobes)	
Cefaclor	Oral, short acting, active vs *H influenzae*
Cefamandole	IM, IV, short acting
Cefmetazole	IV, short acting, good vs. anaerobes
Cefonicid	IM, IV, intermed-long acting
Ceforanid	IM, IV, intermed acting
Cefotetan	IM, IV, intermed-long acting, good vs anaerobes
Cefoxitin	IM, IV, short acting, good vs anaerobes
Cefprozil	Oral, short acting
Cefuroxime	IM, IV, oral, beta-lactamase resist., active vs *H influenzae,* good csf levels
Loracarbef	Oral, short acting, active vs *H influenzae*
Third generation (best gram-neg. spectrum, beta-lactamase resistant, poor vs staph.)	
Cefixime	Oral, intermed-long acting
Cefpodoxime	Oral, intermed acting, similar to cefixime
Cefoperazone	IM, IV, intermed acting, good vs *Pseud*
Cefotaxime	IM, IV, shortest acting, metab, good csf
Ceftazidime	IM, IV, short acting, good vs *Pseud*
Ceftizoxime	IM, IV, short acting, good csf levels
Ceftriaxone	IM, IV, long acting, good vs gonococci
Ceftibuten	Oral, similar to cefixime
Cefdinir	Oral, similar to cefixime
Fourth Generation	
Cefepime	IV, better vs staph and strep than 3rd gen

the presence of beta-lactamases. However, this classification scheme is becoming less reliable because newer agents have led to more exceptions and less precise criteria for differences in antibacterial spectrum.

The *first-generation cephalosporins* (cefazolin, cephalothin, cephapirin, cephradine, cephalexin, and cefadroxil) have the highest activity against gram-positive and the lowest against gram-negative bacteria. In summary, they are effective against the following antibacterial spectrum: good activity against most staphylococci (even penicillinase-producers, but not methicillin-resistant staphylococci) plus most common streptococci (*Strep pyogenes, viridans* and *pneumoniae*), but not enterococci; moderately active against certain gram-negative bacteria, such as *N gonorrhoeae* and *meningitidis*, many *E coli*, some *H influenzae*, and non-hospital-acquired *Klebsiella* and *Pr mirabilis* and some *Salmonella* and *Shigella*.

The *second-generation cephalosporins* (cefuroxime, cefamandole, cefmetazole, cefonicid, cefoxitin, cefotetan, cefaclor, cefprozil, and loracarbef) are more active against gram-negative and less active against gram-positive bacteria than are first-generation members. Notable differences include the increased activity against most *H influenzae* and the efficacy of some cephalosporins (cefoxitin, cefotetan, cefmetazole) against some more resistant hospital-acquired infections due to anaerobic bacteria (*Bacteroides fragilis*) and indole-positive *Proteus*. Like the first-generation, members of this group are inactive against *Ps aeruginosa*.

The *third-generation cephalosporins* (cefotaxime, ceftizoxime, ceftriaxone, cefpodoxime, ceftibuten, moxalactam, ceftazidime, cefoperazone, and cefixime) are considerably less active than first-generation drugs against gram-positive bacteria (especially staphylococci) but have a much expanded spectrum of activity against gram-negative organisms and have more resistance to gram-negative beta-lactamases. They are quite active against gram-negative anaerobes and are frequently active against *Enterobacteriaceae* (*E coli, Enterobacter, K pneumoniae*). Of special interest is the activity some members of this group (ceftazidime and cefoperazone) that have high activity against *Pseudomonas* but possess a weaker overall gram-negative spectrum.

The current *fourth-generation cephalosporin* classification (cefepime) is based on an improved gram-positive spectrum while retaining the expanded gram-negative activity of third-generation cephalosporins.

RESISTANCE—As with the penicillins, one common mechanism of resistance is that of elaboration of a beta-lactamase. Although some cephalosporins are inactivated by penicillinase-types of beta-lactamase, many beta-lactamases are selective for cephalosporins and are called cephalosporinase types. Other resistance mechanisms include failure to bind to PBPs as occurs with methicillin-resistant strains of staphylococci.

INDICATIONS—The cephalosporins are effective in a wide variety of infections because they have a broad spectrum and high therapeutic/toxic ratio. The first- and second-generation cephalosporins are used frequently for prophylaxis during certain surgical procedures to reduce the risk of postoperative wound infections. Cefazolin is preferred over other first-generation analogs because it has a higher serum concentration and longer elimination half-life; also it is less painful upon IM administration. Cefoxitin, cefotetan, and cefmetazole are cephamycins that are preferred for intra-abdominal surgery because of their beta-lactamase resistance and activity against *Bacteroides fragilis*. A number of second- and third-generation cephalosporins are effective alternatives as prophylactic agents for various surgical procedures.

Cephalosporins are generally not the first drug of choice for any bacterial infections because of the availability of equally effective and less expensive alternatives. First-generation cephalosporins are preferred alternatives to antistaphylococcal penicillins or penicillin G for serious staphylococcal and/or streptococcal infection except enterococcal infections or meningitis. The non-cephamycin second-generation cephalosporins such as cefuroxime have similar antimicrobial spectra and may be used as alternatives to treat most serious infections caused by staphylococci and aerobic gram-negative bacilli. Only the third-generation cephalosporins are approved for treatment of meningitis caused by enteric gram-negative bacilli. Cefuroxime may be used to treat meningitis caused by *H influenzae*, although a third-generation cephalosporin is still the preferred choice.

Cefotaxime, ceftizoxime, and ceftriaxone are third-generationcephalosporins that are effective against serious hospital-acquired infections caused by enteric gram-negative bacilli, such as *Enterobacter*, indole-positive *Proteus, Providencia stuartii,* and *Serratia*. Against *H influenzae*, cefotaxime and ceftriaxone are preferred for parenteral therapy, although cefuroxime is an alternative.

Ceftriaxone is the drug of choice for treatment of gonorrhea, and any cephalosporin may be preferred over an extended-spectrum penicillin against *Kl pneumoniae*. The cephalosporins are also alternatives to penicillins to treat infections caused by *Branhamella catarrhalis* and less serious infections of streptococci, staphylococci, *H influenzae*, *N meningitides,* and *E coli*.

Several oral cephalosporins have increased activity against *H influenzae* including cefaclor, cefuroxime axetil, cefixime, cefprozil, and cefpodoxime proxetil. Ceftazidime and cefoperazone are preferred in the treatment of infections caused by *Ps aeruginosa*, *cepacia,* or *maltophilia*. Third-generation cephalosporins such as cefotaxime and ceftizoxime are expensive alternatives against indole-positive *Proteus*, *Providencia,* and nontyphoid *Salmonella*.

ADVERSE EFFECTS—Hypersensitivity occurs in about 5% to 10% of recipients of cephalosporins; manifestations are eosinophilia, drug fever, maculopapular rash, urticaria, serum sickness, angioneurotic edema, anaphylaxis, positive Coombs

test associated with rare hemolytic anemia and infrequent transient hepatic abnormalities (increased SGOT, SGPT and total bilirubin), thrombocytopenia, neutropenia, and interstitial nephritis. There is an appreciable incidence of cross-sensitization with penicillin; when previously manifested, penicillin sensitivity has not been serious. A cephalosporin, especially cefazolin, may be administered cautiously after sensitivity testing, but only if necessary; skin tests often give false negatives. If the previous reaction to penicillin was severe, such as with anaphylaxis or angioneurotic edema, or if the patient reacts to penicillin minor determinants, a cephalosporin usually is discouraged.

Other adverse effects of cephalosporins include pain, induration, sterile abscess, and sloughing at the site of IM injection, thrombophlebitis after IV administration, nausea, vomiting, glossitis, diarrhea, loose stools, abdominal pain and heartburn, especially with oral administration, sodium load, and water retention with sodium salts, antibiotic-associated colitis (especially with poorly absorbed members) and a false-positive urine test for glucose (Benedict, Fehling, and Clinitest, but not Tes-Tape). Present cephalosporins are not significantly nephrotoxic alone but may increase considerably the nephrotoxicity of an aminoglycoside.

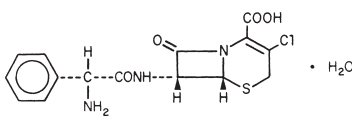
Cephalosporins should not be used in combination with other antibiotics that cause nephrotoxicity or ototoxicity. High-ceiling diuretics (eg, furosemide and ethacrynic acid) also enhance nephrotoxicity and make certain cephalosporins ototoxic. The acquisition costs of some cephalosporins is very high. Suprainfections by gram-negative bacteria and *Candida* may occur. There may be occasional hypoprothrombinemia and disulfiram-like reaction with alcohol; those drugs with *N*-methylthiotetrazole side chains seem to be the serious offenders that include cefamandole, cefoperazone, cefotetan, and cefmetazole.

PHARMACOKINETICS—Cephalosporins vary considerably in their peroral bioavailability (15–86%), protein binding (14–96%) and half-lives (0.5–6.5 hr). Elimination is mainly by glomerular filtration and tubular secretion (except for cefoperazone) and some biliary secretion (and reabsorption), except that most of cephaloglycin and some of cefotaxime, cephalothin, cephapirin, and cephacetrile are deacetylated and subsequently further transformed; consequently, renal failure may greatly increase the half-lives of most cephalosporins. Cephalosporins vary in their penetrance into tissues. Only cefuroxime and third-generation cephalosporins achieve therapeutic concentrations in CSF, and then only in inflammation of the meninges. The first- and second-generation cephalosporins should not be used for meningitis.

Cephalosporins cross the placental barrier and reach plasma concentration in the fetus in about 10% of maternal concentrations; effects on the fetus are unknown, but it is advisable to avoid treatment of pregnant women with cephalosporins if possible. A summary of the cephalosporins is included in Table 90-5.

CEFACLOR

5-Thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, [6*R*-[6α,7β(*R)]]-7-[(aminophenylacetyl)amino]-3-chloro-8-oxo-, monohydrate; Ceclor**



[70356-03-05] $C_{15}H_{14}ClN_3O_4S \cdot H_2O$ (385.82)]. Cefaclor is a semisynthetic cephalosporin related to cephalexin.

Preparation—See *J Med Chem* 1975; 18:403.

Description—White crystalline solid; aqueous solutions are most stable at pH of approximately 3.5, which is the pH of a 2% solution.

Solubility—Soluble in water (1 in 100); practically insoluble in most organic solvents.

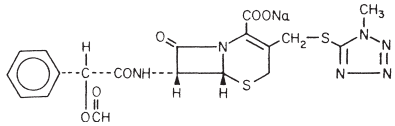
Comments—A *second-generation cephalosporin* with typical antibacterial activities and adverse effects (see the general statement). It was the first orally efficacious member of its group. It is approved for use in the treatment of *upper respiratory tract infections, pharyngitis,* and *tonsillitis* caused by *Strep pyogenes*; lower respiratory tract infections caused by *Strep pneumoniae, pyogenes,* and *H influenzae*; otitis media caused by *Strep pneumoniae or pyogenes*, staphylococci and *H influenzae*; cutaneous infections caused by *Staph aureus* and *Strep pyrogens*; and UTIs caused by *E coli, Pr mirabilis, Klebsiella* spp, and coagulase-negative staphylococci. In plasma, 25% is bound to protein. The volume of distribution is 0.24 to 0.36 mL/g. About 60% to 85% is excreted unchanged into the urine. The half-life is 0.6 to 0.9 hr, except longer in renal failure.

Table 90-5. Carbapenems

DRUG	COMMENTS
Imipenem	IV, metabolized by renal enzymes
Carbapenem	IV, not metabolized by renal enzymes

CEFAMANDOLE NAFATE

5-Thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, [6*R*-[6α,7β(*R)]]-7-[[(formyloxy)phenylacetyl]amino]-3-[[(1-methyl-1H-tetrazol-5-yl)-thio]methyl]-8-oxo-, monosodium salt, Mandol**



[42540-40-9] [34444-01-4(acid)] $C_{19}H_{17}N_6NaO_6S_2$ (512.49).

Preparation—US Pat 3,641,021.

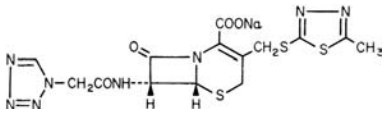
Description—White crystals; melts about 190° with decomposition; pK_a 2.8.

Solubility—Soluble in water or methanol; insoluble in nonpolar solvents.

Comments—A *second-generation cephalosporin* given IM and IV. It is short-acting.

CEFAZOLIN SODIUM

5-Thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 3-[[(5-methyl-(6*R-trans*)-1,3,4-thiadiazol-2-yl)thio]methyl]-8-oxo-7-[[(1H-tetrazol-1-yl)acetyl]-amino]-, monosodium salt; Ancef, Kefzol



[27164-46-1] $C_{14}H_{13}N_8NaO_4S_3$ (476.48). Potency: not less than 850 μg and not more than 1050 μg of cefazolin ($C_{14}H_{14}N_8O_4S_3$)/mg, calculated on the anhydrous basis.

Preparation—The sodium salt of 7-aminocephalosporanic acid is acylated with 1*H*-tetrazole-1-acetyl chloride and the acetoxy group is then displaced by reaction with 5-methyl-1,3,4-thiadiazole-2-thiol; the resulting cefazolin is converted to the sodium salt.

Description—White to off-white, crystalline powder.

Solubility—Freely soluble in water, saline TS or dextrose solutions; very slightly soluble in alcohol; practically insoluble in chloroform or ether.

Comments—A *first-generation cephalosporins* given IV or IM. Some gram-negative organisms and penicillinase-producing staphylococci resistant to both penicillin G and ampicillin are sensitive to cefazolin. Gram-negative activity essentially limited to *E coli, Klebsiella* and *Pr mirabilis*.

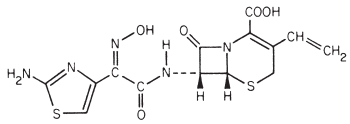
The drug can be used to treat infections of the respiratory tract, skin, soft tissues, bones, joints, and urinary tract and endocarditis and septicemia caused by susceptible organisms. Among UTIs, cystitis responds much better than pyelonephritis. It is the preferred cephalosporin for most surgical prophylaxis, because of its (relatively) long half-life.

The adverse effects are those of cephalosporins in general (see the general statement). It causes some pain at the site of injection and occasional phlebitis. Oral, genital, and vaginal candidiasis and anal pruritus occur. It causes a transient increase in blood urea nitrogen yet seems to have negligible nephrotoxicity.

It is not absorbed orally. It is bound to the extent of 70% to 85% by plasma proteins and has a low volume of distribution of only 0.10 to 0.14 mL/g. From 95% is excreted into urine. The half-life is 1.5 to 2 hr in normal persons but 3 to 42 hr in renal failure.

CEFDINIR

5-Thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, [6*R*-[6α,7β(*Z*)]]-7-[[2-amino-4-thiazolyl) (hydroxyimino)acetyl]amino]-3-ethenyl-8-oxo-, Omnicef



[91832-40-5] $C_{14}H_{13}N_5O_5S_2$ (395.42).

Preparation—US Pat 4,559,334(1985).

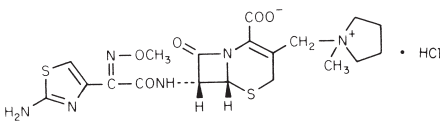
Description—White to slightly brownish yellow powder melting about 170° (dec); pK_a 9.7.

Solubility—Slightly soluble in dilute HCl; sparingly soluble in 0.1*M* phosphate buffer.

Comments—A third generation cephalosporin given orally. It has a similar action as *Cefixime*.

CEFEPIME HYDROCHLORIDE

Pyrrolidinium, [6*R*-[6α,7*β*(*Z*)]]-1-[[7-(2-amino-4-thiazolyl) (methoxyimino)acetyl]amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-3-yl]methyl]-1-methyl-, hydroxide, inner salt hydrochloride; Maxipime



[88040-23-7] $C_{19}H_{24}N_6O_5S_2{\cdot}HCl$ (527.08).

Preparation—US Pat 4,406,899 (1983).

Description—Colorless solid melting about 150° (dec) (base). White to pale yellow powder (HCl); the commercial product is the hydrochloride dihydrate.

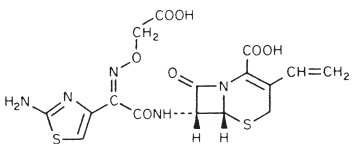
Solubility—Very soluble in water (hydrochloride).

Comments—A *fourth-generation cephalosporin* that retains an extended gram-negative spectrum against gram-negative aerobic bacilli covered by cefotaxime and ceftazidime including some strains resistant to these third-generation cephalosporins. It has improved activity against *Strep pneumoniae* and *Staph aureus* compared to the third-generation cephalosporins. Its activity against *P aeruginosa* is clinically relevant and it has become one of the agents of choice (often in combination with another anti- Pseudomonal drug) to treat this diffuclt pathogen.

The drug may be given IV or IM for treatment of UTIs, pneumonias, and skin infections. It is eliminated like most cephalosporins by renal excretion and has a half-life of 2 hr. Its adverse effects resemble the other cephalosporins.

CEFIXIME

5-Thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, [6*R*-[6α,7β(*Z*)]]-7-[[(2-amino-4-thiazolyl)[(carboxymethoxy)imino]acetyl]amino]-3-ethenyl-8-oxo-, Suprax



[79350-37-1] $C_{16}H_{15}N_5O_7S_2$ (453.44).

Preparation—US Pat 4,098,888.

Description—Off-white crystals; melts over 250°; distinguished from the *E*-trihydrate which melts about 220° with decomposition; pK_a (acid) 2.5.

Solubility—1 g in 125 mL water or 2000 mL alcohol.

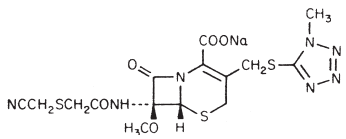
Comments—An oral *third-generation cephalosporin* with excellent activity against most *E coli* and *Klebsiella, H influenzae, Branhamella catarrhalis, N gonorrhoeae* and *meningitidis*, including β-lactamase-producing strains. It is active against common streptococci but staphylococci are resistant. It is used for respiratory infections, otitis media, and uncomplicated UTIs, but its therapeutic role remains to be defined.

It is absorbed slowly and incompletely from the GI tract and has a bioavailability of 40% to 50%. The oral suspension produces peak concentrations that are 25% to 50% higher than equivalent doses of tablet formulations. Food does not affect the amount of cefixime absorbed but delays absorption. Approximately 65% to 70% is bound to plasma protein. Renal excretion is the main route of elimination although biliary excretion is greater than 10%. The serum half-life is 3 to 4 hr but is prolonged with renal impairment.

The most common adverse reactions are gastrointestinal, primarily diarrhea. Other GI side effects may occur such as nausea, dyspepsia, and flatulence. Dizziness, headache, genital pruritus, and hypersensitivity reactions may occur.

CEFMETAZOLE SODIUM

5-Thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, (6*R-cis*)-7-[[[(cyanomethyl)thio]acetyl]amino]-7-methoxy-3-[[(1-methyl-1*H*-tetrazol-5-yl)thio]methyl]-8-oxo-, monosodium salt, Zefazone



[56796-39-5], [5796-20-4 (acid)] $C_{15}H_{16}N_7NaO_5S_3$ (493.51).

Preparation—*J Antibiot* 1976; 29:554.

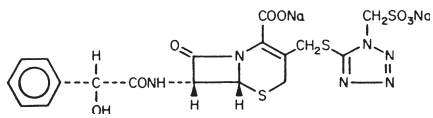
Description—White solid.

Solubility—Very soluble in water or methanol; soluble in acetone.

Comments—A *second-generation cephalosporin* given IV. It is short-acting and has good activity versus anaerobes.

CEFONICID SODIUM

5-Thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, [6*R*-[6α,7β(*R)]-7-[(hydroxyphenylacetyl)amino]-8-oxo-3-[[[1-(sulfomethyl)-1*H*-tetrazol-5-yl]thio]methyl]-, disodium salt, Monocid**



[61270-78-8] $C_{18}H_{16}N_6Na_2O_8S_3$ (586.52).

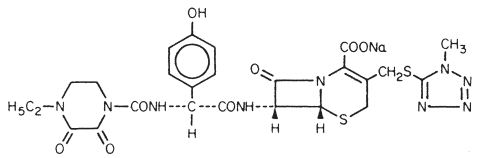
Preparation—Ger Pat 2,611,270; *CA* 1977; 86:2985t.

Description—pH (5% solution) 3.5 to 6.5.

Comments—A *second-generation cephalosporin* given IM and IV. It is intermediate-acting.

CEFOPERAZONE SODIUM

5-Thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, [6*R*-[6α,7β(*R)]]-7-[[[[(4-ethyl-2,3-dioxo-1-piperazinyl)carbonyl]amino]-(4-hydroxyphenyl)acetyl]amino]-3-[[(1-methyl-1*H*-tetrazol-5-yl)-thio]methyl]-8-oxo, monosodium salt, Cefobid**



[62893-20-3] $C_{25}H_{26}N_9NaO_8S_2$ (667.65).

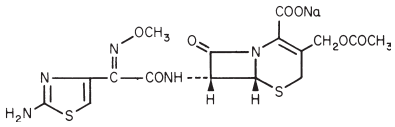
Preparation—See Belg Pat 837,682; *CA* 1977; 87:6002v.

Description—White powder; melts about 170°; pH (25% aqueous solution), 4.5 to 6.5; unstable in alkaline solution.

Comments—A *third-generation cephalosporin* given IM and IV. It is intermediate-acting and has good activity versus *Pseudomonas*.

CEFOTAXIME SODIUM

5-Thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, [6*R*-[6α,7β(*Z*)]]-3-[(acetyloxy)methyl]-7-[[(2-amino-4-thiazolyl)-(methoxyimino)acetyl]amino]-8-oxo-, monosodium salt, Claforan



[64485-93-4] $C_{16}H_{16}N_5NaO_7S_2$ (477.44).

Preparation—*Chem Pharm Bull* 1980; 28:2629.

Description—White to off-white solid; pH (10% solution) approximately 5.5; pK_a (acid) 3.75.

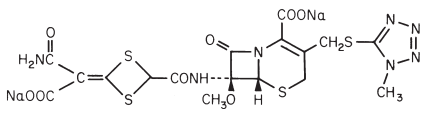
Solubility—Freely soluble in water; practically insoluble in most organic solvents.

Comments—A *third-generation cephalosporin*, given IV or IM, with an antibacterial spectrum characteristic of its class (see the general statement). Against many gram-negative bacilli it is equal to the aminoglycosides, except against *Ps aeruginosa*, *Acinetobacter* and some *Enterobacter*. It is more active against multiple-drug-resistant gram-negative bacilli than are moxalactam ceftazidime and cefoperazone. It is highly resistant to β-lactamases. Against *S aureus*, it is less active than first-or second-generation cephalosporins. It is a preferred third-generation cephalosporin for gram-negative meningitis and other serious gram-negative bacillary infections outside the CNS. It is used for surgical prophylaxis. When appropriate, it may be combined with an aminoglycoside. It has no unique toxicity (see the general statement). It is very expensive.

The drug is absorbed poorly by the oral route. In plasma, 38% is protein-bound. The volume of distribution is 0.25 to 0.39 mL/g. It penetrates into the CSF. About 85% is eliminated in the urine and 8% in the feces. The half-life is 1 to 1.2 hr, except 3 to 12 hr in renal failure. It is 30% to 50% metabolized to an active β-lactamase-stable metabolite.

CEFOTETAN DISODIUM

5-Thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, [6*R*-6α,7α)]-7-[[[4-(2-amino-1-carboxy-2-oxoethylidene)-1,3-dithietan-2-yl]-carbonyl]amino]-7-methoxy-3-[[(1-methyl-1*H*-tetrazol-5-yl)-thio]methyl]-8-oxo-, disodium salt; Cefotan



[74356-00-6] $C_{17}H_{15}N_7Na_2O_8S_4$ (619.57).

Preparation—See *Chem Pharm Bull* 1980; 28:2629.

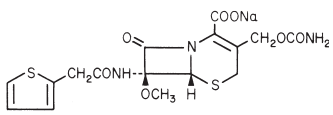
Description—White to pale yellow powder; pH (freshly reconstituted solution) approximately 5.5; pK_a 2.1, 3.3.

Solubility—Very soluble in water (the color varies from colorless to yellow depending on the concentration).

Comments—A *second-generation cephalosporin* given IM and IV. It is intermediate-acting and has good activity versus anaerobes.

CEFOXITIN SODIUM

(6*R-cis*)-5-Thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 3- [[(aminocarbonyl)oxy]methyl]-7-methoxy-8-oxo-7-[(2-thienylacetyl)amino]-, sodium salt; Mefoxin



[33564-30-6] $C_{16}H_{16}N_3NaO_7S_2$ (449.43).

Preparation—A semi-synthetic, broad spectrum cepha antibiotic derived from cephamycin C, which is produced by *S lactamdurans*. See *J Am Chem Soc* 1972; 94:1410.

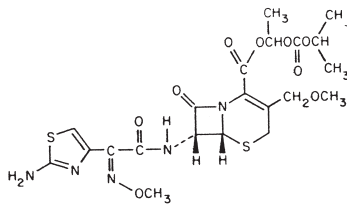
Description—Crystals melting about 150°; pK_a 2.2 (acid).

Solubility—Very soluble in water; soluble in methanol; sparing soluble in ethanol or acetone.

Comments—A *second-generation cephalosporin*. It is not the drug of choice for any infection, but it is an alternative drug for intra-abdominal infections, colorectal surgery, or appendectomy and ruptured viscus because it is active against most enteric anaerobes including *Bacteroides fragilis*. It is approved for use in the treatment of bone and joint infections caused by *S aureus*, gynecological and intra-abdominal infections by *Bacteroides* spp, and other common enteric anaerobes and gram-negative bacilli; lower respiratory tract infections by *Bacteroides* spp, *E coli*, *H influenzae*, *Klebsiella* spp, *S aureus,* or *Streptococcus* spp (except enterococci); septicemia by *Bacteroides* spp, *E coli, Klebsiella* spp, *S aureus,* or *Strep pneumoniae*; skin infections by *Bacteroides* spp, *E coli, Klebsiella* spp, *S aureus* or *epidermidis,* or *Streptococcus* spp (except enterococci) or UTIs by *E coli, Klebsiella* spp, or indole-positive *Proteus*, and for perioperative prophylaxis. It is absorbed poorly by the oral route. Elimination is essentially renal. The half-life is 40 to 60 min, except 13 to 22 hr in renal failure.

CEFPODOXIME PROXETIL

5-Thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, [6*R*-[6α,7β(*Z*)]]-7-[[(2-amino-4-thiazolyl)(methoxyimino)acetyl]amino]-3-(methoxy-methyl)-8-oxo-, 1-[[(1-methylethoxy)-carbonyl]oxy]ethyl ester, Vantin



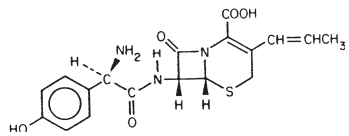
[87239-81-4], [80210-62-4 (acid)] $C_{21}H_{27}N_5O_9S_2$ (557.59).

Preparation—*J Antibiot* 1987; 40:370. The ester is the prodrug of the metabolite, cefpodoxime, with the free carboxyl group at position 4 of the thiazine ring.

Comments—A *third generation cephalosporin* given orally. It is intermediate-acting. It is similar to *Cefixime*.

CEFPROZIL

5-Thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, [6*R*-[6α,7β(*R)]]-, 7-[[amino(4-hydroxyphenyl)acetyl]amino]-8-oxo-3-(1-propenyl)-, Cefzil**

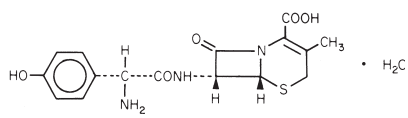


[92665-29-7] $C_{18}H_{19}N_3O_5S$ (389.43).

Comments—A *second-generation cephalosporin* given orally. It is short-acting.

CEFRADROXIL

[6*R*-[6α,7β(*R)]]-5-Thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 7-[[amino-(4-hydroxyphenyl)acetyl]amino]-3-methyl-8-oxo-, monohydrate; Duricef**



[66592-87-8] $C_{16}H_{17}N_3O_5S{\cdot}H_2O$ (381.42).

Preparation—US Pat 4,504,657 (1985); German Pat 2,163,514 (1973).

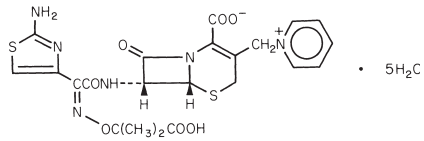
Description—White to yellow-white crystals melting about 197° (dec).

Solubility—Soluble in water; stable in acid solution.

Comments—A *first-generation cephalosporin* given orally. It is intermediate-acting and effective against *Staphylococcus* and some enteric gram-negative bacilli.

CEFTAZIDIME

Pyridinium, [6*R*-[6α,7β(*Z*)]]-1-[[7-[[(2-amino-4-thiazolyl)-[(1-carboxy- 1-methylethoxy)imino]acetyl]amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-3-yl]-methyl]-, hydroxide, inner salt pentahydrate; Fortaz,Tazicef,Tazidime



[78439-06-2] $C_{22}H_{22}N_6O_7S_2 \cdot 5H_2O$ (636.67).

Preparation—See Ger Pat 2,921,316; *CA 92*: 198413c, 1980.

Description—Ivory-colored powder; pK_a 1.8, 2.7, 4.1.

Comments—A *third-generation cephalosporin* given IV or IM. It is a broad-spectrum antibiotic. It is of special interest because of its high activity against *Pseudomonas* and *Enterobacteriaceae* but not enterococci. It is resistant to penicillinases. It is an alternative drug for the treatment of hospital-acquired gram-negative infections. It may be combined with amikacin in the treatment of infections in immunocompromised patients when *Ps aeruginosa* is a potential causative organism.

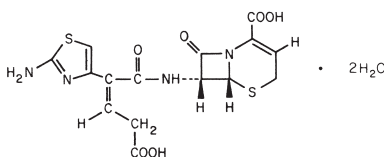
It is approved for use in the treatment of bone and joint infections, CNS infections, gynecological infections, lower respiratory tract infections, septicemia, skin and UTIs.

The adverse effects are those of the cephalosporins in general.

It is absorbed poorly by the oral route. It is 80% to 90% eliminated in the urine. The half-life in normal persons is about 2 hr but longer in renal failure.

CEFTIBUTEN

5-Thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, [6*R*-[6α,7β(*Z*)]]-7-[[2-(2-amino-4-thiazolyl)-4-carboxy-1-oxo-2-butenyl]amino]-8-oxo-, dihydrate; Cedax



[97519-39-6] $C_{15}H_{14}N_4O_6S_2 \cdot 2H_2O$ (410.43).

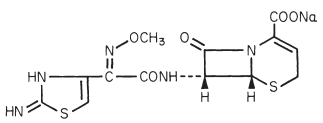
Preparation—US Pat 4,634,697 (1987).

Description—The commercial product is the dehydrate.

Comments—A *third generation cephalosporin* given orally with activity similar to *Cefixime*.

CEFTIZOXIME SODIUM

[6*R*-[6α,7β,(*Z*)]]-5-Thia-1-azabicyclo[4.2.0]-oct-2-ene-2-carboxylic acid, 7-[[(2,3-dihydro-2-imino-4-thiazolyl)(methoxyimino)acetyl]amino]-8-oxo-, monosodium salt; Cefizox



[68401-82-1] $C_{13}H_{12}N_5NaO_5S_2$ (405.38).

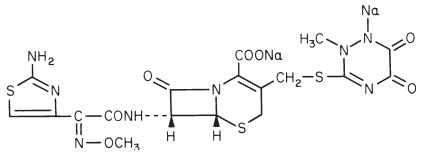
Preparation—See US Pat 4,166,155.

Comments—A *third-generation cephalosporin* given IV with antibacterial activity typical of this class (see the general statement). It is about as active as cefotaxime and more active than cefoperazone against gram-negative enteric bacilli but is less active than cefoperazone against *Ps aeruginosa*. It has unreliable activity against anaerobes. It is not active against enterococci. It is approved for the treatment of bone and joint infections, gonorrhea, intra-abdominal infections, lower respiratory tract infections, meningitis, septicemia, skin infections, or UTIs. In serious infections caused by gram-negative bacilli, it usually is combined with an aminoglycoside.

Its adverse effects are those of cephalosporins in general. The drug is not effective orally. IM and IV doses of 1 g yield respective concentrations of 36 and 80 to 90μg/ mL 30 min after administration. Only 30% is protein-bound in plasma. About 80% is eliminated in the urine. The half-life is about 1.7 hr but much longer in renal failure.

CEFTRIAXONE SODIUM

[6*R*-[6α,7β(*Z*)]]-5-Thia-1-azabicyclo[4.2.0]-oct-2-ene-2-carboxylic acid, 7-[[(2-amino-4-thiazolyl)(methoxyimino)acetyl]amino]-8-oxo-3-[[(1,2,5,6-tetrahydro-2-methyl-5,6-dioxo-1-2,4-triazin-3-yl)-thio]methyl]-, disodium salt; Rocephin



[74578-69-1] $C_{18}H_{16}N_8Na_2O_7S_3$ (598.53).

Preparation—See Brit Pat 2,022,090; *CA* 1980; 93:95289h.

Description—White to yellowish orange crystalline powder (hemiheptahydrate); melts over 155° with decomposition; $pK_a \approx 3$ (COOH); 3.2 (NH_3^+); 4.1 (enolic OH); solution color varies from light yellow to amber depending on concentration and length of storage; pH (1% solution) approximately 6.7).

Solubility—Readily soluble in water (approximately 40g/100 mL at 25°); sparingly soluble in methanol; very slightly soluble in alcohol.

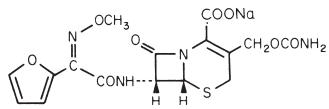
Comments—A *third-generation cephalosporin* that is the drug of choice for uncomplicated and disseminated gonococcal infections. It is an effective alternative for meningitis in infants caused by *H influenzae, N meningitides,* and *Strep pneumoniae*. It is effective against gram-negative bacillary meningitis and other serious gram-negative infections, including complications associated with Lyme disease. It is not used for enterococci. It is approved for the treatment of bone and joint infections, intra-abdominal infections; lower respiratory tract infections, pelvic infections, skin and urinary tract infections. It also is indicated for perioperative prophylaxis, for which it is as effective as cefazolin.

The side effects are those of the cephalosporins. Some patients show symptoms of cholecystitis.

It is not orally effective. Redistribution time is about 2 hr. In plasma, 83% to 96% is protein-bound. Elimination is 40% to 65% renal. The elimination half-life is 6 to 9 hr, except up to 34 hr in renal failure; the long half-life is an important advantage of the drug that permits a single daily administration.

CEFUROXIME SODIUM

5-Thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, (6*R*,7*R*)-7-[2-(2-furyl)glyoxylamido]-3-(hydroxymethyl)-8-oxo-, 7-(*Z*)-mono (*O*-methyloxime) carbamate (ester); Kefurox, Zinacef,



[56238-63-2] $C_{16}H_{15}N_4NaO_8S$ (446.37).

Preparation—See US Pat 3,974,153.

Description—Off-white to white powder; unbuffered aqueous solutions are stable for approximately 12 hr at room temperature; approximately 15% decomposition occurs after 24 hr. Suspensions for IM use and solutions for IV infusion are usually stable for 48 hr if stored between 2° and 10°. May become yellowish on standing; pK_a (acid) 2.5.

Solubility—1 g in 5 mL of water; slightly soluble in alcohol. A 10% aqueous solution has a pH of approximately 7.

Comments—A *second-generation cephalosporin* with antibacterial activity typical of that class (see the general statement). Its activity against *H influenzae* and ability to penetrate into the CSF make it particularly useful for treating meningitis caused by that organism; it also is approved to treat meningitis caused by *Strep pneumoniae, N meningitidis* and *Staph aureus*. It has excellent activity against all gonococci, hence is used to treat gonorrhea. It may be used to treat lower respiratory tract infections caused by *H influenzae and parainfluenzae, Klebsiella* spp, *E coli, Strep pneumoniae* and *pyogenes,* and *Staph aureus*. It is approved for use against UTIs caused by *E coli* and *Klebsiella*, a more limited approval than for other second-generation drugs. It also is approved for bone infections, septicemias, and surgical prophylaxis. The adverse effects are those of cephalosporins in general (see the general statement). Pain at the injection site is usually slight. However, supra infections caused by *Pseudomonas* and *Candida* may occur more frequently than with first- and other second-generation cephalosporins.

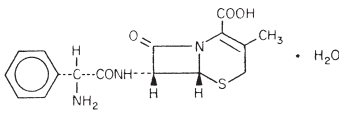
It is absorbed poorly by the oral route. However, the axetil ester is available for oral therapy of otitis media, pneumonia, and UTIs.

In plasma, 33% is protein-bound. The volume of distribution is 0.19 mL/g. It penetrates into CSF. More than 85% is eliminated in the urine; the half-life is 1.3 to 1.7 hr but may be as much as 24 hr in renal failure.

The axetil amide of cefuroxime is more lipid-soluble than the sodium salt, so that it is better absorbed by the oral route. Oral bioavailability without food is 36% compared to 50% fasting. It is approved for the treatment of otitis media caused by *Branhamella catarrhalis, H influenzae,* and *Strep pneumoniae* or *pyogenes;* pharyngitis and tonsilitis by *Strep pyogenes*; lower respiratory tract infections by *H influenzae* or *parainfluenzae* and *Strep pneumoniae*; skin infections by *Staph aureus* and *Strep pyogenes*; and UTIs by *E coli* and *Kl pneumoniae*.

CEPHALEXIN

5-Thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, [6*R*-[6α,7β(*R)]]-7-[(aminophenylacetyl)amino]-3-methyl-8-oxo-, monohydrate; Keflex**



[23325-78-2] $C_{16}H_{17}N_3O_4S{\cdot}H_2O$ (365.40).

Preparation—*J Med Chem* 1969; 12:310.

Description—White crystals; pK_a 5.2, 7.3; pH (0.5% solution) approximately 4.5.

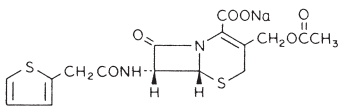
Solubility—1 g in 100 mL water; soluble in dilute aqueous alkaline solutions; very slightly soluble to practically insoluble in organic solvents.

Comments—An *oral first-generation cephalosporin* with antimicrobial activity and adverse effects characteristic of that class (see the general statement). It is approved for use against respiratory infections by pneumococcus and Group A beta-hemolytic streptococci; otitis media by *H influenzae, Branhamella catarrhalis*, pneumococcus, staphylococci and streptococci; bone and joint infections by *Pr mirabilis* and staphylococci; skin and soft tissue infections by staphylococci and streptococci; and UTIs by *E coli, Klebsiella,* and *Pr mirabilis*. It is effective orally.

Elimination is by renal excretion with a half-life of 0.9 hr, except 5 to 30 hr in renal failure.

CEPHALOTHIN SODIUM

5-Thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, (6*R-trans*)-3-[(acetyloxy)methyl]-8-oxo-7-[(2-thienylacetyl)amino]-, monosodium salt, Keflin, Leutral



[58-71-9] $C_{16}H_{15}N_2NaO_6S_2$ (418.41).

Preparation—7-Aminocephalosporanic acid is *N*-acetylated with 2-thiopheneacetyl chloride in a dehydrochlorinating environment. The starting acid may be prepared from the natural antibiotic, cephalosporin C, by either proton-catalyzed or enzymatic hydrolysis. The cephalothin thus prepared may be converted into its sodium salt by interaction with sodium acetate in a suitable organic solvent.

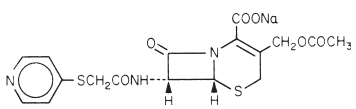
Description—White to off-white, crystalline powder; practically odorless; moderately hygroscopic; decomposes on heating; pK_a 2.2.

Solubility—Freely soluble in water, normal saline or dextrose solution; slightly soluble in alcohol; insoluble in most organic solvents.

Comments—A *first-generation cephalosporin* given IM and IV. It is short-acting and has the weakest spectrum of its class.

CEPHAPIRIN SODIUM

5-Thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, [6*R-trans*]-3-[(acetyloxy)methyl]-8-oxo-7-[[(4-pyridylthio)acetyl]amino]-, monosodium salt; Cefadyl



[24356-60-3]$C_{17}H_{16}N_3NaO_6S_2$ (445.46).

Preparation—From 7-aminocephalosporanic acid by bromomethylation of the amino group to form the bromacetamide and then displacing the bromine with 4-mercapto-pyridine to produce the thioether. Treatment with sodium bicarbonate gives the salt. US Pat 3,578,661 (1970); *J Med Chem* 1973; 16:1413.

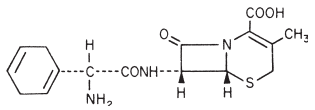
Description—Soluble in water.

Solubility—Soluble in water.

Comments—A short-acting *first-generation cephalosporin* given IM or IV.

CEPHRADINE

5-Thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, [6*R*-[6α,7β- (*R)]]-7-[(amino-1,4-cyclohexadien-1-ylacetyl]amino]-3-methyl-8-oxo-, Velosef**



[31828-50-9 (non-stoichiometric hydrate)] [38821-53-3 (anhydrous)] $C_{16}H_{19}N_3O_4S$ (anhydrous)(349.40).

Preparation—From cephalosporanic acid. US Pat 3,485,819 (1969); *J Med Chem* 1971; 14:117.

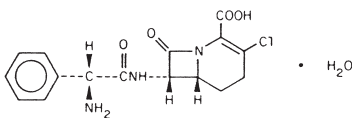
Description—Colorless crystals (monohydrate) melting about 141°; pK_{a1} −2.63, pK_{a2} −7.27.

Solubility—Slightly soluble in acetone or alcohol; soluble in propylene glycol.

Comments—A short-acting first generation cephalosporin given IM or IV. The dosage form contains a non-stoichiometric hydrate containing up to 16% water and products must indicate by the labeling on the package and each label of a bulk shipment, eg, "Each capsule contains X mg of cephradine as the dihydrate."

LORACARBEF

1-Azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, [6*R*-[6α,7β(*R)]]-7-[(aminophenylacetyl)amino]-3-chloro-8-oxo-, monohydrate, Lorabid**



[124750-99-8] $C_{16}H_{16}ClN_3O_4{\cdot}H_2O$ (367.79).

Preparation—US Pat 4,708,956 (1987).

Description—White solid melting about 210°.

Solubility—Slightly soluble in water.

Comments—An oral *second-generation cephalosporin* with good beta-lactamase resistance. It is actually a carbacephem that has an antibacterial spectrum similar to cefaclor, cefprozil, or cefuroxime axetil. It is an alternative agent for upper and lower respiratory tract infections due to *Strep pneumoniae, H influenzae,* or *Branhamella catarrhalis*. It also may be used for uncomplicated UTIs caused by *E coli* or *Staph saprophyticus*.

It has a serum half-life of 1 hr and is eliminated almost entirely by renal excretion. Protein binding is 25%. The most common adverse effect is diarrhea, but limited experience with this beta-lactam antibiotic suggests that one consider its potential for allergic reactions including anaphylaxis. Patients allergic to penicillin may also be allergic to loracarbef.

Carbapenems and Monobactams

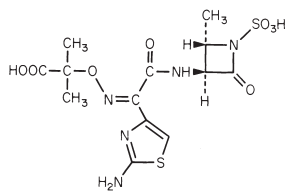
Carbapenems (imipenem and meropenem) are penicillin-related antibiotics in which the sulfur atom in the A ring of penicillanic acid has been replaced by carbon. A double bond in the A ring helps the planarity of the ring to approximate that of penicillanic acid. The carbapenems bind to penicillin-binding Proteins 1 and 2 and thus have antibacterial actions similar to those of the penicillins. However, they also bind to binding-Protein 7, which enables them to kill nongrowing bacteria, a property that undoubtedly will be found to be important in the treatment of infections with large populations of dormant cells (endocarditis, meningitis, ophthalmitis, osteomyelitis, etc). Carbapenems induce beta-lactamases but are resistant to them, which accounts for their efficacy against more than 90% of gram-negative species of bacteria.

Some important advantages of carbapenems include better activity against many highly penicillin-resistant strains of *Strep pneumoniae* and gram-negative aerobes, especially *Enterobacter*. They are not active against methicillin-resistant strains of staphylococci and *Enterococcus*. They also penetrate body tissues and fluids well including the CSF. They are eliminated by the kidney that can inactivate imipenem. Consequently, imipenem is only available with cilistatin, an inhibitor of renal dehydropeptidases. Patients allergic to penicillin may be sensitive to carbapenems. Other common side effects of these parenteral drugs are nausea, vomiting, skin rashes, and reactions at infusion sites. Excessive blood levels in patients with renal failure may lead to seizures, which are less frequently observed with meropenem (Table 90-5).

Monobactams (aztreonam) are natural or synthetic analogs of a monocyclic beta-lactam antibiotic isolated from certain soil bacteria. They bind only to penicillin-binding Protein 3, so that their activity is limited to aerobic gram-negative organisms; gram-positive and anaerobic organisms are insensitive. β-4-Alkyl groups confer resistance to most β-lactamases. Monobactams do not induce β-lactamases.

AZTREONAM

Propanoic acid, [2*S*,2α,3β(*Z*)]]- 2-[[[1-(2-amino-4-thiazolyl)-2-[(2-methyl-4-oxo-1-sulfo-3-azetidinyl)amino]-2-oxoethylidene]amino]-oxy]-2-methyl-, Azactam



[78110-38-0] $C_{13}H_{17}N_5O_8S_2$ (435.43).

Preparation—Neth Pat Appl 81 00571; *CA* 1982; 96:181062x.

Description—White powder; decomposes about 227°; pK_a −0.5, 2.6, 3.7.

Solubility—Very soluble in water; slightly soluble in methanol; soluble in DMF; practically insoluble in nonpolar solvents.

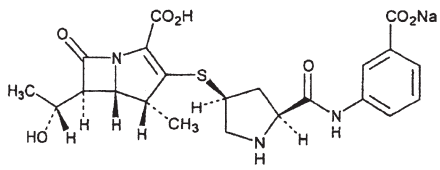
Comments—A monobactam with antibacterial activity against most *Enterobacteriaceae* comparable to that of the extended-spectrum penicillins or third-generation cephalosporins. However, it is not active against *Acinetobacter* and is variably active against *Ps aeruginosa*. Against β-lactamase-producing, nonenteric gram-negative bacilli, such as *H influenzae* and *N gonorrhoeae*, it is as effective as third-generation cephalosporins. This drug and aminoglycosides mutually enhance antibacterial efficacy. In bacteremias, intra-abdominal infections, pneumonias, skin and soft-tissue infections and UTIs, efficacy ranges from 80% to 90%. Gram-positive organisms are not sensitive.

It causes the adverse effects characteristic of penicillins and cephalosporins except that coagulation defects do not occur. However, it does not cause cross-sensitization with penicillins or cephalosporins.

Oral bioavailability is low. In plasma, 56% is protein-bound. The volume of distribution is 0.18 mL/kg. The drug crosses the placental barrier and also is excreted in milk. Renal tubular secretion accounts for about 67% of elimination; 7% is converted to a metabolite and excreted and over 1% is secreted into bile. The half-life is 1.7 hr in healthy adults but longer in renal failure or if given with probenecid.

ERTAPENEM SODIUM

1-Azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid, [4*R*-[3(3*S,5*S**),4α,5β,6β(*R**)]]-3-[[5-[[(3-carboxyphenyl)amino]carbonyl]-3-pyrrolidinyl]thio]-6-(1-hydroxyethyl)-4-methyl-7-oxo-, monosodium salt; Invanz**



[153832-38-3] $C_{22}H_{24}N_3NaO_7S$ (497.50).

Preparation—US Pat 5,952,323 (1009) and *Albany Molecular Research Tech Report*, 7(66):21-28.

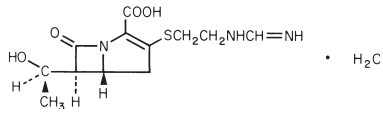
Description—White to off-white hygroscopic, crystalline powder

Solubility—Soluble in water or 0.9% saline; practically insoluble in ethanol; insoluble in isopropyl acetate and THF.

Comments—A carbapenem anti-infective with enhamced stability against beta-lactamase enzymes. Not clinically active against *P aeruginosa* or *A baumannii*. Clinically useful in the treatment of mixed infections and respiratory tract infections in patients at high-risk for poor outcomes. Adverse effects are similar to other beta-lactam anti-infectives.

IMIPENEM

1-Azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid, [5*R*-[5α,6α (*R)]]-6-(1-hydroxyethyl)-3-[[2-[(iminomethyl)amino]ethyl]thio]-7-oxo-, monohydrate; ing of Primaxin**



Imipemide[74431-23-5] $C_{12}H_{17}N_3O_4S{\cdot}H_2O$ (317.36).

Preparation—*J Med Chem* 1979; 22:1435. A crystalline derivative of thienamycin, produced by *S cuttleya*.

Description—White solid; nonhygroscopic; pK_a 3.2, 9.9.

Solubility—1g in 1000 mL water or 2000 mL methanol; practically insoluble in ethanol, DMF or DMSO.

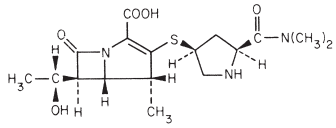
Comments—A *carbapenem*. It binds to bacterial penicillin-binding Proteins 1 and 2 and thus interferes with cell-wall synthesis, so that elongation and lysis occur. It is not destroyed by β-lactamases except those from *Ps maltophila* and occasional strains of *Bacteroides fragilis*. It has a broader antibacterial spectrum than any other β-lactam. It includes all cocci (except methicillin-resistant staphylococci and enterococci), *Enterobacteriaciae*, *Haemophilus*, *Ps aeruginosa*, and most anaerobes, including *Bacteroides fragilis*. It surpasses cephalosporins against staphylococci, equals penicillin G against streptococci, equals third-generation cephalosporins against most aerobic gram-negative bacilli and is comparable to ceftazidime against *Ps aeruginosa*. It is comparable to clindamycin or metronidazole against anaerobes. It is particularly useful for treatment of mixed bacterial infections. It should not be used alone for serious infections due to *Ps aeruginosa* because resistance may occur.

The adverse effects are those of other β-lactams. Nausea and vomiting occur with an incidence of 4%, diarrhea 3%, and hypersensitivity 3%. A reported incidence of seizures in 1.5% of recipients of imipenem-cilastatin requires confirmation; high doses, neurological disorders, and renal failure are said to contribute. The incidence of suprainfections is about 4%.

The induction of β-lactamases jeopardizes other β-lactam therapy. There is acquired resistance in up to 60% of strains of Pseudomonas. The oral bioavailability is low. Inflamed meninges are penetrated by the drug. Elimination is primarily renal, but the renal tubular cells inactivate the drug. The dehydropeptidase inhibitor, cilastatin, prevents inactivation, and enables tubular reabsorption; when it is coadministered, renal excretion of it is about 70%. It is marketed only in combination with cilastatin. Elimination half-life of both imipenem and cilastatin is 1 hr but is increased with decreased renal function.

MEROPENEM

1-Azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid, [4*R*-[3(3*S,5*S**)-4α,5β,6β(*R**)]]-3-[[5-(dimethylamino)carbonyl]-3-pyrrolidino]thio]-6-(1-hydroxyethyl)-4-methyl-7-oxo-, trihydrate; Merrem**



[119478-56-7] $C_{17}H_{25}N_3O_5S{\cdot}3H_2O$ (437.52).

Preparation—US Pat 4,943,569 (1990).

Description—White to pale yellow crystalline powder. Solutions vary from colorless to yellow, depending on the concentration.

Solubility—Sparingly soluble in water; soluble in 5% monobasic sodium phosphate solution; very slightly soluble in alcohol; practically insoluble in acetone or ether.

Comments—A *carbapenem* similar to imipenem with slightly different affinity for specific PBPs (primary targets include PBPs 2 and 3)

depending on the strain of gram-negative bacteria. It has a similar distribution to imipenem. However, it is not degraded by renal dehydropeptidases. It has the same side effects as imipenem but is less likely to cause seizures. Because of this decreased potential, meropenem is the primary carbapenem used in the treatment of central nervous system infections.

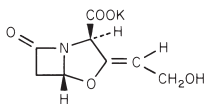
Beta-Lactamase Inhibitors

Enzymes that open the β-lactam rings of penicillins, cephalosporins, and related compounds at the β-lactam bond are known as β-lactamases. There are several classes; classification is based upon general substrate selectivity and inhibition, the acidity or basicity of the enzyme protein, and the intra- and extracellular location of the enzyme. Those that are excreted mainly from the bacterium and the genes for which are located on plasmids are called penicillinases. They are Type II β-lactamases. They are mainly responsible for the penicillin-resistance of gram-positive bacteria, gram-negative cocci, and a number of gram-negative bacilli.

Penicillinase-resistant penicillins bind to the penicillinases but dissociation of the drug-enzyme complex is relatively rapid. They have been supplanted by clavulanate, sulbactam, and tazobactam. These newer inhibitors are β-lactams that acylate the enzyme by forming a double bond and consequently dissociate very slowly. They greatly increase the potency of the penicillins against certain bacteria and thus enhance efficacy. The combinations currently available in the US include clavulanate with amoxacillin and ticarcillin, sulbactam with ampicillin, and tazobactam with piperacillin.

CLAVULANATE POTASSIUM

[2*R*-(2α,3*Z*,5α)]-4-Oxa-1-azabicyclo[3.2.0]heptane-2-carboxylic acid, 3-(2-hydroxyethylidene)-7-oxo-, monopotassium salt; ing of Augmentum and Timentin



[61177-45-5] $C_8H_8KNO_5$ (237.25).

Preparation—A β-lactamase inhibitor, produced by *S clavuligerus.* It is the first reported naturally occurring fused β-lactam containing oxygen. *J Antibiot* 1976; 29:668.

Description—White powder; bitter-tasting.

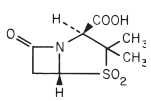
Solubility—1 g in 2.5 mL alcohol or in less than 1 mL water.

Comments—The sulfur at Position 1 of the β-lactam ring has been replaced by oxygen and there is an ethylidene moiety at Position 2, which greatly enhances reactivity with the classic exopenicillinases of *Staph aureus* and *epidermidis* and the gram-negative β-lactamases of the Richmond Types II and III (*Haemophilus, Niesseria, E coli, Salmonella,* and *Shigella*), IV (*Bacteroides, Klebsiella,* and *Legionella*) and V. These are all plasmid-mediated enzymes; chromosomally mediated enzymes are not inhibited. It reacts irreversibly with some but not all β-lactamases. It is not presently available in a single-entity product but is marketed only in combination with amoxicillin and ticarcillin (see the separate monographs for use in particular infections).

It is absorbed well by the oral route but is also suitable for parenteral administration. In plasma, about 30% is protein-bound. About 25% to 50% is eliminated by renal tubular secretion, which is inhibited by probenicid; some is metabolized. The half-life is about 1 hr.

SULBACTAM SODIUM

(2*S-cis*)-4-Thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid, 3, 3-dimethyl-7-oxo-4,4-dioxide, sodium salt; ing of Unasyn



[69388-84-7] $C_8H_{10}NNaO_5S$ (255.22).

Preparation—6-aminopenicillanic is diazotized to form the unstable diazo derivative, which is immediately converted to the 6,6-dibromo compound if the reaction is carried out in the presence of bromine. Catalytic hydrogenolysis of the bromine atoms forms the product. *J Org Chem* 1982; 47:3344.

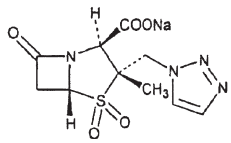
Comments—A greater activity against Type I β-lactamases than clavulanate, but does not penetrate the cell walls of gram-negative bacteria as well. It extends the antibacterial spectrum of ampicillin to include β-lactamase-producing strains of *Acinetobacter, Bacteroides,* and other anaerobes, *Branhamella, Enterobacter, E coli, Klebsiella, Neisseria, Proteus,* and *Staphylococcus*. It has weak antibacterial activity of its own. It is important to note it does possess moderate antimicrobial activity against *Acinetobacter* sp that may be clinically relevant.

It is absorbed by the oral route but is also suitable for parenteral administration. The volume of distribution is about 0.27 mL/g.

Elimination is mostly by renal tubular secretion; however, it does not interfere significantly with the elimination of ampicillin, the only β-lactam antibiotics with which it is combined. It also is secreted into milk. The plasma half-life is about 1 hr. It is not currently available in a single-entity product.

TAZOBACTAM SODIUM

4-Thia-1-azabicyclo[3.2.0]-heptane-2-carboxylic acid, (2α,3α,5α)-3-methyl-7-oxo-3-(1*H*-1,2,3-triazol-1-ylmethyl)-, 4,4-dioxide, sodium salt; Ing of Zosyn



[89785-84-2] $C_{10}H_{11}N_4NaO_4S$ (322.27)

Preparation—*Microbiol Lett* 1997; 57:805.

Solubility—(Acid) Moderately soluble in water (5.5 mg/mL); solubility increases with increase in pH; partially soluble in methanol, acetone, ethanol; slightly soluble in ethyl acetate, ether or chloroform; insoluble in hydrocarbon solvents. (Salt) Soluble in water.

Comments—Enhanced activity against Type I beta-lactamse enzymes. It extends the spectrum of activity of piperacillin to include beta-lactamase producing strains of *Acinetobacter, Bacteroides* and other anaerobes, *Moraxella, Enterobacter, E coli, Klebsiella, Neisseria, Proteus, Pseudomonas,* and *Staphylococcus*. It has weak antibacterial activity of its own.

AMINOGLYCOSIDES

The aminoglycosides each contain one or more aminosugars, such as glucosamine or neosamine, linked by glycoside linkages to a basic (amino or guanidino) 6-membered carbon ring (eg, streptidine or streptamine).

ANTIBACTERIAL SPECTRUM—The major spectrum of activity of aminoglycosides include aerobic gram-negative bacilli and *Staph aureus*. Only gentamicin, tobramycin, amikacin, and netilmicin are reliable against most hospital-acquired infections due to aerobic gram-negative bacteria. Other aminoglycosides have distinct limitations and disadvantages that restrict their uses. It is easier to state what organisms are not affected: anaerobes (*Bacteroides, Clostridium, Entameba histolytica, Trichomonas vaginalis), Rickettsia*, fungi, *Trypanosoma* and viruses (Table 90-6).

MECHANISM—The aminoglycosides combine with bacterial (not mammalian) ribosomes to arrest protein synthesis. The initiation complex can be formed, but cannot pass into, subsequent stages of protein synthesis. The binding is quite firm, so that inhibition is severe enough that a bactericidal effect can result. The drugs also appear to interfere with the binding of aminoacetyl-t-RNA, which prevents chain elongation. They fur-

Table 90-6. Aminoglycosides

DRUG	COMMENTS
Amikacin	More resistant to bacterial enzymes, active vs some gentamicin resistance strains
Gentamicin	Least expensive
Netilmicin	Similar to gentamicin spectrum
Tobramycin	Similar to gentamicin spectrum
Streptomycin	Used mainly for TB

ther appear to cause misreading of some RNA codons, such that inappropriate proteins can be formed when protein synthesis is not prevented completely.

Toxicity in the human is unrelated and, instead, results from blockade of N-type calcium channels and inhibition of lysosomal phospholipase and sphingomyelinase.

RESISTANCE—Resistance to aminoglycosides develops very rapidly with some bacteria, sometimes as a single-step high resistance. With meningococcus, *Hemophilus* and some other bacteria, even dependence on the drug can occur.

Although resistance to one amino glycoside often confers resistance to others, there are important exceptions that may determine the choice of amino glycoside for the treatment of certain infections. Both acquired and natural resistance often resulting from bacterial elaboration of amino glycoside-destructive enzymes; nine such enzymes have been identified. Because of the rapid acquisition of resistance, it is common to employ aminoglycosides only in combination with other antibacterial drugs when the organism is one that rapidly develops high resistance.

COMMENTS—Aminoglycosides have been a very important class of antibiotics to treat infections caused by gram-negative bacilli. Treatment of most nosocomial gram-negative bacillary infections with third-generation cephalosporins, carbapenems, and new fluoroquinolones have made the aminoglycosides alternative drugs unless resistant strains are suspected in immunosuppressed patients.

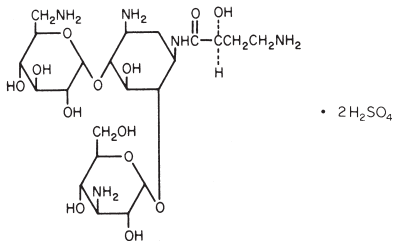
TOXICITY—Most of the toxic actions are common among all aminoglycosides, although there are important quantitative differences in incidence and severity. Hypersensitivity, mostly manifested as rashes but sometimes as drug fever and blood dyscrasias, occurs in 5% to 10% of recipients. Eosinophilia is relatively common. A history of sensitization contraindicates use. Cross-sensitization occurs. Vestibular and auditory function may be impaired; in the early stages it may be reversible, but often it becomes irreversible if medication is not stopped. Headaches, dizziness, and nausea and vomiting during movement are early signs of impairment of vestibular function. Loss of auditory perception of high-frequency sound signals onset of auditory toxicity. Aminoglycosides vary with respect to whether auditory or vestibular function is most affected. High-ceiling diuretics increase risk of ototoxicity. Nephrotoxicity, manifested by albuminuria, hematuria, cylindruria, azotemia, tubular necrosis, and renal failure, is common to all aminoglycosides, although there are marked differences in incidence and severity. Aminoglycosides should not be used in combination with other nephrotoxic substances. Neuromuscular blockade also occurs with high doses, as the result of both postjunctional and prejunctional inhibitory actions, probably because of interference with movement of calcium into nerve terminals and motor endplate. Low plasma-calcium predisposes to the blockade. Aminoglycosides greatly will increase neuromuscular paralysis induced by curare-like drugs and ether anesthetics. Supra infections (*overgrowth*), most often candidal, may occur during prolonged use, as the result of interference with the normal microbial flora.

Therapeutic drug monitoring may be used to determine appropriate drug intervals and renal function must be monitored. Signs and symptoms of toxicity should be monitored. The use of single daily dosing of aminoglycosides may be used if renal function is not compromised. Aminoglycosides have a post-antibiotic effect and the rate of killing is concentration-dependent so that the total daily dose may be given once daily. This approach allows plasma levels to be below the threshold for MIC and decrease drug accumulation in sites that cause toxicities.

PHARMACOKINETICS—At the pH of the lower small bowel, aminoglycosides are polycationic and, hence, are absorbed poorly from the gut. For the same reason, they are confined mostly to the extracellular space and penetrate cells poorly. The distribution coefficients (Δ') range from 0.19 to 0.28 mL/g. Aminoglycosides penetrate the blood-brain barrier only slightly, unless the meninges are inflamed. Binding to plasma protein is low and ranges from 0% to 34%. The drugs are excreted mostly into urine, the amount ranging from 60% to 100%. The average clinically significant half-lives are about 2 to 3 hr, but there is a much slower phase of elimination that relates to the gradual release of tissue-bound drug; there is greater variation among recipients than there is among the drugs. Renal failure greatly prolongs the half-life. Half-lives in the inner ear are 4 to 5 times those in plasma; the half-lives in the renal cortex range from 25 to 700 hr. These facts help explain the predisposition to vestibular, auditory and renal toxicities.

AMIKACIN SULFATE

D-Streptamine, (*S*)-*O*-3-amino-3-deoxy-α-D-glucopyranosyl-(1 → 6)-*O*-[6- amino-6-deoxy-α-D-glucopyranosyl-(1 → 4)]-*N*^{1}-(4-amino-2-hydroxy-1-oxobutyl)-2-deoxy-, sulfate (1:2) salt; Amikin



[39831-55-5] $C_{22}H_{43}N_5O_{23}\cdot 2H_2SO_4$ (781.78).

Preparation—Amikacin, the 1-L-(−)-4-amino-2-hydroxybutyryl derivative of kanamycin, is obtained by acylation of the C-1 amino group of the 2-deoxystreptamine moiety of kanamycin with L-(−)-4-amino-2-hydroxybutyric acid. German Pat 2,234,315, corresponding to US Pat 3,781,268 (*CA* 1973; 78:136615x).

Description—Amikacin base: white to off-white flocculent powder, which is converted to the sulfate salt in preparing injection dosage forms; melts (base) at approximately 203°, (sulfate) about 225° with decomp; pK_a (base) 8.1.

Solubility—Amikacin base: freely soluble in water; insoluble in alcohol.

Comments—The *N*-(4-amino-2-hydroxy-1-oxobutyl) group protects the amino glycoside from all but one of the nine amino glycoside-inactivating enzymes and acetyltransferase. In one study, more than 80% of strains of bacteria resistant to one or more aminoglycosides were sensitive in vitro to this drug. The greatest differences are shown with *Ps aeruginosa* and to a lesser extent with various *Enterobacteriaceae*.

Amikacin is considered the drug of choice for empirical therapy of infections caused by gram-negative bacilli in hospitals where bacterial strains are common that are resistant to gentamicin or tobramycin. Development of resistance to amikacin has not occurred where hospitals have used it as the primary amino glycoside. Septicemia, and serious infections of burns, urinary tract, respiratory tract and various soft tissues, meningitis, peritonitis, osteomyelitis, omphalitis in neonates, and serious surgical infections are indications for use.

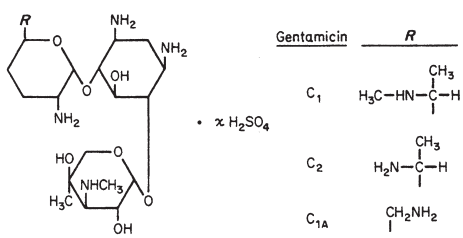
The toxicity is that of the aminoglycosides in general (see the general statement). Tremors, paresthesias, arthralgia, and hypotension also occur. Plasma levels should be monitored where possible, and auditory tests and examination of the urine are mandatory. The effect on the fetus is unknown, and use in pregnancy should be avoided, if possible.

The absorption, distribution, and elimination is that of aminoglycosides in general (see the general statement). The drug is eliminated totally unchanged in the urine. The half-life is 2 to 3 hr in adults with normal renal function but up to 30 hr in renal failure; in neonates it is 4 to 8 hr.

GENTAMICIN SULFATE

Gentamicin, sulfate

Gentamycins sulfate [1405-41-0]; the sulfate salt of the antibiotic substances produced by the growth of *Micromonospora purpurea*. Potency: not less than 590 μg of gentamicin/mg, on the anhydrous basis.



Gentamicin is a mixture of gentamicin C_1, gentamicin C_2 and gentamicin C_{1A}. Gentamicin C_{1A} is *O*-3-deoxy-4-*C*-methyl-3-(methylamino)-β-L-arabinopyronosyl-(1 → 6)-*O*-[2,6-diamino-2,3,4,6-tetradeoxy-α-D-*erythro*-hexopyranosyl-(1 → 4)-2-deoxy-D-streptamine.

Preparation—Recovered from a fermentation broth produced when submerged cultures of two subspecies of *Micromonospora purpurea* are grown in a yeast extract-cerelose medium. US Pat 3,136,704.

Description—White to buff powder; odorless; stable in light, air and heat; melts with decomposition between 220° and 240°.

Solubility—Soluble in water; insoluble in alcohol, acetone, or benzene.

Comments—Currently the most important amino glycoside for use in the treatment of infections caused by most aerobic gram-negative bacteria and many strains of staphylococci. It has broad-spectrum antibacterial activity. The action against *Pseudomonas* is of especial interest, since species of that genus resistant to other antibiotics have become an important cause of surgical infections. They also almost always invade burned skin and, furthermore, cause some serious UTIs. However, because of systemic toxicity, present systemic use is limited mainly to life-threatening infections caused by *Pseudomonas, Klebsiella-Enterobacter-Serratia, Citrobacter,* and *Proteus*. In these infections it may be combined with an appropriate cephalosporin or penicillin.

It is used topically in the treatment of impetigo, infected bed sores, burns and nasal staphylococcal carrier state, pyodermata, and in infections of the external eye.

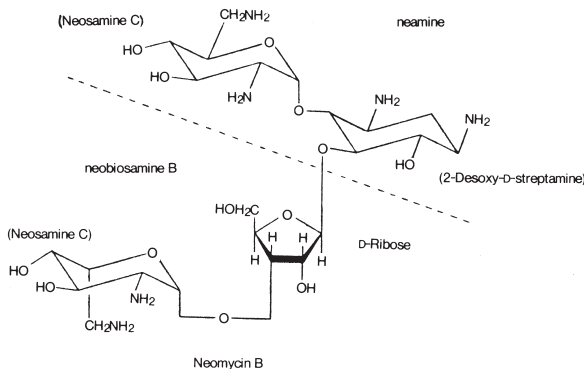
The absorption, distribution, elimination, and toxicity are those of aminoglycosides in general (see the general statement).

NEOMYCIN SULFATE

Fradiomycin Sulfate, Mycifradin Sulfate

Neomycin sulfate [1405-10-3]; the sulfate of an antibacterial substance produced by the growth of *Streptomyces fradiae* Waksman (Fam. *Streptomycetaceae*). Potency: equivalent to not less than 600 μg of neomycin/mg, calculated on the dried basis.

Neomycin consists almost entirely of a pair of $C_{23}H_{46}N_6O_{13}$ epimers designated as neomycin B and neomycin C, and the ratio of B to C has been observed to vary widely among different production lots. The total structure and the common names of the component parts of neomycin C are shown below. One g of salt should contain no less than 600 mg of the base.



Systematically, it is *O*-2,6-diamino-2,6-dideoxy-α-D-gluco-pyranosyl-(1 → 3)-*O*-β-D-ribofuranosyl-(1 → 5)-*O*-[2,6-diamino-2,6-dideoxy-α-D-gluco-pyranosyl-(1 → 4)-2-deoxy-d-streptamine. Neomycin B is identical except that the α-D-glucopyranosyl residue in the neobiosamine moiety is β-L-idopyranosyl.

Description—White to slightly yellow powder or cryodesiccated solid; odorless or practically odorless; hygroscopic; pH (aqueous solution 33 mg/mL) between 5 and 7.5.

Solubility—1 g in approximately 1 mL water; very slightly soluble in alcohol; practically insoluble in acetone, chloroform or ether.

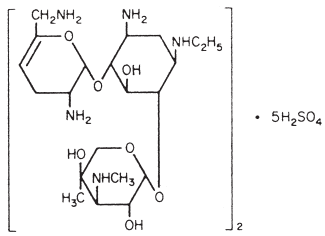
Comments—Used topically in a wide variety of local infections caused by common aerobic gram-negative bacteria in the *Enterobacteriaceae* family plus gram-positive cocci *(Staph* and *Enterococcus* but not streptococci). Some examples include infected dermatoses, burns, wounds, ulcers, impetigo, furunculosis, otitis externa, conjunctivitis and sty, as well as for irrigation of the bladder and urethra during catheterization, as prophylaxis. It mostly is combined with other antibiotics, especially polymyxin B sulfate, bacitracin zinc and gramicidin.

Orally, the drug is used to produce intestinal antisepsis prior to large bowel surgery, for the treatment of gastroenteritis caused by toxigenic *E coli* and to suppress ammonia-producing bowel flora in the management of hepatic coma. Because of rapid overgrowth of nonsusceptible bacteria, including staphylococci, oral therapy should not be continued for longer than 72 hr.

Although the orally administered drug rarely causes systemic toxic effects, it frequently produces loose stools, nausea, vomiting, and malabsorption syndromes. Applied topically, the drug is tolerated well, relatively nonirritating and has a low index of sensitivity. However, contact dermatitis occasionally occurs. Injected parenterally, it causes serious nephrotoxic, ototoxic, and neurotoxic effects. Because of the potential toxicity, parenteral injection and prolonged oral administration are avoided if possible.

NETILMICIN SULFATE

D-Streptamine, *O*-3-deoxy-4-*C*-methyl-3-(methylamino)-β-L-arabino-pyranosyl-(1 → 6)-*O*-[2,6-diamino-2,3,4,5-tetradeoxy-α-D-*glycero*-hex-4- enopyranosyl-(1 → 4)]-2-deoxy-*N*^{1}-ethyl-, sulfate (2:5) (salt), pentahydrate; Netromycin



[56391-57-2] $(C_{21}H_{41}N_5O_7)_2 \cdot 5H_2O$ (1441.54); contains not less than 595 μg of netilmicin base calculated on the dried basis.

Preparation—A semi-synthetic derivative of sisomicin formed by ethylation of the amino group in the 1-position of the 2-deoxystreptamine ring; see *Chem Commun* 1976; 206.

Description—Off-white powder, p (1 in 25 solution) between 3.5 and 5.5; pK_a 8.1.

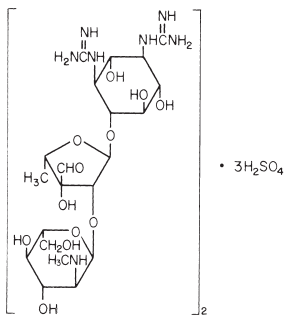
Solubility—Very soluble in water.

Comments—An *aminoglycoside* with a spectrum similar to *Gentamicin*.

PAROMOMYCIN—page 1668.

STREPTOMYCIN SULFATE

D-Streptamine, *O*-2-deoxy-2-(methylamino)-α-L-glucopyranosyl-(1 → 2)-*O*-5-deoxy-3-*C*-formyl-α-L-lyxofuranosyl-(1 → 4)-*N,N′*-bis(aminoiminomethyl)-, sulfate (2:3) (salt)



Streptomycin sulfate (2:3) (salt) [3810-74-0] $(C_{21}H_{39}N_7O_{12})_2 \cdot 3H_2SO_4$ (1457.38). Potency: equivalent to 650 to 850 μg of streptomycin $(C_{21}H_{39}N_7O_{12})$/mg.

Streptomycin is an organic base, consisting of *N*-methyl-*l*-glucosamine and streptidine linked through the carbohydrate streptose. The overall structure is portrayed above.

Preparation—Isolated from soil by Waksman and his colleagues of Rutgers University in 1943.

Streptomycin is produced in organic or synthetic media, in surface or submerged cultures of an actinomycete, *Streptomyces griseus*, a mold-like organism with filaments (mycelium) of bacterial thickness.

Commercially, streptomycin is manufactured much like penicillin, microbiologically in tank fermenters with aeration and agitation.

Description—White or practically white powder; odorless or has not more than a faint odor; hygroscopic; but stable toward air and light; pH (1 in 5 solution) between 4.5 and 7.0.

Solubility—Freely soluble in water; slightly soluble in alcohol; practically insoluble in chloroform.

Comments—Bacteriostatic in low concentrations and bactericidal in high concentrations to a large number of gram-negative and gram-positive bacteria. *Brucella, H ducreyi, Yersinia pestis, Francisella tu-*

larensis, many strains of *Mycobacterium tuberculosis* are sensitive to concentrations that are usually achievable in man.

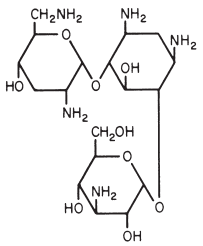
The only infections in which it alone is the drug of choice are tularemia and bubonic plague. In combination with a tetracycline it is used in the treatment of brucellosis and infections caused by *Pseudomonas mallei*. It is an alternate choice drug in the treatment of chancroid, rat-bite fevers (*Spirillum* and *Streptobacillus*) and tuberculosis; in tuberculosis, however, it is never used alone, because of the rapidity of development of resistance.

The toxicity is that of aminoglycosides in general (see the general statement). In addition, malaise and myalgia may occur. Vestibular disturbances are more frequent than loss of hearing.

The absorption, distribution, and elimination are those of aminoglycosides in general.

TOBRAMYCIN

D-Streptamine, *O*-3-amino-3-deoxy-α-D-glucopyranosyl- (1 → 6)-*O*-[2,6-diamino-2,3,6-trideoxy-α-D-*ribo*-hexopyranosyl-(1 → 4)]-2-deoxy-, Tobrex, Nebcin (sulfate)



[32986-56-4] $C_{18}H_{37}N_5O_9$ (467.52). Potency: not less than 900 μg of $C_{18}H_{37}N_5O_9$ /mg, calculated on the anhydrous basis.

Preparation—An antibiotic entity separated from an antibiotic complex produced by *Streptomyces tenebrarius*. In its injection dosage form tobramycin is present as a sulfate.

Description—White or off-white, hygroscopic powder; hygroscopic; pK_a 6.7, 8.3, 9.9.

Solubility—1 g in 1.5 mL water; slightly soluble in alcohol; practically insoluble in chloroform or ether; a 1 in 10 aqueous solution, pH between 9 and 11.

Comments—An *aminoglycoside* with a spectrum similar to *Gentamicin*.

Aminoglycoside-Containing Combinations

Some examples of aminoglycoside-containing combinations (with content/mL or g provided) are as follows:

NEOMYCIN SULFATE AND POLYMYXIN B SULFATE—[Neosporin G.U. Irrigant]—40 mg and 200,000 Units, respectively; G.U. irrigant. [Neosporin, Startol]—3.5 and 10,000 Units, respectively; cream, ophthalmic ointment.—3.5 mg and 16,250 units, respectively; ophthalmic solution.

NEOMYCIN SULFATE, POLYMYXIN B SULFATE AND BACITRACIN ZINC—[Neosporin and Neosporin Ophthalmic, Triple Antibiotic, Mycitracin Triple Antibiotic and Mycitracin Ophthalmic,]—3.5 or 5 mg, 5000 Units and 400 or 500 Units, respectively; ointment and ophthalmic ointment.

NEOMYCIN SULFATE, POLYMYXIN B SULFATE AND GRAMICIDIN—[AK-Spore, Neocidin, Neosporin Ophthalmic]—1.75 mg, 10,000 units and 0.025 mg, respectively; ophthalmic solution.

Macrolides

The macrolides are hydroxylated macrocyclic lactones containing 12 to 20 carbon atoms in the primary ring. There are 37 known members of this class but only erythromycin and its derivatives have been used widely. New macrolides, clarithromycin, dirithromycin and azithromycin were approved in 1991. These are chemically similar to the 14-membered-ring macrolide, erythromycin. Azithromycin is a 15-membered-ring macrolide.

The macrolides are active against gram-positive and gram-negative aerobic bacteria and atypical organisms including chlamydiae, mycoplasmae, legionellae, rickettsiae, and spirochetes. Erythromycin is the prototypical macrolide and has been used in treating a wide variety of infections over the years. However, its use has been diminished by its gastrointestinal intolerance. The newer macrolides are better tolerated, have a broader spectrum of activity (*H influenzae*, *Mycobacterium avium*), and possess longer half-lives

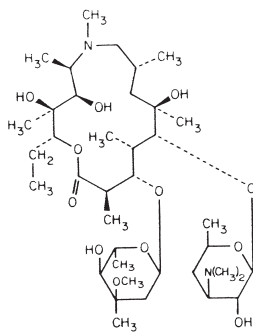
The mechanism of action of the macrolides is inhibition of bacterial protein synthesis by binding to the 50s subunit of the bacterial ribosome. The complex has a relatively low affinity constant that some protein synthesiscan occur, so that these drugs are mainly bacteriostatic in therapeutic concentrations. Macrolides bind equally to ribosomes from gram-positive and gram-negative bacteria; the much greater effect on gram-positive organisms is the result of greater permeation of the cell membrane.

The macrolides in general are considered safe agents. Gastrointestinal effects such as abdominal pain, nausea, and vomiting are most common. The newer macrolides cause fewer GI side effects. Hepatotoxicity related to the macrolides is rare but may be serious. It is also less common with the newer agents. Extremely high doses of IV erythromycin and oral clarithromycin have been associated with ototoxicity. Phlebitis may occur with the intravenous administration of the macrolides.

The macrolides are separated into groups based on clinical significance of drug interactions. It is postulated that structural features of the compounds contribute to their interacting potential. Group 1 includes the prototype, erythromycin, a documented inhibitor of the cytochrome P450 enzyme system. It has been shown to prolong the half-life of an extensive list of agents including cyclosporine, theophylline, rifampin, and the HMG-CoA reductase inhibitors. These interactions are also likely to occur in Group 2 which includes clarithromycin. The newer marcolides in Group 3, azithromycin and Dirithromycin, do not form CYP 450 complexes so the possibility of interactions is low (Table 90-7).

AZITHROMYCIN

Oxa-6-azacyclopentadecan-15-one, 13-[(2,6-dideoxy-3-*C*-methyl-[2*R*-(2*R,3*S**,4*R**,5*R**,8*R**,10*R**,11*R**,12*S**,13*S**,14*R**)]-3-*O*-methyl-α-L-*ribo*-hexopyranosyl)oxy]-2-ethyl-3,4,10-trihydroxy-3,5,6,8,10,12,14-heptamethyl-11-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-*xylo*-hexopyranosyl]oxy]-, Zithromax**



[83905-01-5] $C_{38}H_{72}N_2O_{12}$ (749.00).

Preparation—A semisynthetic macrolide similar to erythromycin A; US Pat 4,517,359.

Description—White crystals; melts about 114°.

Comments—A new alternative macrolide to erythromycin that has a similar spectrum of activity. It is active against staphylococci and

Table 90-7. Macrolides

DRUG	COMMENTS
Azithromycin	Expanded spectrum, less GI effects, does not affect CYP enzymes, long half-life
Clarithromycin	Improved spectrum over erthromycin,less GI effects, inhibits CYP enzymes
Erythromycin	Frequent GI effects, inhibits CYP enzymes

streptococci but is more active than erythromycin against *H influenzae* and some aerobic gram-negative bacilli. Azithromycin suspension should be taken at least 1 hr before or 2 hr after a meal but tablets (as the dihydrate) are unaffected by food. It has a half-life of approximately 50 hours, which is much longer than any other macrolide. Only 6% is recovered from the urine; hepatic metabolism and biliary excretion account for most of its clearance.

Side effects most frequently reported are diarrhea, nausea, and abdominal pain, but these are less than those observed with erythromycin. Antacids containing aluminum or magnesium affect absorption. In addition, this new macrolide does not form complexes with the CYP 450 system so the possibility of interactions is low. Azithromycin is most commonly used in the treatment of respiratory tract infections (sinusitis, bronchitis, pneumonia) as well as for the prophylaxis of Mycobacterium avium infections in AIDS patients.

CLARITHROMYCIN

Erythromycin, 6-*O*-methyl; Biaxin

[81103-11-9] $C_{38}H_{69}NO_{13}$ (747.96). For the structure of *Erythromycin base,* see next monograph.

Preparation—US Pat 4,331,802.

Description—Crystals; colorless; melts about 220° with decomposition.

Comments—An alternative to erythromycin that is two- to fourfold times more active than erythromycin against most streptococci and staphylococci. It has moderate activity against *H influenzae* and *N gonorrhoeae* and is also active against the atypical organisms as well as mycobacteria. Clarithromycin is well absorbed from the GI tract with or without food. Bioavailability is approximately 50%. It is metabolized in the liver, and 30% to 40% of the dose is recovered in the urine. It is 65% to 70% bound to plasma proteins but penetrates well into tissues and cells, including macrophages and polymorphonuclear leukocytes. It may increase serum concentrations of theophylline or carbamazepine. Diarrhea, nausea, vomiting, dyspepsia, and metallic taste may occur but seem to be less frequent than reported with erythromycin.

Clarithromycin is an alternative to erythromycin that has a more convenient twice daily dosage regimen for the treatment of upper and lower respiratory tract infections. It is also a first-line agent used in combination with ethambutol for the treatment of *Mycobacterium avium* infection in AIDS patients.

DIRITHROMYCIN

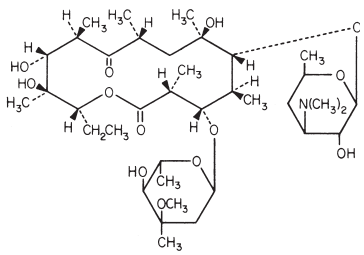
Comments—Prodrug converted to erythromycylamine during intestinal absorption. The bioavailability of the oral formulation is 10%. Dirithromyicin is enteric-coated to protect contents from gastric acid. The protein binding of dirithromycin ranges from 15% to 30%. The agent is primarily eliminated in the bile and undergoes little hepatic metabolism. The mean half-life is estimated to be approximately 8 hours. Rapid distribution of dirithromycin into tissues results in significantly higher concentrations in tissue than in serum. As a result, dirithromycin is not recommended for use in the treatment of known or suspected bacteremias due to inadequate serum levels to provide sufficient coverage of the bloodstream.

ERYTHROMYCIN

(3*R,4*S**,5*S**,6*R**,7*R**,9*R**,11*R**,12*R**,13*S**, 14*R**)-4-[(2,6-Di-deoxy-3-*C*-methyl-3-*O*-methyl-α-L-*ribo*-hexopyranosyl) oxy]-14-ethyl-7,12,13-trihydroxy-3,5,7,9,11,13-hexamethyl-6-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-*xylo*-hexopyranosyl]oxy]oxacyclotetradecane-2,10-dione; Ilotycin; E-Mycin**

[114-07-8] $C_{37}H_{67}NO_{13}$ (733.94). Potency: not less than 850 μg of $C_{37}H_{67}NO_{13}$/mg, calculated on the anhydrous basis.

Preparation—Elaborated during the growth of a strain of *Streptomyces erythreus*. US Pat 2,823,203.



Description—White or slightly yellow crystals or powder; odorless or practically odorless; slightly hygroscopic; pK_a 8.7.

Solubility—1 g in approximately 1000 mL of water; soluble in alcohol, chloroform, or ether.

Comments—The prototypical macrolide with activity against gram-positive, gram-negative, and the atypical organisms (*Mycoplasma*, *Chlamydia*, *Legionella*).

Nausea, vomiting, and occasionally, diarrhea and stomatitis may occur, particularly with large doses. Hypersensitivity, skin eruptions, fever, and eosinophilia occasionally occur. The drug antagonizes lincomycin and chloramphenicol. Hepatic dysfunction, with or without jaundice, occurs in some patients receiving oral erythromycin products (especially the estolate).

It is absorbed variably after oral administration. Food interferes with absorption. The antibiotic is destroyed by gastric acid so enteric-coated preparations of the free base and acid-resistant salts or esters are used. It is 73% bound to plasma proteins. The volume of distribution is 0.72 mL/g. The plasma half-life is 1.2 to 2 hr but may be prolonged up to 5 to 6 hr in renal insufficiency.

The antibiotic does not diffuse readily into CSF, but attains antibacterial concentrations in peritoneal and pleural fluids. Only 2% of oral and 20% of parenteral erythromycin is excreted in active form by the kidney. The antibiotic is concentrated in the liver and excreted in active form in the bile. Erythromycin increases the plasma levels of theophylline, caffeine, alfentanil, carbamazepine, cyclosporine, digoxin, warfarin, and bilirubin.

Polypeptides

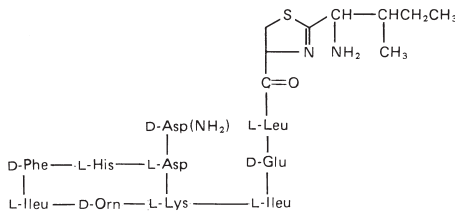
The polypeptide antibiotics (bacitracin and polymyxin B) are restricted to topical use because of their systemic toxicity. They differ from each other in their mechanism of action and antibacterial spectrum. Bacitracin is mainly effective against gram-negative bacteria and inhibits cell wall synthesis by interfering with the transfer of peptidoglycan subunits to the cell wall. Polymyxin are active against gram-negative bacteria by virtue of their cationic detergent-like disruption of bacterial cytoplasmic membranes.

BACITRACIN

Ayfivin; Penitracin; Topitracin; Zutracin

Bacitracin [1405-87-4]; polypeptide produced by the growth of the *licheniformis* group of *Bacillus subtilis* (Fam *Bacillaceae*). It has a potency of not less than 40 USP Units of bacitracin/mg. (The USP Unit of Bacitracin is the bacitracin activity exhibited by the weight of USP Bacitracin Reference Standard indicated on the label of the Standard. The USP unit and that defined by the FDA are equivalent.) Sterile bacitracin has a potency of not less than 50 Units/mg.

Bacitracin is a mixture of at least nine polypeptides, principally bacitracin A, $C_{66}H_{103}N_{17}O_{16}S$ (1411). The structure of bacitracin A has been shown to be



in which the detailed structure at the upper right represents a cyclic condensation moiety derived from cysteine and isoleucine.

Preparation—Several methods for isolation and purification of this antibiotic have been published. For details of certain of these multistep procedures see US Pats 2,498,165, 2,828,246, and 2,915,432.

Description—White to pale-buff powder; odorless or has a slight odor; hygroscopic; solutions rapidly deteriorate at room temperature; precipitated from its solutions and is inactivated by salts of many of the heavy metals; solutions retain their potency for several weeks if kept in a refrigerator.

Solubility—Freely soluble in water; soluble in alcohol; insoluble in chloroform or ether.

Comments—Effective mainly against gram-positive bacteria. It is limited largely in its use to infections that can be treated by topical application or local infiltration. The high incidence of nephrotoxicity (albuminuria, cylindruria, azotemia, accumulation of drug) that follows its parenteral administration precludes systemic use except in life-endan-

gering staphylococcal infections (pneumonia, empyema) in infants in which other antibiotics have proved to be ineffective or in the treatment of antibiotic-associated (pseudomembranous) enterocolitis caused by *Cl difficile*.

It is effective topically in the treatment of the following cutaneous bacterial infections where the pathogen is bacitracin-sensitive:impetigo contagiosa, folliculitis, pyoderma, ecthyma, furunculosis, decubitus ulcer, infectious eczematoid dermatitis, scabies, and dermatophytosis. The drug is used in the treatment of ophthalmological conditions. The zinc salt often is preferred for topical therapy and is the form most often incorporated into combinations. It usually is combined with neomycin and polymyxin B sulfate. Development of bacterial resistance is much less frequent and slower for bacitracin than for penicillin, and for most organisms it is essentially nil.

In addition to renal damage, toxic effects of parenteral use include pain, induration and petechiae at the site of injection, skin rash, malaise, anorexia, nausea, and vomiting. In a few instances tinnitus and a peculiar taste may be noted. Topical application is usually not irritating and rarely induces allergic reactions.

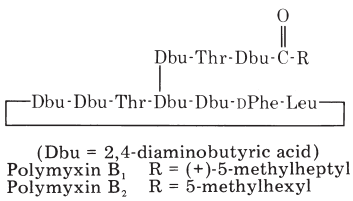
POLYMYXIN B SULFATE

Polymyxin B, sulfate; Aerosporin

Polymyxin B sulfate [1405-20-5]; the sulfate salt of a substance produced by the growth of *Bacillus polymyxa* (Prazmowski) Migula (Fam *Bacillaceae*). It has a potency of not less than 6000 Units of polymyxin B/mg, calculated on the anhydrous basis.

Preparation—The filtered broth from the fermentation step is treated with a certified dye and the polymyxin B-dye salt complex thus precipitated is collected by filtration, washed with water and treated with an alcoholic solution of a lower aliphatic amine sulfate. The polymyxin B sulfate thus formed is filtered off, purified and lyophilized.

There are several polymyxins each of which is an *N*-monoacylated decapeptide with seven of the amino acid residues in cyclic union. Polymyxin B is a mixture of polymyxin B_1 ($C_{56}H_{98}N_{16}O_{13}$) and polymyxin B_2 ($C_{55}H_{96}N_{16}O_{13}$) the only difference being in the composition of the *N*-acyl group:



(Dbu = 2,4-diaminobutyric acid)
Polymyxin B_1 R = (+)-5-methylheptyl
Polymyxin B_2 R = 5-methylhexyl

The close relationship between these polymyxins and the colistins (see preceding article) is readily apparent.

Description—White to buff-colored powder; odorless or a faint odor; solutions are slightly acid or are neutral to litmus (pH 5 to 7.5); pK_a 8 to 9.

Solubility—Freely soluble in water; slightly soluble in alcohol.

Comments—In vitro and in vivo antimicrobial spectrum of activity is restricted to gram-negative bacteria, including *Aerobacter, Acinetobacter, Escherichia, Haemophilus, Klebsiella, Pasteurella, Pseudomonas, Salmonella, Shigella*, most *Vibrio* and *Yersinia*; all strains of *Pr providencia* and most of *Serratio marcescens* are unaffected by the antibiotic. In particular, it possesses activity against many multiply resistant strains of Acinetobacter and Pseudomonas species. All gram-positive bacteria are resistant.

The drug is used topically for the treatment or the prevention and treatment of external ocular infections caused by susceptible microorganisms, especially *Ps aeruginosa*. In topical therapy, it often is combined with neomycin, gramicidin, and bacitracin. It also is included in glucocorticoid ophthalmological topical preparations.

When given parenterally, it adversely can affect the nervous system and the kidney. Substances such as soap, which antagonize cationic surface-active agents, impair the action of the antibiotic.

VANCOMYCIN—page 1662.

Tetracyclines

The tetracyclines are all very much alike with respect to their antimicrobial spectra and the untoward effects they elicit. They differ mainly in their absorption, duration of action and suitability for parenteral administration (Table 90-8).

Table 90-8. Tetracyclines

DRUG	COMMENTS
Chlortetracycline	Short acting, incomplete oral abs
Demeclocycline	Intermed. acting, more phototoxicity
Doxycycline	Long acting, good oral abs, biliary excretion
Minocycline	Long acting, good oral abs, dizziness, and vertigo, metabolized
Methacycline	Intermed acting
Oxytetracycline	Short acting, incomplete oral abs
Tetracycline	Short acting, incomplete oral abs

ANTIMICROBIAL ACTIONS—The tetracyclines are broad-spectrum antibiotics. They are mainly bacteriostatic. They bind to the bacterial 30s ribosomes and prevent t-RNA from combining with m-RNA. Thus, protein synthesis is inhibited. The drugs have activities against both gram-positive and gram-negative bacteria, mycobacteria, *Mycoplasma*, treponemas, leptospira, rickettsia, actinomycetes, *Coxiella*, *Chlamydiae,* and plasmodia. The susceptible gram-positive bacteria are variable.

Although resistance to the tetracyclines is not acquired as rapidly as to penicillin, it nevertheless does occur readily. Among the gram-positive bacteria up to 44% of *Strep pyogenes* are resistant and 74% of *Enterococcus fecalis*. The incidence of resistance among hospital strains of *Staph aureus* may run from 30% to 50% but may increase to as high as 75% after several days of treatment. Highly resistant gonococci have become prevalent; however, topical tetracycline is comparable with silver nitrate in the prophylaxis of ophthalmia neonatorum and does not cause chemical conjunctivitis.

Various streptococci and pneumococci also become resistant. The incidence of resistance among various gram-negative bacteria is also very high, especially among the *Enterobacteriaceae*, which in the intestine can pass resistance-controlling genes from one species, even genus, to another (infectious drug resistance). Resistance to one tetracycline usually confers resistance to all others, except that some tetracycline-resistant strains of streptococci and *E coli* may retain sensitivity to minocycline. Cross-resistance between penicillin and tetracyclines or between other classes of antibiotics and tetracyclines is uncommon, except in infectious drug resistance, in which the acquired episome or plasmid contains more than one gene for resistance to other drugs.

COMMENTS—A tetracycline alone is the drug of choice in the treatment of cholera, relapsing fever, granuloma inguinale and infections caused by rickettsia, *Borrelia, Mycobacterium fortuitum* and *marinum,* and *Chlamydia psittaci* and *trachomatis* (except pneumonia and inclusion conjunctivitis). With erythromycin it shares first-choice status for the treatment of *Mycoplasma pneumonia* (primary atypical pneumonia). A tetracycline is a component of first-choice combinations for the treatment of brucellosis, glanders and infections by *Ps pseudomallei*. It is an alternative drug for the treatment of actinomycosis, anthrax, chancroid, mellioidosis, plague, rat-bite fevers, syphilis, and yaws. However, in the treatment of acne, tetracyclines maintain a favored but challengeable status; if there is inflammation with pustules and cysts, an antibiotic may be indicated.

Doxycycline has been shown to prevent travelers' diarrhea caused by enterotoxigenic *E coli*. In UTIs, other drugs usually are preferred, unless sensitivity testing especially indicates tetracyclines. However, tetracyclines are used in nongonococcal urethritis and in prostatitis (often a mycoplasma). In UTIs and urethritis, the urine should be acidified to favor antibacterial action. In the treatment of the meningococcal carrier state, minocycline, but not other tetracyclines, appears to be effective.

In combination with quinine, a tetracycline is an alternative drug for the treatment chloroquine-resistant *Plasmodium falciparum* malaria.

Tetracyclines are used as an alternative to silver nitrate in the prevention of neonatal ocular prophylaxis of chlamydial and gonococcal conjunctivitis, but studies have shown them to be inferior.

ADVERSE EFFECTS—The tetracyclines cause a number of untoward effects. GI toxicity is common with oral use; it is probably the combined effect of local irritation and alteration of the intestinal flora. Manifestations are heartburn, epigastric distress, nausea, vomiting, diarrhea and rare esophageal ulceration in persons with esophageal obstruction or spastic disease.

The broad-spectrum antibacterial activity of the tetracyclines causes marked alterations in the floral ecology, so that microorganisms formerly held in check overgrow to cause superinfections. This occurs most frequently in the bowel but it also may occur readily in the mouth, lungs, vagina, and occasionally elsewhere. The most common superinfection is candidiasis, but overgrowth from staphylococci, enterococci, *Proteus, Pseudomonas,* or *Cl difficile* (cause of antibiotic-associated colitis) occurs. Staphylococcal enteric superinfections are frequently fatal.

Various hypersensitivity reactions, especially urticaria, asthma or facial edema, occur, but they are uncommon. Phototoxicity can occur with all tetracyclines, but it is most frequent with demeclocycline.

Hepatotoxicity, which is sometimes fatal, occasionally results when the daily dose in adults exceeds 1 g/day, especially if the tetracycline is given intravenously; pregnancy and renal failure predispose to this toxicity. Tetracyclines also may increase the risk of hepatic damage by other hepatotoxic drugs.

Although tetracyclines probably do not affect normal kidney function, they aggravate preexisting renal insufficiency, which can lead to extreme azotemia, but without oliguria. Doxycycline appears to be free of this effect. Old preparations that have undergone decomposition on the shelf are serious offenders in causing nephrotoxicity. Minocycline can cause vestibular toxicity.

Tetracyclines pigment developing teeth and reversibly impair bone growth through complexation with the bone salts and fixation to matrix proteins. The implication is that tetracyclines should be avoided in children up to 8 yr of age, in whom the cosmetically important permanent teeth have not erupted. It also should be avoided in pregnancy.

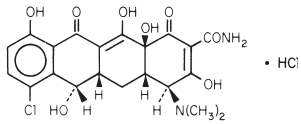
IV tetracyclines may cause thrombophlebitis, caused mainly by the acid required to effect solution. IM injections cause local pain, unless a local anesthetic is included.

ABSORPTION, DISTRIBUTION, AND ELIMINATION—The extent of GI absorption is 58% to 100%. Doxycycline and minocycline are absorbed the best. Tetracyclines complex with bivalent and trivalent metal ions, so that their absorption is greatly impaired by calcium-, magnesium- and aluminum-containing antacids and by iron preparations. Food, especially milk products or other high-calcium foods, also interferes with oral absorption of tetracyclines, although a minimal effect occurs with doxycycline and minocycline. Phosphate appears to improve absorption, in part by removing calcium.

All tetracyclines are bound to plasma proteins, to an extent ranging from 35% to 91%. Volumes of distribution range from 0.14 to 1.79 mL/g. Half-lives vary from 6 to 17 hr in normal persons but 12 to 108 hr in renal failure. Doxycycline and minocycline are longer acting, the most lipophilic and pentrate tissues more efficiently. Therapeutic concentrations of minocycline are achieved in saliva and tears to eradicate the meningococcal carrier state. Renal excretion is the principal mode of elimination, except that minocycline is excreted mostly in the bile and doxycycline is more than 50% metabolized and/or excreted into the colon. The tetracyclines penetrate well into the tissues and body fluids, but penetration into the CSF is low by the oral route. All tetracyclines are excreted somewhat into the bile and not resorbed completely in the intestine, so that even IV doses are capable of altering the bowel flora.

DEMECLOCYCLINE HYDROCHLORIDE

2-Naphthacenecarboxamide, [4*S*-(4α,4aα,5aα,6β,12aα)]-7-chloro-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,6,10,12,12a-pentahydroxy-1,11-dioxo-, monohydrochloride; Declomycin



7-Chloro-6-demethyltetracycline hydrochloride [64-73-3] $C_{21}H_{21}ClN_2O_8 \cdot HCl$ (501.32). Potency: not less than 900 μg of $C_{21}H_{21}ClN_2O_8 \cdot HCl$/mg, calculated on the anhydrous basis.

Preparation—An appropriate mutant strain of *Streptomyces aureofaciens* is grown in an appropriate liquid nutrient medium under controlled conditions of temperature, pH, and aeration. The harvested broth is acidified and filtered, and the antibiotic is isolated from the filtrate, either by solvent extraction or by chemical precipitation, and converted into the hydrochloride.

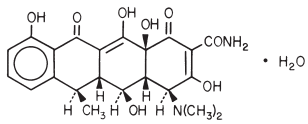
Description—Yellow, crystalline powder; odorless; bitter taste; pH (1 in 100 solution) approximately 2.5; pK_a 3.3, 7.2, 9.3.

Solubility—1 g in approximately 60 mL water, 200 mL ethanol, or 50 mL methanol; sparingly soluble in solutions of alkali hydroxides or carbonates; practically insoluble in chloroform.

Comments—A *tetracycline*. It is intermediate-acting and causes more phototoxicity than other members of its class.

DOXYCYCLINE

2-Naphthacenecarboxamide, [4*S*-(4α,4aα,5α,5aα,6α,12aα)]-4-(dimethyl-amino)-1,4,4a,5,5a,6,11,12a-octahydro-3,5,10,12,12a-pentahydroxy-6-methyl-1,11-dioxo-, monohydrate; Vibramycin



[1086-28-1] $C_{22}H_{24}N_2O_8 \cdot H_2O$ (462.46); anhydrous [564-25-0] (444.44). Potency: 880 to 980 μg of $C_{22}H_{24}N_2O_8$ /mg.

Preparation—6-Deoxy-6-demethyl-6-methylene-5-oxytetracycline (*see Methacycline*) is dissolved or suspended in an inert liquid such as methanol and hydrogenated under the influence of catalytic amounts of noble metals such as rhodium or palladium to give a mixture of the 6α- and 6β-methyl epimers. The desired epimer is then isolated by chromatographic processes. US Pat 3,200,149.

Description—Yellow, crystalline powder; bitter taste; pK_a 3.4, 7.7, 9.7.

Solubility—Very slightly soluble in water; freely soluble in dilute acid or alkali hydroxide solutions; sparingly soluble in alcohol; practically insoluble in chloroform or ether.

Comments—The actions and uses generally are the same as other tetracyclines (see the general statement). Against gram-positive bacteria it is about twice as potent as tetracycline, except that it is up to 10 times as potent against *Strep viridans*. Furthermore, strains of *Enterococcus fecalis* that are resistant to other tetracyclines may be sensitive to the drug.

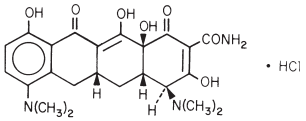
Against gram-negative bacteria it is as potent to twice as potent as tetracycline. It is the drug of first choice for prophylaxis of *travelers' diarrhea*, commonly caused by enterotoxigenic *E coli*. It is the best of the tetracyclines against anaerobes.

It is absorbed more completely (90–100%) after oral administration than other tetracyclines, and its absorption does not appear to be inhibited by foods. Plasma-protein binding is about 93%. It has a volume of distribution of 0.75 mL/g. It readily penetrates cells, body fluids and cavities. Elimination is about 65% by hepatic metabolism and 35% by biliary/renal excretion. The rate of excretion is slow and the half-life is the longest of the tetracyclines, namely, 12 to 22 hr. Renal insufficiency has little influence on plasma levels or duration of action.

The toxicity is that of tetracyclines in general, but there is a threefold greater incidence of GI effects and more frequent skin rashes than with other tetracyclines. Photosensitization occurs much more frequently than with shorter-acting tetracyclines. It complexes calcium to a lesser extent than other tetracyclines not affected by food or dairy products.

MINOCYCLINE HYDROCHLORIDE

2-Naphthacenecarboxamide, [4*S*-(4α,4aα,5aα,12aα)]-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-, monohydrochloride; Minocin



7-Dimethylamino-6-demethyl-6-deoxytetracycline [13614-98-7] $C_{23}H_{27}N_3O_7 \cdot HCl$ (493.94). Potency: equivalent to not less than 785 μg of minocycline ($C_{23}H_{27}N_3O_7$)/mg.

Preparation—6-Demethyltetracycline, dissolved in tetrahydrofuran containing methanesulfonic acid, is reacted with dibenzyl azodicarboxylate to form 7-[1,2-bis(carbobenzoxy)hydrazino]-6-demethyltetracycline. Palladium-catalyzed hydrogenation in the presence of formaldehyde yields minocycline which reacts with an equimolar quantity of HCl to form the monohydrochloride. US Pats 3,148,212 and 3,226,436.

Description—Yellow, crystalline powder; odorless; slightly bitter taste; slightly hygroscopic; stable in air when protected from light and moisture (strong light and/or moist air causes it to darken); potency in solution affected primarily caused by epimerization; pH (1 in 100 solution) between 3.5 and 4.5; pK_{a1} 2.8; pK_{a2} 5; pK_{a3} 7.8; pK_{a4} 9.3.

Solubility—1 g in approximately 60 mL water and approximately 70 mL alcohol; soluble in solutions of alkali hydroxides or carbonates; practically insoluble in chloroform or ether.

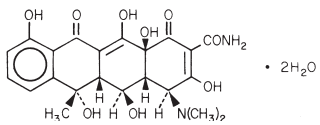
Comments—The actions and uses are essentially the same as those of the tetracyclines in general (see the general statement). Against most gram-positive organisms it appears to be generally two to four times as potent as tetracycline, but it shares an equally low potency against *Enterococcus fecalis*. Against *Strep viridans* it is about eight times as potent. Against gram-negative bacteria it is generally two to four times as potent as tetracycline. It is especially effective against *Mycobacterium marinum*, and it is now the drug of choice for treating infections caused by that bacterium. It differs from other tetracyclines in that bacterial resistance to the drug is of a lower order and incidence; this is especially true of staphylococci, in which cross-resistance has been reported to be as low as 4%.

The incidence and severity of the usual side effects of tetracyclines, effects like phototoxicity and GI upsets, are less than with other tetracyclines. However, nausea and vomiting are frequent, as the result of ototoxicity and CNS effects.

It is 90% to 100% absorbed by the oral route. Its absorption is diminished slightly by food and milk and markedly by nonsystemic antacids and iron preparations. It is 70% to 75% protein-bound in plasma. The volume of distribution is 0.14 to 0.7 mL/g. The half-life is 11 to 17 hr. Only 10% is reported to be excreted unchanged, but the half-life has been reported to be greatly prolonged in renal failure.

OXYTETRACYCLINE

2-Naphthacenecarboxamide, [4*S*-(4α,4aα,5α,5aα,6β,12aα)]-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,5,6,10,12,12a-hexahydroxy-6-methyl-1,11-dioxo-, dihydrate; Terramycin



[6153-64-6] $C_{22}H_{24}N_2O_9 \cdot 2H_2O$ (496.47); *anhydrous* [79-57-2] (460.44). Potency: not less than 832 mg of $C_{22}H_{24}N_2O_9$/mg.

Preparation—By the growth of a selected strain of *Streptomyces rimosus* on a medium consisting of water, proteins, and nutrient salts.

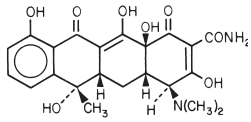
Description—Pale yellow to tan, odorless, crystalline powder; stable in air, but exposure to strong sunlight causes it to darken; deteriorates in solutions of pH less than 2, and is rapidly destroyed by alkali hydroxide solutions; saturated solution is nearly neutral to litmus, having a pH of approximately 6.5.

Solubility—1 g in 4150 mL water, 100 mL alcohol, >10,000 mL chloroform, 6250 mL ether; freely soluble in diluted hydrochloric acid or alkaline solutions.

Comments—A *tetracycline*. It is short-acting with incomplete oral absorption.

TETRACYCLINE

2-Naphthacenecarboxamide, [4*S*-(4α,4aα,5aα,6β,12aα)]-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,6,10,12,12a-pentahydroxy-6-methyl-1,11-dioxo-,



[60-54-8] $C_{22}H_{24}N_2O_8$ (444.44). Potency: equivalent to not less than 975 μg of tetracycline hydrochloride ($C_{22}H_{24}N_2O_8 \cdot HCl$)/mg, calculated on the anhydrous basis.

Preparation—By removal of chlorine from chlortetracycline by hydrogenation. Also obtained from a *Streptomyces* species cultured in an appropriate nutrient medium.

Description—Yellow, crystalline powder; odorless; stable in air, but exposure to strong sunlight causes it to darken; potency is affected in solutions of pH less than 2, and is destroyed rapidly by alkali hydroxide solutions; more soluble than chlortetracycline and within the physiological and moderately alkaline range of pH is more stable; its solutions darken more rapidly than chlortetracycline but less than oxytetracycline; pH (aqueous suspension, 10 mg/mL) between 3.0 and 7.0; pK_a 3.3, 7.7, 7.9.

Solubility—1 g in approximately 2500 mL water and approximately 50 mL alcohol; freely soluble in dilute HCl or alkali hydroxide solutions; practically insoluble in chloroform or ether.

Comments—The antibiotic spectrum, actions, toxicity, absorption, fate and excretion, doses and uses essentially the same as those of the tetracyclines in general (see the general statement). It has been reported to be useful in the treatment of toxoplasmosis; it is not known whether this use can be extended to all tetracyclines. The GI side effects are less than those from chlortetracycline and oxytetracycline but more than from demeclocycline. About 77% of an oral dose is absorbed. In the plasma 25% to 55% is bound to proteins. The volume of distribution is 1.5 mL/g.

About 60% is eliminated by renal excretion. The plasma half-life is 6 to 11 hr in patients with normal renal function; in oliguria it may be as long as 2 to 4 days, and dosage must be adjusted accordingly.

FLUOROQUINOLONES

The quinolone antibacterial drugs have been in use since 1964 when nalidixic acid was released. Oxolinic acid and cinoxacin were introduced later but have fallen into disuse because of their limited antibacterial spectra and rapid development of resistance The introduction of 6-fluoro and 7-(1-piperazinyl) groups to the existing structure has expanded the spectrum, increased potency, and may prevent the development of plasmid-mediated resistance. Since 1990, the fluoroquinolones have become a dominant class of antimicrobial agents. The fluoroquinolones are bactericidal agents. They are strong inhibitors of DNA gyrase (topoisomerase II) and topoisomerase IV. These enzymes are critical to the process of supercoiling DNA. Without such enzymatic activity, DNA replication cannot occur.

In general, the fluoroquinolones possess activity against gram-positive, gram-negative, and the atypical organisms. The older fluoroquinolones (ciprofloxacin, norfloxacin, ofloxacin) are highly active against gram-negative pathogens including *Pseudomonas aeruginosa* but their activity against streptococci and staphylococci is limited. Ciprofloxacin remains the fluoroquinolone with the most potent in vitro activity against *Pseudomonas aeruginosa*. The newer fluoroquinolones (levofloxacin, gatifloxacin, moxifloxacin, trovafloxacin) have enhanced activity against the gram-positive pathogens (*S aureus*, *S pneumoniae*) while maintaining similar gram-negative activity with the exception of *Pseudomonas aeruginosa*. Moxifloxacin is unique in that it possesses anti-anaerobic activity but lacks sufficient activity against *Pseudomonas aeruginosa*. Trovafloxacin has the broadest spectrum and best overall activity including better activity against anaerobes. Resistance to one fluoroquinolone usually confers resistance to all other quinolones but not to other classes of antimicrobial drugs.

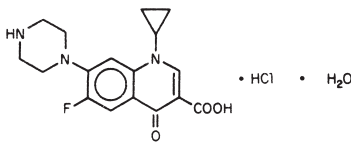
Adverse effects are usually mild and transient. They include GI disturbances (nausea, vomiting, diarrhea, dyspepsia, flatulence, constipation, heartburn, abdominal discomfort); CNS symptoms (ranging from headache and dizziness to seizures); mild or moderate rash and/or pruritus (photosensitivity, especially severe with sparfloxacin); arthropathy in growing children; increased likelihood of tendon ruptures (especially Achilles in adults); and arthralgias. Prolongation of QT interval occurs with some new fluoroquinolones. Some fluoroquinolones prolong the half-life of theophylline. Erosion of cartilage has been documented in young animals so the fluoroquinolones are not recommended for use in children under 18 years old or pregnant or nursing women. However, the agents have been used safely in the childhood population of patients with cystic fibrosis without sequelae.

Fluoroquinolones are all effective orally but also may be administered parenterally. They have large volumes of distribution and reach therapeutic concentrations in most tissues. They have long half-lives and may be administered only once or twice a day (Table 90-9).

Fluoroquinolones are used to treat upper and lower respiratory infections, gonorrhea, bacterial gastroenteritis, skin and soft tissue infections including osteomyelitis and both uncomplicated and complicated UTIs,.

CIPROFLOXACIN HYDROCHLORIDE

3-Quinolinecarboxylic acid, 1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-, monohydrochloride, monohydrate; Ciloxan, Cipro



[8693-32-0] $C_{17}H_{18}FN_3O_3 \cdot HCl \cdot H_2O$ (385.82).

Preparation—From 3-chloro-4-fluoroaniline by condensation with diethyl ethoxymethylenemalonate to form the imine which is thermally cyclized to ethyl 7-chloro-6-fluoro-4-hydroxyquinoline-3-carboxylate. *N*-alkylation with cyclopropyl iodide followed by nucleophilic displacement of the 7-chloro group by *N*-methylpiperazine and hydrolysis of the ester affords the product. *J Med Chem* 1976;19:1138.

Description—Pale-yellow crystals; amphoteric; pK_a 6, 8.8.

Solubility—1 g in 25 mL water.

Comments—It is approved for use in the treatment of bone and joint infections, infectious diarrhea, lower respiratory tract infections, and urinary tract infections. For hospital-acquired infections, ciprofloxacin remains the preferred agent because it possesses the best activity against Pseudomonas aeruginosa. Ciprofloxacin is also recommended for meningococcal prophylaxis.

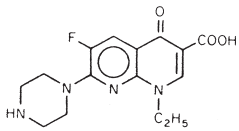
The oral bioavailability is about 70% to 80%. Urinary excretion accounts for the elimination of 40% to 50% of an oral dose. Twenty to 35% is eliminated in the feces. There is hepatic biotransformation of four known metabolites, which accounts for 15% of a dose. The half-life is about 4 hr.

Table 90-9. Fluroquinolones

DRUGS	COMMENTS
Classical Fluoroquinolones	
Ciprofloxacin	Intermed. spectrum, good distribution
Norfloxacin	Incomplete oral absorption, limited spectrum
Ofloxacin	Intermed. spectrum
Levofloxacin	More active than ofloxacin, long acting
Enoxacin	Limited spectrum
Lomefloxacin	Intermed. spectrum, phototoxicity
Pefloxacin	Intermed. spectrum, long acting, phototoxicity
Newest Fluoroquinolones	
Sparfloxacin	Expanded spectrum, long acting, serious phototoxicity problems
Grepafloxacin	Expanded spectrum, long acting
Trovafloxacin	Expanded spectrum, no effect on drug metabolizing enzymes

ENOXACIN

1,8-Naphthyridine-3-carboxylic acid, 1-ethyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-, Penetrex



[74011-58-8] $C_{15}H_{17}FN_4O_3$ (320.32).

Preparation—The active 2-chloro group of 2,6-dichloro-3-nitropyridine is nucleophilically displaced by *N*-carbethoxypiperazine; then the 6-chloro atom is displaced with ammonia and the resulting amined acylated to the acetamide. The nitro group is reduced, diazotized, and treated with HBF_4 to yield the fluoro derivative. The balance of the synthesis is analogous to that for *ciprofloxacin*; *J Med Chem* 1984; 27:292.

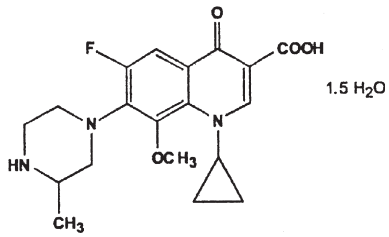
Description—White crystals; bitter taste; melts at approximately 222°.

Solubility—1 g in 3330 mL water.

Comments—A *limited-spectrum fluoroquinolone*.

GATIFLOXACIN

3-Quinolinecarboxylic acid, (±)-1-Cyclopropyl-6-fluoro-1,4-di-hydro-8-methoxy-7-(3-methyl-1-piperazinyl)-4-oxo-, sesquihydrate; Tequin



[160738-57-8](anhydrous) $C_{19}H_{22}FN_3O_4 \cdot \frac{1}{2}H_2O$ (402.42).

Preparation—A 10-step synthesis starting with 2,4,5-trifluoro-3-hydroxybenzoic acid. *J Med Chem* 1995; 38:4478.

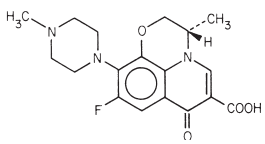
Description—White to pale yellow crystalline powder melting about 160°.

Solubility—Aqueous solubility is pH dependent with maximum (40-60 mg/mL) at pH 2-5.

Comments—An 8-methoxyfluoroquinolone with enhanced activity against gram-positive organisms (especially S. pneumonia). Not clinically active against *P aeruginosa*. Clinically useful in the treatment of upper and lower respiratory tract infections. It is available both orally and parenterally.

LEVOFLOXACIN

7*H*-Pyrido[1,2,3-*de*]-1,4-benzoxazine-6-carboxylic acid, (*S*)-9-fluoro-2,3-dihydro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-, hemihydrate; Levaquin; Cravit



[138199-71-0] $C_{18}H_{20}FN_3O_4 \cdot \frac{1}{2}H_2O$ (369.93).

Preparation—US Pat 4,382,892 (1983); Lednicer D, et al. *Org Chem of Drug Syn*, vol 4, New York: Wiley, 1990, p 141.

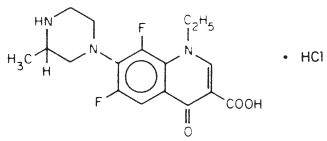
Description—White to light yellow needles melting about 226° (dec). It is the (−) isomer; the racemic form is *ofloxacin*. Forms stable coordination complexes with metal ions (eg, Al > Cu > Zn > Mg > Ca in order if decreasing stability).

Solubility—Essentially constant from pH 0.6 to 5.8 (100 mg/mL). Above pH 5.8 solubility increases rapidly and at pH 6.7 it reaches a max of 272 mg/mL. Above pH 6.7 solubility decreases to a min of 50 mg/mL at pH 6.9.

Comments—The more active *levo* isomer of ofloxacin (a racemic mixture of D,L-isomers) that has improved activity against gram-positive pathogens (in particular against S. pneumoniae) compared to ciprofloxacin. It is well absorbed after oral administration and more than 80% of dose is excreted in urine. Its side effects are similar to other fluoroquinolones. Useful in the treatment of urinary tract infections, lower respiratory tract infections.

LOMEFLOXACIN HYDROCHLORIDE

3-Quinolinecarboxylic acid, (±)-1-ethyl-6,8-difluoro-1,4-dihydro-7-(3-methyl-1-piperazinyl)-4-oxo-, monohydrochloride; Maxaquin



[98079-52-8] $C_{17}H_{19}F_2N_3O_3 \cdot HCl$ (387.81).

Preparation—By a method analagous to that for *Enoxacin*; US Pat 4,528,287.

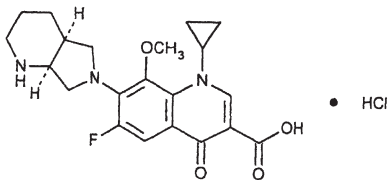
Description—Colorless needles; melts about 295° with decomposition.

Solubility—Soluble in water.

Comments—Another limited-spectrum fluoroquinolone that is similar in antibacterial activity to enoxacin. It is approved only for treatment of UTIs and bronchitis caused by *H influenzae* or *Branhamella catarrhalis*. It covers gram-negative organisms frequently associated with UTIs but does not have the activity to cover the same bacterial infections which respond to ciprofloxacin and ofloxacin.

MOXIFLOXACIN HYDROCHLORIDE

3-Quinolinecarboxylic acid, (4a*S*-*cis*)-1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-(octahydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)-4-oxo-, monohydrochloride; Avelox, Vigamox



[186826-86-8] $C_{21}H_{24}FN_3O_4 \cdot HCl$ (437.89).

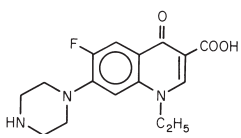
Preparation—US Pats 4,254,135 (1981) and 4,990,517 (1991).

Description—Slightly yellow to yellow crystals melting about 325°. $[\alpha]^{25}_D$ -256° (c = 0.5, water).

Comments—An 8-methoxy fluoroquinolone with enhanced activity against gram-positive organisms (in particular *S pneumoniae*) and moderate anti-anaerobic activity. Not clinically active against *P aeruginosa*. Clinically useful for the treatment of upper and lower respiratory tract infections. It is available both orally and parenterally.

NORFLOXACIN

3-Quinolinecarboxylic acid, 1-ethyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-, Chibroxin, Noroxin



[70458-96-7] $C_{16}H_{18}FN_3O_3$ (319.34).

Preparation—Similar to *Ciprofloxacin*, see *J Med Chem* 1980; 23:1358.

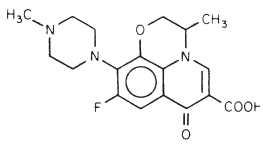
Description—White to pale-yellow crystalline powder; melts about 221°; hygroscopic and forms a hemihydrate in air; pK_a 6.3, 8.8.

Solubility—Very slightly soluble in water, methanol or alcohol; freely soluble in glacial acetic acid.

Comments—A *limited-spectrum fluoroquinolone*. It has incomplete oral absorption.

OFLOXACIN

7*H*-Pyridol[1,2,3-*de*]-1,4-benzoxazine-6-carboxylic acid, (±)-9-fluoro-2,3-dihydro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-, Floxin



[82419-36-1] $C_{18}H_{20}FN_3O_4$ (361.38). The carbon atom to which the methyl group is attached, in the oxazine ring, is chiral and the clinically used substance is a racemic mixture, whereas the (+) form has twice the activity of the (−) form.

Preparation—By a method analogous to that for *Ciprofloxacin*; US Pat 4,382,892.

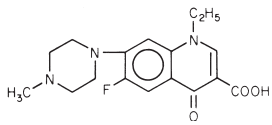
Description—Colorless needles; melts about 255° with decomposition; pK_a 7.9.

Solubility—Poorly soluble in water or ethanol.

Comments—An *intermediate-spectrum fluoroquinolone.*

PEFLOXACIN

3-Quinolinecarboxylic acid, 1-ethyl-6-fluoro-1,4-di-hydro-7-(4-methyl-1-piperazinyl)-4-oxo-,



Preparation—US Pat 4,292,317 (1981); Lednicer D, et al. *Org Chem of Drug Syn*, vol 4, p 141. New York: Wiley, 1990.

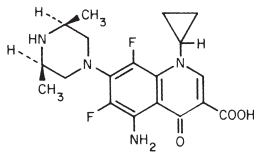
Description—White crystals melting about 271° (dec). It is the *N*-methyl analog of norfloxacin.

Solubility—Slightly soluble in water; soluble in fixed acids or alkalies.

Comments—An intermediate spectrum, long acting fluoroquinolone; causes.

SPARFLOXACIN

3-Quinolinecarboxylic acid, *cis*-5-amino-1-cyclopropyl-7-(3,5-dimethyl-1-piperazinyl)-6,8-difluoro-1,4-dihydro-4-oxo-, Zagam



[110871-86-8] $C_{19}H_{22}F_2N_4O_3$ (392.41).

Preparation—US Pat 4,795,751 (1989); *J Med Chem* 1990; 33:1645.

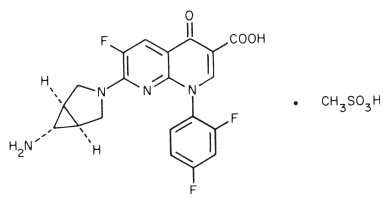
Description—Yellow crystalline powder melting about 268°(dec); pK_{a1} −6.25; pK_{a2} −9.30.

Solubility—Sparingly soluble in glacial acetic acid or chloroform; very slightly soluble in alcohol; practically insoluble in water or ether. Soluble in dilute mineral acids or fixed bases (ca 0.1 *N*).

Comments—It is a newer fluoroquinolone with improved activity against *Strep pneumoniae* and other lower respiratory pathogens covered by grepafloxacin. It is more active against *Mycoplasma* than other fluoroquinolones. It has excellent oral bioavailability (92%) and is metabolized mainly by hepatic glucuronidation rather than cytochrome P450-mediated pathways. Consequently, it does not affect the clearance of other drugs (like theophylline, cimetidine, digoxin, warfarin and cyclosporine) that occurs with some fluoroquinolones. It has a half-life of approximately 20 hr. Its side effects are similarto other fluoroquinolones except that photosensitivity is much more severe.

TROVAFLOXACIN

1,8-Naphthyridine-3-carboxylic acid, (1α,5α,6α)-7-(6-amino-3-azabicyclo[3.1.0]hex-3-yl)-1-(2,4-difluorophenyl)-6-fluoro-1,4-dihydro-4-oxo-, monomethanesulfonate; Trovan



[147059-75-4] $C_{20}H_{15}F_3N_4O_3 \cdot CH_4O_3S$ (512.47).

Preparation—US Pat 5,164,402 (1992).

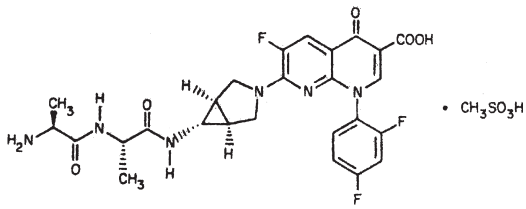
Description—White to off-white powder.

Comments—It is a newer fluoroquinolone that is similar to the antibacterial spectrum of grepafloxacin that involves a better activity against some respiratory pathogens than the older fluoroquinolones

such as ciprofloxacin. It is more active against *Strep pneumoniae* (including penicillin-resistant strains), *Staph aureus* (including methicillin-resistant strains), Enterococcus faecalis, and most important respiratory tract pathogens (*H influenzae, Moraxella, Legionella, Neisseria*). It is highly active against *Chlamydia*, *Mycoplasma*, and *Ureaplasma*, plus covers important anaerobes such as *Bacteroides fragilis* and the gram-negative *Enterobacteriaciae*, including *Ps aeruginosa*. Its use has been very limited secondary to serious adverse events.

ALATROFLOXACIN MESYLATE

L-Alaninamide, (1α,5α,6α)- L-alanyl-*N*-[3-[6-carboxy-8-(2,4-difluorophenyl)-3-fluoro-5,8-dihydro-5-oxo-1,8-naphthyridin-2-yl]-3-azabicyclo[3.1.0]hex-6-yl-, monomethanesulfonate; Trovan (Tablets only)



[157605-25-9] $C_{26}H_{25}F_3N_6O_5 \cdot CH_4O_3S$ (654.63).

Preparation—US Pat 5,164,402 (1992) and *J Chem Soc Perkin Trans* 2000; 1:1615.

Description—White to light yellow powder. *Alatrofloxacin* is *Trovaloxacin* with the L-alanyl-L-alanine side chain appended to the amino group on the 3-member ring of the azabicyclohexyl moiety.

Comments—The intravenous form of trovafloxacin.

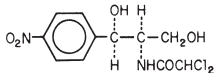
MISCELLANEOUS ANTIBACTERIAL AGENTS

These antibacterial agents are principally second-line drugs because of emerging resistance, concerns with toxicity, or special activity against selected organisms. Chloramphenicol has the potential for causing aplastic anemia but is an alternative for treatment of life-threatening infections such as bacterial meningitis or rickettsial infections. Clindamycin is a unique licosamide antibiotic that is useful for anaerobic infections but is only bacteriostatic against streptococci and staphylococci. It also covers some parasitic infections such as pneumocystis and toxoplasmosis that occur in immunosuppressed patients. Spectinomycin is only used to treat gonococcal infections in patients unable to receive first-line drugs. Rifampin is important for prophylaxis of meningococcal disease and *H influenzae* meningitis plus some cases of *Mycobacterium avium* infections in AIDS patients. Vancomycin is a very specialized glycopeptide antibiotic for serious hospital infections caused by staphylococci (especially methicillin-resistant strains) and enterococci. Consequently, vancomycin should be reserved for those conditions where it is often the only effective drug available for such infections.

AMPHOTERICIN B—page 1670.

CHLORAMPHENICOL

Acetamide, [*R*-(*R,*R**)]-2,2-dichloro-*N*-[2-hydroxy-1-(hydroxymethyl)-2-(4-nitrophenyl)ethyl-, Chloromycetin**



D-*threo*- (−)-2,2-Dichloro-*N*-[β-hydroxy-α-(hydroxymethyl)-*p*-nitrophenethyl]acetamide [56-75-7] $C_{11}H_{12}Cl_2N_2O_5$ (323.13). Potency: not less than 900 μg of $C_{11}H_{12}Cl_2N_2O_5$/mg.

Preparation—Chloramphenicol is believed to be the first naturally occurring compound known to contain a nitro group or to be a derivative of dichloroacetic acid. Its stereochemical configuration is analogous to that of (−)-norpseudoephedrine, and is the only one of the four related stereoisomers that has antibiotic activity.

Chloramphenicol can be obtained from the filtrate of a *Streptomyces venezuelae* culture by extraction with ethyl acetate. If the charcoal extract is rich in chloramphenicol, the latter can be crystallized from the ethyl acetate by diluting with many volumes of kerosene.

Several synthetic methods of preparation are known. One of the better known commences with *p*-nitroacetophenone and, after converting it into *p*-nitro-2-aminoacetophenone, proceeds through the following steps: (a) acetylation of the—NH_2 group, (b) reaction with HCHO to introduce the terminal—CH_2OH group, (c) reduction with aluminum isopropoxide to give a mixture of the racemates of the *threo* and *erythro* forms of *p*-$NO_2PhCH(OH)CH(NH_2)CH_2OH$, (d) isolation of the *threo* racemate and resolution of it using *d*-camphorsulfonic acid, and (e) condensing the (−) enantiomorph with methyl dichloroacetate.

Description—Fine, white to grayish white or yellowish white, needle-like crystals or elongated plates; odorless; intensely bitter taste; pH (saturated solution) between 4.5 and 7.5; reasonably stable in neutral or moderately acid solutions but rapidly destroyed in alkaline solutions; melts between 149° and 153°; pK_a 5.5.

Solubility—1 g in approximately 400 mL water; freely soluble in alcohol; slightly soluble in ether or chloroform.

Comments—A wide spectrum of antibacterial activity. The drug is effective in rickettsial diseases including epidemic, murine and scrub typhus, Rocky Mountain spotted fever, rickettsial pox and Q fever; chlamydial diseases including the psittacosis-lymphogranuloma group and many gram-positive and gram-negative bacterial infections including the anaerobes (especially *Bacteroides fragilis*). Because of serious toxic reactions, the systemic use of the drug should be limited only to very serious infections that cannot be managed by other drugs. It is still the drug of choice for typhoid fever.

It is used topically for superficial conjunctival infections and blepharitis caused by *E coli, H influenzae, Moraxella lacunata, Staph aureus,* and *Strep hemolyticus*. Bone-marrow injury is the major toxic effect. Thrombocytopenia, granulocytopenia, and aplastic anemia are the most serious hematopoietic disturbances observed and have resulted in a number of fatalities.

In neonates it may cause the *Gray syndrome*, a fatal cyanosis (40% of cases) with symptoms of vomiting, abdominal distention, and loose, green stools, owing to the inability of the infant to metabolize the drug in consequence of glucuronyl transferase deficiency. Optic atrophy and blindness occur in a small number of cases, mainly in children on prolonged therapy.

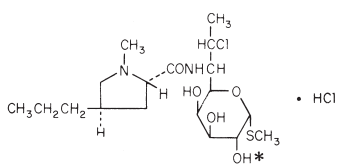
Minor untoward effects such as transient mild euphoria, skin rash, and GI disturbances have been observed; the drug is contraindicated in patients with a history of previous sensitization.

Occasional untoward effects include glossitis, stomatitis, and pharyngitis. Its use, as with other antibiotics, may result in an overgrowth of microorganisms not susceptible to the drug. Oral anticoagulants, oral hypoglycemics, phenytoin, and perhaps acetaminophen inhibit its metabolism and increase the risk of intoxication; appropriate dose adjustments should be made. Rifampin decreases plasma concentrations.

The drug is absorbed rapidly from the GI tract, with a bioavailability of about 90%. Sixty percent of the drug in blood is bound to serum albumin. The volume of distribution is about 0.7 mL/g. From 85% to 95% is biotransformed in the liver. The half-life is 1.5 to 5 hr, except over 24 hr in neonates 1 to 2 days old and 10 hr in infants 10 to 16 days old. Because of considerable variability, plasma levels must be monitored. Also, the clearance increases with continuous use, and dose adjustments are necessary. When there is impaired hepatic function, and sometimes of renal function as well, the dosage must be reduced, according to determined plasma concentrations. It can cross the placental barrier and intoxicate the fetus, so that the drug should be avoided in pregnancy, if possible.

CLINDAMYCIN HYDROCHLORIDE

L-*threo*-α-D-*galacto*-Octopyranoside, methyl (2*S*-*trans*)-7-chloro-6,7,8-trideoxy-6-[[(1-methyl-4-propyl-2-pyrrolidinyl)carbonyl]-amino]-1-thio-, monohydrochloride; Cleocin Hydrochloride



(*) Indicates site of esterification to form the palmitate or phosphate derivatives.

[21462-39-5] $C_{18}H_{33}ClN_2O_5S \cdot HCl$ (461.44). Potency: equivalent to not less than 800 μg of clindamycin/mg.

Preparation—Lincomycin is treated with a solution of Rydon reagent prepared from triphenylphosphine, acetonitrile, and chlorine. The base is ultimately reacted with HCl. *CA* 1970; 73:15185*v*.

Description—White or practically white, crystalline powder; strong, characteristic taste; odorless or has a faint mercaptan-like odor; stable in air and light; pK_a 7.72; melts about 142°.

Solubility—1 g in 2 mL water or 200 mL ethanol.

Comments—An antibacterial spectrum very much like that of *Lincomycin*, from which it is derived. However, among staphylococci and several streptococci it may be as much as 20 times more potent. It is also more potent against certain gram-negative organisms, but not against gram-negative cocci; with the recommended doses the plasma levels usually are not high enough to be effective against gram-negative bacteria. It is especially useful in the treatment of several infections caused by anaerobes; it is the drug of choice for treatment of GI infections caused by *Bacteroides fragilis*. It is important as an alternate drug for treating infections caused by penicillin-resistant *Staph aureus*. It also is used for treatment of respiratory tract infections and pharyngitis or tonsillitis caused by *Strep pyogenes*. It is perhaps the best drug for the topical treatment of acne vulgaris (used as the phosphate).

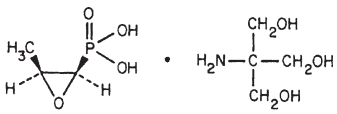
It may cause abdominal pain, nausea, vomiting, diarrhea and loose stools, which may occasionally contain blood and mucus. Incidence of benign diarrhea is about 10% to 20%. Incidence of antibiotic-associated (pseudomembranous) colitis is estimated to be 1:10,000. Allergic rashes and urticaria occur with an incidence of about 10%.

By the oral route, bioavailability is about 90% with low doses. The presence of food in the stomach and intestines does not appear to interfere with absorption. In plasma it is 60% to 95% protein-bound. Its volume of distribution is about 0.66 mL/g. It is distributed widely in most tissues, body fluids and bone.

However, high enough concentrations are not achieved in CSF to be used to treat meningitis. Most of it is eliminated in the liver, only about 10% being excreted in the urine. The half-life is 2.4 to 3 hr, except 3.5 to 5 hr in anuria and 7 to 14 hr in liver disease. Hepatic failure can be expected to reduce the dose requirement more than renal failure.

FOSFOMYCIN TROMETHAMINE

Phosphonic acid, (2*R-cis*)-(3-methyloxiranyl)-, compd with 2-amino-2-(hydroxymethyl)-1,3-propanediol (1:1); Monurol



[78964-85-9] $C_3H_7O_4P{\cdot}C_4H_{11}NO_3$ (259.20).

Preparation—The thermal rearrangement of di-*tert*-butyl 2-propynyl phosphite yields the ester, di-*tert*-butyl propadienyl phosphonate. Selective hydrogenation followed by acid-catalyzed cleavage of the *t*-butyl groups forms *cis*-propenylphosphonic acid. Treatment of the acid with hydrogen peroxide and sodium tungstate gives the epoxide, which is resolved to the 2*R-cis* compound. Final reaction with 2-amino-2-(hydroxymethyl)-1,2-propanediol yields the salt. *J Org Chem* 1970; 35:3510 and US Pat 3,914,231 (1969).

Description—(Acid) White granular solid melting about 133°. $[\alpha]^{28}_{405}$ -2.6° (c = 5, water); + 18.7° (c = 3, DMF).

Comments—A single dose treatrment option for uncomplicated urinary tract infections in women. A less effective treatment alternative than fluorquinolones for this condition, but a viable choice in patients who have a contraindication to fluoroquinolone therapy. Adverse events commonly are gastrointestinal in nature.

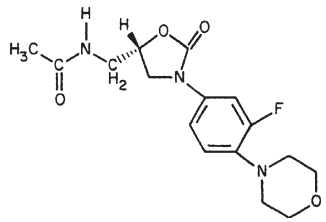
Oxazolidinones

The oxazolidinones are a totally synthetic antibiotic class first investigated in the late 1980s as antidepressant agents. Serendipitously, these agents were discovered to have excellent antibacterial activity. The main reason for their development has been the increase and spread of resistance in gram-positive pathogens. The first agent in this class, l inezolid, was approved by the FDA in April 2000.

The oxazolidinones are protein-synthesis inhibiting compounds that most commonly produces a bacteriostatic effect. They bind to the 50S ribosome at a unique site and disrupt protein synthesis. The principal activity of the class is against gram-positive aerobic organisms including staphylococci, streptococci, and enterococci. In particular, activity against resistant pathogens such as methicillin-resistant staphylococci, penicillin-resistant streptococci, and vancomycin-resistant enterococci, is excellent.

LINEZOLID

Acetamide, (*S*)-*N*-[[3-[3-fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]-, Zyvox



[165800-03-3] $C_{16}H_{20}FN_3O_4$ (337.35).

Preparation—Several multi-step methods starting with *p*-acetylphenyliso-thiocyanate. US Pat 5,688,792 (1997) ; *Tetrahedron Letters* 1999; 40:4855 and *Albany Molecular Research, Tech Reports* 9(17):14-18.

Description—White crystals from ethyl acetate melting about 182°; $[\alpha]^{20}_D$ − 9° (c = 0.919, chloroform).

Comments—The only oxazolidinone commercially available to date. Both intravenous and oral formulations are commercially available. The bioavailability of the oral formulation is 100%. Linezolid is predominately eliminated by nonrenal mechanisms. Its metabolism does not involve the cytochrome P450 system. Two inactive metabolites are the major by-products of this conversion to water-soluble products that are excreted by the kidney.

In general, linezolid is well tolerated. The most common adverse effects are diarrhea, nausea, taste perversion, and vomiting. Thrombocytopenia has been reported in up to 4% of patients in clinical trials and has been associated with more than 2 weeks duration of therapy. Linezolid also possesses weak monoamine oxidase inhibitory activity. Therefore, the potential for drug interactions with sympathomimetic agents or foods rich in tyramine does exist.

Linezolid has proven useful in the treatment of a variety of infections caused by resistant gram-positive pathogens such as MRSA and VRE.

Streptogramins

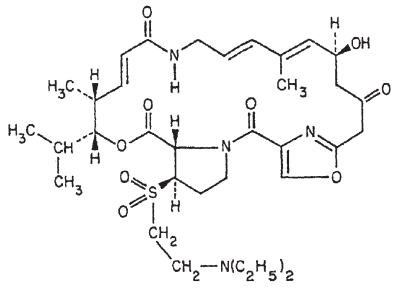
The streptogramin antibiotics are naturally occurring products that have been in clinical use in Europe fpr more than 30 years as oral agents to treat mild to moderate infections. A semisynthetic derivative, quniupristin/dalfopristin, is the first injectable streptogramin antibiotic.

The streptogramins inhibit protein synthesis by binding to the 50S ribosome. The interaction of quinupristin and dalfopristin is synergistic. Either compound alone is bacteriostatic whereas the combination results in a bactericidal effect. The streptogramins are bactericidal against most organisms with the exception of enterococcus.

The principal activity of the streptogramins is against gram-positive aerobic organisms including staphylococci, streptococci, and enterococci. In particular, activity against resistant pathogens such as methicillin-resistant staphylococci, penicillin-resistant streptococci, and vancomycin-resistant *E faecium*, is excellent. Quinupristin/dalfopristin is not active against *Enterococcus faecalis*.

DALFOPRISTIN

Virginiamycin M_1, (26*R*, 27*S*)- 26-[[2-(diethylamino)ethyl]sulfonyl]-26,27-dihydro-, Ing of Synercid, which is approx 30% *Quinupristin* and 70% *Dalfopristin*



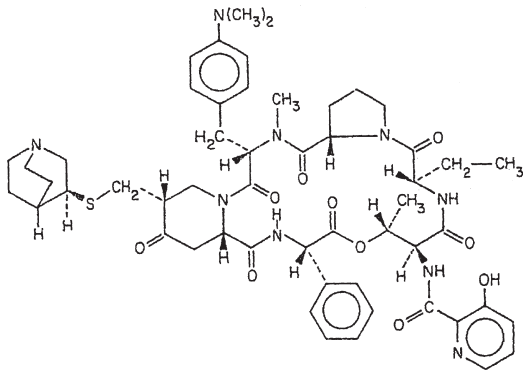
[112362-50-2] $C_{34}H_{50}N_4O_9S$ (690.85).

Preparation—US Pat 4,669,669 (1987).

Description—White to slightly yellow hygroscopic powder melting about 150°. A synthetic polyunsaturated macrolactone type II *Streptogramin* derived from pristinamycin.

QUINUPRISTIN

Virginiamycin S_1, (*S*)-4-[4-(dimethylamino)-*N*-methyl-L-phenylalanine]-5-[5-[(1-azabicyclo[2.2.0]oct-3-ylthio)methyl]-4-oxo-L-2-piperidinecarboxylic acid]-, Ing of Synercid



[120138-50-3] $C_{53}H_{67}N_9O_{10}S$ (1022.23).

Preparation—US Pat 4,798,703 (1987).

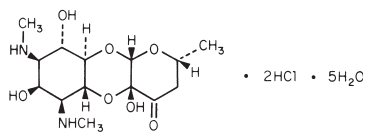
Description—White crystals from methanol.

Comments—The only streptogramin commercially available in the United States. Quinupristin/dalfopristin is not absorbed from the gastrointestinal tract. After intravenous administration, both compounds have a serum half-life of approximately 1 hour. Clearance of both agents is through the liver. Although the cytochrome P450 system is not involved in the metabolism, CYP3A4 is significantly inhibited by quinupristin/dalfopristin, potentially increasing the levels of agents such as cyclosporine, warfarin, and the azoles. The most common adverse effects are infusion related. Infusion site reactions including pain, inflammation, edema and thrombophlebitis have been reported in as many as 75% of patients who received the drug through a peripheral IV catheter. Arthralgias and myalgias have also been reported which may be severe and require discontinuation of therapy. The most common laboratory abnormality is hyperbilirubinemia.

Quinupristin/dalfopristin has been used primarily in the treatment of resistant gram-positive infections including methicillin-resistant staphylococci, penicillin-resistant pneumococci and vancomycin-resistant E. faecium.

SPECTINOMYCIN HYDROCHLORIDE

4*H*-Pyrano[2,3-*b*][1,4]benzodioxin-4-one, [2*R*-(2α,4aβ,5aβ,6β,7β,8β,9α,9aα,10aβ)]-decahydro-4a,7,9-trihydroxy-2-methyl-6,8-bis(methyl-amino)-, dihydrochloride, pentahydrate; Trobicin



[22189-32-8]; $C_{14}H_{24}N_2O_7 \cdot 2HCl \cdot 5H_2O$ (495.35); *anhydrous* [21736-83-4] (405.27). Potency: equivalent to not less than 603 μg spectinomycin/mg.

Preparation—By growth of the soil microorganism *Streptomyces spectabilis*. Reaction with a double equimolar quantity of HCl yields the hydrochloride. *Antibiot Chemother* 1961; 11:118 and 661, US Pat 3,234,092.

Description—White, odorless, crystalline powder; slightly bitter taste; stable in light; nonhygroscopic; stable in air at room temperature; pK_a 6.88, 8.84.

Solubility—1 g in approximately 7 mL water; practically insoluble in alcohol, chloroform or ether.

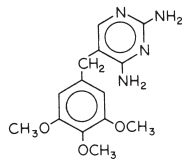
Comments—A wide-spectrum antibiotic with moderate activity against both gram-positive and gram-negative bacteria. However, it is employed clinically for only one purpose, namely, to treat or prevent acute gonorrhea when the organism is resistant to penicillin, or when the patient is allergic to penicillin. It is not as effective as ceftriaxone. Resistance sometimes develops. It is not effective in eradicating pharyngeal gonococcal infections in more than 50% of patients.

Orally, the drug is absorbed poorly and must be given intramuscularly. The distribution coefficient is 0.12 mL/g. About 75% is excreted into urine unchanged. Plasma half-life is approximately 1 to 3 hr.

Untoward effects caused include frequent pain at the site of injection and infrequent headache, nausea, vomiting, insomnia, chills, fever, mild pruritus, and urticaria. It does not eradicate *Treponema* or *Chlamydia trachomatis*, which are common sexually transmitted pathogens.

TRIMETHOPRIM

2,4-Pyrimidinediamine, 5-[(3,4,5-trimethoxyphenyl)methyl]-, Proloprim, Trimpex



2,4-Diamino-5-(3,4,5-trimethoxybenzyl)pyrimidine [738-70-5] $C_{14}H_{18}N_4O_3$ (290.32).

Preparation—By interaction of a-(ethoxymethyl)-3,4,5-trimethoxycinnamonitrile and guanidine, the former prepared by condensing 3,4,5-trimethoxybenzaldehyde with β-ethoxypropionitrile. US Pat 3,049,544.

Description—White to cream-colored crystals or crystalline powder; odorless; bitter taste; melts about 199°; pK_a approximately 6.6.

Solubility—Very slightly soluble in water; 1 g in approximately 285 mL absolute alcohol or 53 mL chloroform.

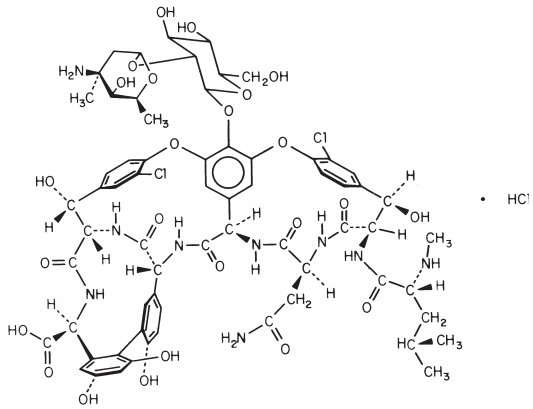
Comments—A congener of pyrimethamine and it similarly inhibits dihydrofolate reductase, although it is considerably less potent. It was introduced as an antimalarial drug (mostly against *Plasmodium falci-parum*) and is still used somewhat for that purpose, usually in combination with an appropriate sulfonamide. However, its most important use is as an antibacterial agent. Bacterial dihydrofolate reductases are generally more susceptible than are the plasmodial ones. Therefore, the drug is effective against all bacteria that must synthesize their own folinic acid (leucovorin). This gives it a wide spectrum of activity that includes *Strep pyogenes, viridans* and *pneumoniae, Staph aureus* and *epidermidis, H influenzae, Klebsiella-Enterobacter-Serratia, E coli*, various *Shigella* and *Salmonella, Bordetella pertussis, Vibrio cholerae, Pneumocystis carinii, Toxoplasma gondii,* and *Plasmodia*. It is not effective against *Ps aeruginosa* but is against *Ps cepaciae* and *pseudomallei*. Many of these same organisms must also synthesize their own folic acid. Sulfonamides and dapsone block the incorporation of *p*-aminobenzoate into folate, thus inhibiting a crucial biosynthetic step just previous to that where this drug acts. Therefore, the combination of this drug and sulfonamides or dapsone is supposedly more effective than either drug alone, although clinical confirmation of significant synergism is lacking. Nevertheless, it is widely used in combination with sulfamethoxazole. It alone is approved for the same uses as the above combination. It would seem prudent to use the combination for UTIs, even though the cost is greater, but the pharmacokinetics are such that sulfamethoxazole in the present formulation adds little to this drug alone for systemic infections. The combination of dapsone and trimethoprim is used in the treatment of leprosy and infections by *Mycobacterium avium*.

Mammalian dihydrofolate reductase is about 1:10,000 to 1:50,000 as sensitive to it as the bacterial enzymes, so that there is little interference with folate metabolism in man. The toxicity is low. It includes occasional nausea and vomiting, diarrhea, malaise, immunosuppression and, rarely, rash, leucopenia, and thrombocytopenia. It increases bone-marrow suppression and immunosuppression by antineoplastics. It is potentially teratogenic.

By the oral route, it is well absorbed and reaches a peak in 2 to 3 hr. About 45% is protein-bound in plasma. The volume of distribution is about 1.8 mL/g. The concentration in CSF reaches 30% to 50% of that in plasma. It is excreted mainly into the urine. The half-life is 9 to 12 hr in normal adults, but may be increased 2- to 3-fold when the creatinine clearance falls below 10 mL/min. It is considerably shorter in infants and children. The drug decreases the renal clearance of procainamide and acecainide. Rifampin accelerates its elimination.

VANCOMYCIN HYDROCHLORIDE

Vancomycin, hydrochloride; Lyphocin; Vancocin, Vancoled



Vancomycin hydrochloride [1404-93-9] is a substance produced by growth of *Streptomyces orientalis* (Fam *Streptomycetaceae*). Potency: equivalent to not less than 900 μg of vancomycin/mg, calculated on the anhydrous basis.

Preparation—Vancomycin is produced by the submerged fermentation process. After purification the base is converted to the soluble hydrochloride with HCl. See *Antibiot Ann* 1955–1956; 606. US Pat 3,067,099.

Description—Tan to brown, free-flowing powder; odorless; bitter taste.

Solubility—Freely soluble in water; insoluble in ether or chloroform.

Comments—A glycopeptide highly active against gram-positive cocci, *Neisseria* and *Clostridia*. It inhibits synthesis of peptidoglycan in cell-wall formation. It is one of the drugs of choice in the treatment of antibiotic-associated colitis and other infections caused by *Cl difficile*. The rapid emergence of methicillin-resistant staphylococci makes this drug valuable in the treatment of severe staphylococcal infections. Development of resistance to vancomycin is uncommon, but has been seen in Enterococci and rarely in Staphylococci. There is no cross-resistance to other antibiotics. Streptococcal (especially *Strep vividans* and *bovis*), enterococcal and pneumococcal infections also are treated with the drug. It is used only in combination with an aminoglycoside in treating enterococcal endocarditis.

It is absorbed poorly from the GI tract, so that it may be used orally against staphylococcal and enterococcal enteritis and antibiotic-associated enterocolitis. In plasma, 55% is protein-bound. It poorly enters the CSF with uninflammed meninges. The volume of distribution is 0.7 L/kg. The distribution half-life is 0.5 hr. The elimination half-life is 4 to 6 hr in adults.

Since the drug is 70% eliminated by excretion in urine, the half-life in anuric patients ranges from 3 to 10 days and doses must be appropriately adjusted.

It is irritating to tissue and may cause thrombophlebitis, or pain at the site of injection and necrosis occurs if extravasated; also chills, fever, occasional urticaria and maculopapular rashes with hypotension (red man's syndrome), nephrotoxicity and ototoxicity and, rarely, thrombocytopenia and neutropenia. True allergy is very rare.

ANTIMYCOBACTERIAL DRUGS

Drugs used in the treatment of tuberculosis, *Mycobacterium avium* and leprosy can be grouped together because all involve slow growing microorganisms that cause chronic diseases. Therapeutic problems are also similar and consist of prolonged therapy regimens with drug toxicity, microbial resistance and the challenges of patient compliance.

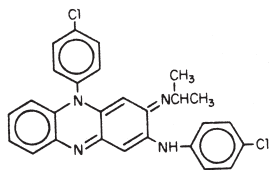
The first-line drugs for tuberculosis include isoniazid, rifampin, ethambutol, pyrazinamide, and streptomycin. Excellent responses can now be obtained with a 6-month regimen: isoniazid, rifampin, and pyrazinamide for the first 2 mo, followed by isoniazid and rifampin for the remaining 4 mo. Isoniazid is the only drug approved for prophylaxis of tuberculosis. Hepatoxicity is observed with chronic use of isoniazid, rifampin, and pyrazinamide. The first new drug approved in the last 25 yr for tuberculosis is rifapentine, a cyclopentyl derivative of rifampin. It has a longer half-life (16 hr vs 3 hr) and shares some of the same problems as observed with rifampin including potential hepatoxicity, drug interactions, and red-orange discoloration of secretions. In areas where resistance occurs therapy involves up to four drugs for as long as 24 mo. Second-line drugs for tuberculosis are more toxic but may be required with resistance problems. These drugs include some fluoroquinolones (ofloxacin and ciprofloxacin), cycloserine, ethionamide, aminosalicylic acid, aminoglycosides (amikacin, kanamycin), clofazimine, and capreomycin.

Mycobacterium avium complex infection as well as tuberculosis are increased because of the high numbers of AIDS patients that coexist in the large inner city populations and homeless shelters. Antimicrobial drugs used to treat *Mycobacterium avium* complex include rifabutin, the new macrolides (clarithromycin and azithromycin), the fluoroquinolones, and combination regimens of ethambutol (or other tuberculosis drugs) with clarithromycin (or azithromycin).

The drugs most frequently used to treat leprosy are dapsone, clofazimine, and rifampin for 6 mo to 2 yr depending on the type of disease. All of these drugs have some serious toxicities that can develop with the prolonged therapeutic regimens required. Therefore, patient compliance must be well supervised and patients should be informed of the need to discuss side effects of their treatment.

CLOFAZIMINE

2-Phenazinamine, *N*,5-bis(4-chlorophenyl)-3,5-dihydro-3-[(1-methylethyl)imino]-, Lamprene



3-(*p*-Chloroanilino)-10-(*p*-chlorophenyl)- 2,10-dihydro- 2 -(isopropylimino)phenazine; [2030-63-9] $C_{27}H_{22}Cl_2N_4$ (473.40).

Preparation—*J Chem Soc* 1958; 859.

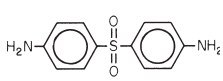
Description—Dark-red crystals; melts about 210°.

Solubility—Practically insoluble in water; soluble in alcohol, acetone, ethyl acetate, chloroform, or benzene.

Comments—In combination with other drugs, used for the treatment of leprosy and infections caused by *Mycobacterium avium* in AIDS patients. It is not significantly active against other bacteria. It binds to mycobacterial DNA and interferes with growth. It is bactericidal, but as long as 50 days may be required before killing is evident. Nausea, vomiting, diarrhea, abdominal pain, and eosinophilic enteritis may occur. Crystalline deposits of the drug in the viscera may cause GI bleeding and/or obstruction. Antimuscarinic actions cause dry skin and dryness, burning, itching, and irritation of the eyes. The drug also causes long-persisting, rufous discoloration of the skin, cornea, conjunctiva, and body fluids. The oral-systemic bioavailability is about 50%. The drug has a predilection for adipocytes, reticuloendothelial cells, and other macrophages, in which crystals may accumulate. During maintenance, the elimination half-life is about 70 days.

DAPSONE

Benzenamine 4,4′-sulfonylbis-, DDS



4,4′-Sulfonyldianiline [80-08-0] $C_{12}H_{12}N_2O_2S$ (248.30).

Preparation—Benzene is condensed with sulfuric acid to yield phenyl sulfone $[(C_6H_5)_2SO_2]$ which is then nitrated by standard procedures to yield the 4,4′-dinitro derivative. Reduction with tin and HCl or with various other appropriate reductants yields dapsone.

Description—White or creamy white, crystalline powder; odorless; slightly bitter taste; melts between 175° and 181°.

Solubility—Very slightly soluble in water; freely soluble in alcohol; soluble in dilute mineral acids.

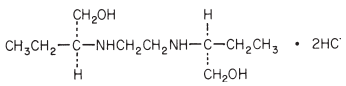
Comments—Has an antibacterial spectrum and mechanism of action similar to those of sulfanilamide (see *Sulfonamides*), of which it originally was studied as a congener. Limited success against tuberculosis has been achieved with it, but it is far surpassed by other agents. However, in combination with rifampin, it is the drug of choice in the chemotherapy of leprosy. Most of the sulfones used in the treatment of this disease owe both their activity and toxicity to dapsone released from the molecule. For this reason, the drug is the preferred sulfone, since it is cheaper than and equally efficacious to the others. However, resistance is becoming common. Combined with trimethoprim, it is as effective as trimethoprim-sulfametoxazole in the treatment of *Pneumocystis carinii pneumonia*. It is also useful as a suppressant in the treatment of dermatitis herpetiformis and relapsing polychondritis.

It is absorbed by the oral route. Absorption is more efficient with low than with high doses. It is eliminated in the liver by acetylation. There are slow and fast acetylators among patients. The half-life is 10 to 50 hr, and at least 8 days are required to reach plateau concentrations.

It may cause hemolytic anemia in glucose 6-phosphate dehydrogenase-deficient persons, methemoglobinemia, GI upset, headache, nervousness, giddiness, tachycardia, motor neuropathy, blurred vision, paresthesias and pruritus, hematuria, liver damage, and jaundice or rash that may become exfoliative. The dermatitis frequently occurs during the 5th week of therapy, followed by *Hypermelanosis*. Lepra reactions (erythema nodosum-like) may occur from a flooding of the body with endotoxins released from killed organisms. Careful initial grading of dose and rest periods avoids much of the toxicity.

ETHAMBUTOL HYDROCHLORIDE

[*R*-(*R,*R**)]-1-Butanol, 2,2′-(1,2-ethanediyldiimino)bis-, dihydrochloride; Myambutol**



(+)-2,2′-(Ethylenediimino)di-1-butanol dihydrochloride [1070-11-7] $C_{10}H_{24}N_2O_2 \cdot 2HCl$ (277.23).

Preparation—(±)-2-Aminobutanol is resolved via its tartrate and the (+)-enantiomorph is condensed with 1,2-dichloroethane in an appropriate dehydrochlorinating environment. The ethambutol thus formed is dissolved in a suitable solvent and reacted with HCl. US Pat 3,297,707.

Description—White, crystalline powder; essentially odorless; a bitter taste; stable in light and heat but is hygroscopic when exposed to high relative humidities; melts between 198° and 202°; pK_a 6.3, 9.5.

Solubility—1 g in 1 mL water or 4 mL alcohol; slightly soluble in ether or chloroform.

Comments—A tuberculostatic drug that is effective against tubercle bacilli resistant to isoniazid or streptomycin. It acts only on proliferating cells, apparently by interfering with synthesis of RNA. When used alone in the treatment of tuberculosis, the drug may clear the sputum of mycobacteria within 3 mo in the majority of patients, but bacterial resistance occurs in 35% of cases, and relapses frequently occur. In combination with isoniazid or other tuberculostatic drugs, relapses are uncommon. It should be used as a companion drug to isoniazid. The ethambutol-isoniazid rifampin combinations are now the most frequently used for patients exposed to drug-resistant organisms.

It occasionally causes optic neuritis, with blurred vision and diminished visual acuity to green light; the effect relates to the duration of use of the drug. Although these effects disappear on discontinuation, the drug should be discontinued at the first indication of a loss in visual acuity. Eye tests should be made before and at monthly intervals after the onset of therapy.

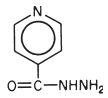
Other untoward effects include dermatitis, pruritus, anorexia, nausea, vomiting, abdominal pain, pyrosis, fever, headache, vertigo, malaise, mental confusion, disorientation, hallucinations, paresthesias, elevated serum urate levels (and gout), and abnormal liver function.

Multivitamins should be given concurrently. Leukopenia and anaphylaxis are rare occurrences.

The oral bioavailability is 75% to 80%. It is distributed well into most tissues and fluids but poorly in CSF. The volume of distribution is 1.6 mL/g. Over 80% is eliminated in the urine. The half-life is 3 to 4 hr but up to 8 hr in renal failure.

ISONIAZID

4-Pyridinecarboxylic acid, hydrazide; Isonicotinylhydrazine; INH



Isonicotinic acid hydrazide [54-85-3] $C_6H_7N_3O$ (137.14).

Preparation—By heating isonicotinic acid or its ethyl ester with anhydrous hydrazine. Isonicotinic acid may be synthesized by various oxidative processes starting with 4-methylpyridine.

Description—Colorless or white crystals, or a white, crystalline powder; odorless; slowly affected by exposure to air and light; solutions are practically neutral to litmus; melts between 170° and 173°; pK_a 1.8, 3.5, 9.5; pH (1 in 100 solution) 5.5 to 6.5.

Solubility—1 g in approximately 8 mL water and approximately 50 mL alcohol; slightly soluble in chloroform and ether.

Comments—The most potent and selective of the known tuberculostatic antibacterial agents. It is tuberculocidal to growing bacteria and regarded as the most effective agent in the therapy of tuberculosis. The fact that it gains access to all organs and to all body fluids, including CSF, renders the drug of special value in treating tuberculous meningitis and other extrapulmonary forms of the disease. The drug is never used alone because of the rapid emergence of resistance. Used in combination with other antitubercular drugs, it enhances the clinical response, permits lower doses of the other active agent(s) to be used and retards emergence of resistant tubercle bacilli. It is the central drug around which various combinations are formulated. The first-choice combination contains isoniazid and rifampin, with or without pyrazinamide. It also is used as a prophylactic.

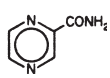
Untoward effects are relatively few except in persons who are slow acetylators, when the dose must be lowered. The effects may include restlessness, insomnia, muscle twitching, hyperreflexia, paresthesia, and even convulsions, toxic encephalopathy, optic neuritis, atrophy, and psychoses. These neurologic disorders result from competition of the drug with pyridoxine; pyridoxine administration suppresses the neurological disorders without antagonizing the antitubercular action. Other signs of pyridoxine deficiency may occur. The drug also may cause nausea, vomiting, epigastric distress, agranulocytosis, hemolytic or aplastic anemia, thrombocytopenia, eosinophilia, fever, various rashes and dermatoses, and rheumatoid and lupoid syndromes. Hepatitis, with jaundice, is uncommon in patients under 35 yr but occurs in about 2% of recipients over 50 yr, but 10% to 20% will show elevations in SGOT and SGPT. The hepatic, hematologic, and dermatologic effects are probably all allergic.

It is mostly acetylated by the liver; the rate varies considerably. In fast acetylators, the half-life is 1 to 1 1/2 hr; in slow ones, it is 2 to 5 hr.

IM injections cause local irritation.

PYRAZINAMIDE

Pyrazine carboxamide



[98-96-4] $C_5H_5N_3O$ (123.11).

Preparation—By thermal decarboxylation of 2,3-pyrazinedicarboxylic acid to form the monocarboxylic acid, which is esterified with methanol and then subjected to controlled ammonolysis. *J Am Chem Soc* 1952; 74:3617.

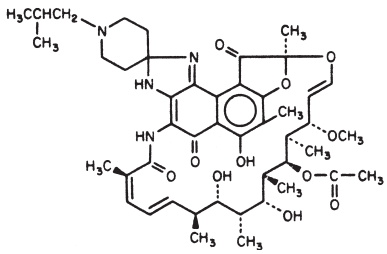
Description—White to practically white, crystalline powder; sublimes about 60°; melts about 190°; pK_a0.5.

Solubility—1 g in 67 mL water, 75 mL methanol, 175 mL absolute ethanol, 135 mL chloroform, 1000 mL ether, or 110 mL alcohol.

Comments—An antituberculosis drug used for initial treatment in combination with isoniazid and rifampin. It generally is administered with isoniazid, which it potentiates. However, it is quite toxic and should be held in reserve until other therapy fails. It may cause fever, anorexia, malaise and hepatic damage, with or without jaundice, and death can occur. All patients intended to be treated with this drug should have prior liver function tests, which tests also must be repeated periodically during therapy. All patients should be hospitalized during treatment. It may cause retention of uric acid.

RIFABUTIN

(9*S*,12*E*,14*S*,15*R*,16*S*,17*R*,18*R*,19*R*,20*S*,21*S*,22*E*,24*Z*)-6,16,18,20-tetrahydroxy-1′-isobutyl-14-methoxy-7,9,15,17,19,21,25-heptamethylspiro[9,4-(epoxypentadeca[1,11,13]trienimino)-2*H*-furo[2′,3′:7,8]naphth[1,2-*d*]imidazole-2,4′-piperidine]-5,10,26-(3*H*,9*H*)-trione-16-acetate; Mycobutin



[72559-06-9] $C_{46}H_{62}N_4O_{11}$ (847.02).

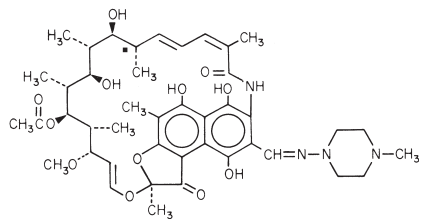
Comments—A semisynthetic ansamycin antibiotic that has antimycobacterial activity. It inhibits DNA-dependent RNA polymerase in susceptible strains of bacteria. It is indicated for prevention of disseminated *Mycobacterium avium* complex (MAC) disease in patients with advanced HIV infection.

It should not be administered to patients with active tuberculosis because single-agent therapy is likely to lead to development of tuberculosis that is resistant both to rifabutin and rifampin. Adverse reactions primarily may include rash (4%), GI intolerance (3%), and neutropenia (2%). Other reactions may include flu-like syndrome, hepatitis hemolysis, arthralgia, parathesia, aphasia, confusion, and nonspecific T-wave changes on ECG.

Oral doses are absorbed readily from the GI tract and slowly eliminated with a half-life of 16 to 69 hr. It has a high volume of distribution and good tissue uptake due to its lipophilicity. About 30% of dose is excreted in the feces, and 53% is excreted in urine primarily as metabolites.

RIFAMPIN

Rifamycin, 3-[[(4-methyl-1-piperazinyl)imino]methyl]-, Rifampicin, Rifadin, Rimactane



[13292-46-1] $C_{43}H_{58}N_4O_{12}$ (822.95). Potency: not less than 900 μg of $C_{43}H_{58}N_4O_{12}$/mg.

Preparation—Rifamycin SV, which may be prepared by the method of Sensi et al (US Pat 3,313,804), is converted to the 8-carboxaldehyde derivative, known also as 3-formylrifamycin SV, and this is condensed with 1-amino-4-methylpiperazine to form a Schiff base, which is rifampin.

Description—Red-brown, crystalline powder; odorless; unstable in light, heat, air, and moisture; melts between 183° and 188° with decomposition; pK_a 1.7, 7.9.

Solubility—1 g in approximately 762 mL water; freely soluble in chloroform; soluble in ethyl acetate or methanol.

Comments—A broad-spectrum antibiotic effective against most gram-positive bacteria, especially *Staph pyogenes, Strep pyogenes, viridans,* and *pneumoniae*, and variably active against gram-negative organisms, especially *H influenzae*, meningococci and gonococci. Both *Mycobacterium tuberculosis* and *Mycobacterium leprae* are very susceptible to the drug. Its clinical use is mainly in the treatment of tuberculosis. The rate of development of resistance of the mycobacterium is low. Nevertheless, it always is used in combination with other antitubercular drugs. It also appears to be an excellent drug for prophylaxis of meningococcal meningitis and pneumonia from *H influenzae* Type B and treatment of meningococcal carrier state. It may cause heartburn, epigastric distress, gas, cramps, diarrhea, anorexia, and nausea and vomiting. Headache, drowsiness, and fatigue commonly occur. Inability to concentrate, confusion, muscular weakness, ataxia, pain in the extremities, visual disturbances, and generalized numbness are other CNS side effects. Jaundice and other manifestations of hepatotoxicity have occurred. It is teratogenic in laboratory animals and should therefore be withheld in pregnancy.

It induces the hepatic drug-metabolizing enzyme system and accelerates the metabolism of digitoxin, methadone, phenytoin, beta blockers, verapamil, theophylline, chloramphenicol, oral contraceptives and estrogens, oral anticoagulants, barbiturates, tolbutamide, and itself.

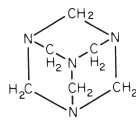
It is 100% absorbed after oral administration, but food in the stomach delays absorption of the drug. The drug is distributed widely in the body, even into CSF. In plasma 98% is protein-bound. The volume of distribution is 0.9 mL/g. About 85% of the drug is eliminated by biotransformation in the liver. An active metabolite is secreted into bile, where it is therapeutically effective. The risk of hepatotoxicity is increased when it is used with isoniazid. It imparts a reddish-orange color to urine, stools, sweat, saliva, and tears. Soft contact lenses may be stained permanently.

MISCELLANEOUS SYSTEMIC URINARY TRACT ANTISEPTICS

These drugs are used for chronic suppressive therapy of UTIs. The primary agents in this group are methenamine and nitrofurantoin. Both drugs are given orally for recurrent urinary tract pathogens and require an acidic urine for efficacy. They are not first-line agents to treat an initial UTI.

METHENAMINE

1,3,5,7-Tetraazatricyclo[3.3.1.1^{3,7}]decane; Aminoform; Cystamin, Cystogen, Hexamine, Uritone, Urised



Hexamethylenetetramine [100-97-0] $C_6H_{12}N_4$ (140.19).

Although a cyclic tetramine, the therapeutic action of this compound depends exclusively on its ability to liberate formaldehyde under suitable environmental conditions.

Preparation—By adding a moderate excess of ammonia water to formaldehyde solution, and evaporating to dryness.

Description—Colorless, lustrous crystals or a white crystalline powder; practically odorless; aqueous solution is alkaline to litmus; sublimes about 260°; when ignited it burns with a smokeless flame.

Solubility—1 g in 1.5 mL water, 12.5 mL alcohol, 10 mL chloroform or 320 mL ether.

Incompatibilities—Alkaline in reaction and forms salts with weak acids. *Strong acids* and concentrated solutions of organic acids decompose it with liberation of formaldehyde. With prolonged contact, weak acids also decompose it, as do acidic vehicles.

It liquefies, in some cases with decomposition, when rubbed with *aspirin, antipyrine, benzoic acid, lithium carbonate, menthol, phenol, potassium acetate, sodium benzoate, sodium salicylate*, etc.

Ammonium salts and *alkalies* darken it. In capsules, it may combine slowly with the gelatin, rendering it insoluble.

Comments—A urinary tract anti-infective, provided it is acting in an acid medium. It is excreted rapidly and thus reaches effective antiseptic concentrations in the urine. The drug depends for its action on the liberation of free formaldehyde. This occurs to the extent of 20% of theoretical at pH 5, 6% at pH 6, and almost not at all at pH 7.6.

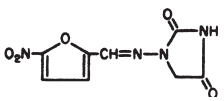
Consequently, precaution must be taken to maintain an acid urine (pH 6 or below) during medication with it. This usually is accomplished by administration of sodium biphosphate, mandelic acid, hippuric acid, ascorbic acid, or cranberry juice. Ammonium chloride should not be used, since NH_4^+ drives the equilibrium to the left. At a pH of 6, a daily dose of 2 g will yield an average 24-hr urine concentration of about 18 to 60 μg/mL, which is about 40 times the minimum to inhibit the growth of most bacteria that cause UTIs. However, it will not prevent growth of *Candida albicans*. It is improbable that products that provide only 40.8 to 81.6 mg/dose can provide a high enough concentration of formaldehyde, since the urine contains substances that bind some of the formaldehyde.

It is of particular value in the treatment of *E coli* infections of the urinary tract. It also is especially useful in patients with renal insufficiency. Because of its low systemic toxicity, failure to excrete the drug causes no harmful consequences, unless renal insufficiency is severe.

Approximately 10% to 30% is converted to formaldehyde in the acid stomach contents unless enteric capsules are employed. Even with enteric coatings, nausea, vomiting, diarrhea, and other GI distress often occur when the dose exceeds 500 mg 4 times a day. Take with food to minimize GI upset. Formaldehyde liberated from the compound presumably is the cause of the distress. Other untoward effects are occasional pruritus and skin rashes and bladder irritation, painful and frequent urination, and hematuria in persons who have taken the drug longer than 3 to 4 wk. Dyspnea, lipoid pneumonitis, and headache occur rarely. In persons with acidosis or renal failure, the acid salts usually given concomitantly may be detrimental. The drug should not be used if hepatic insufficiency exists.

NITROFURANTOIN

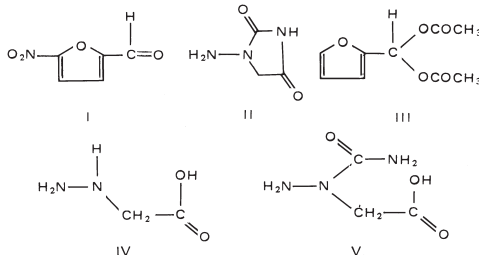
2,4-Imidazolidenedione, 1-[[(5-nitro-2-furanyl) methylene]amino]-, Furadantin, Macrodantin



1-[(-5-Nitrofurfurylidene)amino]hydantoin [67-20-9] $C_8H_6N_4O_5$ (238.16).

Caution—It is discolored by alkali and by exposure to light, and is decomposed upon contact with metals other than stainless steel or aluminum.

Preparation—5-Nitro-2-furaldehyde (1) readily undergoes condensation with 1-aminohydantoin (II) to yield nitrofurantoin. I is synthesized by direct nitration of "2-furfural diacetate" [2-furanmethanediol diacetate (III), prepared by the addition reaction between 2-furaldehyde and acetic anhydride] followed by saponification to regenerate the formyl group which, had it not been so protected, would have been oxidized to carboxyl during the nitration. II may be synthesized by effecting the addition of cyanic acid to hydrazinoacetic acid (IV) to produce the 3-carbamoyl derivative (V) which cyclizes by dehydration to II.



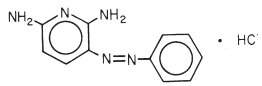
Description—Lemon-yellow crystals or fine powder; odorless; bitter aftertaste; pk_a 7.2.

Solubility—Very slightly soluble in water or alcohol.

Comments—Effective against a majority of urinary tract pathogens, including certain strains of *E coli, Enterobacter, Klebsiella, Proteus* spp, *Staph aureus,* and *Strep faecalis*. It is also effective against many staphylococci, clostridia, and *B subtilis*. It is indicated for the treatment of infections of the urinary tract caused by the above bacteria: pyelonephritis, cystis, and pyelitis. An acid urine favors activity. It is not the drug of first choice in the treatment of any acute infection, and it rarely is used. In chronic bacteriuria, it is a second- or third-choice agent. However, as a prophylactic in the prevention of recurrences it is effective, being slightly superior to methenamine mandelate but inferior to sulfamethizole. It is not indicated for treatment of associated perinephric or renal cortical abscesses, prostatitis, or other genitourinary tract infections, since in these the blood level is more important than urine concentration. The microcrystalline form is absorbed rapidly and completely; the macrocrystalline form is more slowly and less completely absorbed. About 67% is metabolized in the body, and 33% is excreted into the urine unchanged. The half-life is only 0.3 hr; slow absorption helps to sustain urine levels. Dose adjustment must be made in renal failure. Overall, the side effects are high (10% or more). Nausea, vomiting, and diarrhea occur in an appreciable number of patients. Reduction in dosage, or administration with food or milk, lessens the incidence; it is claimed that use of "macrocrystalline" product diminishes the incidence and intensity of GI upsets without affecting potency. Absorption is delayed, but bioavailability is not diminished. GI effects also occur in some patients receiving the drug intravenously. Hypersensitivity reactions with dermatological manifestations also occur. Headache, vertigo, drowsiness, malaise, muscular aches, nystagmus, and polyneuropathy occasionally occur. Neuropathies appear to be more likely to occur if there is renal insufficiency; they appear to be caused by metabolites. Hemolytic anemia, megaloblastic anemia, granulocytopenia, leukopenia, esoinophilia, and maculopapular rashes occur occasionally. It also causes infrequent cholestatic jaundice and hepatocellular damage. Pneumonitis and pulmonary fibrosis can occur, especially in elderly patients. Occasionally, there is transient alopecia. Superinfections may occur. The drug is mutagenic in the Ames test.

PHENAZOPYRIDINE HYDROCHLORIDE

2,6-Pyridinediamine, 3-(phenylazo)-, monohydrochloride; Pyridium



2,6-Diamino-3-(phenylazo)pyridine monohydrochloride [136-40-3] $C_{11}H_{11}N_5 \cdot HCl$ (249.70).

Preparation—Aniline is diazotized with sodium nitrite and excess HCl, and the resulting benzenediazonium chloride is coupled with 2,6-diaminopyridine.

Description—Light or dark red to dark violet, crystalline powder; odorless or has a slight odor; melts about 235° with decomposition.

Solubility—1 g in <10 mL water, 59 mL alcohol, 331 mL chloroform, >5000 mL ether, or 100 mL glycerin.

Comments—A drug used for symptomatic relief of pain, burning, urgency, frequency, and other discomforts arising from irritation of lower urinary tract mucosa caused by infection, trauma, surgery, endoscopic procedures or passage of catheters. When taken systemically, it is excreted quickly into the urine, so that a high local concentration is reached. Thus, the drug either may be administered orally or instilled locally.

However, a considerable proportion of the drug is converted metabolically to an inactive form, so that large oral doses are required to exert a therapeutic effect. The relief of discomfort is attributable mostly to a local anesthetic action rather than to an antibacterial action. Treatment should not continue beyond 2 days because there is no evidence it provides greater benefit than sulfonamides alone. GI irritation, jaundice, hemolytic anemia, and methemoglobinemia have been reported. After oral administration, the color of the urine may be orange red to dark red, if the urine is acidic. Large doses and prolonged treatment can give rise to renal stones of the drug. It is contraindicated in renal insufficiency, severe hepatitis, and pyelonephritis of pregnancy, and it should be used cautiously in the presence of GI disturbances. It often is combined with sulfonamides or methenamine salts.

ANTIMALARIALS

Malaria is caused by several species of the protozoan *Plasmodium*, of which *Plasmodium vivax,* and *Plasmodium falciparum* are the most common. The most serious infections involve *Plasmodium falciparum*, which causes a higher incidence of complications and deaths. They all have complex life cycles involving both the anopheles mosquito and the erythrocyte of the human host. In *Plasmodium vivax*, a persisting tissue phase continues to infect the blood at intervals for many years. Thus, the ideal antimalarial not only should eradicate the microzoan from the blood (ie, to *suppress* the clinical attack) but from the tissues as well, to effect a *radical cure*. The several antimalarials differ in their point of interruption of the cycle of the parasite and in the type of malaria affected. In addition, parasite resistance (especially *Plasmodium falciparum*) to these drugs is an important therapeutic problem.

The 4-aminoquinolines (amodiaquine, chloroquine, and hydroxychloroquine) and quinacrine cause similar adverse effects. GI side effects such as nausea, vomiting, diarrhea, and sialorrhea are common; they can be diminished by administering the drugs with meals and milk.

Oropharyngeal and dermatologic side effects may occur, especially during protracted therapy. They include pigmentation of the skin, nailbeds, and palate (especially quinacrine), bleaching of hair, pruritus, and lichenoid and pleomorphic skin eruptions. They may precipitate severe attacks of psoriasis in patients with that disease. The drugs should not be coadminis-

tered with phenylbutazone or gold salts, which have similar dermatotoxicities. There is cross-sensitization among all the 4-aminoquinolines. The drugs may cause neurologic disturbances, such as fatigue, lassitude, neuromyopathy, polyneuritis, toxic psychosis, and ototoxicity with vertigo and/or decreased auditory sensitivity. The knee and ankle reflexes should be monitored periodically. Ocular disorders, such as corneal opacities, keratopathy, and retinopathy (the drugs are concentrated in the retina) occur, especially during long-term treatment. Periodic ophthalmologic examinations are advised. The drugs are contraindicated if retinal or visual field disease is present.

The 4-aminoquinolines are concentrated in the liver and may cause hepatotoxicity, and they may precipitate attacks of porphyria; they must be used cautiously in persons with liver disease or who are under medication with other potentially hepatotoxic drugs (gold salts, erythromycin estolate, indomethacin, phenylbutazone, certain anabolic steroids, etc).

Hematologic disorders occasionally caused by the 4-aminoquinolines include leukopenia, pancytopenia, and agranulocytosis; periodic white-blood-cell counts are necessary. The drugs may depress the electrocardiographic T-wave.

The drugs pass the placental barrier and can cause cochleovestibular paresis in the fetus; they should be withheld in pregnancy, although chloroquine has been given safely in low doses for chemoprophylaxis.

CHLOROQUINE PHOSPHATE

1,4-Pentanediamine, N^4-(7-chloro-4-quinolinyl)-N^1,N^1-diethyl-, phosphate (1:2); Aralen Phosphate

7-Chloro-4-[[4-(diethylamino)-1-methylbutyl]amino]quinoline phosphate (1:2) [50-63-5] $C_{18}H_{26}ClN_3 \cdot 2H_3PO_4$ (515.87).

Preparation—By addition of concentrated phosphoric acid to a hot ethanolic solution of chloroquine base.

Description—White, crystalline powder; odorless; bitter taste; slowly discolors on exposure to light; pH (aqueous solution) approximately 4.5; is dimorphic; one form melts about 193° to 195° (usual form) or 210° to 215° (other polymorphic form); pK_{a1} 7; pK_{a2} 9.2.

Solubility—Freely soluble in water; practically insoluble in alcohol, chloroform, or ether.

Comments—An *antimalarial* that causes dysfunction of the acid phagosomes in plasmodia and also in human leukocytes and macrophages. It is used both for control of acute attacks of vivax malaria and for suppression against all plasmodia except chloroquine-resistant *Plasmodium falciparum*. The drug is neither a prophylactic nor a radical curative agent in vivax malaria. In regions where *Plasmodium falciparum* is generally sensitive to chloroquine, it is markedly effective in terminating acute attacks of nonresistant falciparum malaria and usually brings about complete cure in this type of malaria. However, in some regions a high incidence of resistance (up to 90%) exists, so that other drugs, such as quinine or quinidine, alone or in combination with pyrimethamine, sulfadiazine, or tetracycline, may have preference. Resistant strains of *Plasmodium vivax* also occur.

It is the drug of choice for the oral treatment of all malaria except that caused by resistant *Plasmodium falciparum*; the hydrochloride is second to quinine or quinidine for parenteral treatment.

Although not useful in intestinal amebiasis, it is an effective agent in the treatment of extraintestinal amebiasis, especially amebic hepatitis. It is not used alone but rather in combination with dihydroemetine or emetine. The combination is only the treatment of second choice, behind metronidazole-diiodohydroxyquin. Since chloroquine is well tolerated, it has been recommended that it be employed routinely even in cases of amebiasis without demonstrable hepatic involvement. Like quinacrine, it also may be of value in chronic discoid lupus erythematosus and rheumatoid arthritis. It is quite effective in the treatment of photoallergic reactions.

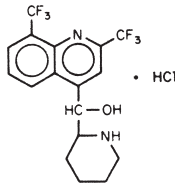
The adverse effects are those of the 4-aminoquinolines (see the general statement). The incidence is low, except for the GI side effects of the oral forms.

The drug is absorbed almost completely from the GI tract and usually is administered orally. It (as the hydrochloride) is given intramuscularly when necessary to resort to parenteral administration. Tissues bind the drug, although not quite to the same degree of quinacrine. It is degraded in tissues to unknown products. The drug is slowly excreted in the urine with an initial half-life of 1 wk, changing to 17 days after 4 wk, then ultimately becoming months.

DAPSONE—page 1662.

MEFLOQUINE HYDROCHLORIDE

4-Quinolinemethanol, (*R, *S**)-(±)-α-2-piperidinyl-2,8-bis(trifluoromethyl)-, hydrochloride; Lariam**



[51773-92-3] $C_{17}H_{16}F_6N_2O \cdot HCl$ (414.78).

Preparation—*J Med Chem* 1971; 14:926.

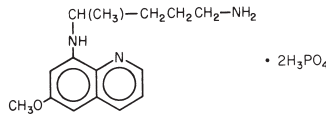
Description—White powder; bitter taste; melts about 260° with decomposition; the secondary alcohol group is chiral, but the racemate is used clinically; pK_a 8.6.

Solubility—1 g in 6 mL water or 250 mL alcohol.

Comments—Can eliminate fever and parasitemia and cause a radical cure in infections caused by *Plasmodium falciparum* and can suppress infections caused by *Plasmodium vivax*; with *Plasmodium vivax*, infections usually recur at a later time. Its mechanism is unknown. Resistance develops rapidly (the WHO is investigating combinations to delay resistance) and it is absorbed well orally. In plasma, it is extensively bound to plasma proteins and is concentrated in the liver and lungs. It is eliminated mainly in the feces, mostly after biliary secretion. The half-life is about 13 to 24 days.

PRIMAQUINE PHOSPHATE

1,4-Pentanediamine, N^4-(6-methoxy-8-quinolinyl)-, phosphate (1:2)



8-[(4-Amino-1-methylbutyl)amino]-6-methoxyquinoline phosphate (1:2) [63-45-6] $C_{15}H_{21}N_3O \cdot 2H_3PO_4$ (455.34).

Preparation—2-Chloropentylamine is condensed with 8-amino-6-methoxyquinoline, and the resulting primaquine base is reacted with a double molar quantity of phosphoric acid.

Description—Orange-red, crystalline powder; odorless; bitter taste; solutions are acid to litmus; melts about 200°.

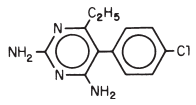
Solubility—1 g in approximately 15 mL water; insoluble in chloroform or ether.

Comments—An *antimalarial* that is very important for the radical cure (ie, prevention of relapse) of relapsing vivax or ovale malaria; it is not employed for suppressive therapy or for control of the acute clinical attacks of the disease. It often is administered in combination with chloroquine. The incidence of serious untoward effects is low. Administration of the drug with milk, food, or antacids lessens GI adverse effects of abdominal cramps and epigastric distress; however, aluminum-containing antacids interfere with absorption. Mild hemolytic anemia, cyanosis (methemoglobinemia), and leukocytosis also may be observed. At higher dose levels these symptoms are accentuated, and leukopenia may be noted. Impairment of liver function has not been noted, even in patients with infectious hepatitis. Persons with tendencies toward granulocytopenia (eg, lupus erythematosus or rheumatoid diseases) should not take it because the blood dyscrasia may be precipitated. Other hemolyzing drugs should not be administered concurrently.

Untoward effects in non-Caucasians are similar, but the incidence and degree of anemia and intravascular hemolysis are greater especially in patients whose erythrocytes are deficient in glucose 6-phosphate dehydrogenase. Bone-marrow depressant drugs (eg, antineoplastics, colchicine, gold salts, penicillamine, phenylbutazone, hydroxyphenylbutazone, or quinacrine) given concurrently can cause excessive bone-marrow depression.

PYRIMETHAMINE

2,4-Pyrimidinediamine, 5-(4-chlorophenyl)-6-ethyl-, Daraprim



2,4-Diamino-5-(*p*-chlorophenyl)-6-ethylpyrimidine [58-14-0] $C_{12}H_{13}ClN_4$ (248.71).

Preparation—Ethyl propionate is condensed with *p*-chlorophenylacetonitrile in the presence of sodium methylate. The resulting α-propionyl-*p*-chlorophenylacetonitrile is reacted with isoamyl alcohol to form the hemiacetal which undergoes dehydration to α-(*p*-chlorophenyl)-β-ethyl-β-isoamyloxylacrylonitrile (I). I is reacted with guanidine whereupon cyclization occurs because of (*a*) the liberation of isoamyl alcohol by condensation involving the imino hydrogen of guanidine and the isoamyloxy group of I, and (*b*) an addition reaction involving an amino group of guanidine and the nitrile group of I.

Description—White, crystalline powder; odorless; melting range 238 to 242°; pK_a 7.3.

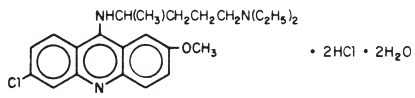
Solubility—Practically insoluble in water; 1 g in approximately 200 mL alcohol or 125 mL chloroform.

Comments—Inhibits dihydrofolate reductase in plasmodia; thus the developing parasite cannot synthesize and use nucleic acid precursors needed for growth. Its action in preventing the development of the erythrocytic phase of the parasite is slow, so that it is of little value in suppression of acute attacks, except as an adjunct to quinine; rather it is used mainly as a suppressive prophylactic for the prevention of clinical attacks by *Plasmodium falciparum* in regions where the organism is resistant to chloroquine, in which use it is combined with sulfadoxine. It also renders the parasites incapable of sporulating in the mosquito, so that the life cycle of the parasite is broken. In some regions, treatment with the drug is successful in up to 90% of cases; addition of quinine increases the success rate to about 95%. Combination of the drug and trisulfapyrimidines is the treatment of choice for toxoplasmosis.

The toxicity is low. Anorexia and vomiting are common with large doses. Skin rashes are rare. In high doses it may cause megaloblastic anemia and, less commonly, leukopenia, thrombocytopenia and pancytopenia as the result of antagonism of folic acid. Atrophic pharyngitis and esophagitis occasionally results. CNS signs of folate deficiency may occur. Because of the intensive dose regimen for toxoplasmosis, semiweekly blood-cell and platelet counts should be made. The hematopoietic toxicity can be reversed by leucovorin. The antifolate actions are damaging to the fetus, so that the drug should be avoided in pregnancy, if possible, or be coadministered with leucovorin.

QUINACRINE HYDROCHLORIDE

1.4-Pentanediamine, N^4-(6-chloro-2-methoxy-9-acridinyl)-N^1,N^1-diethyl-, dihydrochloride, dihydrate, Atabrine Hydrochloride



6-Chloro-9-[[4-(diethylamino)-1-methylbutyl]amino]-2-methoxyacridine dihydrochloride dihydrate, [6151-30-0] $C_{23}H_{30}ClN_3O{\cdot}2HCl{\cdot}2H_2O$ (508.91).

Preparation—2,4-Dichlorobenzoic acid is condensed in alkaline solution with *p*-anisidine, and the product, on treatment with phosphorus oxychloride, is cyclized to methoxydichloroacridine. This is heated with 2-amino-5-(diethylamino)pentane in phenol solution and the reaction mixture is added to acetone containing hydrochloric acid. Quinacrine is precipitated as the dihydrochloride while the phenol is held in solution by the acetone.

Description—Bright-yellow, crystalline powder; odorless; bitter; pH (1 in 100 solution) approximately 4.5; melts about 250° with decomposition.

Solubility—1 g in approximately 35 mL water; soluble in alcohol; almost insoluble in chloroform.

Comments—Now generally considered an alternative choice for giardiasis for patients who do not tolerate metronidazole. It is obsolete for treating of malaria. A small percentage of patients treated with it exhibit untoward effects. These are essentially the same as those caused by the 4-aminoquinolines (see the general statement), of which quinacrine can be considered to be an analog. The GI irritancy is higher than with the 4-aminoquinolines, and it is common to give sodium bicarbonate concomitantly. Children do not tolerate it well, and patients with psoriasis should not receive quinacrine because it may exacerbate the condition. Toxic psychosis has been reported in 1.5% of adults who take it. It is absorbed readily from the GI tract and from IM and intracavitary sites of injection. It is excreted very slowly in the urine and accumulates in tissue on chronic administration. It usually is administered orally; each dose is given with water after a meal. If the oral route cannot be employed, IM injection is preferred over the IV injection.

QUINIDINE GLUCONATE—see page 1364.

QUININE SULFATE

(8α,9*R*)-Cinchonan-9-ol, 6′-methoxy-, sulfate (2:1) (salt), dihydrate

Quinine sulfate (2:1) (salt) dihydrate [6119-70-6]

$(C_{20}H_{24}N_2O_2)_2{\cdot}H_2SO_4{\cdot}2H_2O$ (782.95); *anhydrous* [804-63-7] (746.92); the sulfate of an alkaloid obtained from the bark of *Cinchona officinalis Linné* (*C ledgeriana* Moens) (Fam *Rubiaceae*) or other species of *Cinchona*.

Contains not more than 10.0% of dihydroquinine.

Preparation—The crude sulfate, obtained when quinine is isolated from the bark of *Cinchona* sp, is recrystallized once or twice from hot water slightly acidified with sulfuric acid.

Description—White, fine, needle-like crystals; usually lusterless, making a light and readily compressible mass; odorless; persistent, bitter taste; when exposed to light, it acquires a brown tint; pK_a 4.1, 8.5.

Solubility—1 g in approximately 500 mL water, 120 mL alcohol, 35 mL water at 100°, or approximately 10 mL alcohol at 80°; slightly soluble in chloroform or ether.

Comments—The *original antimalarial drug*. It only affects the erythrocytic form of the plasmodia and hence is used only as a suppressive in the management of acute attacks of vivax, malariae or ovale malaria. It may cure up to 50% of infections caused by falciparum plasmodia, but some strains are resistant. The drug may be combined with pyrimethamine and a sulfonamide, but it appears to be antagonized by chloroquine. The quinine-pyrimethamine-sulfadiazine (or sulfadoxine) combination is presently the treatment of choice for infections caused by chloroquine-resistant *Plasmodium falciparum*; an alternative is quinine with tetracycline. In severe infections, IV dihydrochloride or quinidine gluconate is the drug of choice. The combination, clindamycin-quinine, is the treatment of choice for babesiosis.

It has an effect to suppress neuromuscular transmission. In the symptomatic treatment of a rare myopathy known as myotonia congenita, or Thomsen's disease, it exerts a neuromuscular depressant action. It occasionally benefits patients with spasmodic torticollis (torsion spasm) and also persons with nocturnal leg cramps. It is a frequent constituent of bitter tonics and stomachic preparations.

A syndrome of toxic effects known as *cinchonism*, follows the repeated use of full therapeutic doses. Mild cinchonism is characterized by tinnitus, headache, nausea, and slight disturbance of vision. In severe cinchonism the skin is hot and flushed, rashes are frequent, and the CNS is involved; headache, fever, vomiting, apprehension, excitement, confusion, delirium, and syncope are common. The emesis is due to a central action of the drug as well as to its local irritant action on the intestinal mucosa. In a few cases, renal damage, photosensitivity, and hypoprothrombinemia may occur. Agranulocytosis has been observed rarely. Transient ventricular tachycardia is noted in rare instances after massive acute overdosage. Although it generally exerts vasodilator actions, retinal vasoconstriction, leading to loss of vision, has been described; and these effects mostly have followed rapid IV injections or large overdoses. It is absorbed readily from the GI tract. It is only moderately concentrated in tissues and undergoes degradation particularly in the liver. The drug and its degradation products are excreted rapidly in the urine, and for this reason the drug must be given every 6 hr in order to maintain relatively constant plasma levels. The half-life is 5 to 16 hr.

An alkaline urine prolongs the half-life. See the USP DI for the various pharmacokinetic drug interactions. The drug is given after meals to minimize gastric irritation. IM and SC injections are painful and frequently are followed by local tissue injury. The IV route is used rarely and only in emergencies.

SULFADIAZINE—page 1632.
SULFADOXINE—page 1632.

AMEBICIDES

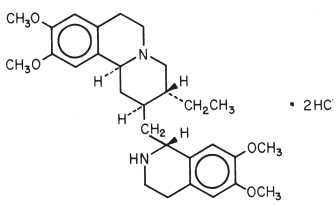
Endemic amebiasis is relatively rare in the US but it still has a prevalence of 2% to 4% in some areas. Most infections are essentially asymptomatic, but the number of severe infections is still large. Amebic infections generally remain confined to the intestines, where they may give rise to dysentery, but in an appreciable fraction of cases the amebae may locate elsewhere, especially in the liver. The chemotherapy of amebiasis thus must provide drugs to treat both the intestinal and extraintestinal forms of the disease. In addition, the ideal amebicide also is capable of eliminating amebic cysts from the intestine. No safe drug exists that will eradicate all of motile forms, cysts, and extraintestinal amebas, but judicious combined therapy can eliminate the parasite from all sites. Metronidazole acts on amebae

within the lumen and wall of the intestine as well as other organs. Diloxanide, iodoquinol, and paromomycin are oral luminal amebicides. Emetine and chloroquine are tissue amebicides.

The most commonly reported intestinal protozoal infection in the US is giardiasis, caused by the flagellated protozoan, *Giardia lamblia*. Most individuals are asymptomatic. However, these organisms cause a diarrhea that can be transient or persistent. Infection results from ingestion of cysts from fecal contamination of water, especially from lakes and streams in back country areas where various mammalian species can serve as reservoirs. Cysts change into motile trophozoites in the upper intestine where disease may be produced. Chemotherapy with metronidazole or quinacrine usually is successful.

EMETINE HYDROCHLORIDE

Emetan, 6′,7′,10,11-tetramethoxy-, dihydrochloride



[316-42-7] $C_{29}H_{40}N_2O_4 \cdot 2HCl$ (553.57); the hydrochloride of an alkaloid obtained from ipecac, or prepared by methylation of cephaeline, or prepared synthetically.

Description—White or slightly yellowish, crystalline powder; odorless; affected by light; pK_a 7.4, 8.3.

Solubility—1 g in 8 mL water or 12 mL alcohol.

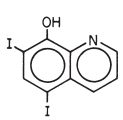
Comments—Eradicates *Entameba histolytica* from both intestinal and extraintestinal sites. It is an alternative drug for severe intestinal amebiasis or amebic hepatitis; it ranks only as an alternative when other drugs fail. It is concentrated in the liver, hence its value in amebic hepatitis; it is also of considerable value in the treatment of amebic abscesses in other locations. Occasionally, the drug may be life-saving. It rapidly relieves symptoms of intestinal amebiasis by destroying motile amebas, but the percentage of cures is below 15%, since cysts are affected little; other agents are not only safer but superior. It may be used initially to control quickly severe intestinal amebiasis; the drug then is followed by treatment with other agents. It has no place in the therapy of mild ambulatory or chronic cases.

The incidence of toxic effects is very high, both by local and systemic administration. Thus, the IV route is contraindicated. Large doses produce acute lesions in the heart, liver, kidney, and intestines, and the dose is now restricted. Nevertheless, deaths still sometimes occur, often because of repeated courses of treatment at close intervals; the drug has a probable half-life on the order of weeks to months. Diarrhea, nausea, and vomiting are frequent, as are also skeletal muscle weakness, stiffness, and aching. Sensory disturbances also occur. By far the most important toxic effects are cardiovascular; they include hypotension, precordial pain, dyspnea, tachycardia, and long-persisting electrocardiographic changes; electrocardiographic and blood-pressure recordings at daily intervals are necessary. It is contraindicated in patients with organic disease of the heart or kidney, unless there is no therapeutic alternative, in pregnancy, and when there has been a previous course of therapy within 6 wk.

A course of the drug should not continue for more than 5 days. The patient should be kept in bed, and carefully watched for toxic effects. Do not give the drug IV. Dehydroemetine is available in US but only from the CDC.

IODOQUINOL

8-Quinolinol, 5,7-diiodo-, Diiodohydroxyquinoline; Diodohydroxyquin; Yodoxin



[83-73-8] $C_9H_5I_2NO$ (396.95).

Preparation—8-Quinolinol is iodinated by treatment with iodine monochloride or with a solution of iodine in potassium iodide.

Description—Light yellowish to tan, microcrystalline powder; wetted by water with difficulty; odorless or nearly so; stable in air; melts about 210° with decomposition.

Solubility—Practically insoluble in water; sparingly soluble in alcohol or ether.

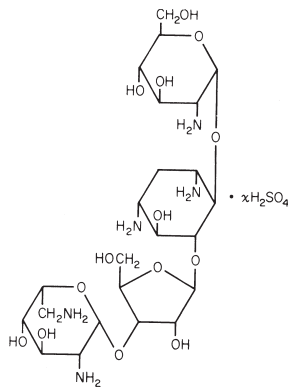
Comments—The drug of choice for the treatment of asymptomatic intestinal amebiasis (cyst carrier state) caused by *Entameba histolytica*. In symptomatic intestinal disease, it follows initial treatment with metronidazole or dehydroemetine. In hepatic abscess, it follows metronidazole or emetine. Bed rest is not required. It is the drug of choice in the treatment of infections caused by *Dientameba fragilis*. It is a second-choice drug in the treatment of balantidial dysentery.

It has caused subacute myelo-optic neuropathy when doses larger than recommended for amebiasis were given for 3 wk, so long term therapy should be avoided. Iodine toxicoderma, chills, fever, mild to severe dermatitis, irritation, abdominal discomfort, diarrhea, and headache occur. The drug may cause goiter. It also can interfere with certain thyroid tests, and protein-bound iodine may remain elevated for as long as 6 mo after termination of a course of treatment. Systemic toxicity can result from topical, especially intravaginal, application. Because of GI irritation, it should be taken after meals.

METRONIDAZOLE—page 1669.

PAROMOMYCIN SULFATE

D-Streptamine, *O*-2-amino-2-deoxy-α-D-glucopyranosyl-(1 → 4)-*O*-[*O*-2,6-diamino-2,6-dideoxy-β-L-idopyranosyl-1(1 → 3)-β-D-ribofuranosyl-(1 → 5)]-2-deoxy-, sulfate (salt); Humatin



[1263-89-4];[7542-37-2;59-04-1 (paramomycin)] $C_{23}H_{45}N_5O_{14}.xH_2SO_4$; the sulfate of an antibiotic substance or substances produced by the growth of *Streptomyces rimosus* var *paromomycinus*, or a mixture of two or more such salts. Potency: equivalent to not less than 675 μg of paromomycin ($C_{23}H_{45}N_5O_{14}$)/mg, calculated on the anhydrous basis.

Preparation—Paromomycin is isolated from fermentation broths by ion-exchange adsorption.

Description—Off-white to light-yellow, amorphous powder; odorless or practically so; hygroscopic.

Solubility—1 g in <1 mL water; >10,000 mL alcohol, chloroform, or ether.

Comments—Effective against most clinically significant gram-negative bacteria, especially various species of *Shigella* and *Salmonella* and strains of *E coli*. It is not effective against *Ps aeruginosa*. Among the gram-positive organisms, only staphylococci are sufficiently sensitive to be of clinical significance. It has been used to treat gastroenteritis or bacterial dysentery caused by these organisms, but resistance develops rapidly, the relapse rate is high and other antibiotics are more successful. It also has been used to reduce the bacterial content of the intestine prior to surgery on the bowel or to rid the bowel of nitrogen-forming bacteria in patients with hepatic coma.

Its principal and approved use (US) is in the treatment of asymptomatic intestinal amebiasis, for which it is an alternative drug. It alters the ecology of the intestinal flora in such a way that growth of intestinal amebas is discouraged and it also helps to prevent secondary infections that may follow or facilitate amebic invasion of the intestinal walls. It is of no value in treating hepatic or other extraintestinal abscesses. It also is used to treat infections caused by *Dientamoeba fragilis*. It is an obsolete drug for the treatment of tapeworm infestations.

It often causes GI hypermotility, nausea, diarrhea, and abdominal cramps, which generally appear on the 2nd or 3rd day of treatment and when the daily dose exceeds 2 g. Occasionally, the drug may cause headache, vertigo, vomiting, abdominal pain, or skin rash.

Overgrowth of enteric staphylococci and other pathogenic bacteria rarely occurs, but may if treatment is prolonged. Malabsorption syndromes have not been reported. There is mutual cross-resistance to kanamycin and neomycin, and often to streptomycin. Although it is absorbed poorly from the gut, there is potential nephrotoxicity, especially in the presence of renal disease.

MISCELLANEOUS ANTIPROTOZOAL DRUGS

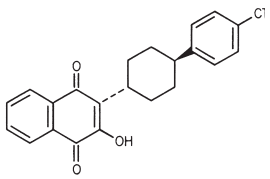
Among the protozoal infections that are endemic to the US are trichomoniasis, amebiasis, giardiasis, and malaria. Other protozoal infections, uncommon in the US, nevertheless constitute serious public health and agricultural problems within the possessions and elsewhere. The amebicides and antimalarials are useful in the treatment of a number of other protozoal infections. The antimalarials and amebicides have been treated in separate sections.

Two important protozoal infections that occur in immunocomprimised patients (especially AIDS) are pneumocystis and toxoplasmosis. The intracellular protozoa *Toxoplasma gondii* is responsible for congenital infections (usually ocular) or encephalitis that are treated with trimethoprim-sulfamethoxazole or pyrimethamine-sulfadoxine. Alternative regimens include spiramycin, clindamycin, trimetrexate and atovaquone. The incidence of pneumonias due to *Pneumocystis carinii* (PCP) are increasing in AIDS patients and drug-induced immunosuppressed patients because more physicians are aware of this life-threatening risk to such patient populations. Therapy for PCP includes trimethoprim-sulfamethoxazole in most cases. However, some patients intolerant to this regimen are treated with pentamidine isethionate or atovaquone.

ANTIMONY POTASSIUM TARTRATE—page 1596.

ATOVAQUONE

1,4-Naphthalenedione, *trans*-2-[4-(4-chlorophenyl)cyclohexyl]-3-hydroxy-, Mepron



[95233-18-4]$C_{22}H_{19}ClO_3$ (366.85).

Preparation—A mixture of acetyl chloride, anhydrous $AlCl_3$, cyclohexene, and chlorobenzene is heated in CS_2 to form 4-(*p*-chlorophenyl)cyclohexyl methyl ketone. The haloform reaction with hypobromite yields 4-(*p*-chlorophenyl)cyclohexanecarboxylic acid. This latter compound with 2-chloro-1,4-naphthoquinone boiled in an aqueous solution containing silver nitrate, CH_3CN and ammonium persulfate yields the title compound with the ring hydroxyl replaced by Cl. The halogen is replaced with OH by boiling with aqueous alkali to yield the product. US Pats 5,053,532 and 4,981,874 (both 1991).

Description—Yellow crystals melting about 218°.

Solubility—Practically insoluble in water.

Comments—An analog of ubiquinone with antiprotozoal activity against *Pneumocystis carinii, Plasmodium* spp, and *Toxplasma gondii*. Its mechanism of action is not fully elucidated but antiprotozoal activity may be explained by an ability to inhibit selectively mitchondrial electron transport that results in inhibition of *de novo* pyrimidine synthesis.

It is highly lipophilic with low aqueous solubility. Bioavailability is increased significantly with food, but especially by fat. It has a half-life of 2.9 days and is believed to be excreted in the bile and to undergo enterohepatic cycling with almost all of the drug eliminated in the feces. It is highly protein-bound (>99.9%).

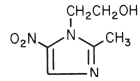
It is indicated for acute oral treatment of mild to moderate *Pneumocystis carinii* pneumonia (PCP) in patients who are intolerant to trimethoprim-sulfamethoxazole. It has not been evaluated adequately as a chronic suppressive agent to prevent PCP in patients at high risk for it.

Adverse effects in one study of 203 patients have included rash (23%), nausea (21%), diarrhea (19%), headache (16%), vomiting (14%), fever (14%), insomnia (10%), asthenia (8%), pruritus (5%), oral monilial (5%), abdominal pain (4%), constipation (3%), and dizziness (3%).

IODOQUINOL—page 1668.

METRONIDAZOLE

1*H*-Imidazole-1-ethanol, 2-methyl-5-nitro-, Flagyl



2-Methyl-5-nitroimidazole-1-ethanol [443-48-1] $C_6H_9N_3O_3$ (171.16).

Preparation—2-Methyl-5-nitroimidazole is condensed with ethylene chlorohydrin by heating with a large excess of the chlorohydrin. After removing the surplus chlorohydrin, the residue is extracted with water and the extract is alkalinized and extracted with chloroform. Evaporation of the chloroform yields crude metronidazole which is recrystallized from ethyl acetate. US Pat 2,944,061.

Description—White to pale-yellow, crystals or crystalline powder; odorless; stable in air, but darkens on exposure to light; melts between 159° and 163°; pK_a 2.62.

Solubility—Sparingly soluble in water, alcohol or chloroform; slightly soluble in ether.

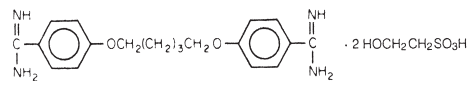
Comments—Bactericidal to anaerobic and microaerophilic microorganisms, including *Bacteroides, Clostridium* sp, *Endolimax nana, Entameba histolytica, Fusobacterium vincentii, Gardnerella vaginalis, Giardia lamblia, Peptococcus, Peptostreptococcus,* and *Trichomonas vaginalis*. These organisms reduce the nitro group and generate metabolites that inhibit DNA synthesis. It long has been the drug of choice for the treatment of trichomoniasis and more recently in combination with iodoquinol for the treatment of symptomatic amebiasis (except in brain). Because it is absorbed well orally, concentrations in the lower bowel sometimes are not high enough to eradicate amebas, so that it is combined with iodoquinol to make a first-choice combination. It is also the drug of choice for the treatment of Dracunculus (guinea worm) infestations. It is the alternative drug to treat giardiasis (although some authorities consider it the drug of first choice), balantidiasis, blastocystitis, and infections by *Entameba polecki*. It is used widely for the treatment and prophylaxis of infections caused by anerobic bacteria; it is a drug of choice against GI strains of *Bacteroides fragilis* and vaginal infections by *Gardnerella vaginalis*. It has been used successfully in the treatment of antibiotic-associated pseudomembranous colitis, for which it may be given orally or intravenously. It also has been reported to be of value in Crohn's disease. The drug sensitizes hypoxic tumor cells to radiation and has been employed as an adjunct to radiation therapy.

The most common untoward effects are nausea, diarrhea, anorexia, epigastric distress, and abdominal cramps. Unpleasant taste, vomiting, furry tongue, and stomatitis are fairly frequent. Urticaria, pruritus, flushing, dysuria, cystitis, dry mouth, dry vulva and vagina, feeling of pelvic pressure, vaginal burning, rash, vertigo, headache, numbness, paresthesias, and insomnia occur occasionally. Incoordination and ataxia are rare. Sudden overgrowth of monilia sometimes occurs. The urine sometimes turns a dark color. During treatment the patient should refrain from drinking alcoholic beverages, since the drug has a mild effect similar to *Disulfiram*. Neutropenia occurs, so that a blood count should be made, especially before a second course of the drug. In patients with blood dyscrasias great care must be exercised. It should not be used in patients with diseases of the CNS. The drug has been found to be carcinogenic in mice and rats, and mutagenic. Substances mutagenic in the Ames test have been found in the urine of recipients. It has been used in pregnancy without consequence, but it is advisable to withhold it during pregnancy, if possible.

It is usually about 80% absorbed by the oral route, but in some patients absorption is low. Bowel surgery decreases presystemic elimination. Feces contain 6% to 20% of an oral dose. Although metabolism is performed by target anaerobes and microaerophiles, the principal route of elimination is hepatic oxidation and glucuronidation. About 20% of unchanged drug and all of the hepatic metabolites are excreted into the urine. The half-life is about 6 to 12 hr. The drug inhibits the oxidation of warfarin.

PENTAMIDINE ISETHIONATE

4,4′-(Pentamethylenedioxy)dibenzamidine, bis(2-hydroxyethanesulfonate; Pentam 300, NebuPent



[140-64-7] $C_{19}H_{24}N_4O_2 \cdot 2C_2H_6O_4S$ (592.68).

Preparation—*J Chem Soc* 1942; 103.

Description—Crystals; hygroscopic; melts about 180°.

Solubility—Soluble in water; slightly soluble in alcohol; insoluble in ether or chloroform; pK_a 11.4 (base).

Comments—The alternate drug to suramin for treatment of the hemolymphatic stage of African sleeping sickness (trypanosomiasis) caused by *T brucci gambiense* and *T brucei rhodesiense*. It is the alternate drug for the treatment and the drug of choice for prophylaxis of infections caused by *Pneumocystis carinii*; some reports indicate an efficacy equal to that of trimethoprim-sulfamethoxazole and comparable toxicity in patients with AIDS. It is also an alternative drug for the treatment of kala azar and visceral leishmaniasis. It concentrates in some organs and is eliminated mainly by the kidney. It has a half-life of 6.4 hr and 9.4 hr after 1 IM or IV administration, respectively. Frequent adverse effects include pain and swelling at the site of injection, hypotension, vomiting, blood dyscrasias, and renal damage. Occasional effects are diabetes, hypoglycemia, shock, and liver damage. Herxheimer reactions are rare. Too-rapid injection causes hypotension.

SULFADOXINE—page 1632.
TRIMETREXATE—see RPS-19, page 1262.

ANTIFUNGAL DRUGS

Human fungal infections have increased in recent years because more patients are now at risk for these pathogens. The increased exposure is explained by more frequent surgeries, the use of broad spectrum antimicrobials, immunosuppressive drug therapy for cancer and organ transplantation patients and the HIV epidemic. The antifungal drugs are grouped into the following categories: drugs for systemic mycoses, oral drugs for mucocutaneous infections and topical drugs for mucocutaneous infections (Table 87-10).

The major drugs for systemic mycoses include amphotericin B (a polyene macrolide), flucytosine (a pyrimidine analog), and the relatively nontoxic, orally-active azoles (ketoconazole, itraconazole, and fluconazole). These azoles are synthetic compounds that possess either an imidazole or triazole group. The major attributes of the lipophilic amphotericin B are its broad fungicidal activity and potential for serious nephrotoxicity. Flucytosine has a very restricted spectrum and causes bone marrow suppression and transient hepatoxicity. In contrast, the azoles have a broad antifungal spectrum and cause only relatively minor GI upset. Ketoconazole inhibits adrenal and gonadal steroid hormone synthesis and some hepatic metabolizing enzymes. However, itraconazole and fluconazole have much less potential for the inhibition of hepatic metabolism of other drugs.

Amphotericin B is relatively selective for fungal membranes because it binds to ergosterol, the predominant sterol in these microbes, whereas the main sterol in bacteria and human cells is cholesterol. Upon binding to ergosterol, amphotericin B alters the permeability of fungal cells resulting in pores allowing leakage of intracellular ions and macromolecules. Resistance occurs if ergosterol binding is impaired.

Flucytosine is converted to 5-fluorouracil and then a monophosphate and triphosphate inside the fungal cell where it inhibits DNA and RNA synthesis. Human cells are unable to convert the parent drug to its active metabolites.

The antifungal activity of azole drugs is based on their inhibition of fungal cytochrome P450 enzymes that participate in ergosterol sytnesis. Ketoconazole (an imidazole) is less selective and inhibits adrenal and gonadal cytochrome P450 enzymes (causing gynecomastia, infertility, and menstrual irregularities) as well as hepatic enzymes involved in drug metabolism. Itraconazole and fluconazole (both triazoles) have less interaction with hepatic microsomal enzymes.

The other major differences in these systemic antifungal drugs involve their pharmacokinetics. Amphotericin B is given by IV infusion and must be formulated as a colloidal suspension because of its low water solubility. Reactions due to IV infusion include fever, chills, headache, and hypotension. New liposomal formulations are now available to reduce the renal toxicity by decreasing its accumulation in renal cell membranes and increase delivery at other sites such as liver, spleen, lymph nodes, and lung.

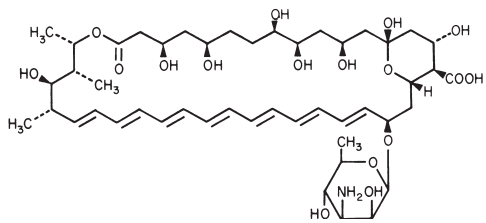
The distribution of flucytosine is very extensive including the CSF in contrast to amphotericin B that must be given intrathecally to treat fungal meningitis. Flucytosine is eliminated by renal excretion, while amphotericin is mainly metabolized. The azoles vary in their water solubility and route of administration. Fluconazole is the most water soluble and best orally absorbed. It also has good CSF levels and is eliminated by renal excretion. Both ketoconazole and itraconazole have low water solubility, variable oral absorption, low CSF levels and undergo metabolism.

Table 90-10. Antifungals

DRUG	COMMENTS
Drugs for Systemic Mycoses	
Amphotericin B	IV only, broad spectrum, nephrotoxicity
Flucytosine	Narrow spectrum, bone marrow suppression
Fluconazole	IV or oral, good oral abs and distribution, long acting
Ketoconazole	Oral abs good unless reduced gastric acid, limited distribution, inhibits CYP3A4
Itraconazole	Very lipophilic, so food improves p oral abs, metabolized, inhibits CYP3A4
Oral Drugs for Cutaneous Mycoses	
Griseofulvin	Food improves oral abs, fungistatic
Terbinafine	Good oral abs., fungicidal, shorter therapy
Topical Drugs for Cutaneous Mycoses	
Clotrimazole	High efficacy vs dermatophytes
Miconazole	Best efficacy vs dermatophytes
Ciclopirox	High efficacy vs dermatophytes
Tolnaftate	Good efficacy vs dermatophytes
Haloprogin	Good efficacy vs dermatophytes
Undecylenic acid	Lower efficacy vs dermatophytes

AMPHOTERICIN B

Fungizone



[1*R* – (1*R**,3S*,5*R**,6*R**,9*R**,11*R**,15*S**,16*R**,17*R**,18*S**,19*E*,21*E*,23*E*,25*E*,27*E*,29*E*,31*E*,33*R**,35*S*,36*S**,37*S**)]-33-[(3-Amino-3,6-dideoxy-β-D-mannopyranosyl)oxy]-1,3,5,6,9,11,17,37-octahydroxy-15,16,18-trimethyl-13-oxo-14,39-dioxabicyclo[33.3.1]nonatriaconta-19,21,23,25,27, 29,31-heptaene-36-carboxylic acid [1397-89-3] $C_{47}H_{73}NO_{17}$ (924.09); a substance produced by the growth of *Streptomyces nodosus*. Potency: not less than 750 μg of amphotericin B/mg.

Preparation—By the growth of selected strains of *Streptomyces nodosus* in an appropriate medium under controlled conditions of temperature, pH, and aeration. After extracting from the medium, the crude product is purified by treatment with various solvents at controlled acidity.

Description—Yellow to orange powder; odorless or practically so; pK_a (acid) 5.7, (amine) 10.0.

Solubility—Insoluble in water, anhydrous alcohol or ether; aqueous solubility can be increased to approximately 50 mg/mL by complexation with sodium desoxycholate.

Comments—The widest spectrum of antifungal activity of any systemic antifungal drug. By the IV route it is an extremely useful drug for therapy of systemic fungus diseases, especially coccidioidomycosis, cryptococcosis, systemic moniliasis, histoplasmosis, aspergillosis, rhodotorulosis, sporotrichosis, phycomycosis (mucormycosis), and North American blastomycosis. It also is used topically in the treatment of superficial monilial infections and by nasal spray in the prophylaxis of aspergillosis in immunocompromised patients.

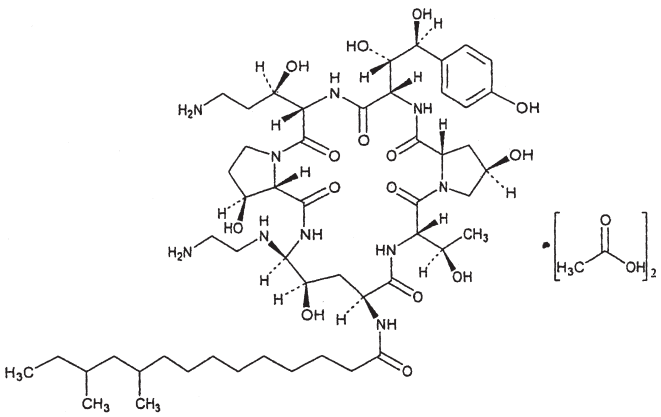
It is absorbed very poorly from the GI tract. It is highly bound predominantly to β-lipoproteins and is excreted slowly by the kidneys but neither renal failure nor hemodialysis has a consistent effect on plasma levels. The initial half-life is 24 hr, is followed by a terminal half-life of about 15 days.

It may induce chills and fever, nausea and vomiting, diarrhea, abdominal *cramps*, hemorrhagic gastroenteritis, dyspepsia, headache, vertigo, pain in the vein injected, thrombophlebitis, muscle and joint pains, anemia, purpura, hypertension, hypotension, cardiac arrest, ventricular fibrillation, skin rashes, hypokalemia, hypomagnesemia, renal damage, blood dyscrasias, loss of hearing, and other untoward effects. When given intrathecally it may cause grand mal convulsions, radiculitis, arachnoiditis, paralysis of the extremities, urinary retention, and other difficulties.

ANTHRALIN—page 1284.
BUTYLPARABEN—page 1627.

CASPOFUNGIN ACETATE

1-[(4*R*,5*S*)-5-[(2-Aminoethyl)amino]-*N*^{2}-(10,12-dimethyl-1-oxotetradecyl)-4-hydroxy-L-ornithine]-5-[(3*R*)-3-hydroxy-L-ornithine]pneumocandin B_0, diacetate (salt); Cancidas



[179463-17-3] $C_{52}H_{88}N_{10}O_{15}\cdot 2C_2H_4O_2$ (1213.42).

Preparation—Synthesized from a fermentation product of *Glarea lozoyensis*.

US Pat 5,378,804 (1995).

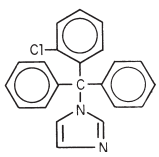
Description—White to off white hygroscopic powder. Saturated solution has pH of about 6.6.

Solubility—Freely soluble in water or methanol; slightly soluble in ethanol.

Comments—A polypeptide antifungal related to pneumocandin B0. It is a glucan synthesis inhibitor of the echinocandin structural class. It is available as a parenteral agent for intravenous injection. This agent is very active against *Candida* species (including azole-resistant strains) and possesses moderate to good activity against *Aspergillus* species. Adverse effects are uncommon but have included histamine release associated with infusion of caspofungin as well as altered liver function tests. Of note, drug intereactions with cyclosporine may occur, and patients should be closely monitored.

CLOTRIMAZOLE

1*H*-Imidazole, 1-[(2-chlorophenyl)diphenylmethyl]-, Gyne-Lotrimin, Lotrimin, Mycelex, Mycelex-G



1-(*o*-Chloro-α,α-diphenylbenzyl)imidazole [23593-75-1] $C_{22}H_{17}ClN_2$ (344.84).

Preparation—From the reaction between imidazole and 2-chlorotriphenylmethyl chloride using trimethylamine as a proton receptor.

Description—White, to pale-yellow, crystalline powder; melts about 147° with decomposition weakly basic; hydrolyses on heating with aqueous acid.

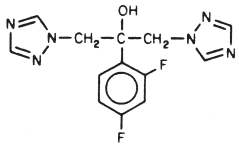
Solubility—Slightly soluble in water; soluble in alcohol or chloroform; slightly soluble in ether.

Comments—A broad-spectrum antifungal agent that inhibits growth of pathogenic dermatophytes. It exhibits fungicidal activity in vitro against isolates of *Trichophyton rubrum* and *mentagrophytes*, *Epidermophyton floccosum, Microsporum canis,* and *Candida albicans*. It shares with econazole and miconazole first-choice status for topical treatment of tinea pedis, tinea cruris, and tinea corporis due to any of the aforementioned organisms, candidiasis due to *Candida albicans.* It is effective for the topical treatment of vulvovaginal and oropharyngeal candidiasis.

Adverse effects from topical use include erythema; stinging, blistering and peeling of the skin; pruritus and urticaria.

FLUCONAZOLE

1*H*-1,2,4-Triazole-1-ethanol, α-(2,4-difluorophenyl)-α-(1*H*-1,2,4-triazol-l-ylmethyl), Diflucan



[86386-73-4] $C_{13}H_{12}F_2N_6O$ (306.27).

Preparation—US Pat 4,404,216.

Description—White crystals; melts about 139°.

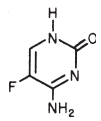
Comments—A highly selective inhibitor of fungal cytochrome P-450 and sterol C-14 α-demethylation that results in inhibition of ergosterol synthesis. It is a broad-spectrum bistriazole antifungal agent that is primarily fungistatic with activity against *Cryptococcus neoformans* and *Candida* spp. In common with other azole antifungal drugs, most fungi are more susceptible in vivo. It is approved for systemic candidiasis, oropharyngeal and esophageal candidiasis, and cryptococcal meningitis.

The bioavailability of oral fluconazole is over 90% compared with IV administration. The volume of distribution is 0.8 g/L and reaches concentrations in the CSF that are 80% of that in serum of patients with meningitis. Plasma protein binding is 11%, and fluconazole is cleared primarily by renal excretion with 80% of the dose unchanged and 11% as metabolites in the urine. The plasma half-life is about 30 hr. Fluconazole may alter cytochrome P-450 pathways of metabolismof several drugs including phenytoin, cyclosporine, warfarin, and sulfonylureas.

The most common adverse effects of fluconazole are nausea, vomiting, bloating, and abdominal discomfort. Elevated hepatic aminotransferase activity and allergic rashes may occur.

FLUCYTOSINE

Cytosine, 5-fluoro-, 5-FC; Ancobon



[2022-85-7] $C_4H_4FN_3O$ (129.09).

Preparation—5-Fluorouracil is reacted with $POCl_3$ to form 2,4-dichloro-5-fluoropyrimidine which is reacted with NH_3 to produce 2-chloro-4-amino-5-fluoropyrimidine. Heating the latter in concentrated HCl yields flucytosine. US Pat 3,368,938.

Description—White to off-white, crystalline powder; odorless or has a slight odor; melts about 295° with decomposition; stable in light; nonhygroscopic; stable for at least 3 months at 45°; pK_a 2.9, 10.7.

Solubility—1 g in approximately 83 mL water or approximately 12 mL 0.1 *N* HCl; slightly soluble in alcohol; practically insoluble in chloroform or ether.

Comments—Converted in the fungus to 5-fluorouracil, which is incorporated into RNA, which interferes with normal protein synthesis. Certain fungal organisms are more sensitive to interference from the drug than are human cells, so that the drug is useful in the treatment of some fungal infections. Most clinical isolates of *Cryptococcus* and 40 to 92% of *Candida* are sensitive to the drug. It is the drug of choice to treat chromomycosis and of second choice to treat systemic candidiasis. It may be combined with amphotericin B for first-choice treatment of aspergillosis or cryptococcosis, especially with meningitis.

Nausea, vomiting, diarrhea, and rash rather commonly are caused by the drug. Bone-marrow depression, manifested by anemia, leucopenia, and thrombocytopenia, occur in about 10% of patients; there have been a few fatalities.

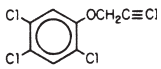
Sedation, confusion, hallucinations, headache, and vertigo occur infrequently. Mild azotemia and an increase in liver enzymes in the plasma are rather common effects. Monitor hepatic function and hematopoietic system during therapy.

About 90% is absorbed orally. It is distributed well among all the tissues, including the CNS. About 80% to 90% is excreted unchanged in the urine with a half-life 0.5 to 1 hr, except 4 to 6 hr in renal failure. The dose needs to be adjusted if renal function is abnormal.

FORMALDEHYDE—page 1628.
GENTIAN VIOLET—see RPS-18, page 1171.

HALOPROGIN

Benzene, 1,2,4-trichloro-5-[(3-iodo-2-propynyl)oxy]-, ing of Halotex



[777-11-7] $C_9H_4Cl_3IO$ (361.39).

Preparation—*CA* 1963; 58:14635g.

Description—White or pale-yellow, crystalline powder; melts about 114°; decomposes at 190°.

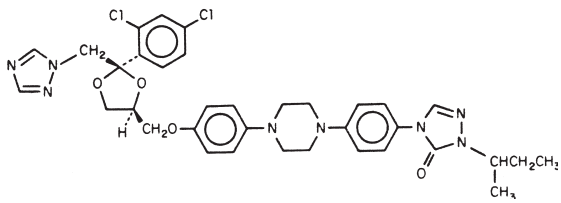
Solubility—Very slightly soluble in water; soluble in alcohol.

Comments—A *topical antifungal* with good efficacy versus dermatophytes, used for cutaneous mycoses.

ICHTHAMMOL—page 1285.
IODINE—pages 1628 and 1716.

ITRACONAZOLE

3*H*-1,2,4-Triazol-3-one, (±)-4-[4-[4-[4-[[2-(2,4-dichlorophenyl)-2-(1*H*-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]-phenyl]-1-piperazinyl]phenyl]-2,4-dihydro-2-(1-methylpropyl)-, Sporanox



[84625-61-6] $C_{35}H_{38}Cl_2N_8O_4$ (705.65).

Preparation—*J Med Chem* 1984; 27:894. The racemate is used clinically.

Description—White crystals; melting about 166°; pK_a approximately 3.5.

Solubility—1 g in 10,000 mL water or 1000 mL of alcohol; more soluble in acidulated polyethylene glycols.

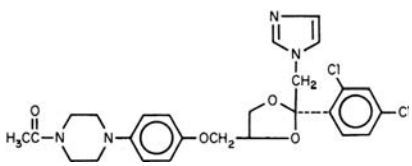
Comments—A triazole antifungal agent with a mechanism of action and broad spectrum similar to fluconazole. It also inhibits chitin synthesis in both yeast-budding and hyphal growth of fungi. It is used to treat fungal infections in immunocompromised and nonimmunocompromised patients who have cryptococcosis, blastomycosis, histoplasmosis and aspergillosis. Unlabeled uses include superficial mycoses, systemic mycoses and subcutaneous mycoses.

Bioavailability is 55% and food enhances oral absorption. It is 99.8% protein bound and is eliminated in urine and bile after extensive hepatic metabolism. The half-life is 20 to 30 hr. Negligible levels reach CSF.

Adverse effects include nausea, epigastric pain, edema, and hypokalemia. Reversible alterations in liver function have been reported in a few cases. Some interactions with drugs metabolized by P450 pathways have been observed in some patients.

KETOCONAZOLE

Piperazine, *cis*-1-acetyl-4-[4-[[2-(2,4-dichlorophenyl)-2-(1*H*-imidazol- 1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-, Nizarol



[65277-42-1] $C_{26}H_{28}Cl_2N_4O_4$ (531.44).

Preparation—*J Med Chem* 1979; 22:1003.

Description—White crystals melting about 146°.

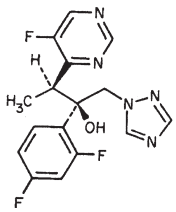
Comments—Blocks the fungal synthesis of ergosterol, which is essential to the integrity of the cell membranes of nearly all the pathogenic fungi. Consequently, it has a broad spectrum of antifungal activity. It or amphotericin B is the drug of choice for the treatment of blastomycosis, coccidiodosis, histoplasmosis, and paracoccidiodosis. It is an alternative drug for candidiasis and chromoblastomycosis. Successful treatment sometimes requires months.

Nausea and vomiting are the most frequent (3–10%) side effects; these can be avoided by taking the drug with food. Pruritus is the next most frequent (1.5%) and abdominal cramps, third (1.2%). Other effects are pruritus, sleepiness, headache, diarrhea, photophobia, fever, thrombocytopenia, gynecomastia, impotence, and oligospermia (from low testosterone levels). A disulfiram-like reaction to alcohol occurs. Most adverse effects are transient and all are reversible, except that three cases of liver necrosis have been fatal. Monitoring of liver function is mandatory. In rats, it is teratogenic; thus, it should not be used during pregnancy. It inhibits certain cytochrome P-450 enzymes; plasma levels of cyclosporine, estradiol, hydrocortisone, methylprednisolone, rifampin, and theophylline can be increased. Cimetidine inhibits and rifampin induces the metabolism of the drug. Ketoconazole inhibits steroid C17-20 lyase and thus decreases the biosynthesis of adrenalcorticoids, androgens, and estrogens. This is the basis of its uses to treat Cushing's syndrome, precocious puberty, and prostatic carcinoma.

It is absorbed well by the oral route. In plasma, 95% to 99% is protein-bound. The principal route of elimination is hepatic metabolism and biliary secretion of the metabolites, less than 4% being renal excretion. There are a number of metabolites. Enterohepatic circulation complicates the pharmacokinetics. During the first 10 hr (alpha-phase), the half-life is 1.4 to 3.3 hr; thereafter (beta-phase), it is 6 to 10 hr.

VORICONAZOLE

4-Pyrimidineethanol, (α*R*,β*S*)-α-(2,4-difluorophenyl)-5-fluoro-β-methyl-α-(1*H*-1,2,4-triazol-1-ylmethyl)-, Vfend



[137234-62-9] $C_{16}H_{14}F_3N_5O$ (349.32).

Preparation—A Friedel-Crafts reaction between 1,3-difluorobenzene and chloroacetyl chloride yields 2,4-difluorophenacyl chloride. This latter compound with

1*H*-1,2,4-triazole forms the1-phenacyl derivative (I). Also, 4-chloro-5-fluoro-6-ethylpyrimidine, with NBS and AIBN forms the 1-bromoethyl product(II). Compounds I and II, with Zn/I_2, couples to form the variconazole nucleus in the *RS*/*SR* configuration of the alkyl side chain, in a 12:1 ratio. The compound is dechlorinated and resolved to yield the product. *Albany Molecular Research Tech Reports* 2003; 8(80):6-9.

Description—White to light yellow powder melting about 127°. $[\alpha]^{25}_D$ -62° (c = 1, methanol).

Comments—Triazole antifungal with enhanced activity against Aspergillus species. Clinically considered to be one of the treatments of choice for infections caused by this species. Also active against most "azole-resistant Candida species". Available both orally and parenterally. Adverse reactions area similar to itraconazole with a noted addition of transient visual disturbances. A potent inhibitor of cytochrome P450 enzymes. Caution should be exercised in patients receiving "narrow index" medications concomitantly with voriconazole.

SYSTEMIC DRUGS FOR MUCOCUTANEOUS INFECTIONS

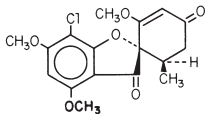
Systemic treatment of dermatophyte infections of skin, hair, and nails has been restricted for many years to the fungistatic drug, griseofulvin. Its action involves deposition in newly formed skin and nail beds where it binds to keratin protecting these sites from new infection. It is given orally for prolonged periods with numerous side effects (headaches, nausea, hepatoxicity, skin rashes, and photosensitivity).

More recently, terbinafine (an allylamine) and itraconazole (an azole) have become available as oral fungicidal drugs for dermatophytes. Terbinafine is especially useful for antifungal therapy of nail beds (onychomycosis) because it is more effective over a shorter time period. It inhibits the fungal enzyme squalene epoxidase leading to the accumulation of the toxic

sterol, squalene. Adverse effects are much less but involve some cases of GI upset and headache. Itraconazole is the azole of choice for treatment of dermatophytoses and onychomycosis.

GRISEOFULVIN

Spiro[benzofuran-2(3*H*),1′-[2]cyclohexene]-3,4-dione, 7-chloro-2,4,6-trimethoxy-6-methyl-, (1′*S-trans*)-,



[126-07-8] $C_{17}H_{17}ClO_6$ (352.77); a substance produced by the growth of *Penicillium griseofulvum* or by other means. It has a potency equivalent to not less than 900 μg of $C_{17}H_{17}ClO_6$/mg.

Preparation—By the submerged process using selected strains of *Penicillium patulum*.

Description—White to creamy white, powder, in which particles of the order of 4 μm in diameter predominate; odorless.

Solubility—Soluble in chloroform; sparingly soluble in alcohol; slightly soluble in water.

Comments—An effective agent in the treatment of superficial fungus infections. It is fungistatic and not fungicidal. Administered systemically, the drug is highly effective in the management of tinea capitis, tinea corporis, tinea unguium (onychomycosis) and the chronic form of tinea pedis caused by the dermatophytes, *Microsporon, Trichophyton,* and *Epidermophyton*.

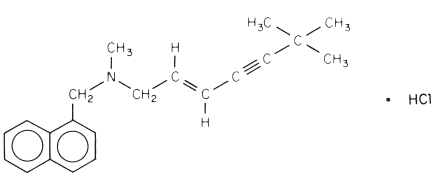
Since it does not kill but only arrests reproduction of the organism, it is necessary to continue medication long enough for the entire epidermis to be shed and replaced in order to remove reinfecting organisms. It is deposited in the keratin precursor cells and is carried outwards into the epidermis as normal skin growth proceeds. This also makes for a long latency from the time medication is begun until evidence of improvement occurs.

Serious untoward reactions are infrequent, but skin eruptions, leukopenia, granulocytopenia, and allergic reactions such as serum sickness or angioneurotic edema are among the serious side effects reported. It also may cause nausea, vomiting, epigastric distress, and diarrhea; these often may be avoided by giving the drug with or shortly following a meal. Headache is also relatively frequent. Infrequently, phototoxicity, proteinuria, lassitude and fatigue occur and, rarely, there is mental confusion and motor incoordination. It is advisable to monitor kidney, blood, and liver functions. Ingestion of alcohol during treatment with the drug causes tachycardia and flushing.

The oral bioavailability depends upon particle size; the smaller the crystal size, the more complete the absorption. The percent absorbed from the microsize preparations is 25% to 70%; from the ultramicrosize preparations it is almost complete. Absorption is greater if the drug is administered with a high-fat meal. The principal route of elimination may be transepidermal loss, although a considerable hepatic metabolism and biliary secretion probably also occur. The half-life is 24 to 36 hr. It induces the hepatic microsomal system, and the metabolism of warfarin, mexiletine and oral contraceptives is increased, thus necessitating dosage adjustments.

TERBINAFINE HYDROCHLORIDE

1-Naphthalenemethaneamine, (*E*)-*N*-(6,6-dimethyl-2-hepten-4-ynyl)-*N*-methyl-, monohydrochloride; Lamasil



[78628-80-5] $C_{21}H_{25}N{\cdot}HCl$ (327.90).

Preparation—*J Med Chem* 1984; 27:1539; Lednicer D, et al. *Org Chem of Drug Syn*, vol 4, Wiley, NY, 1990, p 55.

Description—White to off-white crystalline powder.

Solubility—Freely soluble in methanol and methylene chloride; soluble in alcohol; slightly soluble in water.

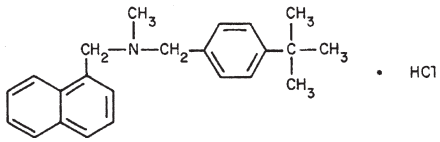
Comments—The *first allylamine* available for systemic use in the treatment of all dermatophytes (*Trichophyton, Epidermophyton*, and *Microspora*). It is also available for topical therapy of dermatophytes including *tinea* infections. It selectively inhibits fungal squalene epoxidase causing a fungicidal action due to the intracellular accumulation of the toxic sterol, squalene; it also exerts a fungistatic action by depletion of ergosterol. One tablet daily for 12 wk achieves a 90% cure rate for onychomycosis that is more effective than griseofulvin or itraconazole. It does not seem to affect the cytochrome P450 metabolism of other drugs. The most common adverse effects are headache, diarrhea, dyspepsia, and abdominal pain. Taste disturbances do occur and may persist for several weeks after discontinuing the drug.

TOPICAL DRUGS FOR MUCOCUTANEOUS INFECTIONS

Nystatin is a topical polyene macrolide analog of amphotericin B with a similar mode of action but too toxic for parenteral use. It is active against most *Candida* spp and may be used for oropharyngeal thrush, vaginal candidiasis, and intestinal candidiasis. However, the most frequently used topical antifungal therapy today for oral thrush and dermatophytic infections are the azoles, clotrimazole and miconazole. Other azoles also available for topical use include econazole, oxiconazole, and sulconazole. The allylamines available of topical treatment of tinea infections are terbinafine and naftifine.

BUTENAFINE HYDROCHLORIDE

1-Naphthalenemethaneamine, *N*-[[4-(1,1-dimethylethyl) phenyl]methyl]-*N*-methyl-, hydrochloride; Mentax



[101827-46-7] $C_{23}H_{27}N{\cdot}HCl$ (353.94).

Preparation—*N*-Methyl-1-naphthylmethaneamine is treated with *p-tert*-butylamine in DMF. Sodium carbonate is added and, after prolonged stirring, butenafine base separates, is filtered and converted to the hydrochloride by usual methods.

Description—White, odorless crystalline powder from methanol/acetic acid melting about 200°.

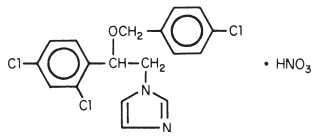
Solubility—Freely soluble in methanol, ethanol, chloroform or methylene chloride; slightly soluble in water.

Comments—Butenafine inhibits ergosterol biosynthesis by blocking squalene epoxidation. Butenafine appears as an alternative for treatment of various dermatophytosis, such as tinea pedis, tinea cruris, tinea corporis, and onychomycosis. Its rapid and persistent antifungal activity is attractive. Butenafine is available for topical administration in 1% cream formulation. The most striking feature of butenafine is its superior fungicidal activity against this group of fungi when compared to that of terbinafine, naftifine, tolnaftate, and clotrimazole. It is active also against *Candida albicans,* and this activity is superior to that of terbinafine and naftifine. Butenafine also generates low MICs for Cryptococcus neoformans and *Aspergillus* spp as well. Butenafine appears as an alternative for treatment of various dermatophytosis, such as tinea pedis, tinea cruris, tinea corporis, and onychomycosis. Its rapid and persistent antifungal activity is attractive.

CLOTRIMAZOLE—page 1671.

ECONAZOLE NITRATE

1*H*-Imidazole, (±)-1-[2-[(4-chlorophenyl)methoxy]-2-(2,4-dichlorophenyl)ethyl]-, mononitrate, Spectrazole



(±)-1-[2,4-Dichloro-β-[(*p*-chlorobenzyl)oxy]phenethyl]imidazole mononitrate [68797-31-9] $C_{18}H_{15}Cl_3N_2O{\cdot}HNO_3$ (440.70).

Preparation—2,4-Dichloroacetophenone is further chlorinated to the phenacyl chloride and this compound treated with imidazole with

loss of HCl to yield 1-(1*H*)-(2,4-dichlorophenacyl)imidazole (I). Reduction of the ketone group of I with sodium borohydride forms the secondary alcohol (II). With sodium hydride, the alcoholate of II is produced, which on reaction with *p*-chlorobenzyl chloride produces econazole base. See *J Med Chem* 1969; 12:784.

Description—White crystals; melts at approximately 162°; pK_a 6.6.

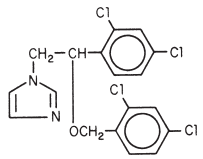
Solubility—Very slightly soluble in water or most organic solvents.

Comments—Antifungal activity against the dermatophytes (*Epidermophyton floccosum, Microsporon auduoni, cani,s* and *gypseum, and Trichophyton rubrum, mentagrophytes,* and *tonsurans*), *Pityrosporon obiculare* (*Malasserzia furfur*) and *Candida albicans*. It is employed in the treatment of *cutaneous Candidiasis*, and *tineas corporis, cruris, pedis,* and *versicolor* (*pityriasis versicolor*). Its efficacy is comparable to that of miconazole or clotrimazole. It readily penetrates into the stratum corneum, where effective concentrations persist for as long as several days. In approximately 3% of recipients, local erythemia, burning sensation, stinging, and itching occur.

MERCURIC OXIDE, YELLOW—see RPS-18, page 1172.
MERCURY, AMMONIATED—see RPS-18, page 1172.

MICONAZOLE

1*H*-Imidazole, 1-[2-(2,4-dichlorophenyl)-2-[(2,4-dichlorophenyl)methoxy]ethyl]-, Micatin, Monistat



1-[2,4-Dichloro-β-[(2,4-dichlorobenzyl)oxy]phenethyl]imidazole [22916-47-8] $C_{18}H_{14}Cl_4N_2O$ (416.12).

Preparation—2,4-Dichlorophenacyl bromide is used to alkylate imidazole followed by reduction of the ketone group to a secondary alcohol which is converted to the alkoxide. Williamson alkylation with α,*p*,-dichlorotoluene yields the product. *J Med Chem* 1969; 12:784.

Comments—Fungicidal to various species of *Aspergillus, Blastomyces, Candida, Cladosporium, Coccidioides, Epidermophyton, Histoplasma, Microsporon, Paracoccidioides,* and *Trichophyton*. It inhibits ergosterol synthesis, which disrupts fungal cell membranes. The drug readily penetrates into the stratum corneum and remains there in high concentration for as long as 4 days, which probably contributes to its efficacy against the dermatophytoses. In tinea pedis (athlete's foot) a mycological cure rate of 96% has been reported with the nitrate salt, which considerably exceeds that of any other drugs except clotrimazole and econazole.

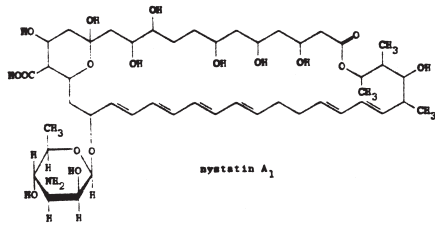
Topically, for vulvovaginal candidiasis, the reported cure rate varies from 80% to 95%, considerably superior to that with nystatin (65%) and amphotericin B (75%). Often pruritus is relieved after a single application. It is also effective against some vaginal infections caused by *Trichophyton glabratus*. The free base is useful in the topical treatment of various ophthalmic mycoses. The base has been used successfully in the systemic treatment of several deep or systemic mycoses, especially those of candidiasis and cryptococcosis.

Burning, itching, and maceration sometimes occurs after application of the nitrate to the skin, as happens frequently with effective antifungal drugs. Intravaginally, burning, itching, pelvic discomfort, urticaria, and headache occur in 6% to 7% of users, especially during the first few days of treatment. Experimental and clinical studies suggest that the drug is safe for use in pregnancy, but systemic use during pregnancy should probably be avoided, if possible. Orally, it appears to be tolerated well, but nausea, vomiting, and diarrhea occur. No evidence of renal or hepatic toxicity has been observed.

IV administration may cause phlebitis, hypercholesterolemia, and hypertriglyceridemia (caused by the vehicle), hyponatremia (from ADH secretion), nausea, vomiting, diarrhea, anorexia, and infrequent allergic and immune reactions, such as fever, chills, pruritus, rashes, thrombocytopenia, anaphylaxis, and anemia. Wheezing and tachypnea and sinoatrial and ventricular tachycardias occur, which can be avoided by slower rates of infusion. Intrathecally, it may cause some meningeal irritation, but the route appears to be safe.

From topical sites, only trace amounts of the drug appear in the blood or urine. Slightly less than 50% of an oral dose is absorbed. In plasma, about 93% is bound to proteins. Less than 1% of an oral dose appears unchanged in urine. The drug manifests three-compartment pharmacokinetics. The terminal (elimination, β) half-life is about 1 day. Systemically, it inhibits the metabolism of warfarin.

NYSTATIN



Nystatin [1400-61-9] is a substance produced by the growth of *Streptomyces noursei* Brown, et al (Fam *Streptomycetaceae*). It contains not less than 4400 Units of nystatin activity/mg. Nystatin is a mixture of 4 different tetraenes, nystatin A, (principally) and nystatin A_2, A_3 and polyfungin B. Nystatin A_1 [34786-70-4] $C_{47}H_{75}NO_{17}$ is closely related to *Amphotericin B*. Each is a macrocyclic lactone containing a ketal ring, an *all-trans* tetraene system and a mycosamine (3-amino-3-deoxyrhamnose) moiety.

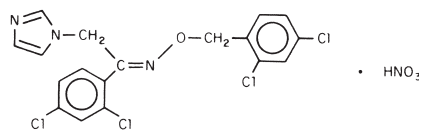
Description—Yellow to light-tan hygroscopic powder; odor suggestive of cereals; hygroscopic; affected by long exposure to light, heat or air; pK_a 4.5, 8.64; gradually decomposes at temperatures higher than 160° without melting.

Solubility—(mg/mL, at approximately 30) Water, 4; alcohol 1.2; methanol 11.2; chloroform, 0.48; or ethylene glycol, 8.75.

Comments—Active *in vitro* against a number of yeasts and molds, but its clinical usefulness is limited to the treatment of *candidiasis*. The antibiotic is absorbed poorly from the gastrointestinal tract; consequently it is not effective against systemic infections, but is effective against *intestinal candidiasis*. It may prevent emergence of candidal suprainfections resulting from oral therapy with broad-spectrum antibiotics, although such suprainfections are so infrequent that routine "prophylactic" use of nystatin is not worthwhile. It does *not* prevent diarrhea from oral broad-spectrum antibiotics. It has been employed with variable success in the treatment of oral "thrush" (moniliasis). It is used alone to treat vulvovaginal candidiasis. For use on the skin, it may be combined with neomycin, gramicidin and triamcinolone acetonide. It is not the drug of first or second choice in any use. It is relatively nontoxic, but nausea, vomiting and diarrhea may occur with oral therapy.

OXICONAZOLE NITRATE

Ethanone, (*Z*)-1-(2,4-dichlorophenyl)-2-(1*H*-imidazol-1-yl)-*O*-[(2,4-dichlorophenyl)methyl]oxime, mononitrate; Oxistat



[64211-46-7]$C_{18}H_{13}Cl_4N_3O{\cdot}HNO_3$ (492.15).

Preparation—An exothermic reaction occurs upon mixing 2,4-dichlorophenacyl chloride and imidazole in acetonitrile. The product, 2,4-dichlorophenacylimidazole, is refluxed with hydroxylamine HCl in pyridine to form the oxime, which is heated with 2,4-dichlorobenzyl chloride in ethanolic pyridine to yield the base of the title compound. US Pat 4,124,767 (1978).

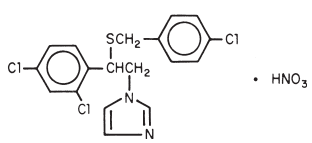
Description—White crystals melting about 138°.

Solubility—Soluble in methanol; sparingly soluble in alcohol, chloroform, or acetone; very slightly soluble in water.

Comments—An antifungal agent used for the topical treatment of *tinea pitryasis versicolor* and for *tinea pedis, tinea cruris* and *tinea corporis* due to *Trichophyton rubrum*, *T mentagrophytes,* or *Epidermophyton floccosum*.

SULCONAZOLE NITRATE

1*H*-Imidazole, (±)-1-[2-[[(4-chlorophenyl)methyl]thio]-2-(2,4-dichlorophenyl)ethyl]-, mononitrate; Exelderm



[61318-91-0] $C_{18}H_{15}Cl_3N_2S{\cdot}HNO_3$ (460.77).

Preparation—US Pat 4,038,409 (1977); Lednicer D, et al. *Org Chem of Drug Syn*, vol 3, NY, Wiley, 1984, p 133.

Description—White to off-white crystals melting about 130°.
Solubility—Freely soluble in pyridine; slightly soluble in alcohol, acetone, or chloroform; very slightly soluble in water.
Comments—Used for various *tinea* conditions (athlete's foot), such as *T corporis, T pedis,* or *T cruris*; action is similar to *oxiconazole*.

POTASSIUM IODIDE—page 1377.
POTASSIUM PERMANGANATE—see RPS-19, page 1270.
PROPYLPARABEN—see RPS-18, page 1173.
SALICYLIC ACID—page 1288.
SODIUM BENZOATE—see RPS-19, page 1271.
SODIUM HYPOCHLORITE SOLUTION—page 1630.

ANTIVIRAL DRUGS

Viruses cause much of the morbidity and mortality in populations worldwide, but the number of drugs available are still quite limited. Antiviral drug development has become a very active area in the last decade, especially with the challenges of the AIDS epidemic. The need to develop more selective inhibitors of viral function has increased the number of antiviral drugs in clinical trials for the human immunodeficiency virus (HIV) and should lead to important advantages in the next decade.

Viruses cannot replicate independently because they use the energy-generating, DNA or RNA replicating, and protein synthesizing pathways of the host cells to replicate. Viral replication can be targeted at several steps:

1. Adsorption to and penetration into susceptible host cells
2. Uncoating of viral nucleic acid
3. Synthesis of early, regulatory proteins (eg, nucleic acid polymerase)
4. Synthesis of RNA or DNA
5. Synthesis of late structural proteins
6. Assembly of viral particles
7. Release of infectious virions from the cell

Replication of the virus peaks after or before manifestation of clinical symptoms, so early initiation of therapy or prevention of infection is important for optimal clinical efficacy. Some good examples of successful early therapy or prevention include acyclovir to treat varicella-zoster infections and amantidine prophylaxis against influenzae A. The development of many pyrimidine and purine nucleoside analogs have lead to new compounds that selectively inhibit viral DNA synthesis. The selectivity of drugs for the HIV retrovirus was derived from reverse transcriptase inhibitors that block transcription of the HIV RNA genome into DNA and protein synthesis. More recently, protease inhibitors have been developed that prevent the synthesis of late protein and packaging of the virion.

The major antiviral drugs will be discussed under the following categories: inhibitors of viral uncoating, inhibitors of viral nucleic acid synthesis, reverse transcriptase inhibitors, protease inhibitors and immunostimulants (Table 90-11).

Amantadine and rimantidine are orally active inhibitors of viral uncoating that are effective for prophylaxis of influenzae A. These antiviral drugs are tricyclic amines that differ only in their pharmacokinetics. Renal excretion predominates for amantidine while rimantidine is extensively metabolized.

Acyclovir and other closely related guanosine analogs (ganciclovir, valacyclovir, and famciclovir) are the most important group of antiherpes drugs that act by inhibition of viral nucleic acid synthesis. These nucleoside antivirals have to be monophosphorylated by viral thymidine kinase and then are further phoshorylated to triphosphates that inhibit virus growth in three ways. First, the acyclovir triphosphate acts as a competitive inhibitor of DNA polymerases, while the human enzyme is much less susceptible than the viral enzyme; second, it can be a chain terminator; and third, it can produce irreversible binding between DNA polymerase and the interrupted chain causing permanent inactivation.

Foscarnet, a phosphonoformic acid, inhibits DNA polymerases, RNA polymerases, and reverse transcriptases. It is used primarily for AIDS patients with CMV retinitis but can be used against CMV herpes viruses resistant to acyclovir.

Table 90-11. Antiviral Drugs

DRUG	COMMENTS
Nucleic Acid Synthesis Inhibitiors	
Purine Analogs	
Acyclovir	Antiherpes (IV, oral, or topical), CNS effects
Cidofovir	For CMV, nephrotoxicity
Famciclovir	Prodrug of penciclovir
Ganciclovir	For CMV, bone marrow suppression
Penciclovir	Topical antiherpes, similar to acyclovir
Ribovarin	For RSV, potential embryotoxicity
Valacyclovir	Prodrug of acyclovir, better oral absorption
Pyrimidine Analogs	
Fluorouracil	Topical for warts
Idoxuridine	Topical for herpes simplex
Trifluridine	Topical for herpes simplex
Nonnucleosides	
Foscarnet	For CMV, acyclovir-resistant herpes, nephrotoxicity
HIV Reverse Transcriptase Inhibitors	
Pyrimidine Nucleosides	
Lamivudine	Well tolerated
Stavudine	Peripheral neuropathy
Zalcitabine	Peripheral neuropathy
Zidovudine	Anemia, neutropenia, GI effects, CNS effects
Purine Nucleosides	
Didanosine	Peripheral neuropathy, pancreatitis, GI effects
Nonnucleosides	
Nevirapine	Rash, fever, nausea, headache
Delavirdine	Rash
HIV Protease Inhibitors	
Indinavir	Good bioavailability, kidney stones, inhibits CYP3A4
Nelfinavir	Less side effects, some dirrhea
Ritonavir	Good bioavailability, more side effects, many drug interactions (CYP3A4 related)
Saquinavir	Lower bioavailability, less side effects, CYP3A4 related drug interactions
Inhibitors of Influenza Viral Penetration or Uncoating	
Amantidine	Renal excretion, more CNS toxicities
Rimantidine	Metabolized, similar toxicity as amantidine

Ribovarin is a synthetic purine nucleoside analog that is phosphorylated by host cell adenosine kinase resulting in a monophosphate that inhibits cellular inosine monophosphate formation. The net result is depletion of guanosine triphosphate and inhibition of viral protein synthesis plus suppression of initiation or elongation of viral mRNA.

The family of nucleoside reverse transcriptase inhibitors includes zidovudine (azidodeoxythymidine) several dideoxynucleosides (didanosine, zalcitabine, lamuvidine, and stavudine) that are competitive inhibitors of the HIV enzyme that converts viral RNA into DNA and act as DNA chain terminators upon phosphorylation to the triphosphate nucleotide derivatives. These nucleoside antivirals also inhibit mammalian DNA polymerases but require higher concentrations than those effective on HIV reverse transcriptase. Resistance to these compounds occurs from mutations in reverse transcriptase, so they need to be used in combination with each other or the HIV protease inhibitors. Two reverse transcriptase inhibitors are usually combined with a protease inhibitor to decrease the development of resistance. Nevirapine and delavirdine are nonnucleoside inhibitors of reverse transcriptase that also disrupts the catalytic site of this enzyme.

Idoxuridine and trifluridine are pyrimidine analogs that are incorporated into viral DNA resulting in inhibition of DNA synthesis. They are only used topically for herpes simplex infections of the cornea because of their toxicity problems. Fluorouracil, another pyrimidine nucleoside, acts by blocking production of thymidylate and interrupts normal cellular RNA and DNA synthesis. Consequently, it is also restricted to topical therapy of warts.

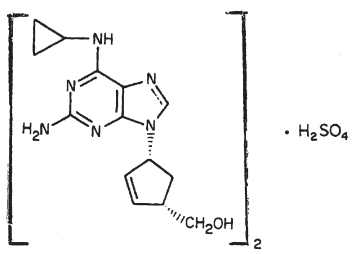
The protease inhibitors (saquinavir, ritonavir, indinavir, and nelfinavir) are peptide analogs that inhibit the HIV-1-specific protein cleaving enzyme necessary for the production of infectious HIV virions and act synergistically with reverse transcriptase inhibitors. It is important to use them in combination HIV therapy because resistance occurs if they are used alone or intermittently. Two reverse transcriptase inhibitors may be used in combination with one protease inhibitor or alternatively two protease inhibitors may be used with a reverse transcriptase inhibitor. The success of individual combination regimens has been variable but the overall success of combination therapy has been able to decrease viral replication, improve the immunologic status (ie, increase $CD4^+$ cell counts), delay complications and prolong life.

Interferons and immunoglobulins are examples of endogenous compounds that stimulate immune responses to virus infections. Interferons are glycoproteins produced by lymphocytes, macrophages, fibroblasts, and other cells. The three distinct immunologic and chemical classes of interferons are alpha, beta, and gamma. They act by inhibiting viral protein synthesis or assembly or by stimulating the immune system. Interferons have specific intracellular actions that result in several effects including inhibition of viral penetration, uncoating, translation of viral proteins plus assembly and release of virus. Immunoglobulins can be used to prevent some viral infections by using antibody preparations with high titers of specific binding to viruses (especially, hepatitis B and rabies).

The limitations of specific oral antiviral drugs are determined by the profile of adverse effects. Amantidine and rimantidine cause GI upset and CNS effects. Acyclovir and its related analogs (valacyclovir and famciclovir) cause CNS effects and decreased renal function. Other specific problems may occur with some analogs such as ganciclovir that causes bone marrow suppression. The nucleoside reverse transcriptase inhibitors have individual differences in their adverse effect profiles, but the most notable side effects include bone marrow suppression (zidovudine, lamivudine), neuropathy (didanosine, zalcitabine, stavudine) and pancreatitis (didanosine). The protease inhibitors vary in their inhibition of cytochrome P450 metabolism (notably CYP3A isoenzyme), but all possess some potential for drug interactions.

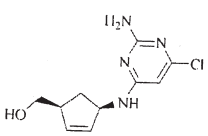
ABACAVIR SULFATE

2-Cyclopentene-1-methanol, (1*S*-*cis*)-4-[2-amino-6-(cyclopropylamino)-9*H*-purin-9-yl-, sulfate; Ziagen

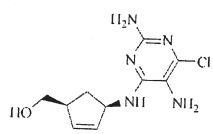


[188062-50-2] $(C_{14}H_{18}N_6O)_2 \cdot H_2SO_4$ (670.74).

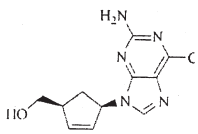
Preparation—2-Amino-4,6-dichloropyrimidine is coupled with *syn*-5-amino-3-cyclopentenemethanol to yield a secondary amine (I) by displacement of one chlorine atom, while retaining the *cis*-configuration. Treatment of I with *p*-chlorobenzenediazonium chloride forms an azo linkage on the sole unsubstituted position of the pyrimidine ring. The azo group is then reduced with zinc and acid to yield the free diamine (II).



I



II



III

Compound II, with ethyl orthoformate and acid forms a 5-membered imidazole ring involving the adjacent primary and secondary amino groups (III). Finally, the halogen atom on the pyrimidine ring is replaced by cyclopropylamino using cyclopropyl amine in alcohol affording the product. US Pat 6,294,540 (1991), US Pat 5,034,394 (1992), US Pat 6,294,540 (2001).

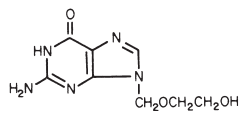
Description—(Base) White to off-white crystals from acetonitrile melting about 165°; $\alpha^{20}/_D$ -59.7° (c = 0.15, methanol); log P 1.22(0.1*M* sodium phosphate); pK_a 5.01. (Salt) log P 1.20, pH 7.1-7.3 buffer at 25°.

Solubility—(Salt) 77 mg/mL in water at 25°.

Comments—A nucleoside analougue used as part of combination therapy for the treatment of HIV infection. It is the most potent nucleoside analogue. Generally a well-tolerated antiretroviral. Adverse reactions include: Hypersensitivity Reaction-fever, rash, fatigue, malaise, GI symptoms, and arthralgia (noted in 2-3% of patients). Mandatory d/c with hypersensitivity rxn. Do not rechallenge. Rare cases of lactic acidosis +/− hepatomegaly w/ steatosis. Rare:Tubular injury

ACYCLOVIR

6*H*-Purin-6-one, 2-amino-1,9-dihydro-9-[(2-hydroxyethoxy)methyl]-, Zovirax



9-[(2-Hydroxyethoxy)methyl]guanine [59277-89-3] $C_8H_{11}N_5O_3$ (225.21).

Preparation—Guanine is alkylated with 2-(chloromethoxy)ethylbenzoate and the resulting ester hydrolyzed to the product; See Ger Pat 2,539,963.

Description—White crystals melting about 257°.

Solubility—In water, 1.3 mg/mL.

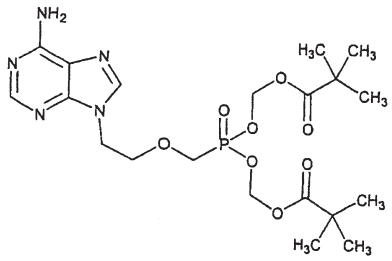
Comments—Activity against *Herpes simplex viruses* (HSV) 1 and 2, varicella-zoster, Epstein-Barr viruses and cytomegalovirus. Inside an infected cell, it is changed into the triphosphate, which then is incorporated into DNA; this terminates elongation of the DNA and prevents viral replication. The sodium salt is approved in the US for the oral treatment of recurrent mucosal and cutaneous infections caused by HSV-1 and HSV-2 in immunocompromised adults and children and for severe initial herpes genitalis infections in immunocompetent patients. However, the drug has been employed effectively in the treatment of HSV encephalitis and neonatal infections and in the treatment of chicken pox, cytomegalovirus, and varicella-zoster infections. The drug also is approved for the topical treatment of nonfulminating HSV-1 and HSV-2 infection (except in the eye), but it is only moderately effective, especially against genital herpes in women. It does not eradicate latent herpes. It is somewhat unpredictable as a topical prophylactic against recurrent infections by HSV-1 and HSV-2. Resistance of herpes simplex and cytomegaloviruses occurs and is a source of concern.

The most frequent adverse effect of systemic treatment is irritation at the site of injection (9%). The drug may crystallize in the urine, cause hematuria, and impair renal function if fluid intake is inadequate, glomerular filtration rate is low, the dosage interval is too short, or the drug is given as a bolus. Metabolic encephalopathy (1%) with hallucinations, confusion, tremors and seizures, bone-marrow depression, and alterations in hepatic function also may result from parenteral therapy. Untoward effects from oral administration are more frequent with long-term than with short-term therapy. In the short term, there may be nausea and vomiting (2.7%), headache (0.6%), diarrhea, dizziness, fatigue, skin rash, sore throat (all 0.3%), anorexia, edema, lymphadenopathy (especially inguinal), and leg pain. In the long term there may be headache (1.9%), diarrhea (2.4%), nausea and vomiting (2.7%), arthralgia, vertigo (both 3.6%), insomnia, fatigue, irritability, depression, rash, acne, alopecia, fever, palpitations, sore throat, muscle cramps,and lymphadenopathy. The drug is mutagenic and should be avoided in pregnancy, if possible. Topically, adverse effects occur in about 30% of recipients and consist of local stinging, burning or pain (28%), itching (4%), vulvitis (0.3%), and rash (0.3%).

In plasma, only 9% to 33% is protein-bound. Renal excretion after IV and oral use accounts for 62% to 91% and 9% to 20%, respectively. The half-life is about 2.5 hr but may be as long as 19.5 hr in renal failure.

ADEFOVIR DIPIVOXIL

Propanoic acid, 2,2-dimethyl-, [[[2-(6-amino-9*H*-purin-9-yl)-ethoxy]methyl]phosphinylidene]bis(oxymethylene) ester; Hepsera, Preveon



[142340-99-6] $C_{20}H_{32}N_5O_8P$ (501.47).

Preparation—*J Med Chem* 1996; 39:4958 and US Pat 6,451,340 (2002).

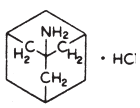
Description—White to off-white crystals melting over 250°. Log P (phosphate buffer, pH 7) 1.91; pK_{a1} 2.0; pK_{a2} 6.8.

Solubility—In water; 19 mg/mL at pH 2.0 and 0.4 mg/mL at pH 7.2.

Comments—A nucleoride analougue used for the treatment of chronic hepatitis B, including patients with clinical evidence of lamivudine-resistant hepatitis B with either compensated or decompensated liver function. Most experts would recommend use in combination with lamivudine. Adverse reactions: Generally well tolerated. Occasional: Increase in creatinine (with underlying renal insufficiency); asthenia, abd pain; h/a; fever; n/v/d; exacerbation of hepatitis (with discontinuation of therapy); pruritus; rash; cough. Rare: nephrotoxicity, lactic acidosis.

AMANTIDINE HYDROCHLORIDE

Tricyclo[3.3.1.1^{3,7}]decan-1-amine, hydrochloride; Symmetrel, Symadine



1-Adamantanamine hydrochloride [665-66-7] $C_{10}H_{17}N{\cdot}HCl$ (187.71).

Preparation—Adamantane is halogenated, with chlorine or bromine in the presence of $AlCl_3$, at the bridgehead carbon atom to yield a reactive tertiary halide, incapable of dehydrohalogenation. Therefore, even with a weak base, such as CH_3CN, it undergoes an S_N1 reaction to the acetamido derivative. Hydrolysis affords the product, which is converted to the salt. *J Med Chem* 1963; 6:760.

Description—White crystals; decompose over 360°; pK_a 10.4, (amino group).

Solubility—1 g in 3 mL water or 5 mL alcohol.

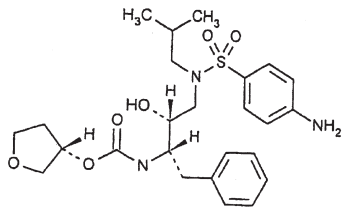
Comments—A *narrow-spectrum antiviral* active against all influenzae A virus strains, some C virus strains, but not effective against B strains. It is approved for chemoprophylaxis and treatment of respiratory tract illness caused by influenzae A virus strains, when immunization is contraindicated or not feasible. It is indicated especially for high-risk patients because of underlying disease (eg, cardiovascular, pulmonary, metabolic, neuromuscular, or immunodeficiency disease), close-household or hospital-ward contacts of index cases, immunocompromised patients, and health-care and community-services personnel.

Amantidine is well tolerated by most patients, but CNS side effects are most common and include difficulty in thinking, confusion, lightheadedness, hallucinations, anxiety, and insomnia. These side effects are reversible upon discontinuation of the drug. More severe adverse effects such as mental depression and psychoses may occur with doses exceeding 200 mg daily. Less common side effects include anorexia, nausea, vomiting, and orthostatic hypotension. The peripheral and central effects of anticholinergic drugs are increased by concomitant use of amantidine.

Oral absorption is rapid and complete. It is not metabolized and 90% of the dose is excreted unchanged in the urine. The half-life is about 20 hr, and it reaches levels in the cerebral spinal fluid that are 60% of the plasma concentration. The dose must be reduced with renal insufficiency and in the elderly who have decreased renal function.

AMPRENAVIR

[3*S*-[3*R(1*R**,2*S**)]]-3-[[(4-Aminophenyl)sulfonyl](2-methylpropyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]tetrahydro-3-furanyl carbamate; Agenerase**



[161814-49-9] $C_{25}H_{35}N_3O_6S$ (505.63).

Preparation—US Pat 5,585,397 (1996).

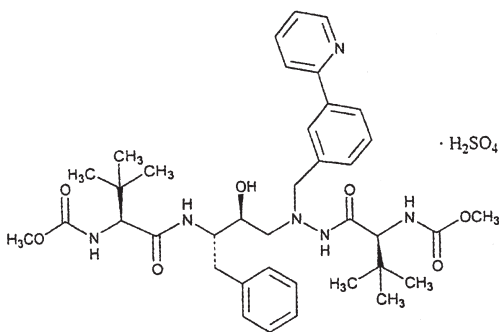
Description—White to cream-colored solid.

Solubility—0.04 mg/mL in water at 25°; soluble in methanol, ethanol, chloroform, DMSO, acetonitrile, and methylene chloride; insoluble in hydrocarbon solvents.

Comments—A protease inhibitor used as part of combination therapy to treat HIV-infection. First once a day PI approved when used with ritonavir. Adverse reactions include: GI intolerance most common (N/V/D); oral paresthesias; headache; rash (in 11% of patients); lipodystrophy syndrome; hyperglycemia; increased triglycerides and/or cholesterol; transaminase elevation. TOXICITY FROM PROPYLENE GLYCOL IN THE ORAL SOLUTION. Co-administration contraindicated with: Terfenadine, astemizole, cisapride, ergot alkaloid, rifampin, bepridil, midazolam and triazolam. Dose modification needed with: Rifabutin, HMG-Coa reductase inhibitors, sildenafil,Dual-protease or NNRTI combination.

ATAZANAVIR SULFATE

2,5,6,10,13-Pentaazatetradecanedioic acid, (3*S*,8*S*,9*S*,12*S*)-3,12-bis(1,1-dimethylethyl)-8-hydroxy-4,11-dioxo-9-(phenylmethyl)-6-[[4-(2-pyridinyl)phenyl]methyl]-, dimethyl ester, sulfate (1:1) salt; Reyataz



[229975-97-7] $C_{38}H_{52}N_6O_7{\cdot}H_2SO_4$ (802.94).

Preparation—US Pat 5,849,911(1998).

Description—White to pale yellow crystalline powder.

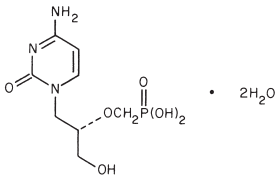
Solubility—Slightly soluble in water; pH of water-saturated solution about 2 at 25°.

Comments—A protease inhibitor used as part of combination therapy for the treatment of HIV-infection. A benefit in terms of lipid profile is consistently shown. This may offer a distinct advantage to patients with established CV disease risks, high lipid levels at baseline or high levels post-therapy with other PIs. Adverse reactions include: Common: Reversible benign hyperbilirubinemia (grade 3-4 occurring in 35-47% of patients), jaundice, and scleral icterus. Occasional: nausea, vomiting, abdominal pain, lipodystrophy, rash, h/a, and mild transaminase elevation (unrelated to UGT 1A1 inhibition). Contraindicated: Rifampin, irinotecan, ergot Alkaloid, cisapride, St. John's Wort, midazolam, triazolam, bepridil, pimozide, simvastatin, lovastatin, indinavir, and all proton pump-inhibitors.

CYTARABINE—page 1568.

CIDOFOVIR

Phosphonic acid, (*S*)-[[2-(4-amino-2-oxo-1(2*H*)-pyrimidin-yl)-1-(hydroxymethyl)ethoxy]methyl]-, dihydrate; Vistide



[149394-66-1] $C_8H_{14}N_3O_6P \cdot 2H_2O$ (315.22).

Preparation—From guanine; US Pat 5,142,051 (1992).

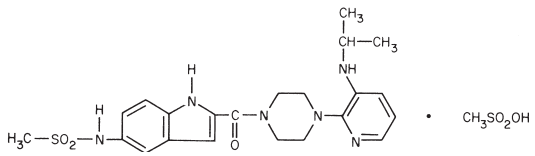
Description—White powder melting about 260°; log P (octanol/pH 7.1 buffer) −3.3.

Solubility—Approximately 170 mg/mL at pH 6–8.

Comments—A nucleic acid synthesis inhibitor (purine analog) used for cytomegalovirus (CMV). It causes nephrotoxicity.

DELAVIRDINE MESYLATE

Piperazine, 1-[3-[(1-methylethyl)amino]-2-pyridin-yl]-4-[[5-[(methylsulfonyl)amino-1*H*-indol-2-yl]carbonyl]-, monomethanesulfonate; Rescriptor



[147221-93-0] $C_{22}H_{28}N_6O_3S \cdot CH_4O_3S$ (552.68).

Preparation—US Pat 5,691,372 (1997); *J Med Chem* 1993; 36:1505.

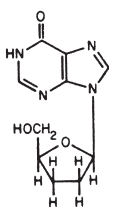
Description—White to tan crystals melting about 227° (base).

Solubility—(Base) Approximately 2.9 μg/mL at pH 1, 295 μg/mL at pH 2 and 0.81 μg/mL at pH 7.4.

Comments—An HIV reverse transcriptase inhibitor (non-nucleoside). It causes rash.

DIDANOSINE

Inosine, 2′,3′-dideoxy-, ddL; Videx



[69655-05-6] $C_{10}H_{12}N_4O_3$ (236.23).

Preparation—*Nucleosides Nucleotides* 1988; 7:147.

Description—White solid; melts about 160° to 163°.

Comments—A nucleoside analog that is incorporated into retroviral DNA contributing to chain termination and inhibition of viral replication. The active metabolite, dideoxyadenosine triphosphate, is a reverse transcriptase inhibitor that is active against the human immunodeficiency virus (HIV) infected T cell and monocyte/macrophage cell cultures.

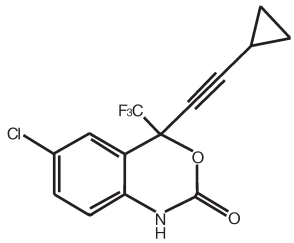
The approved indication is treatment of adult and pediatric patients with advanced HIV infection who have received prolonged prior *zidovudine* therapy or who have demonstrated intolerance or significant clinical or immunological deterioration during zidovudine therapy.

The major clinical toxicities of didanosine are pancreatitis (9%) and peripheral neuropathy (34%). Several other adverse effects are observed frequently including diarrhea (34%), asthenia (25%), insomnia (25%), nausea and vomiting (25%), rash/pruritus (24%), abdominal pain (21%), CNS depression (19%), constipation (16%), stomatitis (14%), myalgia (13%), arthritis (11%), taste loss/perversion (10%), pain (10%), dry mouth (9%), alopecia (8%), and dizziness (7%).

The average bioavailability of didanosine is reported to be 33% after a single dose. The elimination half-life is 1.6 hr and renal clearance is about 50%. There is no evidence of accumulation after either IV or oral dosing.

EFAVIRENZ

2*H*-3,1-Benzoxazin-2-one, (*S*)-6-chloro-4-(cyclopropylethynyl)-1,4-dihydro-4-(trifluoromethyl)-, Sustiva



[154598-52-4] $C_{14}H_9ClF_3NO_2$ (315.67).

Preparation—US Pat 5,519,021 (1996).

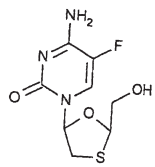
Description—White to slightly pink crystalline powder melting about 179°.

Solubility—Freely soluble in dilute HCl; practically insoluble in water; soluble 6.06 mg/mL in ethanol.

Comment—A non-nucleoside reverse transcriptase inhibitor used as part of combination therapy for the treatment of HIV-infection. Adverse events include: Morbilliform rash in (15-27% of patients with 1-2% requiring discontinuation); one case of Steven Johnson Syndrome reported; CNS effects (confusion, depersonalization, abnormal dreams) usually seen on day 1 (in up to 52% of patients); resolves in 2 to 4 weeks. Coadministration contraindicated with: Ergot alkaloid, midazolam, triazolam, terfenadine, astemizole, cisapride. Dose modification needed with: Saquinavir, amprenavir, indinavir, ethinyl estradiol, and rifabutin.

EMTRACITABINE

2-(1*H*)-Pyrimidinone,)2*R-cis*)-4-amino-5-fluoro-1-[2-(hydroxymethyl)-1,3oxathiolan-5-yl]-, Emtriva, Coviracil



[143491-57-0] $C_8H_{10}FN_3O_3S$ (247.24).

Preparation—A synthetic nucleoside of cytosine. *J Med Chem*, 1993; 36:181.

Description—White to off-white powder from methanol-ether melting about 138°.

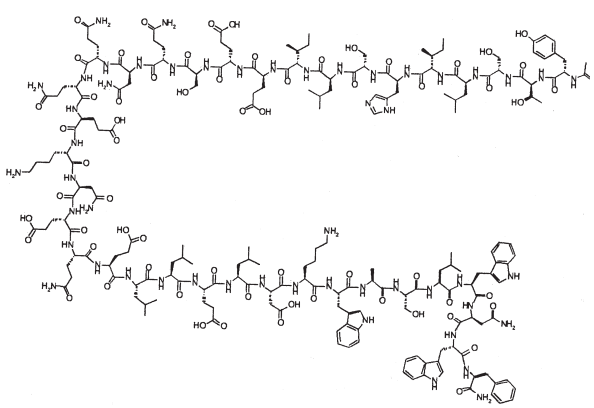
Log P −0.43; pK_a 2.65; $[\alpha]_{25}^{D}$ -133.6° c = 0.23, methanol).

Solubility—112 mg/mL in water at 25°.

Comments—A once-daily nucleoside reverse transcriptase inhibitor used as part of combination therapt for the treatment of HIV-infection. Like lamivudine, possesses activity against the hepatitis-B virus. Adverse reactions include: Common: Generally well tolerated. Mild asymptomatic skin hyperpigmentation on the palm and/or soles. Asymptomatic and transient CPK elevation. Occasional: Headache, diarrhea, nausea, asthenia, and rash that required discontinuation in approx. 1% of patients. Emtricitabine is not a substrate, inhibitor, or inducer of any CYP450 isoforms, likelihood of clinically significant drug interactions are low.

ENFUVIRTIDE

Enfuvirtide; Fuzeon



[159519-65-0] $C_{204}H_{301}N_{51}O_{64}$ (4491.93).

Preparation—US Pat 6,333,395 (2001).

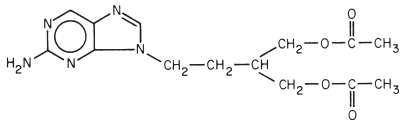
Description—White to off-white solid. A segment of the transmembrane envelope glycoprotein (gp41) of human immunodeficiency virus, type (HIV-1).

Solubility—Practically insoluble in water. Solubility increases in buffered solutions; in pH 7.5 buffer, 0.85–1.42 g/mL.

Comments—The first "fusion inhibitor" used in combination for the treatment of HIV-infection. It is administered subcutaneously. It is most commonly used in patients who have been previously treated with a variety of other antiretroviral agents. A clear advantage of enfuvirtide is the lack of cross-resistance with currently available antiretrovirals, however, as with other antiretrovirals and as seen in clinical trials, salvage therapy with enfuvirtide is only as good as the background regimen with which it is combined. Adverse reactions include: Common ADR: local site reaction (grade 3 or 4) including pain (9%), erythema (32%), pruritus (4%), induration (57%), and nodules or cysts (26%)(with 3% requiring d/c).Occ: Eosinophilia; Bacterial pneumonia (in 4.68 events vs. 0.61 events per 100 pts-years.

FAMCICLOVIR

1,3-Propanediol, 2-[2-(2-amino-9*H*-purin-9-yl)ethyl-, diacetate (ester); Famvir



[104227-87-4] $C_{14}H_{19}N_5O_4$ (321.34).

Preparation—One method involves first the formation of 5-(2-hydroxy- ethyl)-2,2-dimethyl-1,3-dioxolane(**I**) by the reaction of triethylethane-1,1,2-tricarboxylate with THF and lithium aluminum hydride to form an oil which reacts with 2,2-dimethoxypropane in the presence of *p*-toluenesulfonic acid to yield **I**. The OH group is replaced by bromine using CBr_4 and trimethyl phosphine. The bromo derivative is combined with 2-amino-6-chloropurine to alkylate in the 7-position. The dioxalane ring is opened by warming with dilute HCl and the resulting diol esterified with acetic anhydride using 4-(dimethylamino)pyridine as the acid scavenger. US Pat 5,075,445 (1991); *J Med Chem* 1989; 32:1738.

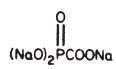
Description—White to pale yellow platelets melting about 103° Non-hygroscopic below 80% relative humidity. Partition coefficient; octanol/water(pH 4) P = 1.09; octanol/pH 7.4 phosphate buffer P = 2.08.

Solubility—In water at 25° it initially is freely soluble (up to 25%) but forms a sparingly soluble monohydrate (about 3% soluble) which precipitates. Freely soluble in methanol or acetone; sparingly soluble in alcohol or 2-propanol.

Comments—An purine analog which is an inhibitor of nucleic acid synthesis; a prodrug of *penciclovir*.

FOSCARNET SODIUM

Phosphinecarboxylic acid, dihydroxy-, oxide, trisodium salt; Foscavir



Phosphonoformic acid, trisodium salt [63585-09-1] CNa_3O_5P (191.95).

Preparation—*Ber* 1924; 57B:1023.

Description—White crystals (usually as the hexahydrate); melts above 250°; pK_a 7.27, 3.41, 0.49.

Solubility—Soluble in water; insoluble in alcohol.

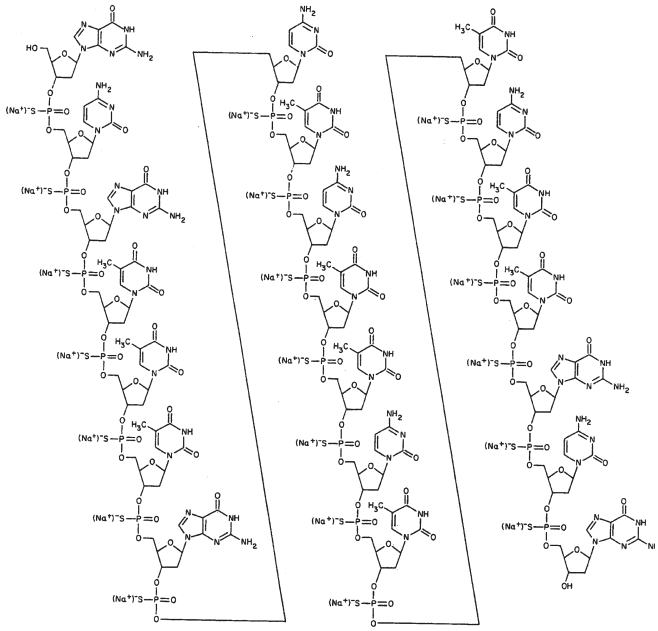
Comments—An antiviral agent that acts at the pyrophosphate-binding site and inhibits viral DNA polymerases and reverse transcriptases at concentrations that do not affect cellular DNA polymerases. It does not require activation (phosphorylation) by a kinase. All known *herpes* viruses are inhibited in vitro including cytomegalovirus (CMV), *herpes simplex* 1 and 2 (HSV-1, HSV-2), human *herpes* virus 6 (HHV-6), *Epstein-Barr* virus (EBV) and *varicella zoster* virus (VZV). The only approved indication is the treatment of CMV retinitis in patients with AIDS.

The major toxicity is renal impairment that occurs in 33% of all patients, so everyone receiving it should be monitored for renal function. The other frequent adverse reactions include fever (65%), nausea (47%), anemia (33%), diarrhea (30%), vomiting or headache (26%), and seizures (10%). Electrolyte abnormalities must be monitored because of the propensity of foscarnet to chelate divalent cations. The drug is only administered by controlled IV infusion to decrease the incidence of toxicity as a result of excessive plasma levels.

Approximately 80% to 90% of IV foscarnet is excreted unchanged in the urine. Plasma half-life of foscarnet increases as renal function is impaired, but initial half-lives of 2 to 8 hr have been reported for patients with normal renal function. The safety and efficacy of foscarnet in children has not been studied because it is deposited in teeth and bone, and deposition is greater in young and growing animals. Development of tooth enamel is adversely affected in studies of animals.

FOMIVIRSEN SODIUM

Deoxyribonucleic acid, d(*P*-thio)G-C-G-T-T-T-G-C-T-C-T-T-C-T-T-C-T-T-G-C-G), eicosasodium salt; Vitravene



[160369-77-7] $C_{204}H_{243}N_{63}O_{114}P_{20}S_{20}$ (7122.04).

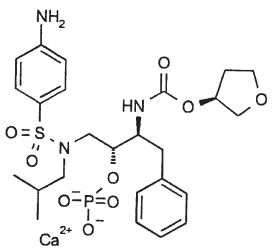
Preparation—One method involves a recombinant M 13 phage containing a negative stranded viral DNA or recombinant DNA vector containing the double-stranded viral DNA which may be produced by growing *E coli* harboring these vectors. Vectors containing the viral genes are isolated and subjected to restriction endonuclease for excision of the viral genes. The viral gene and vector DNA mixture is separated by chromatography. The DNA molecules so obtained are shortened by partial digestion or ultrasonics. The chain length of the viral DNA fragments are adjusted to between 9 and 100 nucleotides using gel electrophoresis or sephadex chromatography. The double-stranded DNA is then converted to isolate the negative strand using affinity chromatography.

Description—White to off-white hygroscopic, amorphous, powder. The IV preparation has an osmolality of 290 mOsm/L at pH 8.7.

Comments—An antisense phosphorothioate oligonucleotide inhibits CMV by binding to complementary sequences on messenger RNA transcribed from the major immediate-early transcriptional unit of the virus. Used as an intraveitreal injection for the treatment of cytomegalovirus retinitis.Active against strains of CMV that are resistant to ganciclovir, cidofovir, and foscarnet. Adverse reactions include: Ocular inflamation (iritis and vitritis) in 15% to 25%-usually respond to topical steroid. Increased intraocular pressure-transient (19%), but should be monitored.

FOSAMPRENAVIR CALCIUM

Carbamic acid, [(1*S*,2*R*)-3-[[(4-aminophenyl)sulfonyl](2-methylpropyl)amino]-1-(phenylmethyl)-2-(phosphonooxy)propyl]-, *C*-[(3*S*)-tetrahydro-3-furanyl] ester, monocalcium salt; Lexiva



[226700-80-7] $C_{25}H_{34}CaN_3O_9PS$ (623.67).

Preparation—*J Med Chem* 2003; 46:4124.

Description—White to cream-colored solid. A prodrug of amprenavir to which it is converted in vivo by cellular phosphatases.

Solubility—About 0.31 mg/mL in water at 25°.

Comments—Fosamprenavir is a prodrug of amprenavir developed to overcome the high (16) pill burden associated with amprenavir. Adverse reactions include: Common: Rash 12% to 33% (severe in <1%). Severe GI intolerance in up to 5% to 10%. Occasional: Elevated triglyceride(less common without RTV) and LDL, insulin resistance, hepatitis. Do not co-administer: Ergot Alkaloid, Midazolam, Triazolam, Terfenadine, Astemizole, Cisapride, Pimozide, Flecainide, propafenone.

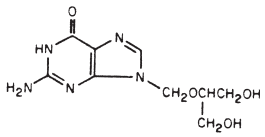
FLUOROURACIL

For the full monograph, see page 1573.

Comments—A *nucleic acid synthesis inhibitor* (pyrimidine analog) used topically for warts.

GANCICLOVIR SODIUM

6*H*-Purin-6-one, 2-amino-1,9-dihydro-9-[[2-hydroxyl-1-(hydroxymethyl)ethoxy]methyl]-, Cytovene



9-[[2-Hydroxyl-1-(hydroxymethyl)ethoxy]methyl]guanine [82410-32-0] $C_9H_{13}N_5O_4$ (255.23).

Preparation—US Pat 4,355,032; *J Med Chem* 1983; 26:759.

Description—White powder.

Solubility—1 g in 250 mL water.

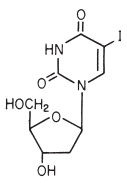
Comments—An antiviral drug active against cytomegalovirus (CMV), *herpes simplex* virus-1 and -2 (HSV-1, HSV-2), *Epstein-Barr* virus and *viricella zoster* virus. It is approved for treatment of CMV retinitis in immunocompromised patients, including those with AIDS and prevention of CMV disease in transplant patients at risk for CMV disease. Upon entry into host cells, CMV induce kinases that phosphorylate ganciclovir to its active triphosphate form that is believed to inhibit viral DNA synthesis by competitive inhibition of viral DNA, resulting in termination of viral DNA elongation.

The major clinical toxicities of ganciclovir include granulocytopenia (40%) and thrombocytopenia (20%). In animal studies it is carcinogenic, teratogenic, and causes aspermatogenesis. Other adverse effects that have led to its withdrawal or interrupted its use in clinical trials are headache (17%), confusion (6%), abnormal thoughts or dreams, ataxia, dizziness, nervousness, parasthesia, psychosis, somnolence, tremor, arrhythmia, hypertension, rash, pruritus, alopecia, urticaria, nausea, vomiting, anorexia, diarrhea, abdominal pain, sepsis, fever, chills, edema, malaise, and dyspnea. Retinal detachment has occurred before and after initial treatment of CMV retinitis, so ophthalmological evaluations are advised. Renal toxicity may occur in heart allograft recipients, so renal function should be monitored during therapy.

Ganciclovir is given by IV infusion. Phlebitis and pain at the site of injection occur. The high pH (11) of solution may result in severe tissue irritation if given SC or IM. It is eliminated unmetabolized by renal excretion that accounts for 90% of the administered dose. The plasma half-life with normal renal function is about 3 hr but is increased to more than 10 hr with severe renal impairment. There is limited evidence to suggest that ganciclovir crosses the blood-brain barrier in adequate concentrations.

IDOXURIDINE

Uridine, 2′-deoxy-5-iodo-, IDU; Herplex; Stoxil



2′-Deoxy-5-iodouridine [54-42-2] $C_9H_{11}IN_2O_5$ (354.10).

Preparation—By refluxing a solution of deoxuridine in aqueous mineral acid in the presence of iodine. Brit Pat 1,024,156. For the preparation of deoxuridine, see *J Chem Soc* 1958:3035.

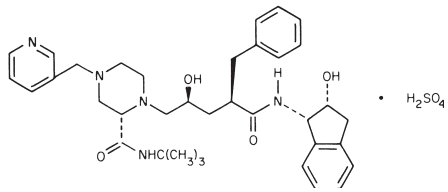
Description—White, crystalline powder; practically odorless; turns black 171°; pH (0.1% aqueous solution) about 6; a 0.1% solution in distilled water and preserved with 1:50,000 thimerosal is stable at room temperature for over a year; pK_a 8.25.

Solubility—Slightly soluble in water or alcohol; practically insoluble in chloroform or ether; 1g in 2.5 mL DMSO.

Comments—A *nucleic acid synthesis inhibitor* (pyrimidine analog) used topically for herpes simplex.

INDINAVIR SULFATE

D-*erythro*-Pentanamide, [1(1*S*,2*R*,5(*S*)]-2,3,5-trideoxy-*N*-(2,3-dihydro-2-hydroxy-1*H*-inden-1-yl)-5-[2-[[(1,1-dimethylethyl)amino]carbonyl]-4-(3-pyridinylmethyl)-1-piperazinyl]-2-(phenylmethyl)-, sulfate(1:1 salt), monohydrate; Crixivan



[157810-81-6] $C_{36}H_{47}N_5O_4 \cdot H_2SO_4$ (711.88).

Preparation—US Pat 5,413,999 (1995).

Description—White to off-white hygroscopic powder; (as the monoethanolate) melts at 152°(dec). Loses ethanol on exposure to moist air and forms the hydrate.

Solubility—Very soluble in water or methanol.

Comments—A synthetic peptide analog that is a specific inhibitor of HIV-1 and -2 proteases that are essential enzymes for production of mature infectious virions. It has excellent oral bioavailability but must be consumed on an empty stomach. Resistance is mediated by expression of multiple and variable protease amino acid substitutions. Cross-resistance commonly occurs for indinavir, saquinavir, and ritonavir. Combination therapy with nucleoside reverse transcriptase inhibitors is used to decrease resistance. Adequate water consumption is important to prevent kidney stones (nephrolithiasis). Other side effects include thrombocytopenia, nausea, vomiting, diarrhea, hemolytic anemia, hepatitis, and irritability. Inhibition of cytochrome P450 enzymes (notably CYP3A4) results in numerous drug interactions. Increased serum levels of antihistamines, cispride, benzodiazepines, and riftabutin occur because they are metabolized by CYP3A4 and results in an increase in their potential toxicity. Serum levels of indinavir may be increased by antifungal azoles and decreased by riftabutin and rifampin.

INTERFERONS—see also Chapter 29.

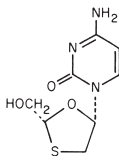
INTERFERON ALFA

(available as 2a, 2b or 2c)

Comments—This glycopeptide is produced by genetic engineering techniques based on the human sequence. It affects many stages of viral infections but primarily inhibits viral protein translation. It is used for therapy of hepatitis B and C. The drug is administered by SC or IM injection. It is rapidly inactivated, but the effects outlast the plasma concentration. Toxicities include flu-like syndrome, bone marrow suppression, and neurotoxicity. Drug interactions can result from its ability to reduce hepatic cytochrome P450-mediated metabolism.

LAMIVUDINE

2(1*H*)-Pyrimidinone, (2*R-cis*)-4-amino-1-[2-(hydroxy-methyl)-1,3-oxathiolan-5-yl]-, Epivir; 3TC



[134678-17-4] $C_8H_{11}N_3O_3S$ (229.26).

Preparation—*J Org Chem* 1992; 55:2217.

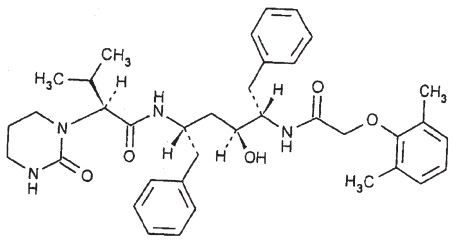
Description—White to off-white powder melting about 161°.

Solubility—About 70 mg/mL in water at 20°.

Comments—An HIV reverse transcriptase inhibitor (pyrimidine nucleoside) which is well tolerated.

LOPINAVIR

1(2*H*)-Pyrimidineacetamide, [1*S*-[1*R(*R**),3*R**,4*R**]]-*N*-[4-[[2,6-dimethylphenoxy)acetyl]amino]-3-hydroxy-5-phenyl-1-(phenylmethyl)pentyl]tetrahydro-α-(1-methylethyl)-2-oxo-, Ing of Kaletra (in combination with *Ritonavir*).**



[192725-17-0] $C_{37}H_{48}N_4O_5$ (628.81).

Preparation—US Pat 5,914,332 (1999).

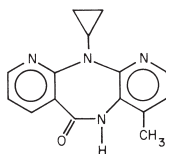
Description—White to light tan powder from ethyl acetate; melts about 126°.

Solubility—Freely soluble in methanol and ethanol; soluble in 2-propanol; practically insoluble in water.

Comments—A protease inhibitor that is formulated as a combination product along with ritonavir. Very potent and currently among the first-line treatment options for HIV-infection. Adverse reactions include: Frequent: Diarrhea in 13.8% to 23.8% of patients. Occasional: Nausea, vomiting, abdominal pain, asthenia, headache, and rash have also been reported. Like other protease inhibitors, class adverse events such as hyperlipidemia, fat redistribution, and hyperglycemia. Contraindicated: Flecainide, propafenone, astemizole, terfenadine, dihydroergotamine, ergonovine, ergotamine, methylergonovine, cisapride, pimozide, midazolam, triazolam, Rifampin, hypericum perforatum (St John's wort), lovastatin, and simvastatin.

NEVIRAPINE

6*H*-Dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one, 11-cyclopropyl-5,11-dihydro-4-methyl-, Viramune



[129618-40-2] $C_{15}H_{14}N_4O$ (266.30).

Preparation—US Pat 5,075,455 (1991); *J Med Chem* 1991; 34:2331.

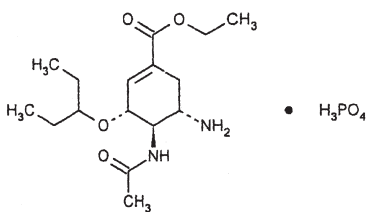
Description—White crystals melting about 248°; pK < 3.

Solubility—Slightly soluble in water at pH7; very soluble at pH < 3.

Comments—An HIV reverse transcriptase inhibitor (pyrimidine nucleoside). It causes rash fever, nausea and headache.

OSELTAMIVIR PHOSPHATE

1-Cyclohexene-1-carboxylic acid, [3*R*-(3α,4β,5α)]-4-(acetyl- amino)-5-amino-3-(1-ethylpropoxy)-, ethyl ester, phosphate salt (1:1); Tamiflu



[204255-11-8] $C_{16}H_{28}N_2O_4 \cdot H_3PO_4$ (410.40).

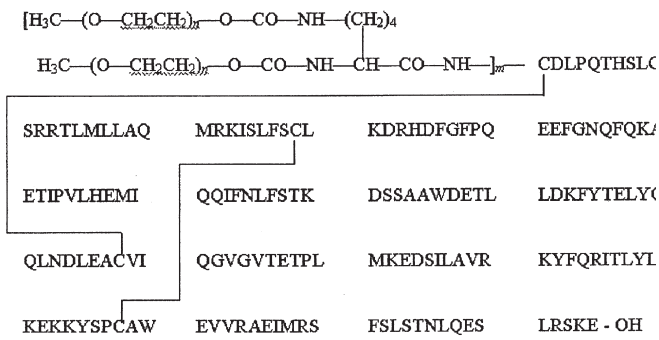
Preparation—A multi-step synthesis beginning with either (-)shikimic acid or (−)quinic acid. Shikimic acid is obtained from star anise by fermentation using genetically engineered *E coli*. Quinic acid is derived from cinchona bark. US Pat 5,763,483(1998); *J Org Chem* 1981; 46:2381 and *Albany Molecular Research Tech Reports* 2000; 4(39):7-9.

Description—White, crystalline solid. Oseltamivir is a pro-drug requiring the hydrolysis of the ethyl ester to form the free acid, which is the active principle.pK_a = 7.7 (base).

Comments—An oral neuramidase inhibitor that is active against influenza A and B. Treatment must be started within 48 hours of the onset of symptoms. Adverse reactions include nausea, vomiting, diarrhea.

PEGINTERFERON ALFA-2A

Interferon αA (human leucocyte), mono(N^2, N^6-dicarboxyl-L-lysyl) derivative, diester with α-methyl-ω-hydroxypoly(oxy-1,2-ethanediyl)-, Pegasys



[198153-51-4]

Preparation—By pegylation of the interferon with polyethylene glycol (PEG). Many protein drugs suffer rapid enzyme degradation and clearance from the body. The optimal mass of a PEG required to retard renal and cellular clearance of protein molecules is estimated to be between 40 and 60 kDa. Pegylation of IFN alfa-2a has optimized pharmacological activity and minimized adverse effects. *J Adv Drug Deliv Rev,* 2002; 54: 571 and http://www.americanpeptide.com/corp/PEGylation.pdf

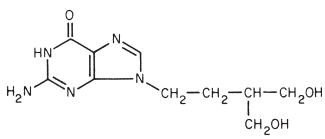
PEGASYS, peginterferon alfa-2a, is a covalent conjugate of recombinant alfa-2a interferon (approximate molecular weight [MW] 20,000 daltons) with a single branched bis-monomethoxy polyethylene glycol (PEG) chain (approximate MW 40,000 daltons). The PEG moiety is linked at a single site to the interferon alfa moiety via a stable amide bond to lysine. Peginterferon alfa-2a has an approximate molecular weight of 60,000 daltons. Interferon alfa-2a is produced using recombinant DNA technology in which a cloned human leukocyte interferon gene is inserted into and expressed in *Escherichia coli*.

Solubility—The drug product contains approximately 1.3 mL of solution containing 180 μg of drug..

Comments—Pegylated formulation of interferon alpha-2a or 2-b. Results in improved pharmacokinetic profile offering patients a once-weekly dosing schedule with greater efficacy, less side effects, and better patient adherence. Used as monotherapy or combination therapy (most commonly) for the treatment of chronic hepatitis C vius infection. Adverse reactions include: Common: Flu-like symptoms, headache, dizziness, fatigue, fever, rigor, injection site inflamation, depression (29%), insomnia, alopecia, GI (abdominal pain, anorexia, n/v/d). Occasional: thrombocytopenia, neutropenia, hypo- and hyperthyroidism, LFTs elevation.

PENCICLOVIR

6*H*-Purin-6-one, 2-amino-1,9-dihydro-9-[4-hydroxy-3-(hydroxymethyl)butyl]-, Denavir



[39809-25-1] $C_{10}H_{15}N_5O_3$ (253.25).

Preparation—US Pat 5,075,445 (1991); *J Med Chem* 1987; 30:1636.

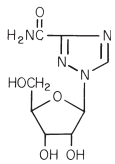
Description—White to pale yellow non-hygroscopic crystals melting at approximately 275° (monohydrate); log P (octanol/water, pH 7.5) 1.62.

Solubility—Approximately 1.7 mg/mL in water at 20°; 0.2 mg/mL in methanol; 1.3 mg/mL in propylene glycol; or 10mg/ml in pH 2 buffer.

Comments—A nucleic acid synthesis inhibitor (purine analog) similar to *acyclovir* and used topically for *herpes*.

RIBAVIRIN

1*H*-1,2,4-Triazole-3-carboxamide, 1-β-D-ribofuranosyl-, Virazole



Tribavirin; [36791-04-5] $C_8H_{12}N_4O_5$ (244.21).

Preparation—*J Med Chem* 1972; 15:1150.

Description—Colorless, crystalline powder existing in two polymorphic forms: melts about 167° (from aqueous ethanol) and melts about 175° (from ethanol).

Solubility—142 mg/mL in water at 25°; slightly soluble in alcohol.

Comments—A nucleoside analog with significant activity against influenza B, respiratory syncytial virus (RSV), and herpes simplex virus. It also has lesser activity against a wide variety of other viruses, such as those of herpes, varicella, Lassa fever, infectious hepatitis, dengue fever, measles, and AIDS. It is converted to metabolites that inhibit the 5′ capping of viral mRNA, so that ultimately viral protein synthesis of both DNA and RNA viruses are affected. It is approved for use only in the treatment of severe upper respiratory infections caused by RSV in infants and children. If the duration of the infection is judged to be less than that of a full course of treatment, the drug is contraindicated. It has been used successfully as an aerosol in the treatment of influenza A and B. Varying success has been achieved against infectious hepatitis, measles, Lassa fever, and Asian hemorrhagic fever.

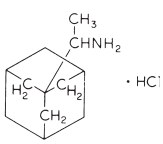
IV or oral doses of more than 1 g a day suppress erythropoiesis, characterized mostly by normocytic anemia and reticulocytosis. The effect is reversible. There is also occasional hypotension, cardiac arrest, or digitalis intoxication. Adverse effects of the inhalation aerosol include occasional rash and conjunctivitis. In chronic obstructive pulmonary disease, pulmonary function often deteriorates. It antagonizes the effect of zidovudine on human immunodeficiency virus replication. It is contraindicated in pregnancy and during breast-feeding.

Systemic absorption occurs after aerosol administration, but bioavailability is unknown. It is highly accumulated in erythrocytes but is not bound to plasma proteins. In the cells, the drug is degraded by deribosylation and amide hydrolysis and the product is mono-, di-, and triphosphorylated.

The triphosphate is thought to be the active metabolite. It is formed more in lung and liver than in other tissues, hence the drug is most effective against infections in these organs. It does not pass the blood-brain barrier. Drug and known metabolites are excreted in the urine (50%) and feces (15%). The plasma half-life is 9.5 hr, while the half-life in erythrocytes is about 40 days.

RIMANTADINE HYDROCHLORIDE

Tricyclo[3.3.1^{3,7}]decane-1-methaneamine-, α-methyl-, hydrochloride; Flumadine



[1501-84-4] $C_{12}H_{21}N{\cdot}HCl$ (215.77)

Preparation—From 1-bromoadamantane by addition of vinyl bromide, using $AlCl_3$ catalyst, to yield the 1-(2,2-dibromoethyl) derivative which undergoes classical dehydrohalogenation by heating with alkali to form the corresponding acetylene. The ketone is formed from the triple bond using mercury-catalyzed hydration with aqueous sulfuric acid. The carbonyl group is converted to the oxime which is the reduced with $LiAlH_4$ to form the product. US Pat 3,352,912 (1967).

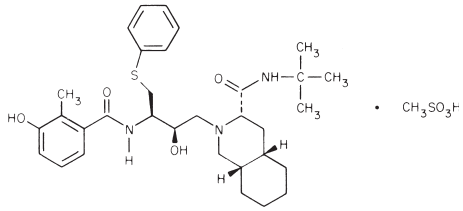
Description—White to off-white crystals melting about 376° (sealed tube).

Solubility—Freely soluble in water (50 mg/mL at 20°).

Comments—An inhibitor of influenza viral penetration or *uncoating*. When metabolized it exhibits toxicity similar to *amantidine*.

NELFINAVIR MESYLATE

3-Isoquinolinecarboxamide, [3*S*-[2(2*S,3*S**),3α,4aβ,8aβ]]-*N*-(1,1-dimethylethyl)decahydro-2-[2-hydroxy-3-[(3-hydroxy-2-methylbenzoyl)amino]-4-(phenylthio)butyl]-, monomethanesulfonate (salt); Viracept**



[159989-65-8] $C_{32}H_{45}N_3O_4S{\cdot}CH_4O_3S$ (663.91).

Preparation—*Drugs of the Future* 1997; 22:371–377.

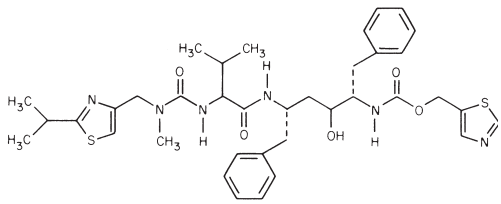
Description—White to off-white amorphous powder.

Solubility—Slightly soluble in water at pH ≥ 4; freely soluble in methanol, ethanol, isopropyl alcohol, or propylene glycol.

Comments—Similar to other peptide analogs that inhibit HIV-1 specific cleaving enzyme. It is used in combination with reverse transcriptase inhibitors to prevent resistance. Resistance to other protease inhibitors may not lead to cross-resistance with nelfinavir. Oral absorption is moderate and may be increased if drug is taken with a meal. It is similar in its adverse effects and drug interactions due to inhibition of CYP3A enzymes. The most common side effect is diarrhea.

RITONAVIR

2,4,7,12-Tetraazatridecan-13-oic acid, [5*S*-(5*R,8*R**,10*R**,11*R**)]-10-hydroxy-2-methyl-5-(1-methylethyl)-1-[2-(1-methylethyl)-4-thiazolyl]-3,6-dioxo-8,11-bis(phenylmethyl)-5-thiazolylmethyl ester; Norvir, Ing of Kaletra**



[155213-67-5] $C_{37}H_{48}N_6O_5S_2$ (720.96).

Preparation—PCT Int Pat Appl 94 14,436(1994); *Drugs of the Future* 1996; 21:700-705.

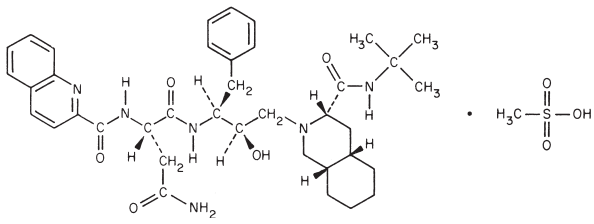
Description—White to light tan powder with a bitter metallic taste.

Solubility—Freely soluble in methanol or ethanol; soluble in isopropyl alcohol; practically insoluble in water.

Comments—A synthetic peptide analog and inhibitor of HIV-1 and -2 proteases. It has high oral bioavailability (60–80%) and is taken with meals. Used as part of combination therapy to treat HIV-infection. Most commonly used to increase the serum levels of other antiretroviral agents due to its ability to potently inhibit cytochrome P450 enzymes. Commercially available alone or in a combination product along with lopinavir. Adverse reactions include: Severe GI intolerance (N/V/D; abdominal pain, common with 600 mg bid dosing); taste perversion; asthenia; circumoral and peripheral paresthesias; lipodystrophy syndrome; hyperglycemia; increased triglycerides and/or cholesterol; transaminase elevation. Co-administration contraindicated with: Terfenadine, astemizole, cisapride, ergot alkaloid, midazolam, triazolam, propafenone, quinidine, flecainide, amiodarone, bepridil, pimozide, simvastatin, lovastatin.

SAQUINAVIR MESYLATE

Butanediamide, [3*S*-[2(1*R(*R**),2*S**],3α,4aβ,8aβ]]-*N*^{1}-[3-[3-[[(1,1-dimethylethyl)amino]carbonyl]octahydro-2(1*H*)-isoquinolinyl]-2-hydroxy-1-(phenylmethyl)propyl]-2-[(2-quinolinylcarbonyl)amino]-, monomethanesulfonate; Invirase**

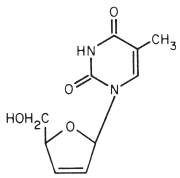


[127779-20-8] $C_{38}H_{50}N_6O_5{\cdot}CH_4O_3S$ (766.96).

Preparation—US Pat 5,196,438 (1993); *J Org Chem* 1994; 59:3656.
Description—White to off-white fine powder.
Solubility—Water; 2.22 mg/mL at 25°.
Comments—A synthetic peptide analog and inhibitor of HIV-1 and -2 proteases. It is used in combination with reverse transcriptase inhibitors, but is has less cross-resistance with other protease inhibitors. It has poor oral bioavailability (4%) and should be taken within 2 hr of a full meal for enhanced absorption. Adverse effects include GI disturbances and rhinitis. Potential drug interactions occur with drugs metabolized by CYP3A4.

STAVUDINE

Thymidine, 2′,3′-didehydro-3′-deoxy-, Zerit; d4t

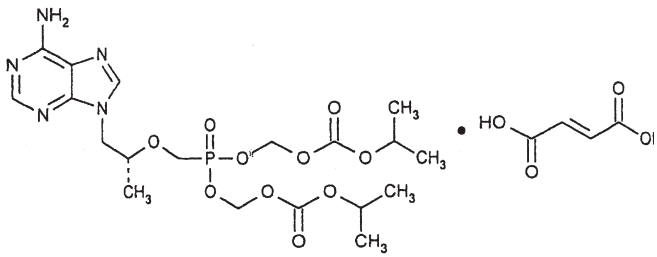


[3056-17-5] $C_{10}H_{12}N_2O_4$ (224.22).
Preparation—US Pat 5,130,421 (1992).
Description—White to off-white crystals melting about 166° (174°). Octanol-water partition coefficient 0.144 at 23°.
Solubility—At 23°; water, 83 mg/mL, propylene glycol 30 mg/mL.
Comments—An HIV reverse transcriptase inhibitor (pyrimidine nucleoside). It causes peripheral neuropathy.

SURAMIN—see RPS-19, page 1326.

TENOFOVIR DISOPROXIL FUMARATE

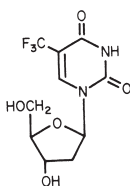
2,4,6,8-Tetraoxa-5-phosphanonanedioic acid, (*R*)-5-[[2-(6-amino-9*H*-purin-9-yl)-1-methylethoxy]methyl]-, bis(1-methylethyl) ester, 5-oxide, (*E*)-2-butenedioate (1:1); Viread



[202138-50-9] $C_{19}H_{30}N_5O_{10}P{\cdot}C_4H_4O_4$ (635.51).
Preparation—One method involves a 9 step synthesis beginning with D- (+)-isobutyl lactate. *Tetrahedron Lett* 1998; 39:1853 and US Pat 5,922,695 (1999).
Description—White to off white crystalline powder. Log P, 1.25 (pH 6.5 phosphate buffer at 25°).
Solubility—13.4 mg/mL, water at 25°.
Comments—A nucleotide analog used as part of combination therapy for the treatment of HIV-infection. Advantages includes: once daily administration, good side effect profile, active against hep B, active against strains that are often resistant to nucleosides. Adverse reactions include: Nausea and vomiting. Asymptomatic elevation of CPK and transaminase levels in 10% [AAC 2001;45:2733]. Neutropenia in 7% and increased amylase in 6%.

TRIFLURIDINE

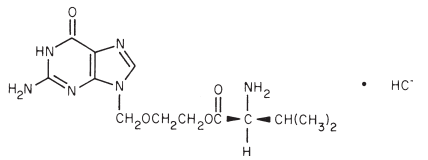
Thymidine, α,α,α-trifluoro-, Viroptic



2′-Deoxy-5-(trifluoromethyl)uridine [70-00-8] $C_{10}H_{11}F_3N_2O_5$ (296.20).
Preparation—*J Am Chem Soc* 1962; 84:3597.
Description—White crystals; melts about 188°.
Comments—A *nucleic acid synthesis inhibitor* (pyrimidine analog) used topically for herpes simplex.

VALACYCLOVIR HYDROCHLORIDE

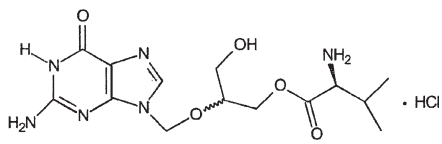
L-Valine, 2-[(2-amino-1,6-dihydro-6-oxo-9*H*-purin-9-yl)-methoxy]ethyl ester, monohydrochloride; Valtrex



[124832-27-5] $C_{13}H_{20}N_6O_4{\cdot}HCl$ (360.80).
Preparation—US Pat 4,957,924 (1990).
Description—White to off-white crystals, pK_{a1} 1.90, pK_{a2} 7.47, pK_{a3} 9.43.
Solubility—174 mg/mL in water at 25°.
Comments—A nucleic acid synthesis inhibitor (purine analog). A prodrug of *acyclovir* but with better oral absorption.

VALGANCYCLOVIR HYDROCHLORIDE

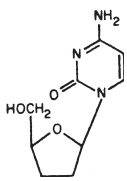
L-Valine, ester with 9-[[2-hydroxy-1-(hydroxymethyl)ethoxy]-methyl]guanine, monohydrochloride; Valcyte



[175865-59-5] $C_{14}H_{22}N_6O_5{\cdot}HCl$ (390.82).
Preparation—*Org Biomol Chem*, 2004, 2(8):1164.
Description—The L-valyl ester (prodrug) of *ganciclovir* (page XXXX). White to off-white crystalline powder. Melting about 175°. Log P 0.009 (1-octanol/pH 6.9 buffer); pKa 7.6.
Solubility—10.4 mg/mL (95% ethanol); 30 mg/mL (acetone).
Comments—The valine-prodrug of ganciclovir. Has a 10-fold improvement in absorption over oral ganciclovir. The AUC of oral valganciclovir 900 mg is comparable to 5 mg/kg IV ganciclovir. Oral valgancicovir is equivalent to IV ganciclovir for the treatment of CMV retinitis in HIV-positive patients. Adverse reactions include: Frequent: diarrhea, nausea, vomiting, neutropenia and anemia (comparable to IV ganciclovir). Occasional: thrombocytopenia, headache, fever, rash, confusion, abnormal LFTs. Contraindicated if ANC<500/mm3, Plt <25,000/ml or hemoglobin <8g/dl. Myelosuppressive drugs (ie, zidovudine)-increased risk of hematologic toxicity. Didanosine- potential increase in didanosine serum level. Probenecid-potential increase in ganciclovir serum level (monitor for ganciclovir toxicity).

ZALCITABINE

Cytidine, 2′,3′-dideoxy-, ddC, Hivid



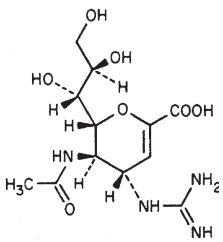
[7481-89-2] $C_9H_{13}N_3O_3$ (211.22).
Preparation—*Chem Pharm Bull* 1974; 22:128.
Description—White crystals; melts about 216°.
Comments—Antiviral activity against human immunodeficiency virus (HIV) is mediated by its conversion within infected cells to the active nucleoside triphosphate metabolite that inhibits HIV reverse transcriptase and viral DNA synthesis. It is approved for combination therapy with *zidovudine* in advanced HIV infection (CD4 cell

count\H300/mm^3) who have demonstrated significant clinical or immunological deterioration.

The major clinical toxicities of *zalcitabine* are peripheral neuropathy (17–31%) and pancreatitis (<1%). It may exacerbate hepatic dysfunction and a greater risk of toxicity may occur in patients with renal impairment. Infrequent cases of esophageal ulcers have been attributed to zalcitabine therapy. Other adverse effects include oral ulcers, nausea, dysphagia, anorexia, abdominal pain, vomiting, diarrhea, rash, pruritus, headache, dizziness, myalgia, arthralgia, fatigue, pharyngitis, fever, rigors, chest pain, and weight decrease. The mean oral bioavailability is >80%, but food decreases the extent and rate of absorption. Renal excretion is the major route of excretion with little if any degree of hepatic metabolism. The half-life is 1 to 3 hr, but impaired renal function prolongs elimination.

ZANAMIVIR

D-*Glycero*-D-*galacto*-Non-2-enonic acid, 5-(acetylamino)-4-[(aminoiminomethyl)amino]-2,6-anhydro-3,4,5-trideoxy-, Relenza



[139110-80-8] $C_{12}H_{20}N_4O_7$ (332.32).

Preparation—From (-)shikimic or (-)quinic acid; *J Am Chem Soc* 1997; 119:681.

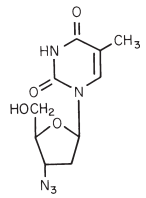
Description—White to off white powder; $[\alpha]^{20}_D$ + 40.9° (c = 0.9, water)

Solubility—18 mg/mL in water at 20°.

Comments—An aerosolized neuramidase inhibitor anti-infuenza agent with activity against influenza A and B. Effective for treatment only if treatment is started within 48 hours of onset of symptoms. Adverse reactions include: Occasional: bronchospasm (caution in patients with COPD or asthma); cough. Rare: headache; diarrhea; nausea; vomiting; dizziness; increase in liver enzyme and CPK; lymphopenia and neutropenia.

ZIDOVUDINE

Thymidine, 3′-azido-3′-deoxy-, AZT; Retrovir



Azidothymidine; [30516-87-1] $C_{10}H_{13}N_5O_4$ (267.24).

Preparation—*Tetrahedron Letters* 1988; 29:5349.

Description—White needles; from petroleum ether melts about 110°; from water, melts about 121°; pK_a 9.68.

Solubility—1 g in 40 mL water or 15 mL alcohol.

Comments—Incorporated into retroviral DNA by reverse-transcriptase to make a nonsense sequence that terminates DNA chain synthesis. The reverse-transcriptase is 100 times more susceptible to the drug than mammalian DNA polymerase. It has activity against human immunodeficiency virus; consequently, it is used for the treatment of AIDS and AIDS-related complex (ARC). It increases the survival and improves the quality of life of patients with complications, such as severe weight loss, fever, pneumocystosis, herpes zoster, herpes or thrush. Because it crosses the blood-brain barrier, it has a favorable effect on the neurological symptoms of AIDS. During prolonged therapy resistance may occur.

It causes severe anemia from bone-marrow depression in patients with AIDS; 25% of infected persons without AIDS develop anemia. It causes granulocytopenia and/or thrombocytopenia in about 5% of AIDS patients. However, it may increase platelet count if the count is depressed as the result of the disease. Nausea (46%), headaches (42%), GI pain (20%), rash (17%), fever (16%), diarrhea (12%), anorexia (11%), myalgia (8%), somnolence (8%), malaise (8%), vomiting, dizziness, paresthesias (each 6%), insomnia, dyspnea, sweating (all 5%), and macrocytosis occur. Polymyositis sometimes occurs. It is weakly mutagenic and should be withheld in pregnancy, if possible. In vitro antagonism of AZT inhibition of HIV-1 by ribovarin has been demonstrated, so those agents should not be used simultaneously. Drugs that inhibit hepatic glucuronidation, such as acetaminophen, aspirin, indomethacin, probenecid, pyrimethamine, and trimethoprim decrease elimination and increase toxicity.

Oral bioavailability is 52% to 75%. CSF levels are nearly the same as in plasma. The drug is metabolized rapidly in liver with a half-life of 0.8 to 1.9 hr. Only 14% of intact drug is eliminated in urine.