CHAPTER 71

Cholinomimetic Drugs

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The autonomic nervous system (ANS) may be divided into two efferent portions called the sympathetic (thoracolumbar) and parasympathetic (craniosacral) divisions. The terms sympathetic and parasympathetic are anatomic terms that do not refer to the neurotransmitter being released at nerve terminals or the type of effects produced. The neurotransmitter of all preganglionic autonomic fibers, postganglionic parasympathetic fibers, and a few postganglionic sympathetic fibers (sweat glands) is acetylcholine (ACh). Most postganglionic sympathetic fibers use norepinephrine as the neurotransmitter. An historically important classification of autonomic nerves is dependent on the type of neurotransmitter released from nerve fibers. Hence, fibers that release ACh are cholinergic and include all autonomic preganglionic neurons, somatic nerve endings, parasympathetic postganglionic neurons, and certain neurons of the central nervous system. Those releasing norepinephrine are noradrenergic or adrenergic fibers and include most postganglionic sympathetic neurons and some neurons of the central nervous system.

The cholinergic neurotransmitter system is known to play an important role in both peripheral (PNS) and central nervous system (CNS) function. Cholinergic receptors are divided into nicotinic and muscarinic receptors based on the preferential binding of the alkaloids, nicotine or muscarine, respectively. Molecular biological studies, radio-ligand binding studies and functional assays have identified numerous subtypes of muscarinic and nicotinic receptors that exist in both the PNS and CNS. Acetylcholine binds nonselectively to each of these widely distributed receptors to elicit a large range of pharmacological actions. Cholinomimetic drugs may act at receptors in ganglia, neuromuscular junctions, in the central nervous system, and in parasympathetic neuroeffectors. By contrast, parasympathomimetic drugs are limited primarily to effects at the parasympathetic neuroeffectors innervated *via* muscarinic receptors. It is important to remember that selectivity for a particular receptor subtype is highly dependent on drug concentration. Thus, high concentrations of a muscarinic agonist can produce effects at receptors in the ganglia and/or the neuromuscular junction. Nonetheless, compounds that specifically target subtypes of muscarinic or nicotinic receptors may provide therapeutic agents that lack the side effect profiles of the currently available nonselective drugs.

Acetylcholine synthesis takes place in the cytoplasm of cholinergic neurons through the action of choline acetyltransferase. The newly synthesized ACh is transported into vesicles for storage. Following the release of ACh from the nerve terminal, it is rapidly hydrolyzed to choline and acetate by acetylcholinesterase. The enzyme is found in high concentrations in cholinergic neurons, surrounding neuromuscular junctions, and in other tissues. Butyrylcholinesterse (also known as serum esterase, pseudo-cholinsterase, cholinesterase) has a lower specificity for acetylcholine and is found in plasma, erythrocytes, liver, glia, and other tissues. Drugs that inhibit these enzymes prolong the life of ACh and elicit a variety of effects associated with muscarinic and nicotinic agonists. For this reason, acetylcholinesterase inhibitors generally are classified as cholinomimetics. These drugs have received considerable attention as therapeutic agents, insecticides, and as agents for chemical warfare. The discussion in this chapter will focus on those acetylcholinesterase inhibitors with therapeutic actions in the PNS and the CNS.

CHOLINOMIMETICS

The rapid destruction of systemically administered ACh by cholinesterases makes the endogenous neurotransmitter of limited clinical value. Clinically useful cholinomimetic drugs are either cholinergic agonists that are resistant to the hydrolytic action of cholinesterases, or agents that inhibit cholinesterases. Based on these mechanisms of action, cholinomimetic drugs may be classified as direct acting (agonists) and indirect acting agents (anticholinesterases). The cholinomimetic drugs are used for their effects at muscarinic receptors in the PNS and find utility in ophthalmologic, gastrointestinal, genitourinary, cardiovascular, and pulmonary practice. In addition to these uses, specific indirect acting drugs (anticholinesterases) are used for their CNS actions and in the treatment of Alzheimer's disease. Finally, nicotine is included as a cholinomimetic drug and is available as a smoking cessation aid.

The effects of drugs acting at muscarinic receptors in the periphery are varied. In the eye, stimulation of muscarinic receptors results in contraction of the ciliary muscle to produce accommodation while contraction of the iris sphincter muscle causes miosis. The prominent effects observed in the cardiovascular system are modified by important homeostatic reflexes and involve reduction of peripheral vascular resistance and changes in heart rate. In the gastrointestinal (GI) tract, muscarinic agonists increase the secretory activity of salivary and gastric glands and increase peristalsis activity. In the genitourinary tract muscarinic agonists promote urination due to contraction of the detrusor muscle and relaxation of the trigone sphincter. In the respiratory system, the bronchiolar smooth muscle is contracted, and the tracheobronchial glands are stimulated.

Widespread neuronal degeneration, neuritic plaques containing β-amyloid, and tau-rich neurofibrillary tangles are hallmark findings in Alzheimer's disease. The loss of markers for cholinergic neurotransmission has called attention to a cholinergic component in the disease. Presently, the only FDA-approved drugs for Alzheimer's disease are cholinomimetic drugs. The drugs are palliative and have no effect on the progression of the disease.

USES—Cholinomimetic drugs are used most commonly in ophthalmology where they reduce elevated intraocular pressure in glaucoma and/or induce miosis. The muscarinic agonists are used in the topical treatment of open-angle, angle-closure, and acute congestive glaucoma, before, during, and after intraocular surgery, and following iridectomy procedures. The drugs may be used in alternation with mydriatic drugs to break adhesions between the iris and lens, to antagonize the effects of mydriatics, and occasionally to treat accommodative esotripia. Acetylcholine chloride is limited to intraocular use because is it rapidly hydrolyzed by cholinesterases following topical application.

In GI disorders that involve decreased smooth muscle contraction without obstruction, specific muscarinic agonist drugs may be used in the treatment of atonic constipation, congenital megacolon, postoperative and postpartum adynamic intestinal ileus, and postvagotomy gastric atony. Pancreatic function tests may utilize muscarinic drugs to stimulate pancreatic secretions. Bethanechol has been used to increase the tone of the lower esophageal sphincter in the diagnosis (treatment) of reflux esophagitis. In the genitourinary tract, muscarinic agonists are useful in the treatment of postoperative and postpartum non-obstructive urinary retention and neurogenic atony of the urinary bladder with retention. The primary use of the drug in the cardiovascular field is in the diagnosis and possible arrest of paroxysmal atrial tachycardia. While therapeutic doses usually do not depress normal cardiac functioning, a conduction block in the aberrant conduction pathway within the atrioventricular node may be induced by the drugs. In pulmonary practice, the hypersensitivity of asthmatic patients to bronchiolar constriction induced by cholinomimetics makes methacholine useful in the diagnosis of asthma. Vasospastic peripheral vascular disorders such as Raynaud's disease and dermatitis congelationis (frost-bite) have been treated with these agents. However, superior drugs are available and cholinomimetic drugs are seldom used for this purpose. Lastly, muscarinic agonists are known to increase secretory activity in glands including the salivary and lacrimal glands and are used in the treatment of symptoms of dry mouth caused by radiotherapy for cancer of the head and neck, and symptoms associated with Sjogren's syndrome.

The cause of Alzheimer's disease is unknown, but abnormal processing of neuronal lipoproteins and marked changes in the level of many neurotransmitters including ACh have been implicated. A significant decrease in cholinergic neuronal activity is observed during the progression of the disease that is consistent with the observed deficits in memory and cognition. Based on these observations, drugs with cholinomimetic properties in the CNS are used in the treatment of Alzheimer's disease.

ADVERSE EFFECTS—Adverse effects produced by the cholinomimetics can be predicted based on the pharmacodynamic activity of the drugs. Thus, undesirable effects may include flushing, sweating (that may interfere with body temperature control), abdominal cramps, difficulty in visual accommodation, headache, and convulsions at high doses. Specific GI adverse effects include epigastric distress, belching, diarrhea, involuntary defecation, nausea and vomiting, and colic. In the genitourinary tract, there may be a feeling of tightness in the urinary bladder, urinary frequency, and enuresis. With regard to respiratory effects, bronchiolar constriction leading to bronchspasm and excessive salivary, nasopharyngeal, and bronchial secretions can result and lead to life-threatening blockade of the airway. In low doses, vasodilatation mainly may be confined to the skin (flush, burning sensation). Moderate to high doses may cause moderate-to-severe hypotension, leading to syncope and even shock. Excessive doses may cause severe bradycardia, even cardiac arrest, and atrioventricular conduction disturbances, especially heart block. Furthermore, reflex sympathoadrenal discharge coupled with direct muscarinic effects on conduction sets the stage for serious cardiac arrhythmias.

Topical muscarinic drugs applied to the conjunctiva or intraocularly may interfere with near vision (accommodative myopia) and cause blurred vision, ocular pain, browache, headache, ciliary and conjunctival congestion, twitching of the eyelids, and decreased vision in poor light. After conjunctival application, there may be enough local absorption and nasolacrimal drainage into the bloodstream to produce systemic side effects.

PRECAUTIONS AND CONTRAINDICATIONS—Muscarinic drugs should be used cautiously in patients with hypertension, especially those under treatment with antihypertensive drugs, and when there is arteriosclerosis (since reflex adjustments to the hypotensive effects may be impaired). Systemic muscarinic drugs are contraindicated in the presence of atrioventricular conduction defects, coronary insufficiency, pheochromocytoma (catecholamine release and hypertensive crisis may be initiated), hyperthyroidism (atrial fibrillation may result), asthma, and peptic ulcer. While systemic absorption following topical application in ophthalmology is rare, care must be exercised in patients with the conditions mentioned above. Digital compression of the nasolacrimal ducts following instillation of solutions into the conjunctival sac will minimize drainage and systemic absorption of the drugs.

The actions produced by cholinomimetic drugs are dose dependent, and at toxic levels nicotinic activity may be observed. In case of overdose, anticholinergic drugs may be useful to reverse and/or control some symptoms. The muscarinic actions of the drugs are antagonized by atropine (or other muscarinic antagonists) and the drug serves as an antidote in the treatment of overdose. The nicotinic actions in the PNS (ganglionic and neuromuscular stimulation) can be antagonized with ganglionic blocking drugs and neuromuscular blocking agents, respectively.

ACETYLCHOLINE CHLORIDE

Ethanaminium, 2-(acetyloxy)-*N,N,N*-trimethyl-, chloride; Miochol

$$CH_3CO(CH_2)_2N^+(CH_3)_3Cl^-$$

Choline chloride acetate [60-31-1] $C_7H_{16}ClNO_2$ (181.66).

Preparation—Trimethylamine is reacted with 2-chloroethyl acetate as described in *Bull Soc Chim France* 1914; 15(4):544.

Description—Hygroscopic, crystalline powder.

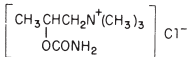
Solubility—Very soluble in cold water or alcohol; decomposed by hot water or alkalies; practically insoluble in ether.

Comments—Principally a topical ophthalmological drug to *induce miosis* during certain intraocular surgical procedures, such as cataract surgery (*after* the lens is delivered), iridectomy, penetrating keratoplasty, and other anterior segment surgery. It is given as an irrigant into the anterior chamber. When applied to the intact cornea, the poor absorption and rapid hydrolysis of ACh preclude its clinical use as a miotic agent.

There are no clinical uses for systemically administered ACh because it is rapidly hydrolyzed by acetylcholinesterase. When deaths due to huge doses have been reported, it is usually a hypoxic death from mucous plugs in the bronchial tree and/or a cardiac death due to arrhythmias.

BETHANECHOL CHLORIDE

1-Propanaminium, 2-[(aminocarbonyl)oxy]-*N,N,N*-trimethyl-, chloride; Duvoid; Urebeth; Urecholine Chloride



(2-Hydroxypropyl)trimethylammonium chloride carbamate [590-63-6] $C_7H_{17}ClN_2O_2$ (196.68).

Preparation—By treating propylene chlorohydrin with phosgene, reacting the condensation product (2-chloro-1-methylethyl chloroformate) with ammonia in ether solution, and heating the resulting urethan with trimethylamine.

Description—Colorless or white crystals or a white crystalline powder, usually having a slight, amine-like odor; slightly hygroscopic; pH (1% solution) between 5.5 and 6.5; exhibits polymorphism (one form melts about 211° and the other about 219°).

Solubility—1 g in 0.6 mL water or 13 mL alcohol; less soluble in dehydrated alcohol; insoluble in chloroform or ether.

Comments—A carbamate ester analog of ACh, bethanechol chloride is resistant to hydrolysis by the cholinesterases, and it has a relatively prolonged duration of action. The drug has minimal nicotinic activity and has somewhat stronger muscarinic activity for the GI and urinary tracts than for the cardiovascular system. Hence it is employed systemically only for the gastroenterological and genitourinary uses indicated in the general statement. See the general statement for adverse effects, precautions, and contraindications.

Bethanechol chloride is supplied for subcutaneous and for oral administration. It should be taken on an empty stomach. It should not be administered by the intravenous or intramuscular route as cholinergic crisis may result. Even with subcutaneous administration, adverse systemic effects may occur.

CARBACHOL

Ethanaminium, 2-[(aminocarbonyl)oxy]-*N,N,N*-trimethyl-, chloride; Miostat

$$[NH_2COOCH_2CH_2N^+(CH_3)_3]Cl^-$$

Choline chloride, carbamate [51-83-2] (182.65).

Preparation—By reaction of ethylene chlorohydrin with phosgene, the resulting chloroethyl chloroformate is treated with ammonia to produce chloroethyl urethan, which yields carbachol when reacted with aqueous trimethylamine.

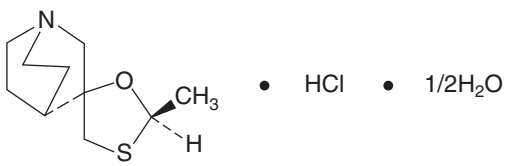
Description—White or faintly yellow crystals or crystalline powder; odorless or with a slight amine-like odor; hygroscopic; melts between 200° and 204°; pK_a 4.8.

Solubility—1 g in about 1 mL water or 50 mL alcohol; practically insoluble in chloroform or ether.

Comments—A carbamate ester analog of ACh, carbachol is resistant to hydrolysis by the cholinesterases, and it has a relatively prolonged duration of action. It is a potent cholinergic agonist exhibiting both muscarinic and nicotinic activity. Currently, it is used in ophthalmology, mainly for the treatment of narrow-angle glaucoma and to induce miosis prior to ocular surgery. See the general statement for actions, adverse effects, and contraindications.

CEVIMELINE HYDROCHLORIDE

Spiro[1-azabicyclo[2.2.2]octane-3,5′-[1,3]oxathiolane], *cis*-2′-methyl-, hydrochloride, hydrate (2:1); Evoxac



(±)-*cis*-2′-Methylspiro[1,3-oxathiolane-5,3′-quinuclidine], hydrochloride, hemihydrate (2:1)

[153504-700-2]; free base [107233-08-9] $C_{10}H_{17}NOS.HCl.1/2H_2O$ (244.79).

Preparation—By reacting 3-hydroxy-3-mercaptomethylquinuclidine with acetaldehyde as described in Japanese Patent 2,804,797 (1986) and referenced in US Patent 5,340,821 (see also, *Drugs of the Future*, (2000), 25(6), 558–569).

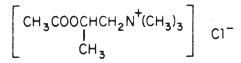
Description—A white to off-white crystalline powder with a melting range of 201–203°. The pH of a 1% solution ranges from 4.6 to 5.6.

Solubility—Freely soluble in alcohol and chloroform, very soluble in water, and virtually insoluble in ether.

Comments—Muscarinic agonist that increases secretion of exocrine glands. Indicated for the treatment of symptoms of dry mouth associated with Sjogren's syndrome. The recommended dosage is 30 mg three times daily. Muscarinic agonists can increase secretion and increase tone of smooth muscle in the gastrointestinal and urinary tracts. The most commonly observed adverse effects (in order of frequency) included excessive salivation, nausea, rhinitis, diarrhea, and urinary frequency. The drug is contraindicated in patients with uncontrolled asthma, known hypersensitivity to cevimeline, and when miosis is undesirable (eg, acute iritis, narrow-angle glaucoma). The drug should be used with caution in patients with cardiovascular disease, pulmonary disease, and in other disorders where cholinomimetic effects may lead to complications. Cevimeline should be administered with caution in patients taking beta-adrenergic antagonists due to the possibility of conduction disturbances. The drug may interfere with the effects of antimuscarinic drugs when co-administered. (See the general statement for additional actions, adverse effects, and contraindications). Cevimeline is metabolized by CYP2D6 and CYP3A4 and drugs that inhibit these enzymes may inhibit cevimeline metabolism. Use in caution in patients suspected of CYP2D6 deficiency. Exposure of CYP450 enzymes to cevimeline produced no inhibition in *in vitro* studies.

METHACHOLINE CHLORIDE

Propanaminium, 2-(acetyloxy)-*N,N,N*-trimethyl-, chloride; Provocholine



(2-Hydroxypropyl)trimethyl ammonium chloride acetate [62-51-1] $C_8H_{18}ClNO_2$ (195.69).

Preparation—From trimethylacetonylammonium chloride by reduction followed by acetylation. (US Pat 2,040,145).

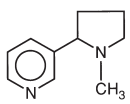
Description—Highly deliquescent; faint, fishy odor; aqueous solutions are neutral and stable for only short periods even when refrigerated; alkaline excipients promote degradation.

Solubility—Freely soluble in water, alcohol, or chloroform.

Comments—The presence of a methyl group beta to the quaternary nitrogen of ACh results in decreased susceptibility to hydrolysis and selectivity for muscarinic receptors. However, weak nicotinic actions are manifested at the neuromuscular junction in myasthenic persons and at adrenal medullary tumors in pheochromocytoma. The drug is marketed only for the diagnosis of bronchial asthma. Persons with asthma are much more sensitive to the bronchoconstrictor actions than are normal persons. A positive test result is a 20% or greater decrease in the forced expiratory volume. However, there is a tendency toward false positives among nonasthmatic smokers and relatives of asthmatics; there is also a small percentage of false negatives. Hypertensives are excessively sensitive to the hypotensive effects, but persons with pheochromocytoma respond with an acute hypertension. Adverse effects of the inhaled drug are syncope and cardiac arrest, for which 0.5 to 1 mg of atropine is given. There is a rare incidence of vertigo, throat irritation, and itching. Methacholine is contraindicated in the presence of β-adrenoreceptor-blocking drugs. Cromolyn may attenuate the bronchoconstrictor response.

NICOTINE

Pyridine, 3-(1-methyl-2-pyrrolidinyl)-,



[54-11-5] $C_{11}H_{14}N_2$ (162-23). An alkaloid from *Nicotiana tabacum* or *N rustica*.

Preparation—Commercially, it is a byproduct of the tobacco industry where it occurs to the extent of 2–8%. It is extracted from waste tobacco with organic solvents and purified through the zinc chloride double salt.

Description—Poisonous, oily liquid; unpleasant tobacco-like odor; burning taste; strongly alkaline reaction; pK_1 6.16; pK_2 10.96 at 15°.

Solubility—Soluble in water, alcohol, chloroform, and most common organic solvents.

Comments—Nicotine is the prototype of cholinomimetics of the so-called nicotinic type. Because it was used by early investigators to determine both cholinomimetic agonist and antagonist actions at the ganglia, at the adrenal medulla, and at the neuromuscular junction, the cholinergic receptors at these sites are designated as the nicotinic subtypes. The action of nicotine in the body is characterized by a primary transient stimulation followed by a persistent depression of all sympathetic and parasympathetic ganglia. The actions are explained by a common mechanism, namely, that of depolarization of the postsynaptic membrane. During the onset of depolarization, nerve action potentials are generated. Once the postsynaptic membrane becomes fully depolarized, further action potentials cannot be initiated, since they require a polarized postsynaptic membrane at their outset. Thus, a block of synaptic transmission results from the persisting depolarization induced by nicotine. Even after the membrane potential is restored, the block may persist. The synaptic stimulatory and depressant effects of nicotine cannot be overcome by atropine.

Nicotine likewise stimulates then paralyzes skeletal muscles and thus induces a succinylcholine-like action, which is the major reason for the toxic effect of the alkaloid on respiration. However, nicotine is more active on ganglia than on skeletal muscles, whereas the reverse is true of succinylcholine. In addition to the above well-established actions, nicotine also first stimulates then depresses the central nervous system (CNS).

Cardiovascular effects of nicotine are hypertension (which may tend to shift to hypotension with time), a smearing of circadian cardiovascular rhythms, tachycardia, a positive inotropic effect (only a part of which can be explained by an effect on nicotinic receptors), and, in large doses, a variety of abnormal electrocardiographic effects. The relationship of these effects to the cardiomyopathy of smoking is unknown.

The CNS effects of nicotine probably are the most important to the initiation and maintenance of the smoking habit. Nicotine is a CNS stimulant that resembles psychomotor stimulants, and it may induce subtle, complex changes in behavior. Although it is often dysphoric in the naive user, it is euphorigenic in tobacco habitues. It increases alertness and attention and, consequently, may improve memory. It decreases irritability and appetite. Deep tendon reflexes and skeletal muscle tone are diminished, which may contribute to a feeling of relaxation. However, nicotine also may induce skeletal muscle tremor and even cause convulsions in large doses. Death may be either consequent to convulsions or respiratory arrest as the result of CNS depression and skeletal muscle paralysis. The adult lethal dose is 40 to 60 mg. Even low doses may cause nausea and vomiting by actions at the chemoreceptor trigger zone and the *vomiting center* in the medulla oblongata. The CNS actions result from a combination of the stimulation of nicotinic and dopaminergic receptors, blockade of some central cholinergic synapses, inhibition of choline acetylase, and release of acetylcholine, dopamine, norepinephrine, and serotonin. Nicotine also causes the release of several hormones, to which some effects are secondary.

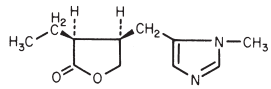
Nicotine is metabolized to cotinine in the liver. The plasma half-life is about 2 hours. Nicotine, along with various other constituents of tobacco smoke, induces various hepatic microsomal enzymes in both phase 1 and phase 2 metabolism. Estrogen elimination is accelerated and may cause menopausal-like consequences. Nicotine also increases the elimination of hydrocortisone, which is counterbalanced by greater release of the hormone from the adrenal cortex because of enhanced ACTH release. The metabolism of caffeine, theophylline, imipramine, pentazocine, propranolol, propoxyphene, mexiletine, and numerous other drugs may be accelerated.

Nicotine delivery systems have been developed to be used as part of comprehensive behavioral smoking cessation programs. The systems are intended to help suppress withdrawal symptoms in chronic tobacco users who are trying to quit. The strategy attempts to substitute nicotine previously obtained from tobacco products with nicotine in the delivery systems. Specific quantities of nicotine are incorporated into the delivery device to permit tapering of the dose (over a period of weeks or months) until tobacco dependency subsides.

In nicotine *gum*, nicotine is complexed with a polyacrylic resin. Release from the resin is slow, so that euphorigenesis is less apparent. Nevertheless, nicotine dependence is maintained. Adverse effects from the nicotine content include (in decreasing order of incidence) nausea and vomiting, eructations, vertigo, sialorrhea, headache, and irritability. Effects from constant chewing are oropharyngeal soreness and jaw muscle ache. Each square contains 2 or 4 mg of nicotine; it should be chewed for 20 to 30 min, during which time about 90% of the nicotine is absorbed. Nicotine *transdermal systems* are attached to hairless, clean skin once a day and deliver a rapid initial release of nicotine followed by a slow release over the next 24 hours. A new patch must be applied every 24 hours to a different site to avoid skin irritation. Daily dosage (5–21 mg) is regulated and tapered by using patches of differing sizes (3.5–30 cm^2) and nicotine content. The most common adverse effect is a reversible erythema, pruritus, or burning at the site of application. Hypersensitivity reactions occur in 2% of patients. A *nasal spray* is available in which each activation of the pump delivers a metered 50 μL spray containing 0.5 mg of nicotine. One dose is considered two sprays and delivers 1 mg of nicotine to the nasal mucosa. The maximum recommended duration of treatment is 3 months, and the maximum number of doses recommended in one day is 40. A nicotine *inhaler* has been developed that delivers 4 mg of nicotine from a cartridge (10 mg/cartridge) attached to a mouthpiece. Successful patients using this nicotine delivery system used 6 to 16 cartridges per day for a duration of 3 months and then were weaned off the inhaler over 6 to 12 weeks. The inhaler is not recommended for more than 6 months. Most recently a nicotine *lozenge* was introduced and is available as 2 mg and 4 mg strengths. The product is allowed to slowly dissolve to release nicotine in place of the usual tobacco product. Headache, insomnia, abnormal dreams, nervousness, insomnia, and GI complaints are relatively common with the nicotine systems. Serious toxicity can result from oral ingestion of patches or from application of multiple patches and overuse/misuse of the gum, lozenge, nasal spray or inhaled products (see effects of nicotine mentioned in the comment section above for additional effects).

PILOCARPINE

2(3*H*)-Furanone, (3*S*-*cis*)-3-ethyldihydro-4-[(1-methyl-1*H*-imidazol-5-yl) methyl]-, Ocusert



Pilocarpine monohydrochloride [92-13-7] $C_{11}H_{16}N_2O_2$ (208.25).

Preparation—The total alkaloids are extracted from the dried crushed leaves of *Pilocarpus microphyllus* or other suitable *Pilocarpus* species with alcohol containing a small amount of hydrochloric acid. The solvent is distilled, and the aqueous residue neutralized with ammonia and allowed to stand until the resins are all deposited. It is then filtered, and the filtrate is evaporated to a small bulk. Ammonia is added in excess, and the free alkaloids are extracted with chloroform. The solvent is removed by distillation, and the residue is allowed to crystallize.

Description—Colorless, translucent, odorless, faintly bitter crystals; hygroscopic and affected by light; solutions acid to litmus; melts within a range of 3° between 199° and 204°; pK_{a1} 6.8, pK_{a2} 1.3.

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

Incompatibilities—See *Alkaloids,* Chapter 26. Since the free alkaloid is quite soluble in water, *alkalies* do not readily cause a precipitation when added to solutions of its salts. It reduces *silver nitrate.*

Comments—See *Pilocarpine Hydrochloride.*

PILOCARPINE HYDROCHLORIDE

2(3*H*)-Furanone, (3*S*-*cis*)-3-ethyldihydro-4-[(1-methyl-1*H*-imidazol-5-yl)methyl]-, monohydrochloride; Isopto Carpine, Salagen

Pilocarpine monohydrochloride [54-71-7] $C_{11}H_{16}N_2O_2.HCl$ (244.72)

Description—Colorless, translucent, odorless, faintly bitter crystals; hygroscopic and affected by light; solutions acid to litmus; melts within a range of 3° between 199° and 204°; pK_{a1} 6.8, pK_{a2} 1.3.

Solubility—1 g in 0.3 mL water, 3 mL alcohol, or 360 mL chloroform; insoluble in ether.

Incompatibilities—See *Alkaloids* (Chapter 26). Since the free alkaloid is quite soluble in water, *alkalies* do not readily cause a precipitation when added to solutions of its salts. It reduces *silver nitrate.*

Comments—A muscarinic agonist that is devoid of nicotinic activity but is nonselective with respect to muscarinic targets. Because it is a tertiary amine, it is reversibly protonated at physiological pH and penetrates membranes more effectively than do quaternary ammonium cholinomimetics. Consequently, it lends itself well to topical administration in ophthalmology (see below).

Pilocarpine is tolerated better than other miotics. It rarely causes irritation or hypersensitivity, and systemic responses following topical application are uncommon; however, absorption from solutions of high concentration may result in systemic side effects. Lens opacities may result from prolonged use. Ocular controlled-release systems may cause mechanical irritation of the conjunctiva and sometimes a slight increase in mucus secretion, which usually wanes during continued use.

The free base, pilocarpine, is employed in the ocular controlled-release system, since only the nonionized form can diffuse readily through the *hydrophobic* membrane. The hydrochloride or nitrate salt is employed to make solutions, gels, and tablets (see below); the less hygroscopic nitrate is the more convenient to handle pharmaceutically but offers no therapeutic advantage.

In narrow-angle glaucomatous patients who are responsive to pilocarpine and who can maintain the unit within the conjunctival sac, the ocular controlled-release system has the advantage of long duration; the system needs changing but once a week. Topically applied drops are suited better to the acute antagonism of antimuscarinic mydriatics. The salts also may be used in the management of both narrow-angle glaucoma and chronic simple glaucoma of the open-angle type.

Muscarinic agonists are known to increase secretory activity in glands including the salivary and lacrimal glands. Pilocarpine HCl is administered orally for the treatment of symptoms of dry mouth caused by radiotherapy for cancer of the head and neck, and symptoms associated with Sjogren's syndrome. The recommended dosage is 5 mg three times daily. See the adverse effects, contraindication sections for cholinomimetic drugs mentioned above for additional information.

PILOCARPINE NITRATE

2(3*H*)-Furanone, (3*S*-*cis*)-3-ethyldihydro-4-[(1-methyl-1*H*-imidazol-5-yl)methyl]-mononitrate; P.V. Carpine Liquifilm

Pilocarpine mononitrate [148-72-1] $C_{11}H_{16}N_2O_2.HNO_3$ (271.27).

Description—Shining, white crystals; stable in air but is affected by light; solutions are acid to litmus; melts within a range of 3° between 171° and 176°.

Solubility—1 g in 4 mL water or 75 mL alcohol; insoluble in chloroform or ether.

Incompatibilities—See *Pilocarpine Hydrochloride.*

Comments—See *Pilocarpine Hydrochloride.*

ANTICHOLINESTERASES

Cholinomimetic drugs may be classified as direct acting and indirect acting agents depending on their mechanism of action. The direct acting agents exert their effects by stimulating muscarinic and/or nicotinic receptors whereas indirect acting agents inhibit acetylcholinesterase. The activity of the indirect acting cholinomimetics is due primarily to inhibition of cholinesterase enzymes though several drugs have direct nicotinic actions. Drugs that inhibit acetylcholinesterase cause ACh to accumulate at cholinergic receptor sites and thereby facilitate cholinergic neurotransmission. The term *cholinesterase* is a generic term that includes all enzymes capable of hydrolyzing acetylcholine. There are two main categories of cholinesterase. The term *acetylcholinesterase* is applied to any or all of a family of serine-dependent isoenzymes that very selectively hydrolyze acetylcholine and hence are called true, or specific, cholinesterases; they are not truly specific, since other choline esters may be hydrolyzed at low velocities. Acetylcholinesterase is concentrated in the region of the motor endplate, at autonomic ganglia, in cholinergic neurons in and outside the CNS, and in erythrocytes. The term *butyrylcholinesterase* (also called cholinesterase, pseudocholinesterase, or nonspecific cholinesterase) is applied to a number of enzymes that may hydrolyze acetylcholine but for which butyrylcholine, not acetylcholine, is the optimal substrate. Butyrylcholinesterase is present in glial and satellite cells in the CNS and autonomic ganglia, in smooth muscle, exocrine glands, and various organs such as the liver, and plasma; its concentration in cholinergic neurons is usually insignificant.

The hydrolysis of the ACh molecule is carried out in several steps. Firstly, ACh binds to the catalytic site of the enzyme that includes an esteratic site and an anionic site. The next step involves attack by the hydroxyl group of an active-site serine on the acetate carbonyl of ACh. The resulting transition state is unstable and decomposes to produce free choline and the acetylated enzyme. The acetylated enzyme is hydrolyzed rapidly to regenerate the active enzyme and acetic acid. By changing the "acylating" group on the substrate (ACh) or on an enzyme inhibitor (eg, ester, carbamate, or phosphate), the rate of regeneration of the enzyme and hence the duration of inhibition can be controlled (see below).

Inhibition of acetylcholinesterase and butyrylcholinesterase has various consequences, depending on where the enzymes are inhibited. The function of the butyrylcholinesterase in plasma and the acetylcholinesterase in erythrocytes are poorly understood, and their inhibition has no known physiological consequences, but inhibition may cause moderate increases in the plasma half-life and concentration of acetylcholine and certain other hydrolyzable choline esters. Important effects accrue to inhibition at sites of cholinergic neuroeffector transmission. The preservation of acetylcholine at such sites prolongs and intensifies the cholinergic activity there. Thus, at the neuromuscular junction, anticholinesterases facilitate neuromuscular transmission, with an early increase in muscle strength (by recruiting subliminal junctions) and a late decrease in muscle strength, even paralysis, if many motor endplates remain depolarized by persisting levels of acetylcholine. Excessive muscular fasciculations and fibrillations also occur, which also decrease muscle strength, by causing asynchrony among motor units and fibers. At the autonomic ganglia, the predominant effect is to facilitate transmission, and the final result depends on the effector organ system innervated by the excited postganglionic nerves. In the case of the atria and the atrioventricular node, the activity in both adrenergic and cholinergic postganglionic nerves will be increased, so that the effects mediated by the parasympathetic nerves will be antagonized by those of the sympathetic nerves. However, in the parasympathetic innervation, acetylcholine is preserved by the anticholinesterase at two sites, the ganglia and the innervated heart cells, which amplifies the action, whereas, in the sympathetic innervation, transmission is facilitated only at the ganglia. Therefore, where there is dual and antagonistic innervation, as in the atria, atrioventricular node, pupil, stomach and intestines, urinary tract, etc, the parasympathetic effects predominate. Thus, bradycardia, partial heart block, miosis, increased gastric secretion and motility, and tendency to urination all result from significant anticholinesterase activity. The blood pressure may be elevated, because there is little cholinergic innervation of the vascular tree, and the facilitation in the sympathetic pathway is not antagonized at the vascular smooth muscle. Ciliary spasm may be intense, because there is a negligible antagonistic sympathetic innervation of the ciliary body. Facilitation in both sympathetic and parasympathetic pathways causes increased salivation and sweating (which is mostly cholinergic). Anticholinesterase action within the CNS may cause a mixture of stimulation and depression.

Most of the cholinesterase inhibitors fall into three chemical categories: (1) alcohols with quaternary ammonium groups (edrophonium), (2) carbamate esters of alcohols containing a tertiary or quaternary ammonium group (physostigmine; also bis-quaternary compounds), (3) and organic derivatives of phosphoric acid (echothiophate). *(Note: anticholinesterase drugs used to treat Alzheimer's disease do not fall into these categories.)* These drugs interact with the anionic sites and/or with the esteratic site of cholinesterase to inhibit the enzyme. The molecular details of the inhibition differ based on the chemical class of each drug. Thus, the quaternary amine containing alcohol, edrophonium, inhibits the enzyme through reversible electrostatic interactions. Interaction between the enzyme and the inhibitor does not involve covalent interactions, and consequently the duration of action is short-lived (minutes). The carbamate-containing group of drugs *(with the possible exception of bis-quaternary ammonium-containing compounds)* undergo hydrolysis by the enzyme as described for ACh. However, during the hydrolysis step, the carbamoylated enzyme (carbamate moiety rather than an acetate) is resistant to hydrolysis, and the regeneration of the active enzyme takes longer. Consequently, the duration of action of the drugs in this category is prolonged (hours). The organophosphate-type anticholinesterases result in a phosphorylated enzyme active site that is extremely stable to hydrolysis and may undergo additional reactions (aging) to further strengthen the bond. With these organophosphate-type drugs (like isofluorphate), the duration of action is dependent on the time for resynthesis of cholinesterase (weeks to months). The organophosphate-like agents are sometimes referred to as irreversible inhibitors due to their long duration of action.

The presence of a permanent positive charge on the quaternary amine containing carbamates limits their absorption from the lungs, skin, conjunctiva, and especially into the CNS. Amines like physostigmine (tertiary amine), however, are reversibly protonated at physiological pH. The drug is well absorbed from the eye, lungs, and other sites, can enter the CNS and is more toxic in overdose than the quaternary carbamates. The quaternary ammonium containing carbamates often may enhance neuromuscular function with only minimal-to-moderate autonomic side effects. The quaternary compounds have a nicotinic agonist activity, which, at the ganglia and neuromuscular junction, adds to the cholinomimetic effect. Due to this dual effect, these agents are often chosen to enhance neuromuscular function. Because of their confinement to the periphery, the quaternary agents also may be preferred for peripheral actions. The organophosphate-type anticholinesterases are lipophilic molecules that are absorbed through the skin, readily distribute throughout the body, and penetrate the blood-brain barrier to cause CNS effects. Their

effects are long-lasting and consequently, overdoses are dangerous and include a significant CNS component. They generally do not enhance neuromuscular transmission without excessive effects on glands and smooth muscle.

USES—The anticholinesterases are applied topically to the eye in the treatment of primary *wide-angle glaucoma, accommodative convergent strabismus,* and *accommodative esotropia* and for the *emergency treatment of acute congestive glaucoma*. They also may be used to *treat marginal corneal ulcers*. In myasthenia gravis, topical application may be used to improve the function of the extraocular muscles and eyelids. The reversibly acting anticholinesterases may be alternated with mydriatics to *break adhesions between lens and iris*.

The quaternary ammonium anticholinesterases are used systemically to abolish muscular paralysis from competitive *neuromuscular blocking drugs,* to improve muscle function in *myasthenia gravis,* to treat *intestinal distention,* such as congenital *megacolon,* postoperative and postpartum *adynamic intestinal ileus, postvagotomy gastric atony, and functional urinary retention*. Edrophonium or neostigmine are used also in the differential *diagnosis of myasthenic crisis,* in which case they will improve muscle function; *cholinergic crisis,* in which case they will worsen function; and to diagnose *myotonia congenita*. Anticholinesterases, especially physostigmine, are used to treat atropine or tricyclic antidepressant poisoning.

Physostigmine, a blood-brain-barrier-penetrant amine anticholinesterase, is employed to *antagonize the toxic CNS effects of antimuscarinic drugs, tricyclic antidepressants, and H_1-antihistamines. An approach to protect against exposure to chemical warfare agents like the organophosphates involves pretreatment with reversible inhibitors (physostigmine). This prophylactic measure is used only when lethal exposue to chemical warefare agents is anticipated and very likely to occur.*

Alzheimer's disease is a neurodegenerative disorder that is characterized by the progressive loss of memory and cognitive functions (dementia). The cause of the disorder is unknown but abnormal processing of neuronal lipoproteins and marked changes in the functioning of many neurotransmitters (ACh, cholinergic, serotonin, glutamate, dopamine, norepinephrine, somatostatin) systems have been implicated. A significant decrease in cholinergic neuronal activity has been observed during the progression of Alzheimer's disease. Based on these observations, drugs that increase ACh levels (anticholinesterases) in the CNS are used in the treatment of Alzheimer's disease. If this purported mechanism of action is correct, these drugs will be beneficial only while cholinergic neurons are still intact (ie, early stages of the disease). There is no evidence that the cholinomimetic agents alter the progression of the disease.

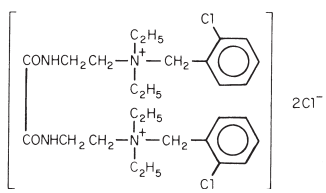
ADVERSE EFFECTS AND INTOXICATION—Conjunctivally applied anticholinesterases locally may cause stinging, lacrimation, ocular pain and brow ache (from ciliary spasm), blurring of vision, blepharospasm, conjunctival and intraocular hyperemia, transient early rise in intraocular pressure, iridocyclitis, pigment cysts of the iris, anterior and posterior synechiae, and, rarely, retinal detachment. Atropine can antagonize some of these effects. Allergies also may occur. In addition, organophosphates may cause fibrinous iritis cataracts, especially in elderly patients (in 50% of cases chronically treated), and uveitis.

Adverse systemic effects, from systemic administration or systemic absorption after topical application, include excessive salivation, sweating, tracheobronchial secretion, lacrimation, bronchoconstriction, marked miosis, blurring of vision, nausea and vomiting, diarrhea, abdominal cramps and colic, involuntary defecation, pallor, hypertension or hypotension, bradycardia, and urinary frequency, urgency, and enuresis. These effects can be antagonized with sufficiently large doses of atropine. Laryngospasm, tremors, muscle fasciculations and twitching, weakness (even respiratory paralysis), potentiation of succinylcholine, and dizziness are nicotinic effects that cannot be antagonized with atropine. These effects usually occur only after quite large overdoses. Pralidoxime will antagonize these actions if given early enough. Acute intoxication caused by large doses of physostigmine or organophosphates also induces CNS effects, such as confusion, ataxia, loss of reflexes, slurred speech, Cheyne-Stokes respiration, convulsions, coma, and respiratory and circulatory paralysis. Huge doses of atropine and pralidoxime, if used early, can suppress these effects. General supportive measures also are necessary in the management of both peripheral and central toxicity. Neuropathy associated with a latent demyelination of various nerve axons has been associated with chronic exposure to some organophosphates.

PRECAUTIONS AND CONTRAINDICATIONS—When systemic anticholinesterases are used, the margin between the first appearance of side effects and serious toxic effects is small. The first signs may be quite subtle. Furthermore, there is wide variation among patients and in the same patient from time to time, so each patient must be approached cautiously. Therefore, careful medical supervision is mandatory. Anticholinesterases should be used cautiously, or withheld, in patients with bronchial asthma, mechanical intestinal or urinary obstruction, peptic ulcer, vagotonia, bradycardia, hypotension, recent myocardial infarction, epilepsy, parkinsonism, or a known hypersensitivity to depolarizing neuromuscular blocking drugs and when cholinomimetics are to be used. Quinidine and quinine antagonize the neuromuscular effects of the anticholinesterases. They should not be applied topically to the eye when there is a history of retinal detachment, uveitis, or angle-closure glaucoma. Their potential systemic effects command the same precautions as for systemic anticholinesterases. Systemic anticholinesterases will antagonize ganglionic blocking drugs. The safety of the amine and quaternary ammonium agents in mother and fetus during pregnancy has not been established; systemic organophosphates are absolutely contraindicated.

AMBENONIUM CHLORIDE

Benzenemethanaminium, *N,N'*-[(1,2-dioxo-1,2-ethanediyl)bis-(imino-2,1-ethanediyl)]bis[2-chloro-*N,N*-diethyl]-, dichloride; Mysuran; Mytelase



[Oxalylbis(iminoethylene)]bis[(*o*-chlorobenzyl)diethylammonium] dichloride [115-79-7] $C_{28}H_{42}Cl_4N_4O_2$ (608.48); *tetrahydrate* [52022-31-8] (680.54).

Preparation—*N,N*-Diethylethylenediamine is reacted with ethyl oxalate to give *N,N'*-bis[2-(diethylamino)ethyl]oxamide which is doubly quaternized with 2-chlorobenzyl chloride. US Pat 3,096,373.

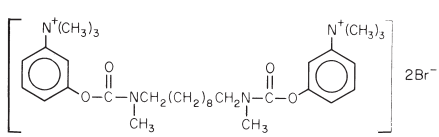
Description—White, odorless powder melting about 200°.

Solubility—1 g in 5 mL water, 20 mL alcohol, >1000 mL chloroform or >1000 mL ether.

Comments—A quaternary ammonium *anticholinesterase* drug with actions similar to those of neostigmine; ambenonium chloride is 2 to 4 times more potent, and its duration of action after oral administration (4 hr) may be slightly longer. It also is claimed to have a lower incidence of side effects than neostigmine, particularly of the GI tract. It is used in the treatment of *myasthenia gravis*. For side effects and precautions, see the general statement, above.

DEMECARIUM BROMIDE

Benzenaminium, 3,3'-[1,10-decanediylbis(methylimino)carbonyloxy]-bis[*N,N,N*-trimethyl-, dibromide; Humorsol



m-(Hydroxyphenyl)trimethylammonium bromide, decamethylenebis [methylcarbamate]

(2:1) [56-94-0] $C_{32}H_{52}Br_2N_4O_4$ (716.60).

Preparation—*N,N′*-Dimethyl-1,10-decamethylenediamine is added to molten 3-(dimethylamino)phenyl carbonate to produce 1,10-decamethylenebis {3-(dimethylenebis[3-(dimethylamino)phenyl]-N-methylcarbamate}. This ester, a viscous oil, is dissolved in ethanol and doubly quaternized with an acetone solution of methyl bromide. US Pat 2,789,981.

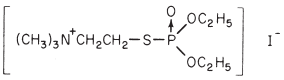
Description—White, or slightly yellow, slightly hygroscopic, crystalline powder; melts about 165° with decomposition; pH (1 in 100 solution) between 5 and 7.

Solubility—Freely soluble in water or alcohol; sparingly soluble in acetone; soluble in ether; aqueous solutions are stable and may be heat-sterilized.

Comments—A reversible anticholinesterase. It is used as a solution with a duration of action from 3 to 5 days.

ECHOTHIOPHATE IODIDE

Ethanaminium, 2-[(diethoxyphosphinyl)thio]-*N,N,N*-trimethyl iodide; Ecodide; Phospholine Iodide



(2-Mercaptoethyl)trimethylammonium iodide *S*-ester with *O,O*-diethyl phosphorothioate [513-10-0] $C_9H_{23}INO_3PS$ (383.22).

Preparation—β-(Dimethylamino)ethanol is reacted with sodium, and the resulting sodium alkoxide is condensed with *O,O*-diethyl phosphorochloridothioate [ClP(S)$(OC_2H_5)_2$] to yield *S*-[2-(dimethylamino)ethyl] *O,O*-diethyl phosphorothioate. This ester is quaternized with methyl iodide. US Pat 2,911,430.

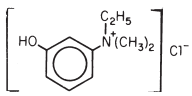
Description—White, crystalline, hygroscopic solid with slight mercaptain-like odor; its solutions have a pH of about 4.

Solubility—1 g in 1 mL water, 3 mL methanol, or 25 mL dehydrated alcohol; practically insoluble in other organic solvents.

Comments—Due to a long duration of action, the drug may be considered an irreversible anticholinesterase. It is used as a solution with a duration of action from 3 to 7 days.

EDROPHONIUM CHLORIDE

Benzenaminium, *N*-ethyl-3-hydroxy-*N,N*-dimethyl-, chloride; Enlon-Plus; Tensilon



Ethyl (*m*- hydroxyphenyl) dimethylammonium chloride [116-38-1] $C_{10}H_{16}ClNO$ (201.70).

Preparation—*m*-Dimethylaminophenol is dissolved in a suitable organic solvent and quaternized with ethyl iodide. The dimethylethyl(3-hydroxyphenyl)ammonium iodide precipitates and is converted to the chloride in various ways, one of which involves treatment with moist silver oxide to form the quaternary base followed by neutralization with hydrochloric acid.

Description—White, odorless crystalline powder; 1 in 10 solution is practically colorless, pH (1 in 10 solution) between 4 and 5; melts between 165° and 170° with decomposition.

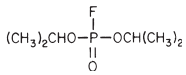
Solubility—1 g in 0.5 mL water or 5 mL alcohol; insoluble in chloroform or ether.

Comments—Inhibits cholinesterase primarily at the neuromuscular junction and very little at other sites. It also has some direct nicotinic stimulant actions at the neuromuscular junction but not at the autonomic ganglia. The duration of action of a single small dose is only about 5 min, but large doses may act for 1 to 2 hours. It is used to *abolish neuromuscular paralysis due to d-tubocurarine* or similarly acting motor endplate–stabilizing drugs. It also is used as a *diagnostic agent for myasthenia gravis* or to differentiate a myasthenic crisis from a cholinergic crisis. It may be used occasionally to treat *myasthenic crises*.

Transient blurring of vision, lacrimation, perspiration, and dizziness may accompany its use. It causes muscle fasciculations in the normal human. When it is used to differentiate myasthenic from cholinergic crisis, facilities for endotracheal intubation and artificial respiration must be available.

ISOFLUROPHATE

Phosphorofluoridic acid, bis(1-methylethyl) ester; DFP; Floropryl



Diisopropyl phosphorofluoridate [55-91-4] $C_6H_{14}FO_3P$ (184.15).

Preparation—Isopropyl alcohol is reacted with PCl_3 to form diisopropyl phosphite. Oxidation with chlorine gives diisopropyl phosphorochloridate, which metathesizes with NaF to yield the phosophorofluoridate.

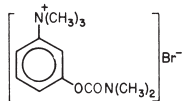
Description—Clear, colorless, or faintly yellow liquid; boils about 183°; specific gravity about 1.05; vapor is extremely irritating to the eye and mucous membranes; in the presence of moisture, it decomposes with formation of hydrogen fluoride.

Solubility—Sparingly soluble in water; soluble in alcohol.

Comments—Due to a very long duration of action, this organophosphate may be considered an irreversible anticholinesterase. It is used as an ointment with a duration of action from 2 to 4 weeks.

NEOSTIGMINE BROMIDE

Benzenaminium, 3-[[(dimethylamino)carbonyl]oxy]-*N,N,N*-trimethyl-, bromide; Prostigmin Bromide



(*m*-Hydroxyphenyl)trimethylammonium bromide dimethylcarbamate [114-80-7] $C_{12}H_{19}BrN_2O_2$ (303.20).

Preparation—It may be prepared by reacting dimethylcarbamoylchloride [$(CH_3)_2NCOCl$] with potassium *m*-(dimethylamino)phenolate, then quaternizing with methyl bromide.

Description—White, crystalline powder; odorless and with a bitter taste; solutions are neutral to litmus; melts between 171° and 176° with decomposition.

Solubility—1 g in about 0.5 mL water; soluble in alcohol; practically insoluble in ether.

Comments—A quaternary ammonium anticholinesterase. It acts at the ester site of the enzyme to form the inactive dimethylcarbamoyl enzyme. Its effects are more prominent on certain structures than on others, being particularly effective on the bowel, urinary bladder, and skeletal muscle; the pupil, heart, blood pressure, and secretions are affected to a much lesser extent at doses that are ordinarily effective on the structures listed above. The duration of action by the oral route is 3 to 6 hours and by the intramuscular route, 2 to 4 hours.

Neostigmine can be employed for the genitourinary and neuromuscular uses indicated in the general statement. However, it is seldom used today to antagonize curare-like drugs or in the diagnosis of myasthenia gravis due to its long duration of action.

Orally, neostigmine is absorbed poorly; sometimes as little as 1%. Changes in bowel condition can alter absorption considerably, which may make management difficult. Neostigmine is administered parenterally as the methylsulfate and orally as the bromide salt.

NEOSTIGMINE METHYLSULFATE

Benzenaminium, 3-[[(dimethylamino)carbonyl]oxy]-*N,N,N*-trimethyl-, methyl sulfate; Prostigmin Methylsulfate

(*m*-Hydroxyphenyl)trimethylammonium methyl sulfate dimethylcarbamate [51-60-5] $C_{13}H_{22}N_2O_6S$ (334.39).

Preparation—It is made by the method outlined under *Neostigmine Bromide,* using dimethyl sulfate in place of methyl bromide.

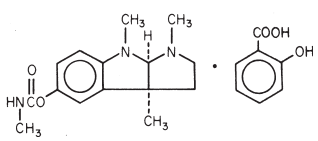
Description—White, crystalline powder, odorless and has a bitter taste; solutions are neutral to litmus; melts between 144° and 149°.

Solubility—Very soluble in water; soluble in alcohol.

Comments—See *Neostigmine Bromide.*

PHYSOSTIGMINE SALICYLATE

Pyrrolo[2,3-*b*]indol-5-ol, (3a*S-cis*)-1,2,3,3a,8,8a-hexahydro-1,3a,8-trimethyl-, methylcarbamate (ester); mono-(2-hydroxybenzoate); Eserine Salicylate; Isopto-Eserine; Antilirium



Physostigmine monosalicylate [57-64-7] $C_{15}H_{21}N_3O_2.C_7H_6O_3$ (413.47).

Preparation—By extracting powdered *Physostigma* seeds with hot alcohol. After distilling off the alcohol, the residue is mixed with sodium carbonate and extracted with ether, from which solution the physostigmine is removed with dilute sulfuric acid. The free alkaloid may be obtained by alkalinizing the acid solution. The salicylate may be made by adding 2 parts of physostigmine to a solution of 1 part of salicylic acid in

35 parts of boiling distilled water and allowing the salt to crystallize on cooling.

Description—White or faintly yellow odorless powder or shining crystals; acquires a red tint when exposed to light and air; melts about 184°.

Solubility—1 g in 75 mL water, 16 mL alcohol, 6 mL chloroform, or about 250 mL ether.

Incompatibilities—Aqueous solutions tend to develop a red color on standing; a pink solution does not necessarily indicate complete ineffectiveness, but as the color deepens to red, the product rapidly loses its potency. Boric acid retards the change, but alkalies hasten decomposition. Alkali-free glass should be used. It is precipitated by the usual alkaloidal precipitants.

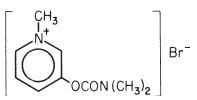
Comments—The oldest of the anticholinesterases. It combines with the enzyme at the esteratic site to yield the inactive methylcarbamoyl enzyme. It shares with neostigmine marked stimulatory actions on the bowel but causes more secretion of glands, more effect on blood pressure, more constriction of the pupil, and less action on skeletal muscle. Since it is a tertiary amine, it penetrates readily into the eye. Although its main use in medicine is topically in ophthalmology, for the purposes indicated in the general statement, there is some interest in its CNS uses. The salicylate is used for both its CNS and ophthalmological actions; the sulfate is used only in the eye. The duration of the ocular effects after topical application is 6 to 12 hours; the duration of systemic effects is less than 2 hours. The systemic bioavailability after oral administration is about 5 to 12%.

Physostigmine, a tertiary amine can penetrate the blood-brain-barrier and is employed to *antagonize the toxic CNS effects of antimuscarinic drugs, tricyclic antidepressants, and* H_1-antihistamines. An approach to protect against exposure to chemical warfare agents like the organophosphates involves pretreatment with reversible inhibitors like physostigmine. The rationale is to protect the enzyme by blocking it with a reversible agents rather than allowing the essentially irreversible inhibitors access to the enzyme. This prophylactic measure is used only when lethal exposure to chemical warfare agents is anticipated and very likely to occur.

The salicylate has the advantage of being less deliquescent than the sulfate. Addition of a small amount of boric acid to a solution of the salt is said to inhibit formation of the red decomposition product produced by alkalies, which frequently occurs in solutions of physostigmine salts dispensed on prescription. A solution that has developed a red color should not be used.

PYRIDOSTIGMINE BROMIDE

Pyridinium, 3-[[(dimethylamino)carbonyl]oxy]-1-methyl-, bromide; Mestinon; Regonal



3-Hydroxy-1-methylpyridinium bromide dimethylcarbamate [101-26-8] $C_9H_{13}BrN_2O_2$ (261.12).

Preparation—3-Pyridinol is condensed with dimethylcarbamoyl chloride in the presence of a suitable basic catalyst such as dimethylaniline, magnesium oxide, etc. The resulting ester, 3-pyridyl dimethylcarbamate, is isolated, dissolved in a suitable organic solvent, and quaternized with methyl bromide.

Description—White or practially white, crystalline, hygroscopic powder, with an agreeable, characteristic odor; melts between 154° and 157°.

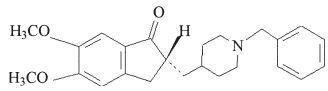
Solubility—Freely soluble in water, alcohol, or chloroform; slightly soluble in hexane; practically insoluble in ether.

Comments—A quaternary ammonium anticholinesterase drug that is approximately one-fourth as potent as neostigmine at the neuromuscular junction and about one-eighth as potent on the bowel, genitourinary tract, and exocrine glands. Its duration of action by the oral route usually is somewhat longer and absorption is less erratic than with neostigmine, which are advantages. Because of its relative affinity for the neuromuscular junction, its principal use is in the treatment of *myasthenia gravis,* in which use it causes fewer side effects than does neostigmine. It is also superior to neostigmine in that the patient may be carried through the night without the necessity of interrupting sleep to take medication. However, in some patients, it provides less control of muscular weakness than does neostigmine. Pyridostigmine is administered orally except when the patient is to undergo surgery or childbirth or is in myasthenic crisis. Neonates born of myasthenic mothers also may be given parenteral pyridostigmine to improve respiration, swallowing, and suckling. The drug also is used to antagonize competitive neuromuscular-blocking drugs.

Anticholinesterases for Alzheimer's Disease

DONEPEZIL HYDROCHLORIDE

Inden-1-one, (±)-2,3-dihydro-5,6-dimethoxy-2-[[1-(phenylmethyl)-4-piperidinyl]methyl]-1*H*- hydrochloride; Aricept



(±)-2-[(1-Benzyl-4-piperidyl)methyl]-5,6-dimethoxy-1-indanone [120014-06-4 (base)] $C_{24}H_{29}NO_3$. HCl (415.96).

Preparation—In a crossed aldol reaction, 1-benzyl-4-piperidinecarboxaldehyde and 5,6-dimethoxy-2(1*H*)-indenone are reacted in the presence of butyl lithium with subsequent dehydration to form the alkene. Catalytic reduction yields the product. *Drugs of the Future* 1997; 22: 397.

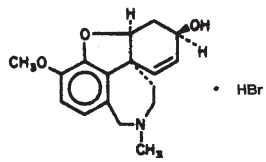
Description—Donepezil hydrochloride is a white crystalline powder**.**

Solubility—Freely soluble in chloroform, soluble in water or glacial acetic acid, slightly soluble in ethanol or acetonitrile and practically insoluble in ethyl acetate or hexane.

Comments—A reversible cholinesterase inhibitor used to treat mild-to-moderate Alzheimer's disease. It is completely absorbed from the GI tract and has a half-life of about 70 hours. Clinical trials indicate modest improvement in cognitive function and activities of daily living; a minority of patients showed greater improvement. Muscarinic side effects and insomnia occur in some patients. Hepatic toxicity has not been reported. Cholinomimetics may have the potential to cause generalized convulsions. However, seizures may be a result of the neurological disorder and not the drugs. Donepezil may interfere with the effects of antimuscarinic drugs or other cholinomimetics (synergy) when co-administered. (See the general statement for additional actions, adverse effects, and contraindications). It is metabolized by CYP2D6 and CYP3A4 and drugs that inhibit or induce these enzymes may alter Donepezil metabolism. Use in caution in patients suspected of CYP2D6 deficiency. Exposure of CYP450 enzymes to donepezil produced no significant inhibition in *in vitro* studies. There is no evidence that the cholinomimetic agents alter the progression of the disease.

GALANTAMINE HYDROBROMIDE

6*H*-Benzofuro[3a,3,2-*ef*][2]benzazepin-6-ol, (4a*S*,6*R*,8a*S*)-4a,5,9,10,11,12-hexahydro-3-methoxy-11-methyl-, hydrobromide; Reminyl, Nivalin



Galanthamine Hydrobromide [1953-04-4] $C_{17}H_{21}NO_3$.HBr (368.27).

Preparation—It has been isolated from Caucasian snowdrop *Galanthus woronoyi*. Galanthamine may be isolated/derived from other plant sources including the bulbs of the daffodil, *Narcissus pseudonarcissus* (see US Pat 5,877,172). It may be synthesized by treating (-)narwedine with L-selectride in tetrahydrofurane followed by treatment with a 60% solution of HBr in ethanol. US Pat 6,407,229.

Description—White to off-white crystalline powder; melts about 245° (decomposition).

Solubility—Sparingly soluble in water, soluble in ethyl acetate, $CHCl_3$.

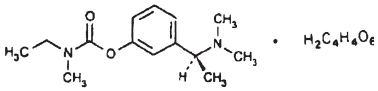
Comments—Tertiary alkaloid isolated from Caucasian snowdrop *Galanthus woronoyi* and other plant sources including the bulbs of the daffodil, *Narcissus pseudonarcissus*. The precise mechanism of action of the drug is unknown. It is a reversible competitive inhibitor of acetylcholinesterase and enhances cholinergic function in the CNS. In addition, it is postulated that the drug is a modulator of nicotinic receptors. These mechanisms may explain the clinical benefits of the drug. If this purported mechanism of action is correct the drug will be beneficial only while cholinergic neurons are still intact (ie, early stages of the disease). There is no evidence that the cholinomimetic agents alter the progression of the disease.

The drug is available as tablets (4 mg, 8 mg, and 12 mg dosages) and as an oral solution (4 mg/mL) supplied with a calibrated pipette. The dose should be titrated up starting with 4 mg twice daily (8 mg/day) and increased to 8 mg twice daily (16 mg/day) after 4 weeks. The recommended dosage range is 16–24 mg/day given twice daily**.** Dosage adjustments may be necessary in patients with hepatic renal impairment.

The most commonly observed adverse effects reported for the drug included nausea, vomiting, diarrhea, dizziness, and headache. The drug is contraindicated in patients with known hypersensitivity to galantamine. The drug should be used with caution in patients with cardiovascular disease, gastrointestinal conditions, pulmonary disease (asthma, COPD) and in other disorders where cholinomimetic effects may lead to complications. Cholinomimetics may have the potential to cause generalized convulsions. However, seizures may be a result of the neurological disorder and not the drugs. Galantamine may interfere with the effects of antimuscarinic drugs or other cholinomimetics (synergy) when co-administered. (See the general statement for additional actions, adverse effects, and contraindications). It is metabolized by CYP2D6 and CYP3A4 and drugs that inhibit or induce these enzymes may alter galantamine metabolism. Use in caution in patients suspected of CYP2D6 deficiency. Exposure of CYP450 enzymes to galantamine produced no significant inhibition in *in vitro* studies.

RIVASTIGMINE TARTRATE

Carbamic acid, *N*-ethyl-*N*-methyl-, 3-[1(*S*)-(dimethylamino)ethyl]phenyl ester, 2*R*,3*R*-dihydroxybutanedioate (1:1); Exelon



m-[(*S*)-1-(Dimethylamino)ethyl]phenyl ethylmethylcarbamate, hydrogen tartrate (1:1); [129101-54-8] $C_{14}H_{22}N_2O_2.C_4H_6O_6$ (400.42).

Preparation—Reaction of *N*-ethyl-*N*-methylcarbamoyl chloride and α-(*m*-hydroxy-phenylethyl)dimethylamine yields a racemic mixture of the product, which is resolved by heating with (+)- bis-[(*O,O*)-*p*-toluyl)tartaric acid in aqueous methanol. On cooling the solution is made alkaline and the *S*-enantiomer extracted with ether. US Pat 5,620,176 (1991).

Description—White to off-white crystals from ethanol melting about 124°. pK_a 8.85, distribution coefficient 3.0 (octanol-phosphate buffer, pH 7 at 37°); $[\alpha]^{20}_D$ +4.7, c = 5, ethanol).

Solubility—Very soluble in water, soluble in ethanol and acetonitrile, slightly soluble in octanol, and very slightly soluble in ethyl acetate.

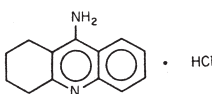
Comments—The precise mechanism of action of the drug is unknown. It is a reversible competitive inhibitor of acetylcholinesterase and enhances cholinergic function in the CNS. If this purported mechanism of action is correct the drug will be beneficial only while cholinergic neurons are still intact (ie, early stages of the disease). There is no evidence that the cholinomimetic agents alter the progression of the disease.

The drug is available as capsules containing rivastigmine tartrate equivalent to 1.5, 3.0, 4.5 and 6.0 mg and as an oral solution containing rivastigmine tartrate equivalent to 2.0 mg/mL of rivastigmine base for oral administration. The starting dose is 1.5 mg twice daily. The dose should be titrated up to the recommended dosage range (6–12 mg/day) based on how well it is tolerated. The drug should be taken with meals in the morning and evening. Dosage adjustments may not be necessary in patients with hepatic and renal impairment.

The most commonly observed adverse effects reported for the drug included nausea, vomiting, diarrhea, loss of appetite, dizziness and headache. The drug is contraindicated in patients with known hypersensitivity to rivastigmine, other carbamate derivatives or components of the formulation. The drug should be used with caution in patients with cardiovascular disease, gastrointestinal conditions, pulmonary disease (asthma, COPD) and in other disorders where cholinomimetic effects may lead to complications. Cholinomimetics may have the potential to cause generalized convulsions. However, seizures may be a result of the neurological disorder and not the drugs. Rivastigmine may interfere with the effects of antimuscarinic drugs or other cholinomimetics (synergy) when co-administered. (See the general statement for additional actions, adverse effects, and contraindications). The drug is metabolized primarily via cholinesterases. Based on in vitro and animal studies the CYP450 enzyme system is not a major route of metabolism and drug interactions related to the CYP450 enzymes have not been observed.

TACRINE HYDROCHLORIDE

Acridine, 9-amino-1,2,3,4-tetrahydro-, hydrochloride; Cognex



[1684-40-8] $C_{13}H_{14}N_2.HCl$ (234.73).

Preparation—By heating 9-chloro-1,2,3,4-tetrahydroacridine with ammonium carbonate in phenol at 130° followed by usual conversion to the hydrochloride. (See *J Soc Chem Ind* 1945; 64: 169.)

Description—Yellow needles melting about 284°; bitter taste; pH of 1.5% solution about 5.

Solubility—Soluble in water.

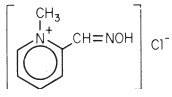
Comments—Tacrine or tetrahydroacridineamine (THA) possesses both an anticholinesterase action and an action to block potassium channels in cell membranes. The latter action causes prolonged action potentials, which, at cholinergic nerve endings, increase the release of acetylcholine. Thus, the two actions complement each other. Since the drug can penetrate the blood-brain barrier readily (in the nonionized form) and gain access to the CNS, it is of special interest as an anticholinesterase for actions in the CNS. The current focus is on its effects to improve learning, memory, and mood in patients with Alzheimer's type of senile dementia. AS with other agents used for Alzheimer's disease, the drug is only palliative and does not prevent the eventual degeneration of the affected nerve tracts. Typical muscarinic side effects occur in about 25–35% of recipients, but they are usually minimal and tolerated; they include belching, nausea, emesis, enuresis, abdominal discomfort, diarrhea, and sweating. Evidence of hepatic toxicity requires dosage reduction or discontinuation.

CHOLINESTERASE REACTIVATORS

Consumption of certain wild mushrooms, exposure to anticholinesterase insecticides, or exposure to organophosphate-like anticholinergics (chemical warfare agents) can result in acute cholinergic poisoning. This is a medical emergency that requires rapid treatment with appropriate supportive measures and anticholinergic medications. To ensure appropriate penetration into the CNS, tertiary amine-containing drugs (atropine) should be used to antagonize muscarinic effects. There is no effective way to antagonize the nicotinic effects of the drugs. However, there is class of compounds that can regenerate the active enzyme following exposure to the organophosphate-type inhibitors. As mentioned above, the phosphorylation of the enzyme active site by organophosphates is extremely stable to hydrolysis and may undergo additional reactions (aging) to further strengthen the bond. Several substances are capable of regenerating the active site by hydrolyzing the phosphorylated esteratic sites of cholinesterases poisoned by the drugs. The reactivators are site-directed nucleophiles designed with a cationic moiety to direct the molecule to the anioinic site of the enzyme. Once bound, the nucleophile (oxime) is in close proximity to the phosphorylated enzyme and a nucleophilic attach of the phosphorous by the oxime results. The oxime-phosphonate is split off to provide the free enzyme. Unfortunately, within a period of minutes to hours after poisoning with organophosphates, there is a change in the phosphorylated enzyme (*aging,* dealkylation of the alkyl phosphate moiety), so that the alkylphosphate-enzyme bond becomes too stable to be displaced by reactivators. The efficacy of reactivators may vary according to which organophosphate drug is involved because of the differences in electrophilicity of the phosphorus in the various phosphate radicals. Anticholinesterase agents have been reported that are refractory to displacement by cholinesterase reactivators. The CNS penetration of reactivators is a consideration in order to treat central effects of the drugs. Atropine also must be used concomitantly with reactivators for optimal therapy. The reactivators may be used prophylactically.

PRALIDOXIME CHLORIDE

Pyridinium, 2-[(hydroxyimino)methyl]-1-methyl-, chloride; 2-PAM Chloride; Protopam Chloride



2-Formyl-1-methylpyridinium chloride oxime [51-15-0] $C_7H_9ClN_2O$ (172.61).

Preparation—Picolinal is converted to its oxime, which is then quaternized with dimethyl sulfate. Metathesis of the resulting pralidoxime methosulfate with HCl yields the official chloride. US Pat 3,123,613.

Description—White to pale-yellow, crystalline powder; odorless; stable in air; melts between 215° and 225° with decomposition.

Solubility—Freely soluble in water.

Comments—A reactivator most effective in the regeneration of cholinesterase associated with neuromuscular junctions. The positively charged quaternary pyridine nitrogen prevents effective penetration into the CNS. The drug is used in the treatment of poisoning by organophosphate anticholinesterases; it has questionable value in poisoning by neostigmine or physostigmine. The therapeutic effect (remission) usually occurs within 1 hour. Pralidoxime also is given prophylactically to handlers of organophosphates and to those expected to come into contact with the organophosphate drugs used as chemical weapons. Pralidoxime does not enter the CNS and does not antagonize all anticholinesterase compounds; the manufacturer's package literature should be consulted to ascertain whether the drug will be effective. After a period of time, organophosphate-inhibited cholinesterase undergoes a change (aging) that makes reactivation difficult; with isoflurophate, this time is only about 1 hour. The plasma half-life of pralidoxime is about 2.5 hours. When pralidoxime is injected more rapidly than at the recommended rate, dizziness, nausea, headache, mild weakness, blurred vision, diplopia, or tachycardia may result.

CHAPTER 72

Adrenergic Antagonists and Adrenergic Neuron Blocking Drugs

The term *blockade* is used to indicate interference with a response system such that the final effect is prevented. Thus, *adrenergic blockade* indicates interference with response systems involving the catecholamine neurotransmitters, epinephrine (adrenaline), norepinephrine (noradrenaline, levarterenol), and dopamine. Adrenergic blocking agents can be classified into two categories: adrenergic receptor (adrenoceptor) antagonists and adrenergic neuron blocking drugs. Adrenergic receptor antagonists are compounds that are devoid of intrinsic activity *per se* and instead exert effects by inhibiting the interaction of catecholamines or sympathomimetic agents with adrenergic receptors. In contrast, the term *adrenergic neuron blocking drugs* generally refers to those drugs that reduce delivery of catecholamines to the adrenergic receptors by disrupting catecholamine synthesis, storage, or release. Adrenergic blocking agents sometimes are called sympatholytics, because they abolish *(lyse)* the response to stimulation of the sympathetic nerves, or adrenolytics, because they abolish certain responses to epinephrine.

ADRENERGIC ANTAGONISTS

Based on their pharmacological properties, adrenoreceptors have been divided into three classes: alpha (α), beta (β), and dopamine. Whereas drugs that block peripheral dopamine receptors are of no established clinical importance, those that block central dopamine receptors are important psychopharmacological agents and are discussed in Chapter 82.

The α and β adrenoreceptors have been defined classically into four subclasses: α_1, α_2, β_1, and β_2. The respective pharmacological effects of activating these receptor subclasses is described in Chapter 70. Nonselective and selective antagonists targeting these subclasses are of considerable therapeutic importance and are described below. Recently, molecular biological studies have further identified at least three α_1 (α_{1A}, α_{1B}, α_{1D}) and three α_2 (α_{2A}, α_{2B}, α_{2C}) subtypes with specific regional distributions in the body. Moreover, an additional β subclass, β_3, has been identified in mammalian tissue. Although a few selective antagonists have been identified, therapeutic utility for selectively targeting these newly described adrenergic subclasses has yet to be demonstrated clinically.

α-ADRENERGIC RECEPTOR ANTAGONISTS

α-Adrenergic antagonists can bind reversibly (eg, phentolamine, prazosin) or irreversibly (eg, phenoxybenzamine) to their receptors. Blockade of α_1-adrenoreceptors causes readily apparent effects, whereas blockade of α_2-receptors generally causes subtle effects. Blockade of α_1-adrenergic impulses to the arterioles decreases vascular resistance, thus tending to lower blood pressure and cause a pink, warm skin. α_1-Receptor blockade at the venules (capacitance vessels) increases venous capacitance and causes postural hypotension. These drugs decrease only that component of vascular resistance that is due to sympathetic activation.

Nonselective α-antagonists (eg, phentolamine, phenoxybenzamine) can cause palpitations and reflex tachycardia. These effects are partially attributable to activation of baroreflexes resulting from the hypotension produced by α_1-blockade. There also can be increased norepinephrine release from adrenergic nerve endings (transmitter *overflow*) as the result of concurrent block of α_2-adrenoreceptors, which subserve a negative- feedback function to decrease the release of transmitter. Consequently, tachycardia and palpitations may occur even when blood pressure falls very little. These reflex/overflow effects are counterproductive in the major uses of nonselective α-blocking drugs.

Other effects associated with α-receptor blockade include improved urine flow rates as a consequence of smooth muscle relaxation in the bladder neck and prostate. Miosis and nasal stuffiness also can occur after α-receptor antagonist administration.

Selective α_1-antagonists approved for use in the US include prazosin, terazosin, and doxazosin. Because these agents have little affinity for α_2-receptors, they do not increase catecholamine release and thereby do not cause excessive tachycardia. The most adverse side effect of α_1-blockade can be severe postural hypotension and syncope, especially early in treatment.

Selective α_2-antagonists include yohimbine and rauwolscine. Theoretically, such agents could be used to correct autonomic insufficiencies, since these agents increase norepinephrine release by blocking the inhibitory effects of norepinephrine at presynaptic α_2-receptors. Although there are presently no approved therapeutic indications for α_2-blockade, yohimbine has been used to treat diabetic neuropathy and impotence.

Some nonselective α-adrenoreceptor antagonists have been approved for use in the treatment of pheochromocytoma. The drugs may be used in advance of surgery to prevent hypertensive episodes caused by manipulation of the tumor or for the long-term treatment of an inoperable, metastatic pheochromocytoma. Other uses for nonselective α-antagonists have been reported, including treatment of:

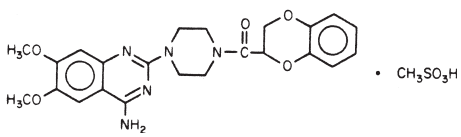
1. Peripheral vascular disorders in which there is an adrenergically mediated vasospastic component, such as Raynaud's syndrome and frostbite.
2. Micturition disorders resulting from neurogenic bladder.

Theoretically, selective α_1-receptor antagonists should be useful in treating many of the same disorders as are the nonselective α-blockers, but α_1-antagonists are currently approved only

for the treatment of hypertension and benign prostatic hyperplasia. However, these agents enjoy considerable use in the treatment of refractory heart failure and of vasospasm associated with Raynaud's disease.

DOXAZOSIN MESYLATE

Piperazine, 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-[(2,3-dihydro-1,4-benzodioxin-2-yl)carbonyl]-, monomethanesulfonate; Cardura



[77883-43-3] $C_{23}H_{25}N_5O_5 \cdot CH_4O_3S$ (547.58).

Preparation—See US Pat 4,188,390.

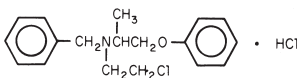
Description—Off-white powder; pK_a 6.93.

Solubility—Sparingly soluble in water and most common organic solvents.

Comments—A selective α_1-antagonist.

PHENOXYBENZAMINE HYDROCHLORIDE

Benzenemethanamine, *N*-(2-chloroethyl)-*N*-(1-methyl-2-phenoxyethyl)-, hydrochloride; Dibenzyline Hydrochloride



N-(2-Chloroethyl)-*N*-(1-methyl-2-phenoxyethyl)benzylamine hydrochloride [63-92-3] $C_{18}H_{22}ClNO \cdot HCl$ (340.29).

Preparation—One method starts with phenol undergoing addition to propylene oxide to give 1-phenoxy-2-propanol, which is reacted with thionyl chloride to yield 1-phenoxy-2-chloropropane. Refluxing the latter with excess ethanolamine gives *N*-(phenoxyisopropylamino) ethanol and additional refluxing of this with benzyl chloride in the presence of $NaHCO_3$ yields 2-[*N*-benzyl-*N*-(1-methyl-2-phenoxyethyl) amino]ethanol. Treatment with thionyl chloride and HCl in $CHCl_3$ completes the synthesis. US Pat 2,599,000.

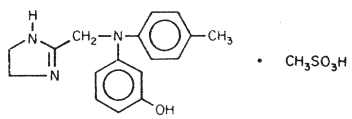
Description—White, crystalline, odorless powder; melts between 136° and 141°.

Solubility—1 g in 25 mL water, 6 mL alcohol, 3 mL chloroform or >1000 mL ether.

Comments—An irreversible antagonist with nonselective actions.

PHENTOLAMINE MESYLATE

Phenol, 3-[[(4,5-dihydro-1*H*-imidazol-2-yl)methyl](4-methylphenyl)-amino]-, monomethanesulfonate (salt); Regitine Mesylate



[65-28-1] $C_{17}H_{19}N_3O.CH_4O_3S$ (377.46)

Preparation—*m*-(*p*-Toluidino)phenol is refluxed with 2-chloromethylimidazoline hydrochloride and the resulting phentolamine base treated with an equimolar portion of methanesulfonic acid.

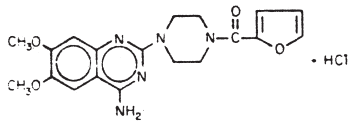
Description—White or off-white, odorless, crystalline powder; solutions are acid to litmus, having a pH of about 5, and deteriorate slowly; melts about 178°.

Solubility—1 g in 1 mL water, 4 mL alcohol or 700 mL chloroform.

Comments—Phentolamine is a nonselective α-adrenoreceptor antagonist with an immediate onset and short duration of action. In addition to α-blocking activity, it has weak muscarinic activity in the gastrointestinal (GI) tract and weak-to-mild histaminergic activity in the stomach. These effects limit the dose that can be used; hence, α-blockade is usually incomplete. Its pharmacological effects are described in the general statement. This drug is approved therapy for treating individuals with a pheochromocytoma and the treatment or prevention of dermal necrosis and sloughing resulting from extravasation or intravenous administration of norepinephrine. Additional uses include the management of hypertensive crises caused by drug interactions with monoamine oxidase inhibitors (MAOIs) or the abrupt withdrawal of clonidine. It is used as a diagnostic agent for pheochromocytoma, although determination of blood and/or urinary concentrations of catecholamines and/or their metabolites is a safer method. It has been combined with papaverine for intracavernous injection in impotence. The adverse effects are those of α-blockade (see the general statement), in addition to which there is weakness.

PRAZOSIN HYDROCHLORIDE

Piperazine, 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-(2-furanylcarbonyl)-, monohydrochloride; Minipress



1-(4-Amino-6,7-dimethoxy-2-quinazolinyl)-4-(2-furoyl)piperazine monohydrochloride [19237-84-4] $C_{19}H_{21}N_5O_4 \cdot HCl$ (419.87).

Preparation—4,5-Dimethoxyanthranilamide is treated with sodium cyanate to form the corresponding tetrahydroquinazoline-2,4-dione. The carbonyl groups are converted to chlorine and the heterocyclic ring aromatized using $POCl_3$ plus PCl_5. Subsequent treatment with ammonia replaces the chlorine atom adjacent to the benzenoid ring with an amino function, and the resulting monochloro derivative is condensed with 1-(2-furoyl)-piperazine to yield the product. See British Pat 1,156,973.

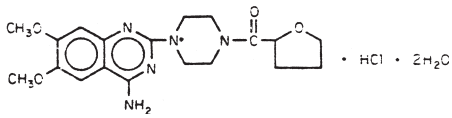
Description—White, crystalline powder; pK_a (in 1:1 water-ethanol solution) 6.5.

Solubility—Slightly soluble in water; very slightly soluble in alcohol.

Comments—A selective α_1-antagonist.

TERAZOSIN HYDROCHLORIDE

Piperazine, 1-(4-amino-6,7-dimethoxy-2-quinazolinyl-4-[(tetrahydro-2-furanyl)carbonyl], monohydrochloride, dihydrate; Hytrin



[70024-40-7] $C_{19}H_{25}N_5O_4 \cdot HCl \cdot 2H_2O$ (459.93)

Preparation—See *Prazosin Hydrochloride;* 1-(tetrahydrofuroyl) piperazine is condensed with the monochloroquinazoline.

Description—White crystalline powder.

Solubility—Freely soluble in water.

Comments—A selective α_1-antagonist.

β-ADRENERGIC RECEPTOR ANTAGONISTS

Most β-adrenergic receptor antagonists *(β-blockers)* reversibly and competitively inhibit the binding of norepinephrine to its receptors. Although most are pure antagonists, a few clinically relevant β-blockers have partial agonist activity. β-Blockers can be distinguished by several factors including relative affinity for the various β-receptor subtypes, duration of effect, local anesthetic activity, and lipid solubility.

Blockade of myocardial β_1-receptors causes bradycardia, suppression of some ectopic pacemakers, decreased force of myocardial contraction, and slowing of atrioventricular conduction. Impaired exercise tolerance can result. β-Blockers can decrease myocardial oxygen demand by preventing catecholamine-induced increases in heart rate and contractility. However, these agents can also increase myocardial oxygen demand by increasing end-diastolic pressure and the duration of systolic injection. Still, the net effect of β-receptor blockade on oxygen demand is usually advantageous. β-blockers are of value in the treatment of angina pectoris.

β-Antagonists are used for the management of both supraventricular and ventricular arrhythmias. These drugs also can be used to suppress tachycardia in thyrotoxicosis and

pheochromocytoma. Many β-blockers act as sodium channel blockers and thereby as local anesthetics. This membrane-stabilizing activity was once considered to be responsible for the antiarrhythmic action of these agents, although it is now recognized that this effect is likely of little consequence, since the dose of β-blockers employed in treatment of arrhythmias is generally too low to exert this effect.

β-Antagonists are used in the treatment of essential hypertension. Although the precise mechanism for this effect has not been determined, it has been suggested that β-blockers decrease blood pressure by (1) a direct effect on the heart and blood vessels, (2) decreasing sympathetic outflow from the central nervous system (CNS), and/or (3) affecting the renin- angiotensin-aldosterone system. Although many β-blockers increase peripheral resistance acutely (probably by opposing β_2-mediated vasodilation), chronic therapy can result in a decreased peripheral resistance that contributes to the long-term hypotensive effects of the drug. β-Antagonists are especially useful in combination with antihypertensive vasodilators (ie, hydralazine, minoxidil) to prevent reflex tachycardia.

The rate of formation of intraocular fluid is decreased by β-antagonists; this effect is useful in the treatment of glaucoma. β-Blockers with significant local anesthetic activity generally are not used for this purpose, so as to prevent local anesthesia of the cornea. Betaxolol, carteolol, levobunalol, metipranolol, and timolol are applied topically in this disorder.

β-Antagonists have varied usefulness in the prophylaxis of migraine headache, diminishing pain in many instances but increasing it in others. Propranolol and timolol are approved for migraine treatment. The mechanism of action is presently unknown.

In the treatment of certain kinds of anxiety, such as stage fright and examination apprehension, β-antagonists are frequently effective. The efficacy is likely attributable to the prevention of the peripheral manifestations of sympathoadrenal discharge (ie, of tachycardia, palpitations, or muscle tremor) rather than to a central action. Their value in the treatment of pathological anxiety disorders is controversial, as they appear to have little effect on the underlying disorder.

Selective β_1-antagonists theoretically can be used for all the purposes listed under the nonselective blockers, although they have not been approved universally for these uses.

Not all β-antagonists penetrate into the CNS, nor do these drugs have similar CNS effects. Some, for example, block certain serotonin receptor subtypes. Central actions explain the increase in sleep disturbances, dizziness, and ataxia that can result from β-blocker administration. Drowsiness, lassitude, headache, vertigo, visual disturbances, depression, hallucinations, and mental confusion may also result from β-blocker administration. Tolerance to these effects is frequent. β-Blockers that are highly lipid soluble are more likely to penetrate the CNS.

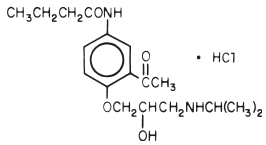
Antagonism of β-receptors in the bronchioles causes an increase in airway resistance. This can cause bronchospasm in bronchial asthma, bronchitis, emphysema, and chronic obstructive pulmonary disease. Laryngospasm also may occur. In insulin overdosage, β_2-blockade may prevent the mobilization of glucose from the liver to offset hypoglycemia; furthermore, the prevention of reflex tachycardia deprives the patient of an early warning signal of impending insulin shock. β-Blockers can inhibit the lipolysis resulting from sympathetic nervous stimulation.

Other adverse effects of β-blockade include loss of libido in both men and women, impotence, increased very low-density and decreased high-density lipoproteins, occasional nausea and vomiting, mild diarrhea or constipation, and rare allergic responses, such as rashes, fever, and purpura.

Some β-antagonists also stimulate β-adrenoreceptors (ie, have intrinsic sympathomimetic activity, or ISA). For instance, carteolol and pindolol have appreciable partial agonist properties. Some authorities believe that partial agonist activity offers no advantage over full antagonist activity. Others contend that partial agonist properties may be advantageous in patients prone to bradycardia.

ACEBUTOLOL HYDROCHLORIDE

Butaneamide, (±)-*N*-3-acetyl-4-[2-hydroxy-3-[(1-methylethyl)-amino[propoxy] phenyl-, hydrochloride; Sectral



(±)-3′-acetyl-4′[2-hydroxy-3-(isopropylamino)propoxy]butyranilide hydrochloride [34381-68-5] $C_{18}H_{28}N_2O_4 \cdot HCl$ (372.93)

Preparation—S Afr Pat 68 08,345.

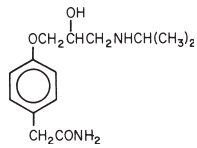
Description—White to slightly off-white powder melting about 142°.

Solubility—Freely soluble in water; partially soluble in alcohol.

Comments—A β_1-selective drug with low lipid solubility.

ATENOLOL

Benzeneacetamide, 4-[2-hydroxy-3-[(1-methylethyl) amino]propoxy]-; Tenormin



2-[*p*-[2-Hydroxy-3-(isopropylamino)propoxy]phenyl]acetamide [29122-68-7] $C_{14}H_{22}N_2O_3$ (266.34)

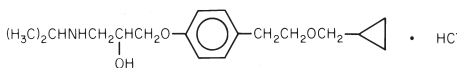
Preparation—From *p*-hydroxyphenylacetamide, ethylene chlorohydrin and isopropylamine (US Pat 3,836,671).

Description—White crystals melting about 147°.

Comments—A β_1-selective drug with low lipid solubility.

BETAXOLOL HYDROCHLORIDE

2-Propanol, 1-[4-[2-(cyclopropylmethoxy)-ethyl]phenoxy]-3-[(1-methylethyl)amino]-, hydrochloride; Betoptic; Kerlone



[63659-19-8] $C_{18}H_{29}NO_3 \cdot HCl$ (343.89)

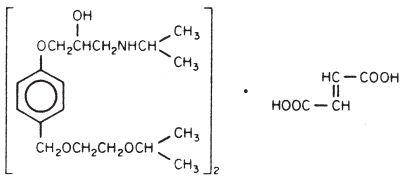
Preparation—The methyl ester of 2-(cyclopropylmethoxy)ethanesulfonic acid and *p*-benzyloxyphenol react to form 2-(cyclopropylmethoxy)ethoxyphenyl benzyl ether, which is debenzylated to yield the free phenol, treated with epichlorhydrin to form the glycidyl ether, followed by ring opening with isopropylamine to yield the product as the base. Treatment of the base in dry ether with HCl forms the salt. US Pat 4,252,984; *Chem Abstr* 87:13454.

Description—Crystals melting about 116°.

Comments—A β_1-selective drug with low lipid solubility. It is used to treat open-angle glaucoma.

BISOPROLOL FUMARATE

2-Propanol, (±)-1-[4-[[2-(1-methylethoxy)ethoxy]methyl]phenoxy]-3-[(1-methylethyl)amino]-, *(E)*-2-butenedioate (2:1) (salt); Zebeta



[104344-23-2] $(C_{18}H_{31}NO_4)_2 \cdot C_4H_4O_2$ (766.97).

Preparation—Cyclization of 1-(isopropylamino)-3-phenoxy-2-propanol with $COCl_2$ forms a cyclic carbamate. Treatment with paraformaldehyde and HCl yields the *p*-chloromethyl derivative, which undergoes an S_N reaction with 2-isopropoxyethanol to form the ether.

Aqueous base opens the protective carbamate ring, yielding the product. See US Pat 4,258,062.

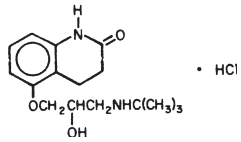
Description—White crystals melting about 100°; pK_a (amine) 4.8.

Solubility—Very soluble in water; 1 g dissolves in 20 mL of alcohol.

Comments—A β_1-selective drug with low lipid solubility.

CARTEOLOL HYDROCHLORIDE

2(1*H*)-Quinolinone, 5-[3-[(1,1-dimethyl-ethyl)amino]-2-hydroxypropoxy]-3,4-dihydro-, monohydrochloride; Cartrol; Ocupress



[51781-21-6] $C_{16}H_{24}N_2O_3 \cdot HCl$ (328.84)

Preparation—It is synthesized from 3,4-dihydro-5-hydroxycarbostyril and epichlorhydrin to afford the 2,3-epoxypropyl ether. Opening the epoxide with *t*-butylamine yields the base, which is converted to the hydrochloride. See *J Med Chem* 1974; 17:529.

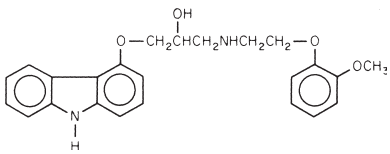
Description—White crystals melting about 278°.

Solubility—Soluble in water; slightly soluble in alcohol.

Comments—A nonselective drug with low lipid solubility. It is used to treat open-angle glaucoma.

CARVEDILOL

2-Propanol, (±)-1-(9*H*-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl]-amino]-, Coreg



[72956-09-3] $C_{24}H_{26}O_4$ (406.48).

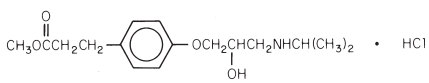
Preparation—By condensation of 4-(2,3-epoxy-1-propyl)carbazole with 2-(2-methoxyphenoxy)ethyl amine. See US 4,503,067 (1985).

Description—Colorless crystals melting about 115°.

Comments—Has both nonselective β-antagonist and α-antagonist activity.

ESMOLOL HYDROCHLORIDE

Benzenepropanoic acid, (±)-4-[2-hydroxy-3-[(1-methylethyl)-amino]propoxy]-, methyl ester, hydrochloride; Brevibloc



[84057-94-3] $C_{16}H_{25}NO_4 \cdot HCl$ (331.84)

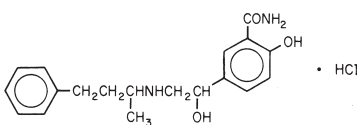
Preparation—*J Med Chem* 1982; 25: 1408.

Description—White crystals melting about 85°.

Comments—A β_1-selective drug with low lipid solubility. It has an ultrashort duration of action.

LABETALOL HYDROCHLORIDE

Benzamide, 2-hydroxy-5-[1-hydroxy-2-[(1-methyl-3-phenylpropyl)amino]ethyl]-, monohydrochloride; Normodyne; Trandate



5-[1-hydroxy-2-[(1-methyl-3-phenylpropyl)amino]ethyl]salicylamide monohydrochloride [32780-64-6] $C_{19}H_{24}N_2O_3 \cdot HCl$ (364.87).

Preparation—US Pat 4,012,444.

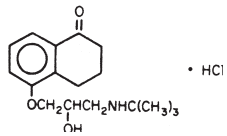
Description—White crystals.

Solubility—Soluble in water or ethanol; insoluble in ether or chloroform.

Comments—Has both nonselective β and selective α_1-antagonist activity.

LEVOBUNOLOL HYDROCHLORIDE

1(2*H*)-Naphthalenone, (−)-5-[3-[(1,1-dimethylethyl)-amino]-2-hydroxypropoxy]-3,4-dihydro-, hydrochloride; Betagan Liquifilm



[27912-14-7] $C_{17}H_{25}NO_3 \cdot HCl$ (327.85)

Preparation—See *J Med Chem* 1970; 13:684.

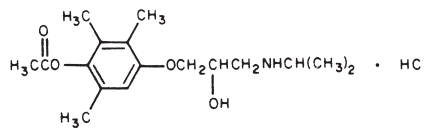
Description—White crystals melting about 210°.

Solubility—Soluble in water; slightly soluble in alcohol.

Comments—A nonselective drug used for open-angle glaucoma.

METIPRANOLOL HYDROCHLORIDE

Phenol, (±)-4-[2-hydroxy-3-[(1-methylethyl)amino]propoxy]-2,3,6-trimethyl-, 1-acetate, hydrochloride; MPR; OptiPranolol



[22664-55-7(base)] $C_{17}H_{27}NO_4$ (345.86).

Preparation—Czech Pat 128,471.

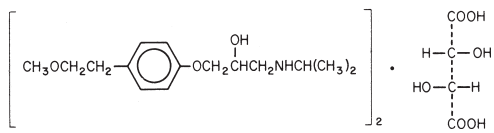
Description—White crystals melting about 106°.

Solubility—Slightly soluble in water.

Comments—A nonselective drug used for open-angle glaucoma.

METOPROLOL TARTRATE

2-Propanol, (±)-1-[4-(2-methoxyethyl)phenoxy]-3-[(1-methylethyl) amino]-, [*R*[(*R,*R**)]-2,3-dihydroxybutanedioate (2:1) (salt); Lopressor; Toprol XL**



(±)-1-(Isopropylamino)-3-[*p*-(2-methoxyethyl)phenoxy]-2-propanol L-(±)-tartrate (2:1) (salt) [56392-17-7] $(C_{15}H_{25}NO_3)_2 \cdot C_4H_4O_6$ (684.82).

Preparation—From 4-(2-methoxyethyl)phenol, 3-chloro-1,2-propanediol and isopropylamine (Swedish Pat 368,004).

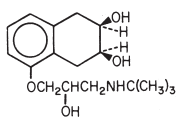
Description—White, odorless powder; bitter taste; melts about 120°.

Solubility—Very soluble in water; soluble in alcohol or chloroform; insoluble in acetone or ether.

Comments—A β_1-selective drug with moderate lipid solubility.

NADOLOL

2,3-Naphthalenediol, *cis*-5-[3-[(1,1-dimethylethyl)amino]-2-hydroxypropoxy]-1,2,3,4-tetrahydro-, Corgard



1-(*tert*-Butylamino)-3-[(5,6,7,8-tetrahydro-*cis*-6,7-dihydroxy-1-naphthyl)oxy]-2-propanol [42200-33-9] $C_{17}H_{27}O_4$ (309.40).

Preparation—US Pat 3,935,267.

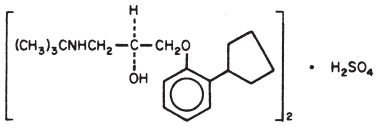
Description—White crystalline powder melting about 130°; pK_a 9.68.

Solubility—Freely soluble in alcohol; slightly soluble in water or chloroform; insoluble in acetone or hydrocarbon solvents.

Comments—A nonselective drug with low lipid solubility.

PENBUTOLOL SULFATE

2-Propanol, (*S*)-1-(2-cyclopentylphenoxy)-3-[(1,1-dimethylethyl)amino]-, sulfate (2:1) (salt); Levatol



[38363-32-5] $C_{18}H_{29}NO_2)_2 \cdot H_2SO_4$ (680.94).

Preparation—See US Pat 3,551,493.

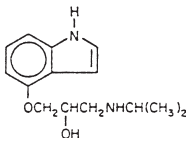
Description—White crystals melting about 217°.

Solubility—Soluble in water; slightly soluble in alcohol.

Comments—A nonselective drug with high lipid solubility. It has some agonist activity.

PINDOLOL

2-Propanol, 1-(1*H*-indol-4-yloxy)-3-[(1-methyl-ethyl)amino]-, Visken



[13523-86-9] $C_{14}H_{20}N_2O$ (248.32).

Preparation—Swiss Pat 472,404.

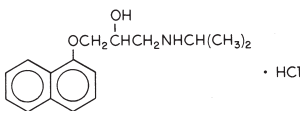
Description—Off-white, crystalline powder; almost odorless; melts about 172°.

Solubility—Practically insoluble in water; slightly soluble in anhydrous alcohol or chloroform.

Comments—A nonselective drug with moderate lipid solubility. It has partial agonist activity.

PROPRANOLOL HYDROCHLORIDE

2-Propanol, 1-[(1-methylethyl)amino]-3-(1-naphthalenyloxy)-, hydrochloride; Inderal



[318-98-9] $C_{16}H_{21}NO_2 \cdot HCl$ (295.81).

Preparation—α-Naphthol is reacted with epichlorohydrin in aqueous alkali to form 2,3-epoxypropyl α-naphthyl ether, and the epoxy ring is ruptured by reaction with isopropylamine. The base is converted to hydrochloride with HCl.

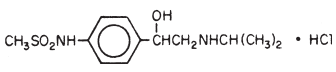
Description—White or almost white powder that is odorless, with a bitter taste; stable to heat, unstable in light, and nonhygroscopic; melts about 161°; pK_a 9.45.

Solubility—1 g in 20 mL water or 20 mL alcohol; slightly soluble in chloroform; practically insoluble in ether.

Comments—The prototype nonselective β-antagonist, with all the actions, uses, adverse effects, and contraindications characteristic of this class of drugs (see general statement), except that it is not used to treat glaucoma. The drug penetrates into the CNS and causes the central effects in the general statement. It has been reported to be of value in more than 20 noncardiovascular disorders, many of which are associated with the CNS. Its elimination $t_{1/2}$ is 4 to 6 hr.

SOTALOL HYDROCHLORIDE

Methanesulfonamide, *N*-[4-[1-hydroxy-2-[(1-methylethyl)-amino]ethyl]phenyl]-, monohydrochloride; Betapace



[959-24-0] $C_{12}H_{20}N_2O_3S \cdot HCl$ (308.82).

Preparation—One method involves the reaction of methanesulfonyl chloride with *p*-aminoacetophenone to form the sulfonamide, which is then brominated by a free radical procedure to yield the phenacyl bromide. A nucleophilic substitution of bromine by isopropyl amine affords the base which is converted to the salt. See *J Med Chem* 1967; 10:462.

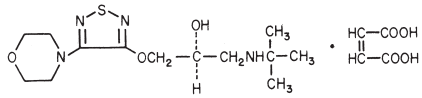
Description—White crystals melting about 207°; pK_1 8.3, pK_2 9.8.

Solubility—Freely soluble in water; insoluble in alcohol.

Comments—A nonselective drug with low lipid solubility.

TIMOLOL MALEATE

2-Propanol, 1-[(1,1-dimethylethyl)amino]-3-[[4-(4-morpholinyl-1,2,5-thiadiazol-3-yl]oxy]-(*S*)-, (*Z*)-2-butenedioate (1:1) (salt); Blocadren, Timoptic



(−)-1-(*tert*-Butylamino)-3-[(4-morpholino-1,2,5-thiadiazol-3-yl)oxy]-2-propanol maleate (1:1) (salt) [26921-17-5] $C_{13}H_{24}N_4O_4 \cdot S \cdot C_4H_4O_4$ (432.49).

Preparation—*J Med Chem* 1972; 15:651.

Description—White crystals melting about 202°; pH (5% aqueous solution) about 4; stable in aqueous solution up to about pH 12.

Solubility—Freely soluble in water; soluble in alcohol; sparingly soluble in chloroform; practically insoluble in ether.

Comments—A nonselective drug with moderate lipid solubility. It is used for open-angle glaucoma.

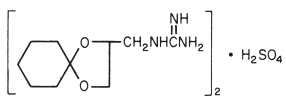
ADRENERGIC NEURON BLOCKING DRUGS

The adrenergic neurotransmitter, norepinephrine, is synthesized in sympathetic adrenergic neurons. 3,4-Dihydroxyphenylalanine (DOPA), which is formed in the adrenergic neuron by the hydroxylation of tyrosine, is decarboxylated (by aromatic amino acid decarboxylase) to produce the catecholamine dopamine (3,4-dihydroxyphenylethylamine). Within the adrenergic neuron in the region of the nerve endings are granular organelles that contain the enzyme dopamine β-hydroxylase, which introduces the side-chain hydroxyl group onto dopamine to form norepinephrine. Norepinephrine is stored in the granular organelles. Nerve impulses cause the influx of calcium, which releases norepinephrine from the storage granules.

Adrenergic neuron blocking drugs reduce the delivery of catecholamines (eg, norepinephrine) to adrenergic receptors. As noted above, this can occur by disrupting catecholamine synthesis, storage, or release. The pharmacology of some such agents is described below.

GUANADREL SULFATE

Guanidine, (1,4-dioxaspiro[4.5]dec-2-ylmethyl)-, sulfate (2:1); Hylorel



[22195-34-2] $(C_{10}H_{19}N_3O_2)_2 \cdot H_2SO_4$ (524.63).

Preparation—US Pat 3,547,951.

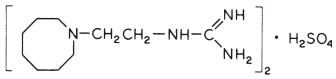
Description—White solid melting about 235° with decomposition.

Solubility—1 g dissolves in about 13.5 mL water.

Comments—An adrenergic neuron blocking drug with a mechanism of action and hemodynamic properties like those of guanethidine, to which it is related chemically. Guanadrel inhibits vasoconstriction by inhibiting norepinephrine release in response to sympathetic nerve stimulation. The resulting antihypertensive effect is greater when standing than in the supine position. Orthostatic hypotension occurs frequently. Unlike guanethidine, it is used in the treatment of mild and moderate essential hypertension. Tricyclic antidepressants and other drugs that inhibit the amine reuptake into the adrenergic neurons prevent neuronal uptake of guanadrel and hence attenuate its effects. Frequent side effects include palpitations, shortness of breath, coughing, fatigue, headache, drowsiness, GI disturbances (diarrhea or constipation), edema, and excessive weight gain/loss.

GUANETHIDINE MONOSULFATE

Guanidine, [2-(hexahydro-1(2*H*)-azocinyl)ethyl-, sulfate (2:1); Ismelin Sulfate



[60-02-6] $(C_{10}H_{22}N_4)_2 \cdot H_2SO_4$ (494.69)

Preparation—Cycloheptanone oxime undergoes Beckmann rearrangement to form hexahydro-2(1*H*)-azocinone,—$CH_2(CH_2)_5$ CO—NHl, which is then reduced to heptamethyleneimine [—$CH_2(CH_2)_6$—NH]. This is condensed with chloracetonitrile, and the resulting nitrile is hydrogenated to 1-(2-aminoethyl)-heptamethyleneimine. Condensation with 2-methyl-2-thiopseudourea [NH═ $C(SCH_3)NH_2$] sulfate eliminates CH_3SH to produce crude guanethidine sulfate. See *Experientia* 1959; 15:267.

Description—White to off-white, crystalline powder.

Solubility—Sparingly soluble in water; slightly soluble in alcohol; practically insoluble in chloroform.

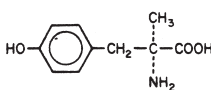
Comments—It is taken up into into noradrenergic nerve terminals via the same transporter responsible for uptake of the transmitter. Once inside, the drug is transported into, and concentrated within, vesicles, wherein it replaces norepinephrine. By replacing norepinephrine, guanethidine causes a gradual depletion of the catecholamine from the nerve terminal. Its onset of action is slow, requiring several hours to 2 or 3 days for its full effect, and its duration of action may be 4 or more days.

Guanethidine causes vasodilation and increases venous capacitance. The drug lowers blood pressure very effectively, especially when an individual is standing or exercising. Since blood pressure can fall to dangerously low levels in some patients, the drug usually is employed in submaximal doses and is combined with thiazides or hydralazine, to permit some adrenergic function. It usually is not employed to treat mild to moderate hypertension, only moderately severe to severe hypertension.

The most common untoward effects of guanethidine are those that obligatorily accrue because of the effects of sympathetic blockade. They include orthostatic hypotension with its attendant vertigo, weakness, lassitude, nausea and occasional syncope, bradycardia, dry mouth, diarrhea, urinary incontinence, and nocturia. Tricyclic antidepressants and other drugs that inhibit the amine reuptake into the adrenergic neurons prevent neuronal uptake of guanethidine and hence attenuate its effects. Guanethidine potentiates the pressor effects of norepinephrine and certain other directly acting α sympathomimetics by inhibiting uptake into the adrenergic nerve terminals and by causing supersensitivity of receptors. It also may cause release of catecholamines from pheochromocytomas and hence precipitate hypertensive crises. The drug is contraindicated in pheochromocytoma, in patients hypersensitive to the drug, and when MAOIs are in use.

METYROSINE

L-Tyrosine, (−)-α-methyl-, Demser



[672-87-7] $C_{10}H_{13}NO_3$ (195.22).

Preparation—*J Org Chem* 1967; 32:4074.

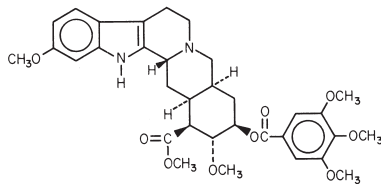
Description—White, crystalline solid; melts about 310°.

Solubility—About 1 g in 1750 mL water.

Comments—Metyrosine inhibits the activity of the catecholaminergic neurons since it blocks tyrosine hydroxylase and thus suppresses the synthesis of catecholamines. This causes depletion of catecholamines in adrenergic neurons in both the sympathetic and central nervous systems and in the pheochrome cells in the adrenal medulla and accessory tissue. The drug is used to treat pheochromocytoma. Sedation is the most common side effect, but some tolerance occurs during the first week of treatment. Extrapyramidal dyskinesias occur in about 10% of recipients. Other adverse CNS effects include anxiety, confusion, depression, disorientation and hallucinations. GI side effects include diarrhea, nausea, vomiting, and abdominal pain. Other adverse effects are nasal stuffiness, impotence, dry mouth, headache, gynecomastia, galactorrhea, peripheral edema, urticaria, and eosinophilia. Metyrosine potentiates the extrapyramidal effects of phenothiazines and butyrophenones.

RESERPINE

Yohimban-16-carboxylic acid, (3β,16β,17α,18β,20α)-11,17-dimethoxy-18-[(3,4,5-trimethoxybenzoyl)oxy]-, methyl ester



[50-55-5] $C_{33}H_{40}N_2O_9$ (608.69)

Reserpine, one of more than 20 alkaloids in *Rauwolfia serpentina,* was first isolated in pure crystalline form by Müller *et al,* (*Experientia* 1952; 8: 338). Subsequently it was found also in other species of *Rauwolfia.* A procedure for its separation is described in US Pat 2,833,771 (1958). Although it has been synthesized (Woodward *et al, J Am Chem Soc* 1956; 78:2023), its production by this route is not economically feasible.

Description—White or pale-buff to slightly yellowish, odorless, crystalline powder; darkens slowly on exposure to light, but more rapidly when in solution; melts between 255° and 265° with decomposition.

Solubility—Insoluble in water; very slightly soluble in ether; 1 g in about 1800 mL alcohol or about 6 mL chloroform; slightly soluble in benzene; freely soluble in acetic acid.

Comments—Reserpine is an alkaloid derived from the roots of *Rauwolfia serpentina*. It acts to inhibit both neuronal and chromaffin granule transporters. As a consequence, catecholamine accumulation is blocked. Depletion is slower and less complete in the adrenal medulla than in other tissues. By preventing such storage, reserpine initially causes catecholamine release. This is followed by a profound depletion of transmitter that can persist for days to weeks. The effects of reserpine appear to be irreversible.

Reserpine was the first rauwolfia alkaloid to be recognized officially. It was used first for the symptomatic management of patients with anxiety or tension psychoneuroses or chronic psychoses involving anxiety, psychomotor hyperactivity, or compulsive aggressive behavior. It is a sedative and may cause mental depression. Extreme caution must be exercised when administering reserpine to patients with a history of depression, since reserpine can unmask or worsen this condition.

Because of the seriousness of side effects, reserpine is rarely used as an antianxiety or antipsychotic drug. Instead, reserpine is used in antihypertensive therapy. By depleting peripheral amines, reserpine lowers blood pressure. Central actions may also contribute to this antihypertensive effect. The drug is used chiefly in combination with thiazide diuretics for the management of mild-to-moderate essential hypertension.

Nasal congestion, scleroconjunctival congestion, drowsiness, bradycardia, nausea, vomiting, anorexia, weight gain, and diarrhea are frequently noted side effects. Dry mouth, headache, dizziness, dysuria, myalgia, and dull sensorium can also occur. Suicidal depression is the most serious untoward effect. Other serious reactions are orthostatic hypotension, fatigue, weakness, insomnia, nightmares, excitement, paradoxical anxiety, parkinsonian-like rigidity, glaucoma, angina-like symptoms, deafness, pruritus, rash, purpura, and optic atrophy.

The drug is absorbed poorly and erratically from the GI tract, which causes considerable differences in efficacy of oral doses. It characteristically has a long latency of onset and a prolonged duration of action. For example, with daily oral administration the effects of the drug usually are not fully manifest for several days to 2 weeks and may persist for as long as 4 weeks after oral medication is discontinued. Tolerance to the drug does not develop with continued administration.

ACKNOWLEDGMENTS—Annette E Fleckenstein, PhD is acknowledged for her efforts in previous editions of this work.

CHAPTER 73

Antimuscarinic and Antispasmodic Drugs

Daniel J Canney, PhD

The preferential binding of the alkaloids nicotine and muscarine to cholinergic receptors has been used to classify them as nicotinic and muscarinic receptors, respectively. Further subtypes of muscarinic and nicotinic receptors have been identified in both the peripheral (PNS) and central nervous systems (CNS). Acetylcholine binds nonselectively to each of these widely distributed receptors to elicit a large range of pharmacological actions. Anticholinergic drugs or *cholinergic blocking drugs* may antagonize the effects of ACh at cholinergic receptors in ganglia, neuromuscular junctions, in the central nervous system or in parasympathetic neuroeffectors. By contrast, antimuscarinic drug actions are limited to antagonist effects at the parasympathetic neuroeffectors and certain central synapses innervated via muscarinic receptors. With the exception of certain quaternary ammonium antimuscarinics, these agents have little effect on nicotinic receptors. The quarternary ammonium-containing antimuscarinics have greater affinity for nicotinic receptors than other drugs in the class and may cause neuromuscular paralysis and/or ganglionic blockade even at therapeutic doses. In general, it is important to remember that the selectivity of drugs for a particular receptor subtype is highly dependent on the concentration (dose). Thus, at autonomic ganglia where ACh acts primarily at nicotinic receptors, antimuscarinic drugs may produce blockade at high doses. In the neuromuscular junction where receptors are almost exclusively nicotinic, antimuscarinic drugs may have slight effects at exceedingly high doses. Drugs that effectively target a specific subtype(s) of muscarinic or nicotinic receptor may provide therapeutic agents that lack the side effect profiles of nonselective drugs.

Atropine, the prototypic antimuscarinic agent, is an alkaloid isolated from the dried leaf and flowering or fruiting top of *Atropa belladonna* Linné. *Antimuscarinic* drugs are competitive antagonists that act on the cholinergic receptors at smooth muscle, secretory cells and certain central synapses. Other synonyms for the term antimuscarinic are *anticholinergic, cholinolytic, parasympatholytic,* and *parasympathetic blocking drugs*. Antagonist drugs that specifically target nicotinic receptors will be handled in the chapter on skeletal muscle relaxants.

ACTIONS AND SELECTIVITY—The effects of antimuscarinic drugs on the whole are predicted readily by considering the consequences of interruption of parasympathetic (and sympathetic cholinergic) nerve stimulation. Thus, the effects are decreased gastrointestinal (GI) motility, decreased gastric secretion, dry mouth, drying of the mucous membranes in general, mydriasis, loss of accommodation (with consequent tendency to increased intraocular pressure), urinary retention, decreased sweating and compensatory cutaneous flush, bronchial and biliary dilation, tachycardia (although effective block of the cardiac inhibitory nerves is difficult to achieve), etc. Some antimuscarinics have important actions in the CNS and are used in the treatment of Parkinson's disease (see below).

Current evidence suggests that there are at least five subtypes of muscarinic receptors that differ in their distribution and function. For example, the M1 subtype is distributed in the CNS, sympathetic postganglionic cell bodies, and at various presynaptic sites. The M2 receptors are found in smooth muscle organs, and the myocardium, and in the CNS while M3 are most commonly found on effector cell membranes of glandular and smooth muscle. Structure-activity relationship (SAR) studies indicate that each subtype differs in its structural requirements for blockage. Hence, subtype-selective muscarinic antagonists may provide therapeutic agents with more favorable side effect profiles than nonselective drugs.

Atropine is the prototypic antimuscarinic drug that guided early attempts to design additional drugs in the class. A close inspection of the molecule reveals a similarity to ACh that results in recognition and nonselective binding to muscarinic receptors. There are considerable differences in the effects elicited by currently available antimuscarinic drugs. These differences may be attributed to varying pharmacokinetic profiles (absorption, distribution, metabolism, excretion) and/or pharmacodynamic profiles (degree of receptor subtype selectivity). For example, scopolamine has excellent mydriatic and cycloplegic activity yet cannot block cardiac vagal activity in nontoxic doses, whereas its derivative methscopolamine is the most efficacious drug for the antagonism of vagally mediated cardiac effects. SAR studies indicate that numerous structural characteristics and functional groups may contribute to the different pharmacological and therapeutic profiles of the antimuscarinic drugs. One moiety of particular importance appears to be the amine group within the molecules. Hence drug with quaternary ammonium groups differ in important ways from the corresponding tertiary or secondary amine-containing drugs.

SOME DIFFERENCES BETWEEN QUATERNARY AND TERTIARY AMINE-CONTAINING ANTIMUSCARINICS—Quaternary ammonium groups in drug molecules carry a positive charge that makes the drug highly ionized. In general, these charged molecules do not penetrate cell membranes or the blood-brain barrier (BBB) very effectively. These properties result in erratic absorption from the GI and little to no CNS penetration. Similarly, the quaternary ammonium compounds poorly penetrate into the eye from the bloodstream or cornea and are less likely than the tertiary amines to cause mydriasis and cycloplegia. The quaternary compounds have a greater affinity for nicotinic receptors, so that some degree of ganglionic blockade may result from therapeutic doses of some quaternary ammonium antimuscarinic drugs. Some analogs also have a potential for neuromuscular paralysis, especially in drug interactions in persons with myasthenia gravis or when taken in toxic doses. The quaternary ammonium group seems to confer various degrees of selectivity for gastric secretory and, perhaps, other GI functions. The extent

to which ganglionic blockade may be involved is not known. The quaternary ammonium-containing drugs tend to be excreted unchanged in the urine. In contrast, the tertiary (and secondary) amine containing antimuscarinic drugs are reversibly protonated at physiological pH and consequently can penetrate cell membranes and the BBB in the non-ionized form. Most topical mydriatic antimuscarinic drugs are tertiary amines. These drugs are may be useful for the treatment of CNS disorders and lead to CNS toxicities also. Lastly, the tertiary amine containing antimuscarinic drugs tend to undergo significant metabolic biotransformation in the liver.

USES—In gastroenterology, antimuscarinic drugs are used sometimes for their GI effects, although parasympathetic effects in the bowel are difficult to suppress completely (Table 73-1). In the *irritable colon syndrome* (spastic colon) they may provide some relief initially, but some refractoriness usually develops later. *Functional GI disorders (functional diarrhea, spastic constipation, cardiospasm, pylorospasm, neurogenic colon, general hypermotility)* may respond, as may mild-to-moderate, irritative or infectious disorders, such as *mild diarrhea;* however, severe infectious dysenteries, regional enteritis, and ulcerative colitis do not. *Acute enterocolitis, mucous colitis,* and *the splenic flexure syndrome* may respond erratically. *Diverticulitis* sometimes may be improved. Antimuscarinic drugs may be used in combination with meperidine in the relief of *biliary dyskinesia*. In these uses, belladonna alkaloids commonly are employed; although they are less expensive than nonsolanaceous antimuscarinic drugs, they also cause more intense side effects than many synthetic, especially quaternary ammonium, drugs (Table 73-2). Atropine is available in combination with diphenoxylate, a non-analgesic analog of meperidine, for the treatment of mild GI hypermotility (eg, traveler's diarrhea). Several antimuscarinic drugs are available for GI use in combination with barbiturates, benzodiazepines, and ergotamine. The therapeutic effectiveness of these combinations is questionable.

The levorotatory alkaloids of belladonna, homatropine hydrobromide, and hyoscyamine sulfate are of historical importance in the treatment of peptic ulcer disease. These agents were used extensively in spite of the fact that doses required to produce modest reduction of *gastric acid secretion* also produced significant, often intolerable, side effects. *Pirenzepine* (Gaotrozepine, *Boehringer Ingelheim)* is an M_1 selective antimuscarinic drug that effectively reduces acid secretion and promotes ulcer healing with a low incidence of antimuscarinic side effects. Although available in many countries, it is not yet approved in the United States. The introduction of several highly effective, well tolerated classes of drugs (H_2 antagonists (eg, cimetidine) and the proton pump inhibitors (eg, *omeprazole*) led to the replacement of the antimuscarinic drugs in the treatment of peptic ulcer. In addition, recurrent ulcers are often associated with infections of the acid-stable bacteria, *Helicobacter pylori* (*H pylori*). Hence, therapy for recurrent ulcers involves regimens that include appropriate antibacterial therapy administered with an H_2 antagonist or a proton pump inhibitor.

In genitourinary practice, antimuscarinic drugs are used to relieve symptoms of bladder instability in patients with uninhibited and reflex neurogenic bladder that include *urinary frequency, urgency, leakage,* and *dysuria.* They also are used to control urinary incontinence and to control enuresis in children (Table 73-1).

In ophthalmology, antimuscarinic drugs are used topically to *dilate the pupil* (*cause mydriasis* to facilitate visualization of the optic fundus) and to *paralyze accommodation (cause cycloplegia* for refractive examination); some of these drugs (eg, homatropine) cannot effect a complete cycloplegia, so they are not all equivalent. Generally, short-acting topical antimuscarinic drugs (cyclopentolate, tropicamide, homatropine) are preferred for examination, so that interference with vision or intraocular tension will last for the shortest possible time. They are given in combination with phenylephrine to *promote maximal widening of the pupil* to allow greater surgical access and, after surgery, to *prevent adhesions* and, in alternation with miotics or with phenylephrine, to *break adhesions between the iris and lens* (synechiae). They also are used to *treat acute iritis, uveitis, iridiocyclitis, and keratitis*. Paradoxically, these drugs may be used to treat malignant (ciliary block) glaucoma; in this, the rationale is that relaxation of the ciliary muscle helps to push the lens/diaphragm posteriorly and reestablish an anterior direction of flow of intraocular fluid.

Antimuscarinic drugs, especially atropine, are used sometimes for *anesthetic premedication,* to *inhibit excessive salivary* and *bronchial secretions* (aspiration prophylaxis) and *prevent bronchospasm* and *laryngospasm*. The antisecretory effects also are sought in the treatment of *sialorrhea, acute coryza, hay fever,* and *rhinitis.* Several medications used to treat allergic rhinitis, for example, contain various belladonna alkaloids (eg, methscopalamine) in combination with antihistamines and de-

Table 73-1. Examples and Potential Uses of Products Containing Antimuscarinic Drugs

THERAPEUTIC USE	DRUG EXAMPLE
Antidiarrheals	Atropine sulfate (Various combinations)
Antispasmodic	Dicyclomine hydrochloride (Bentyl; Various)
Antivertigo (Motion sickness)	Scopalamine Transderm-Scop
Aspiration prophylaxis (inhibit secretions)	Atropine sulfate (Various)
Cardiology (bradycardia, cardiopulmonary resuscitaion)	Atropine sulfate (Various)
Ophthomology (Mydriasis, cycloplegia)	Tropicamide (Mydriacyl; various)
Overactive bladder	Tolterodine tartrate (Detrol) Oxybutynin hydrochloride (Ditropan; Various)
Parkinson's disease	Benztropine mesylate (Cogentin; Various)
Pulmonary (Asthma)	Ipratropium bromide (Atrovent and with albuterol)
Pulmonary (upper respiratory combinations)	Methscopalamine nitrate (Dallergy; Various)

Table 73-2. Antimuscarinic/Antispasmodic Drugs Used for Effects on the Gastrointestinal Tract[a]

QUATERNARY AMINES DRUG (TRADE NAME)	TERTIARY AMINES DRUG (TRADE NAME)	ANTISPASMOTIC/MISC DRUG (TRADE NAME)
Clidinium bromide (Quarzan: in Librium)	L-alkaloids of belladonna (Various)	Dicyclomine hydrochloride (Bentyl)
Glycopyrrolate (Robinul)	Belladonna alkaloids (Various)	Oxybutynin chloride (Ditropan; Various)
Mepenzolate bromide (Cantil)	L-hyoscyamine hydrobromide, sulfate (Various)	
Methantheline bromide (Banthine)	Oxyphencyclimine hydrochloride (Daricon)	
Methscopalamine bromide (Pamine)	Scopolamine hydrobromide (Various)	Pirenzepine (M1 selective-not in USA)
Propantheline bromide (Pro-Banthine)		
Tridihexethyl chloride (Panthilon)		

[a] For further information, see RPS-18, Chap 46, page 907.

congestants for this purpose. The therapeutic effectiveness and the adverse effects resulting from the combination of drugs is questionable, especially at the doses being administered.

The effects to antagonize parasympathetically mediated bronchospasm and bronchorrhea are employed also in the treatment of *bronchial asthma* and other chronic obstructive pulmonary diseases. When administered by inhalation, systemic side-effects are infrequent and often negligible. Ipratropium is available in aerosol form either alone or in combinations with sympathomimetic drugs for the treatment of asthma.

In cardiology and anesthesiology, antimuscarinic drugs (atropine) are used to prevent or suppress *vagally mediated bradyarrhythmias* (such as occur after coronary occlusion), *heart block,* or *cardiac syncope* due to hyperactive carotid sinuses.

Certain antimuscarinic drugs may be used for their CNS actions in the treatment of *parkinsonism* and to treat *extrapyramidal symptoms (pseudoparkinsonism)* associated with antipsychotic drugs (dopamine antagonists). Parkinson's disease is a chronic, progressive degenerative disorder involving areas of the brain that maintain posture and muscle tone, as well as, regulate voluntary motor activity. Patients have great difficulty translating the desire to move into the act of moving. Current drug therapy is based on the observation that dopaminergic neurons in certain brain areas are lost. It is hypothesized that the progressive loss of the inhibitory influence of dopamineric neurons and a relative increase in the influence of ACh leads to an imbalance that results in the symptoms. Current treatment options are palliative and include the use of drugs to increase dopaminergic neurotransmission or to decrease cholinergic neurotransmission in the CNS. Hence, centrally acting antimuscarinic drugs like benztropine (Cogentin), biperiden (Akineton), trihexyphenidyl, and procyclidine (Kemadrin) are used in the treatment of Parkinson's disease (see Chapter 74 under the discussion on *Antiparkinson Drugs*). These drugs are generally used in combination with other drugs and are especially useful in the treatment of tremor.

Antimuscarinic drugs (especially atropine) also are used as antidotes for central and peripheral muscarinic toxicity in *anticholinesterase intoxication and for* poisoning by *Amanita muscaria*. Atropine is available in combination with the cholinesterase reactivator, pralidoxime, for use by the military as a parenteral preparation to treat organophosphate poisoning. Scopolamine is highly effective against motion sickness and is sometimes used for its sedative and amnesic effects, but these effects are not typical of antimuscarinic drugs.

ADVERSE EFFECTS—With nearly all antimuscarinic drugs, *dry mouth* is the first and dry skin is the second most common side effect. *Thirst* and *difficulty in swallowing* occur when the mouth and esophagus become sufficiently dry; chronic dry mouth also fosters dental caries. Suppression of sweating causes reflexive *flushing* and *heat intolerance* and can result in heat exhaustion or heat stroke in a hot environment; it also contributes to the hyperthermia seen in intoxication. *Mydriasis* frequently occurs, especially with secondary and tertiary compounds; *photophobia* and *blurring of vision* are consequences of mydriasis. With the secondary and tertiary amines, *cycloplegia* (which exacerbates blurred vision) occurs approximately concomitantly with mydriasis, but usually higher doses are required with many quaternary ammonium antimuscarinic drugs. In susceptible persons, especially the elderly, cycloplegia may contribute to an *elevation of intraocular pressure*. Difficulty in urination and urinary retention may occur, especially in elderly males with prostate enlargement. Tachycardia is a common side effect. *Constipation,* even *bowel stasis,* may occur. Antimuscarinic drugs relax the lower esophageal sphincter and thus promote gastroesophageal reflux, heartburn, and reflux esophagitis. They are, therefore, contraindicated in these conditions.

At high therapeutic doses, the secondary and tertiary amine antimuscarinic drugs may cause *dizziness, restlessness, tremors, fatigue,* and *locomotor difficulties*. Serious systemic intoxication can occur even from topical ophthalmological application, especially in children, since both local absorption and nasolacrimal drainage into the gut can deliver considerable amounts to the circulation. In serious intoxication, *hyperpyrexia, flushing, nausea, vomiting, drowsiness, disorientation, stupor, hallucinations, leukocytosis, nonallergic rashes, circulatory or respiratory collapse,* and even *death,* in addition to all aforenamed effects, may occur. Children, especially *infants and children with Down's syndrome, spastic paralysis, or brain damage,* are more sensitive than adults to the toxic effects.

When barbiturates or benzodiazepines are included in an antimuscarinic product, adverse effects of these drugs must be anticipated. The possibility that chronic use will lead to dependence should be considered.

The quaternary ammonium drugs mostly have a low CNS component of toxicity but instead may *cause orthostatic hypotension* (from ganglionic blockade) and *neuromuscular paralysis*.

Hypersensitivity with a variety of manifestations, usually rash, may follow the use of any antimuscarinic drug, but it is more common with the solanaceous alkaloids.

Other drugs, such as phenothiazines, tricyclic antidepressants, certain antihistamines, meperidine, and others that have significant antimuscarinic activity, may intensify considerably the effects of antimuscarinic drugs. Drugs with neuromuscular paralyzant activity (neuromuscular blocking drugs, aminoglycosides, polymyxin, etc) and ganglionic blocking drugs will summate with quaternary ammonium antimuscarinic drugs. Aluminum and magnesium trisilicate–containing antacids have been shown to decrease the absorption of some antimuscarinic drugs.

PRECAUTIONS—If there is mydriasis and photophobia, *dark glasses* should be worn. The patient also should be warned that *driving or other vision-dependent capabilities* may be impaired. Appropriate dosage precautions must be taken with *infants, children, and persons with Down's syndrome, brain damage, spasticity, or light irides.* Elevated intraocular pressure, urinary difficulty and retention, and constipation are more probable in *elderly persons*. Men with *prostatic hypertrophy,* especially, should be monitored for urinary function. Antimuscarinics should be used cautiously in *toxic megacolon*. Because of the tachycardic effects of the drugs, care must be exercised when *tachycardia,* other *tachyarrhythmias, coronary heart disease, congestive heart disease,* or *hyperthyroidism preexist.* Persons with *hypertension* may experience both exaggerated orthostatic hypotension and tachycardia. Similarly, *autonomic neuropathy* requires caution. Persons with a history of *allergies* or *bronchial asthma* will show a higher than normal incidence of hypersensitivity reactions. Quaternary ammonium antimuscarinic drugs, especially, may cause neuromuscular paralysis (with fatal respiratory arrest) in persons with *myasthenia gravis*. Although these drugs sometimes are used in the treatment of *adhesions between lens and iris,* damage can occur, and expert precautions must be taken. When solutions of antimuscarinic drugs are applied topically to the eye, pressure should be applied just below the internal canthus of the eye to prevent nasolacrimal drainage.

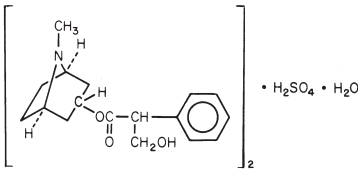
Precautions are appropriate in *ulcerative colitis*. In *hiatus hernia or gastroesophageal reflux,* reflux and esophagitis are exacerbated by antimuscarinic drugs, because the lower esophageal sphincter is stimulated by cholinergic nerves. In a *hot environment,* the user is more susceptible to disruption of heat regulation. *Hepatic disease* for some and *renal disease* for other antimuscarinic drugs may decrease the rate of elimination. Cognizance should be taken of possible *drug interactions*. Lastly, until proven otherwise, it must be assumed that all antimuscarinic drugs can pass the placental barrier; the threat to the fetus *in utero* is unknown, but an infant born with an effective amount of drug aboard may have GI difficulties and problems in early nutrition.

CONTRAINDICATIONS—An antimuscarinic drug generally is contraindicated in *narrow-angle glaucoma, pyloric* or *intestinal obstruction, intestinal atony* of the elderly, *paralytic*

ileus, achalasia of the esophagus, frank *bladder neck obstruction,* or when there is *hypersensitivity* to the drug or a closely related one. There are specific exceptions depending on the route employed and the degree of selectivity (profile of activity) of the drug used.

ATROPINE SULFATE

Benzeneacetic acid, *endo*-(±)-α-(hydroxymethyl)-, 8-methyl-8-azabicyclo[3.2.1]oct-3-yl ester, sulfate (2:1) (salt), monohydrate



1αH,5αH -Tropan-3α-ol (α)-tropate(ester) sulfate (2:1) (salt) monohydrate [5908-99-6] $(C_{17}H_{23}NO_3)_2.H_2SO_4.H_2O$ (694.82); *anhydrous* [55-48-1] (676.82).

Caution—Atropine Sulfate is very poisonous.

Preparation—Atropine is dissolved in warm acetone, sufficient dilute sulfuric acid is added to form the 2:1 sulfate, and atropine sulfate is crystallized from the solution.

Description—Colorless crystals or a white, crystalline powder; odorless; effloresces in dry air; slowly affected by light; when previously dried at 120° for 4 hr, it melts not lower than 187°.

Solubility—1 g in 0.4 mL water, 5 mL alcohol, or about 2.5 mL glycerol.

Comments—Atropine is a tertiary amine antimuscarinic drug with all of the actions and most uses and adverse effects described in the general statement at the beginning of this chapter. The antimuscarinic activity mostly resides in the *l-isomer (l-hyoscyamine).* By historical precedence, it has become the prototype and most widely used of antimuscarinic drugs.

Because atropine is obtained from species of *belladonna,* the word atropine often has been used as synonymous with belladonna. Actually, several genera of *Solanaceae* produce atropine and related alkaloids, so atropine and other related natural or semisynthetic congeners are sometimes called *solanaceous* alkaloids.

Atropine is absorbed rapidly and completely from the gut and is distributed rapidly throughout the body. Atropine is available in combination with diphenoxylate, a nonanalgesic analog of meperidine, for the treatment of mild GI hypermotility (eg, traveler's diarrhea). Following topical application atropine penetrates readily into the eye. It produces prolonged mydriasis and cycloplegia for more than 1 week. It is metabolized mainly in the liver. The plasma half-life of *l-hyoscyamine* is less than 4 hr. The half-life in the eye is long, and effects may last for 7 to 12 days after topical application to the eye. Intraocular inflammation, however, greatly shortens the half-life in the eye.

BELLADONNA

Deadly Nightshade Leaf; Belladonna Herb; Black Cherry Leaf; Dwale; Dwayberry Leaf

The dried leaf and flowering or fruiting top of *Atropa belladonna* Linné or of its variety *acuminata* Royle ex Lindley (Fam *Solanaceae*); it yields not less than 0.35% of the alkaloids of Belladonna Leaf USP.

Comments—Its actions are those of the principal alkaloids, hyoscamine and atropine (see the general statement).

LEVOROTATORY ALKALOIDS OF BELLADONNA

A synthetic mixture of the pure salts of the levorotatory alkaloids found in belladonna. The ratio of the salts is such that a single dose contains the approximate amount of each of the following: scopolamine hydrobromide, 0.006 mg; atropine sulfate, 0.02 mg and hyoscyamine sulfate, 0.1 mg.

Comments—See *Belladonna.*

HOMATROPINE HYDROBROMIDE

Benzeneacetic acid, (±)-α-hydroxy-, *endo*-8-methyl-8-azabicyclo[3.2.1]oct-3-yl ester hydrobromide

1αH,5αH-Tropan-3α-ol mandelate (ester) hydrobromide [51-56-9] $C_{16}H_{21}NO_3.HBr$ (356.26); the hydrobromide of tropine mandelate.

Preparation—By heating *tropine* with *mandelic acid* in the presence of hydrochloric acid; ammonia is added, and the liberated homatropine extracted with chloroform; the solution is evaporated, hydrobromic acid added and the homatropine hydrobromide crystallized.

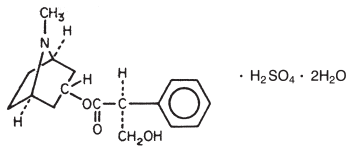
Description—White crystals, or a white crystalline powder; affected by light; melts between 214° and 217° with slight decomposition; aqueous solution is practically neutral or only faintly acid to litmus.

Solubility—1 g in 6 mL water, 40 mL alcohol or about 420 mL chloroform; insoluble in ether.

Comments—For ophthalmological use only. It has a duration of action from 0.5 to 2 days.

HYOSCYAMINE SULFATE

Benzeneacetic acid, α-(hydroxymethyl)-, [3(*S*)-*endo*]-8-methyl-8-azabicyclo[3.2.1]oct-3-yl ester, sulfate (2:1), dihydrate; Cystospaz



[6835-16-1] $(C_{17}H_{23}NO_3)_2.H_2SO_4 2H_2O$ (712.85); *anhydrous* [620-61-1] (676.82). The sulfate of an alkaloid usually obtained from species of *Hyoscyamus* Linné or other genera or Fam *Solanaceae.*

Caution—Hyoscyamine Sulfate is extremely poisonous.

Preparation—Isolated from the alkaloids of belladonna by resolution of atropine.

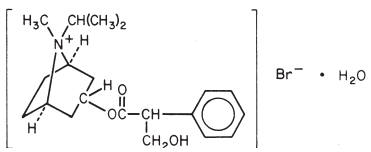
Description—White, odorless crystals or a crystalline powder; deliquescent; affected by light; when previously dried at 105° for 4 hr, does not melt below 200°; pH (1 in 100 solution) about 5.3.

Solubility—1 g in 0.5 mL water or 5 mL alcohol; practically insoluble in ether.

Comments—The levorotatory isomer of atropine. It is used as an *antispasmodic.*

IPRATROPIUM BROMIDE

(±)-(*endo, syn*)-8-Azoniabicyclo[3.2.1]octane, 3-(3-hydroxy-1-oxo-2-phenylpropoxy)-8-methyl-8-(1-methylethyl)-, bromide monohydrate; Atrovent



(8*r*)-3α-Hydroxy-8-isopropyl-1αH,5αH-tropanium bromide (±)-tropate monohydrate [66985-17-9]; anhydrous [22254-24-6] $C_{20}H_{30}BrNO_3.H_2O$ (430.38).

Preparation—Atropine is quaternized with isopropyl bromide.

Description—White, crystalline substance with a bitter taste.

Solubility—Freely soluble in water or alcohol; insoluble in chloroform or ether.

Comments—A quaternary ammonium antimuscarinic drug used for the treatment of *bronchial asthma* and *chronic obstructive pulmonary disease,* for which it is given as an inhalant aerosol. It appears to be approximately equivalent to β_2-agonists in its efficacy against bronchial asthma, but the duration of action is longer. It appears to be more effective than β_2-agonists against chronic obstructive pulmonary disease. It seems to act mainly on the larger airways.

By inhalation, the incidence and severity of side effects is low, the most common effects being dry mouth, irritation in the throat, cough, and unpleasant taste. Other effects are quite rare and include blurring of vision, drowsiness, dizziness, *mild bradycardia,* and airway obstruction caused by sputum made viscous by diminished tracheobronchial secretions.

By inhalation, ipratropium causes bronchodilatation in doses 1/1000 those of oral or intravenous doses, which avoid most systemic side effects. Bronchodilatation occurs within a few minutes, peaks at 1 to 2 hr, and lasts 4 to 8 hr. About half the dose is eliminated in the feces. The half-life is 3 to 4 hr. Nasal sprays of ipratropium (0.03% and 0.06%) are now available for topical treatment of allergic rhinitis or rhinorrhea associated with the common cold, respectively.

SCOPOLAMINE HYDROBROMIDE

Benzeneacetic acid, [7(*S*)-(1α,2β,4β,5α,7β)]-α-(hydroxymethyl)-, 9-methyl-3-oxa-9-azatricyclo[3.3.1.$0^{2,4}$]non-7-yl ester, hydrobromide, trihydrate; Transderm-Scop

6β,7β-Epoxy-1αH,5αH-tropan-3α-ol (-)-tropate(ester) hydrobromide trihydrate [6533-68-2] $C_{17}H_{21}NO_4.HBr.3H_2O$ (438.31); *anhydrous* [114-49-8] (384.27).

Preparation—Scopolamine, an alkaloid occurring in several solanaceous plants, may be obtained from such plants by alkaloid extraction procedures followed by fractionation of the extract to remove other alkaloids, notable hyoscyamine.

Description—Colorless or white crystals or white, granular powder; odorless; slightly efflorescent in dry air; the anhydrous salt melts between 195° and 199°; pH (1 in 10 solution) between 4 and 5.5.

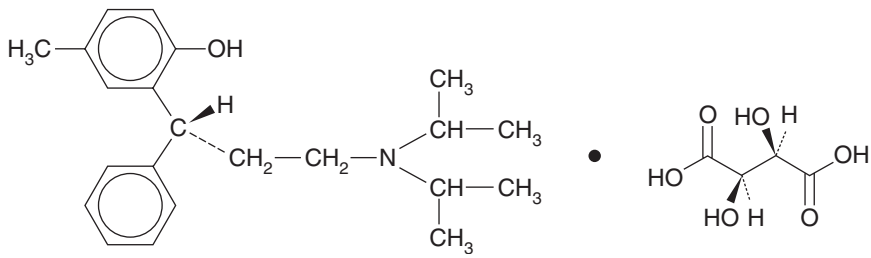
Solubility—1 g in 1.5 mL water or 20 mL alcohol; slightly soluble in chloroform; insoluble in ether.

Comments—It differs from other antimuscarinic drugs in that in therapeutic doses it is a sedative and tranquilizing depressant to the CNS. In its peripheral actions, it differs from atropine in that it is a stronger blocking agent for the iris, ciliary body, and salivary, bronchial, and sweat glands but is weaker in its action on the heart (in which it is incapable of exerting actions in tolerated doses), the intestinal tract, and the bronchial musculature. It is sometimes given as a *preanesthetic* medication for both its sedative-tranquilizing and antisecretory actions. It is effective as a prophylactic against *motion sickness,* for which slow-release transdermal dosage forms have been devised. Transdermal systems provide sustained release for 3 days. It also is used sometimes in other types of *vertigo*. It occasionally is used to suppress *delirium*. It is used as an *amnesic* agent in *obstetrics* (combined with morphine it was used formerly to produce *twilight sleep*). As a *mydriatic* and *cycloplegic,* it has a somewhat shorter duration (3–7 days), and intraocular pressure is affected less markedly than with atropine.

Except for drowsiness, its side effects are those of tertiary amine antimuscarinic drugs. Occasionally, with therapeutic doses a patient may experience excitement, restlessness, hallucinations, delirium or disorientation, confusion, memory loss, stupor, and, rarely, coma. Infants and young children are quite susceptible to the CNS toxicity. After a transdermal system has been in use for 3 or more days, removal sometimes causes a withdrawal syndrome consisting of dizziness, disequilibrium, nausea, vomiting, and headache. Rarely, there may be hypersensitivity, characterized by edema of the uvula, glottis, and lips. The toxic effects of overdoses, precautions, and contraindications are like those of tertiary amine antimuscarinic drugs.

TOLTERODINE TARTRATE

Phenol, (*R*)-2-[3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-methyl-, [*R*-(*R,*R**)]-2,3-dihydroxybutanedioate (1:1) salt; Detrol, Detrol LA**

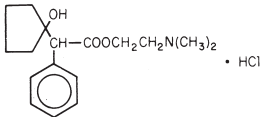


bladder outflow obstruction and gastrointestinal obstructive disorders. The drug is extensively metabolized by CYP2D6 and potent inhibitors of the may lead to adverse effects. CYP3A4 inhibitors also may lead to elevated serum concentrations of the drug.

OPHTHALMOLOGICAL DRUGS

CYCLOPENTOLATE HYDROCHLORIDE

Benzeneacetic acid, α-(1-hydroxycyclopentyl)-, 2-(dimethylamino)ethyl ester, hydrochloride; AK-Pentolate; Cyclogyl



2-(Dimethylamino)ethyl 1-hydroxy-α-phenylcyclopentaneacetate hydrochloride [5870-29-1] $C_{17}H_{25}NO_3.HCl$ (327.85).

Preparation—The acid moiety of the ester, 1-hydroxy-α-phenylcyclopentaneacetic acid (I), may be prepared by adding sodium phenylacetate to an ethereal solution of isopropyl magnesium bromide; treatment of the resulting sodium phenylacetate magnesium bromide with an ethereal solution of cyclopentanone produces a Grignard addition product that on hydrolysis yields I. The ester is produced by metathesis between the sodium salt of I and 2-dimethylaminoethyl chloride in isopropyl alcohol. After crystallization from acetone, the ester is converted to the hydrochloride with HCl.

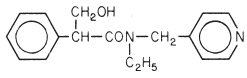
Description—White, crystalline powder, which on standing develops a characteristic odor; melts between 137° and 141°; pH (1 in 100 solution) between 4.5 and 5.5.

Solubility—Very soluble in water; freely soluble in alcohol; insoluble in ether.

Comments—An *antimuscarinic* drug used primarily for its *ophthalmological* actions. After application to the cornea, cyclopegia is complete in 25 to 75 min; recovery is complete in 6 to 24 hr. The side effects and CNS toxicity are those of antimuscarinic drugs, but the duration of the effects is very short.

TROPICAMIDE

Benzeneacetamide, *N*-ethyl-α-(hydroxymethyl)-*N*-(4-pyridinylmethyl)-, Mydriacyl



N-Ethyl-2- phenyl - *N*- (4 - pyridylmethyl) hydracrylamide [1508-75-4 $C_{17}H_{20}N_2O_2$ (284.36).

Preparation—Tropic acid is esterified with acetyl chloride, and the resulting tropic acid acetate is converted to the corresponding acid chlo-

(+)-(*R*)-2-[1-[2-Diisopropylamino)ethyl]benzyl]-*p*-cresol L-tartrate (1:1) salt
[124937-52-6] $C_{22}H_{31}NO.C_4H_6O_6$ (475.58).

Preparation—Crude 3-(2-methoxy-5-methylphenyl)3-phenylpropionyl chloride is added dropwise to a stirred solution of diisopropylamine in dichloromethane at 0°. *N,N*-diisopropyl-3-(2-methoxy-5-methylphenyl)-3-phenylpropionamide is filtered, dried, and added to a stirred suspension of lithium aluminum hydride in dry ether and refluxed for 2 days. The compound was treated with BBr_3 to provide the free phenol. The amine was treated with a solution of L(+)-tartaric acid to provide the desired enantiomer. US Patent 5,382,600.

Description—White crystalline powder; pK_a 9.87.

Solubility—Solubility in water is 12 mg/mL, soluble in methanol, slightly soluble in ethanol, and practically insoluble in toluene. The partition coefficient (octanol/water) is 1.83 at pH 7.3.

Comments—Competitive muscarinic antagonist with pronounced effects on bladder function. The drug is extensively metabolized by the liver following oral administration. The primary route of metabolism involved the oxidation of the 5-methyl group mediated by the CYP2D6. The 5-hydroxymethyl metabolite exhibits antimuscarinic activity similar to the parent drug and contributes significantly to the therapeutic effects of the drug. Certain individuals (7% of caucasian population) are devoid of the CYP2D6 enzyme. These patients are considered poor metabolizers and require dosage adjustments.

Immediate release tablets (1 mg and 2 mg) and extended release capsules (2 mg and 4mg) are available. The initial recommended dosage range for the immediate release product is 1–2 mg twice daily based on individual response and tolerability. The recommended dose for patients with impaired liver function and those taking CYP3A4 inhibitors is 1 mg twice daily.

The recommended dose for the extended release capsules is 2–4 mg once daily (taken with liquids and swallowed whole) based on individual response and tolerability. The recommended dose for patients with significantly impaired liver or renal function and those taking CYP3A4 inhibitors is 2 mg daily.

The drug is contraindicated in patients with known hypersensitivity to tolterodine or its ingredients and in patients with urinary retention, gastric retention, or uncontrolled narrow-angle glaucoma. Adverse effects include dry mouth, headache, constipation, abdominal pain, and abnormal vision. The drug should be used with caution in patients with

ride by reaction with thionyl chloride. Condensation of the acid chloride with 4-[(ethylamino)methyl] pyridine in the presence of an appropriate dehydrochlorinating agent yields the tropicamide acetate ester, which saponifies readily to tropicamide. US Pat 2,726,245.

Description—White or practically white, crystalline powder; odorless or has not more than a slight odor; melts between 96° and 100°.

Solubility—1 g in 500 mL water or 3 mL chloroform; freely soluble in alcohol or solutions of strong acids.

Comments—An *antimuscarinic* drug that is used to induce *mydriasis* and *cycloplegia* in ophthalmological practice. Applied topically to the eye, it has a short duration of action. The time to a maximal effect is usually 20 to 25 min. The duration of maximal effect is only about 15 to 20 min, but full recovery requires 5 to 6 hr. However, photophobia and other subjective indices of an effect may disappear as early as 2 hr after application. The drug, thus, has an obvious advantage over belladonna alkaloids in its shorter duration of action and over homatropine in its ability to induce cycloplegia. It is disadvantageous in that the ophthalmologist must time the examination to coincide with the time of maximal effect and has a brief time for examination or else it is necessary to repeat administration at 30-min intervals to obviate the timing problem.

Although tropicamide does not increase intraocular pressure in normal persons, it may do so in patients with glaucoma or those who have certain structural deformities of the anterior chamber of the eye. It should, thus, be used cautiously in such patients. If an antimuscarinic drug must be employed in such patients, tropicamide is indicated because of its brief duration of action.

Side effects can occur from passage of solutions through the nasolacrimal duct and subsequent absorption. Dry mouth and tachycardia have occurred. Although intoxication in children has not been reported, it must be kept in mind. Tropicamide usually stings transiently when applied.

ANTISPASMODIC DRUGS

The term *antispasmodic* is a general one that might be applied to the actions of many drugs with diverse mechanisms of action. Spasm may result from a local disorder in which cellular injury initiates the contractile process and local hormones or other excitatory or irritant substances are released (or local reflexes are activated) or it may be the result of hyperactivity in efferent excitatory autonomic nerves or electrolyte disturbances that favor increased neuronal and muscular activity. Therefore, according to the locus, cause, and mediators of a spastic condition, one or more of a number of classes of selective drugs may be employed, eg, neuromuscular blocking or centrally acting muscle relaxants for various spastic conditions of skeletal muscle, local anesthetics for some localized neurally mediated spasm, α-adrenoreceptor-blocking drugs or β_2-adrenoreceptor agonists for vasospasm, β_2-agonists for bronchial and uterine spasms, antimuscarinic drugs for ciliary spasm or spastic bowel, calcium for hypocalcemic tetany, calcium channel blockers for various smooth muscle spasms, etc. Thus, the term antispasmodic might apply to many different types of drugs.

The term antispasmodic should be reserved, however, for those drugs that relax smooth muscle nonselectively. Only flavoxate hydrochloride and oxybutinin chloride potentially influence all smooth muscle, regardless of the type of innervation and neurotransmitter affected. Calcium channel–blocking drugs are discussed elsewhere. The selective antagonists are treated in the appropriate chapters. Long before the selective competitive antagonistic actions of antimuscarinic drugs were known, some antimuscarinic preparations and drugs were known to relieve certain spastic conditions of the bowel. Therefore, the term antispasmodic came to connote antimuscarinic drugs that have important GI uses, and it has become common to include antispasmodics in chapters on antimuscarinic drugs.

CHAPTER 74

Skeletal Muscle Relaxants

John E Hoover, BSc Pharm, RPh

Skeletal muscle may be relaxed by blocking the effect of somatic motor nerve impulses, by depressing the appropriate neurons within the central nervous system (CNS) so that somatic motor nerve impulses fail to be generated, or by decreasing the availability of calcium ions to the myofibrillar contractile system. Interruption of certain afferent reflex pathways, as by local anesthesia, also may effect relaxation of circumscribed muscle groups; local anesthetic block of efferent somatic motor outflow also is employed sometimes to relieve localized skeletal muscle spasm. In this chapter only those drugs that act at the myoneural junction, the *neuromuscular blocking drugs,* and those drugs that act upon central neurons, the *centrally acting muscle relaxants,* are discussed.

NEUROMUSCULAR BLOCKING DRUGS

Neuromuscular blocking drugs prevent somatic motor nerve impulses from initiating contractile responses in the effector skeletal (striated) muscles and hence cause a paralysis of the muscles. There are two categories of such drugs: the *competitive (or stabilizing)* paralyzants and the *depolarizing* paralyzants, discussed separately.

USES—Competitive and depolarizing neuromuscular blocking drugs have the same major uses, in general. The pharmacokinetics and pattern of side effects, rather than their mechanism, determine the uses of any given agent. The principal use is to provide *adequate skeletal muscular relaxation* during *surgery, controlled respiration,* and *orthopedic manipulations*. The short-acting drugs are used to relax the laryngeal muscles during *endotracheal intubation* and *bronchoscopy*. Neuromuscular paralyzants may be employed to *decrease the severity of muscle contraction* during *electroconvulsive* treatment. Competitive neuromuscular paralyzants have been used in the management of *tetanus* and in *various spastic disorders,* but the results usually have been disappointing. Competitive blocking drugs may be used in the *diagnosis of myasthenia gravis;* the myasthenic patient is extremely sensitive to the paralyzant actions.

Competitive Neuromuscular Blocking Drugs

When impulses in the somatic motor nerves arrive in the nerve terminals in the motor end-plate region, they evoke the release of acetylcholine, which diffuses to the postsynaptic motor end-plate membrane. There, acetylcholine combines with nicotinic cholinergic receptors to activate them, which leads to the opening of transmembrane ion channels, ion flow, and consequent membrane depolarization. End-plate membrane depolarization is followed by depolarization of the muscle membrane and subsequent contraction. Any interruption of the above sequence of events leads to muscular paralysis.

The competitive neuromuscular blocking drugs combine with the nicotinic receptors and occupy them without activating them. Acetylcholine cannot activate the already occupied receptors, so motor nerve impulses cannot elicit contractions, and paralysis ensues. Some of them also lodge in the receptor-operated ionophore and, thus, decrease electrical activation of the postsynaptic membrane.

PHARMACOLOGICAL ANTAGONISM—The interaction of blocking drug and receptor is reversible and dynamic. Drug molecules combine, dissociate, recombine, etc, thus leaving receptor molecules transiently unoccupied. The probability that an acetylcholine molecule will find an unoccupied receptor is directly proportional to the concentration. If the concentration is elevated sufficiently, dissociated blocking drug molecules will find the receptors occupied with acetylcholine and will be prevented from recombining with the receptors to maintain blockade. Thus, a blockade can be overcome competitively. In practice, the acetylcholine concentration is raised by inhibiting acetylcholinesterase in the end-plate region. Neostigmine and edrophonium are the most commonly employed anticholinesterases for antagonizing competitive neuromuscular paralyzants. The anticholinesterases are discussed in Chapter 71.

SIDE EFFECTS AND PRECAUTIONS—The competitive neuromuscular blocking drugs are quite selective for the nonrespiratory muscles, so that it is possible to achieve surgical relaxation of the abdominal, limb, neck, or laryngeal muscles without significant loss of respiratory function. However, respiration often may be depressed to the point of danger, even apnea, so *these drugs should be used only when facilities for prolonged respiratory assistance are at hand and the trachea is intubated,* in case respiratory assistance is needed. In hypothermic procedures such as cardiopulmonary bypass surgery, blockade is less complete, so that larger than standard doses are required; excessive paralysis may ensue subsequently when body temperature is elevated.

The two other principal side effects are the release of histamine from mast cells and ganglionic blockade. The extent to which histamine release occurs varies among the several drugs; it is greatest with tubocurarine. The histamine released may cause vasodilation and consequent hypotension and reflex tachycardia, bronchospasm, urticaria, rash, and, rarely, even angioneurotic edema. *Histamine-releasing neuromuscular blocking drugs should be avoided in persons with a history of bronchial asthma, angioneurotic edema, or anaphylaxis.*

Ganglionic blockade may occur, because the postsynaptic ganglionic cholinergic receptors are nicotinic. However, these receptors have somewhat different structural requirements from those at the neuromuscular junction, so ganglionic block-

ade is only slight to moderate with the usual clinical doses of neuromuscular blocking drugs. The types of effects of ganglionic blockade depend upon which ganglia are blocked. Blockade of sympathetic ganglia contributes to hypotension and of vagal ganglia, to tachycardia. Some curimimetics have a *vagolytic* action of unknown mechanism at cardiac muscarinic sites; this action also contributes to tachycardia. Ganglionic blockade is salutary when adverse reflexes to surgical manipulation are attenuated.

All of the marketed neuromuscular blocking drugs are quaternary ammonium compounds, hence they do not penetrate the blood-brain barrier and thus lack CNS actions. However, some cross the placental barrier into the fetus.

DRUG INTERACTIONS—Any drug with an effect to depress the excitability of the postsynaptic membrane at the motor end-plate will increase the blocking effect of competitive neuromuscular blocking drugs. The anesthetic ethers, halothane, and propranolol, are among such drugs.

A number of antibiotics can cause neuromuscular paralysis in high doses and in therapeutic doses may increase neuromuscular blockade by the competitive blocking drugs. Some of these (gentamicin, kanamycin, neomycin, streptomycin, tobramycin, and paromomycin) apparently also act competitively on the nicotinic receptor and, hence, may be antagonized by anticholinesterases. Others (polymyxins, colistin, colistimethate, tetracyclines, lincomycin, and clindamycin) have a more obscure action and are not antagonized by anticholinesterases, although anticholinesterases will antagonize the neuromuscular blocking drug and relieve the exaggerated paralysis; calcium partially antagonizes these drugs. Local anesthetics (quinine, quinidine, ganglionic blocking drugs, and magnesium ion) also potentiate the neuromuscular blocking actions of the competitive blocking drugs.

Depolarizing Neuromuscular Blocking Drugs

The depolarizing neuromuscular blocking drugs are nicotinic agonists, which, like acetylcholine, interact with the postsynaptic nicotinic receptors to effect a depolarization of the membrane at the motor end-plate. Unlike acetylcholine their sojourn at the end-plate is long, so the postsynaptic membrane may remain depolarized. Since the muscle membrane and consequent contraction can be excited only by a fresh depolarization, the muscle remains paralyzed. That is to say, the trigger for the conducted muscle impulse is the transient fall in end-plate membrane potential and not the persisting depolarization.

Eventually, the motor end-plate membrane repolarizes despite the continuing presence of the drug (phase two block), owing to a shift in receptor conformation. Nevertheless, despite the fact that the membrane is poised for a new depolarization, motor nerve impulses and acetylcholine fail to elicit a response, because the nicotinic receptor is not in its appropriate configuration. During this phase, the neuromuscular blockade takes on some characteristics of competitive blockade and even may be antagonized partially by anticholinesterases. This second phase is erratic in onset among the various muscles, and blockade may be of a mixed type, thus complicating the treatment of overdoses. Furthermore, not all drug recipients respond alike. Electrolyte status, muscle condition, disease, genetic factors, the presence of other drugs, and temperature all affect the time of onset and extent of phase two block. Moreover, not all depolarizing drugs are identical in the pattern of blockade. Clinically, phase two is usually significant only when the drug dose is repeated or the drug is infused and blood levels sustained beyond the normal single-dose limit. Monitoring neuromuscular function by nerve stimulation to avoid overdose and/or conversion to phase two paralysis is advisable.

SIDE EFFECTS AND PRECAUTIONS—During the onset of the drug-induced depolarization, as the membrane potential depolarizes to the critical firing potential, there may arise conducted impulses that will cause random contraction (fibrillation) of the muscle fibers. Motor nerve terminals are stimulated to generate axon reflexes that fire off entire motor units. In addition, the depolarizing neuromuscular blocking drugs stimulate both the intrafusal fibers and the muscle spindle afferent nerve endings, which results in facilitatory nerve traffic entering the spinal cord. Thus, there usually is an organized contraction pattern, namely *fasciculations* and even *twitching*. The result is muscle soreness. Fasciculations and twitching can exacerbate spasm and also cause damage in the presence of broken bones; consequently, the depolarizing drugs should be avoided in these conditions.

The muscles of respiration (intercostal and diaphragmatic) are more resistant to the paralyzing effects than are other skeletal muscles, and it usually is possible to achieve surgical relaxation of abdominal, limb, neck, or laryngeal muscles without significant loss of respiratory function. Nevertheless, respiration often may be depressed, sometimes to the point of apnea. This is likely especially after prolonged use, which favors considerable loss of potassium from the motor end-plate region. Consequently, *the depolarizing neuromuscular blocking drugs should be used only with tracheal intubation and when facilities for prolonged assisted respiration are at hand*. Care should be used when respiration already is depressed and also when the lithotomy or Trendelenburg positions are employed, especially in young children and the aged.

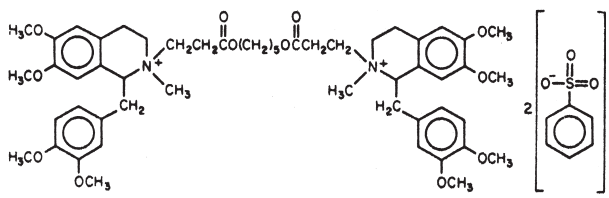
During the depolarizing phase of neuromuscular block, potassium is lost rapidly from the muscles, which may cause hyperkalemia. If a sufficient amount of the mobilized potassium is excreted, there may be a later hypokalemia. Various cardiac arrhythmias, even cardiac arrest, may result, especially if the patient is digitalized. Prolonged paralysis by these agents may lead to malignant hyperthermia.

The effects of depolarizing blocking drugs on autonomic ganglia and histamine stores are variable.

DRUG INTERACTIONS—Muscle paralysis with depolarizing neuromuscular blocking drugs is increased by hypothermia, hypokalemia, hypermagnesemia, polymyxin B, colistin, colistimethate, and aminoglycoside antibiotics (streptomycin, kanamycin, gentamicin, tobramycin, and neomycin).

ATRACURIUM BESYLATE

Isoquinolinium, 2,2′-[1,5-pentanediylbis[oxy(3-oxo-3,1-propanediyl)]]-bis[1-(3,4-dimethoxyphenyl)methyl]-1,2,3,4-tetrahydro-6,7-dimethoxy-2-methyl-, dibenzenesulfonate; Tracrium



[64228-81-5] $C_{65}H_{82}N_2O_{18}S_2$ (1243.49).

Preparation—Acryloyl chloride and 1,5-pentanediol are reacted to produce the diester, which then is treated with tetrahydropapaverine to yield the di-tertiary amine. This latter product, with methyliodide, forms the bis-quaternary iodide, which is converted to the besylate with benzenesulfonic acid. See US Pat 4,179,507.

Description—Off-white powder; melts at 87°. The molecule has the potential to conform to any of 16 different isomers, but due to its symmetry, only 10 exist. The drug entity consists of a mixture of several possible isomers, and the synthetic procedure results in the production of a consistent ratio of isomers, but in unequal amounts. The isomer that predominates (approximately in a 3:1 ratio) is that in which the quaternary methyl group and the dimethoxybenzyl group assume a *trans* configuration about the tetrahydroisoquinoline parent.

Solubility—1 g in 20 mL water.

Comments—A competitive neuromuscular paralyzant that is 2.5 times as potent as tubocurarine. Its effects are more predictable than are those of tubocurarine, especially with respect to repeated doses. Its duration of action is 33–50% of that of tubocurarine, 90% of recovery of

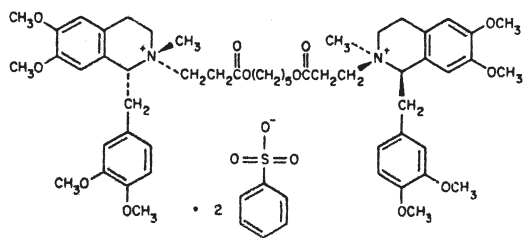
muscle function occurring in 60 to 70 min. The drug thus lends itself to use in surgical procedures of short-to-intermediate duration. In therapeutic doses, side effects are minimal, but moderate degrees of histamine release and consequent sequelae occur occasionally.

Drug interactions and antagonism by anticholinesterases essentially are the same as with tubocurarine, but the potentiating effects of anesthetics are less marked.

It neither is metabolized appreciably in the liver nor excreted into the urine. Rather, the bridge between the isoquinoline moieties is ruptured spontaneously by Hoffman elimination and by hydrolysis in plasma. This unique elimination makes the effects and duration of action independent of liver and/or renal insufficiency. The elimination half-life is about 20 min.

CISATRACURIUM BESYLATE

Isoquinolinium, [1*R*-[1α,2α(1′*R,2′*R**)]]-2,2′-[1,5-pentanediylbis[oxy(3-oxo-3,1-propanediyl)]bis[1-[3,4dimethoxyphenyl)methyl]-1,2,3,4-tetrahydro-6,7-dimethoxy-2-methyl-, dibenzenesulfonate; Nimbex**



[96946-42-8] $C_{65}H_{82}N_2O_{18}S_2$ (12243.51).

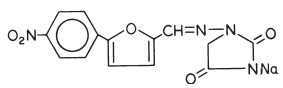
Preparation—From racemic tetrahydropapaverine which is resolved to the *R*-form (**I**). A coupling compound (**II**) is made by forming the diacrylate estser of 1,5-pentanediol with 2-bromopropionic acid using p-toluenesulfonic acid and triethylamine. Two molecules of **I** are condensed with **II** at the piperidine nitrogen atoms using oxalic acid, to form the base. Benzenesulfonic acid converts the base to salt. Drugs of the Future 21:14, 1996. See also US Pat 4,179,507 (1979).

CURARE

Comments—A name applied to extracts principally of the bark and other parts of plants of certain species of *Chondodendron* or *Strychnos,* especially *Chondodendron tomentosum* and *Strychnos toxiferin,* prepared by South American Indians of the Upper Amazon and Orinoco basins for use as arrow poisons. The extracts contain neuromuscular paralyzant alkaloids and numerous other contaminants. The chondodendron alkaloids contain tertiary and quaternary benzylisoquinoline derivatives such as *d*-tubocurarine (see *Tubocurarine Chloride*), *curine,* and related compounds. The strychnos alkaloids contain β-carboline alkaloids such as the toxiferins and calabash *curarines*. None of the crude preparations currently is used in therapeutics. Only purified preparations or alkaloids from *Chondodendron tomentosum* are available commercially.

DANTROLENE SODIUM

2,4-Imidazolidinedione, 1-[[[5-(4-nitrophenyl)-2-furanyl]methylene]amino]-, sodium salt, hydrate (2:7); Dantrium



1-[[5-(*p*-Nitrophenyl)furfurylidene]amino]hydantoin sodium salt hydrate [24868-20-0] $C_{14}H_9N_4NaO_5.31/2H_2O$ (399.29).

Preparation—See *J Med Chem* 1967; 10:807, and US Pat 3,415,821.

Description—Orange powder; *free acid* melts about 280°; pK_a about 7.5.

Solubility—Slightly soluble in water; more soluble in alkali.

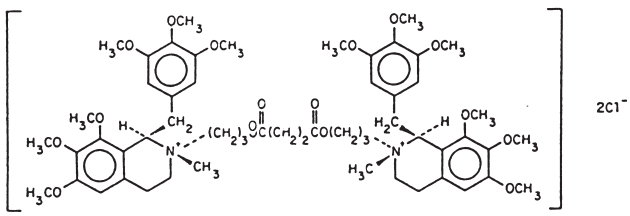
Comments—Differs from the classical neuromuscular blocking drugs in that its action is distal to the nicotinic receptors and neuromuscular junction. Instead, it suppresses excitation-contraction coupling by interfering with release of calcium from the sarcotubular reticulum. The muscle fibers still respond to nerve impulses; the contractile response is lessened but not abolished. Therefore, muscle weakness, rather than paralysis, is the result. Fast muscle fibers (white) are affected more than slow muscle fibers (red). Because the contractility of the intrafusal fibers in the muscle spindles also is decreased, spinal cord–mediated stretch reflexes are attenuated, which provides the primary explanation of its ability to relieve certain types of spasm. It is used to treat *spasticity resulting from upper motor neuron* lesions, such as those in *spinal cord injury, stroke, multiple sclerosis,* and *cerebral palsy* but not spasticity resulting from musculoskeletal injury, lumbago, or rheumatoid disorders. It is possible that a direct effect on the motor neuron may be involved in this limited spectrum of activity, since the drug does exert some CNS-depressant actions. In fact, the drug is used to treat the *neuroleptic malignant syndrome*. Its effect on intracellular calcium also lends itself to the treatment of *malignant hyperthermia,* which can be triggered by general anesthesia and neuromuscular blocking drugs.

Interference with muscle function may cause weakness and fatigue, poor posture with consequent backache and myalgia, a feeling of suffocation, difficulties in swallowing, diplopia, and other visual disturbances. Effects on the CNS include drowsiness, dizziness, malaise, headache, nervousness, slurred speech, confusion, depression, and, rarely, convulsions. Other adverse effects include constipation, diarrhea, abdominal cramps, gastric irritation, GI bleeding, increased urinary frequency yet oliguria, lacrimation, sweating, disorders of taste, urticaria, acneiform rash, eczematoid dermatitis, pleural effusions and pericarditis, hepatitis, chills, and fever. It is contraindicated in liver and pulmonary disease, in situations in which alertness is essential, and when gross postural abnormalities result from its use. It may color the urine orange to red.

Orally, it is absorbed poorly but more or less consistently, so that blood levels are proportional to the dose. It is metabolized in the liver to several products. It is stated that the plasma half-life is 5 hr by the intravenous route but 9 hr by the oral route. The former is probably an approximation of the distribution (α) half-life and the latter of the elimination (β) half-life.

DOXACURIUM CHLORIDE

Isoquinolinium dichloride, 2,2′-[(1,4-dioxo-1,4-butanediyl)bis(oxy-3,1-propanediyl)] bis[1,2,3,4-tetrahydro-6,7,8-trimethoxy-2-methyl-1-[(3,4,5-tri-methoxyphenyl)methyl]-, Nuromax



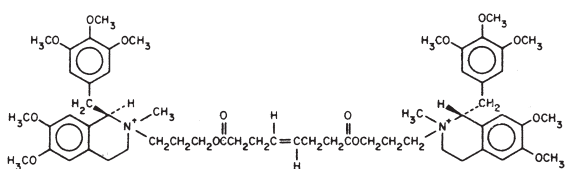
[106819-53-8] $C_{56}H_{78}Cl_2N_2O_{16}$ (1106.15).

Comments—A long-acting, nondepolarizing, competitive, neuromuscular blocking drug whose action is reversed by anticholinesterases. Doxacurium is indicated as an adjunct to general anesthesia. Its time to onset following an intravenous dose is approximately 1.5 to 2 times longer than that of the intermediate-acting nondepolarizing agents atracurium and vecuronium and 4 to 5 times longer than that of the short-acting depolarizing agent succinylcholine. Time to 25% recovery is approximately 10 to 15 times longer than that of succinylcholine and 2 to 3 times longer than that of the intermediate agents. Doxacurium does not appear to cause histamine release. The major elimination pathway for doxacurium is through excretion of unchanged drug in the urine and bile. The duration of action of doxacurium is increased in patients with end-stage kidney and hepatic disease.

METOCURINE IODIDE—see RPS-20, page 1335.

MIVACURIUM CHLORIDE

Isoquinolinium, [*R*-[*R, *R**-(*E*)]]-2,2′-[(1,8-dioxo-4-octene-1,8-diyl)bis(oxy-3,1-propanediyl)]bis-[1,2,3,4-tetrahydro-6,7-dimethoxy-2-methyl-1-[(3,4,5-trimethoxyphenyl)methyl]-, dichloride; Mivacron**



[106861-44-3 (total racemate)] $C_{58}H_{80}Cl_2N_2O_{14}$ (1100.18).

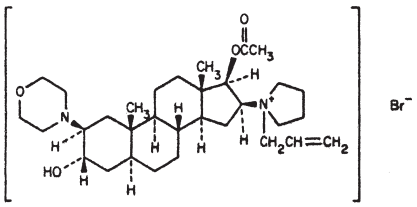
Comments—A short-acting, nondepolarizing, competitive, neuromuscular blocking drug whose action is reversed by anticholinesterases. Its time to onset following a bolus dose is equivalent to the intermediate-acting nondepolarizing agents atracurium and

vecuronium and two to three times longer than the short-acting depolarizing agent succinylcholine. Time to 25% recovery is approximately 2 times longer than with succinylcholine (16 versus 8 min, respectively) and two to three times shorter than with the intermediate agents (16 versus 25 to 45 min, respectively). For short-duration procedures not requiring rapid induction of anesthesia, mivacurium represents a viable alternative to succinylcholine. Bolus doses of mivacurium can cause histamine release that leads to cutaneous flushing of face and neck, increased heart rate, and hypotension. Like succinylcholine, mivacurium is metabolized rapidly by plasma cholinesterase. The duration of action of mivacurium is increased in patients with end-stage kidney and hepatic disease and patients with a deficiency of plasma cholinesterase.

PANCURONIUM BROMIDE—see RPS-20, page 1336.

ROCURONIUM BROMIDE

Pyrrolidinium, 1-(2β,3α,5α,16β,17β)-17-(acetyloxy)-3-hydroxy-2-(4-morpholinyl)androstan-16-yl]-1-(2-propenyl)-, bromide; Zemuron



1-Allyl-1-(3α,17β-dihydroxy-2β-morpholino-5α-andro-stan-16β-yl)pyrrolidinium bromide, 17-acetate [119302-91-9] $C_{32}H_{53}BrN_2O_4$ (609.69).

Preparation—US Pat 4,894,369 (1990).

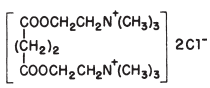
Description—Crystals melting about 161–169°; $[\alpha]_D^{20}$ +18.7° (c = 1.03, $CHCl_3$); Octanol/water partition coefficient 0.5 at 20°.

Solubility—Soluble in water.

Comments—The injection is a nondepolarizing neuromuscular blocking agent with a rapid to intermediate onset depending on the dose and intermediate duration. It acts by competing for cholinergic receptors at the motor and end-plate. This action is antagonized by acetylcholinesterase inhibitors, such as neostigmine and edrophonium.

SUCCINYLCHOLINE CHLORIDE

Ethanaminium, 2,2′-[(1,4-dioxo-1,4-butanediyl)bis(oxy)]bis[*N,N,N*-trimethyl-, dichloride; Suxamethonium Chloride; Quelicin



Choline chloride succinate (2:1) *anhydrous* [71-27-2] $C_{14}H_{30}Cl_2N_2O_4$ (361.31); *dihydrate* [6101-15-1] (397.34); usually occurs as the dihydrate.

Preparation—It may be prepared by condensing succinyl chloride with β-dimethylaminoethanol and quaternizing the resulting ester with methyl chloride.

Description—White, odorless, crystalline powder; solutions are acid to litmus (pH of about 4); the dihydrate melts about 160°, the anhydrous about 190°; hygroscopic.

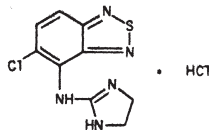
Solubility—1 g in about 1 mL water or about 350 mL alcohol; slightly soluble in chloroform; practically insoluble in ether.

Comments—A depolarizing neuromuscular blocking agent; see the introductory statement for actions, uses, side effects, precautions, and drug interactions. It usually has a very transient duration of action because of rapid hydrolysis of the drug by serum butyryl (pseudo)cholinesterases. The effects of a single injection usually last only a few minutes; consequently, it is of special use for muscle relaxation during brief manipulations. Prolonged muscular relaxation is achieved by continuous intravenous infusion, and the intensity of muscle paralysis is controlled readily by adjustment of the infusion rate. Alternatively, prolonged muscular relaxation may be achieved with periodic injections when the drug is given in combination with *hexafluorenium bromide* (above). Although a stabilizing phase of action can occur, its occurrence is erratic and usually results only from prolonged use.

It does not cause liberation of histamine, but hypersensitivity reactions sometimes occur. As the drug depolarizes the motor end-plate, axon reflex-conducted impulses and contractions of motor units (fasciculations) may occur. Muscle aching resulting from its transient stimulatory action is minimized by slow administration. Hyperkalemia, due to potassium loss from muscle, and myoglobinemia sometimes result from these stimulatory actions. Excessive salivation may occur; this is preventable by premedication with atropine or scopolamine. It may induce a bradycardia that can be suppressed by atropine or methscopolamine but not by scopolamine. It may cause cardiac arrhythmias in patients with myocardial damage. Among neuromuscular blocking drugs, it is unique in its effect to increase intraocular pressure; it is contraindicated in persons with glaucoma or retinal detachment and in persons with known hypersensitivity. Rarely, it may cause a severe (malignant) hyperthermia when an ether anesthetic or cyclopropane is used. No specific pharmacological antagonist of the skeletal muscle effects is available, but dantrolene can suppress malignant hyperthermia. Calcium channel–blocking drugs also are useful in this regard. Its actions may be prolonged in individuals with reduced plasma cholinesterase activity, such as results from a genetic defect or from liver disease or cachexia.

TIZANIDINE HYDROCHLORIDE

2,1,3-Benzothiadiazole-4-amine, 5-chloro-*N*-(4,5-dihydro-1*H*-imidazol-2-yl)-, monohydrochloride; Sirdalud; Zanaflex



5-Chloro-4-(2-imidazolin-2-ylamino)-2,1,3-benzothiadiazole monohydrochloride [51322-75-9] $C_9H_8ClN_5S.HCl$ (290.18).

Preparation—4-Amino-5-chloro-2,1,3-benzothiadiazole is treated with thiophosgene to form the 4-thiocyanato derivative which is reacted with ethylene-diamine yielding the thiourea. Heating the latter compound in methanol evolves H_2S forming the imidazoleamino ring on the 4-position, which is the product.

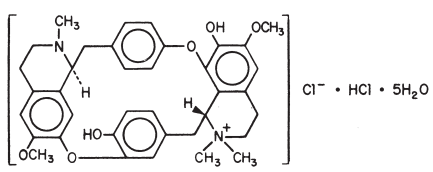
Description—White to off-white odorless crystals from methanol melting about 222°.

Solubility—Slightly soluble in water or methanol; solubility decreases as pH increases.

Comments—An agonist at the α_2-adrenergic receptor sites and presumably reduces spasticity by increasing presynaptic inhibition of motor neurons. In animal models, it has no direct effect on skeletal muscle fibers or the neuromuscular junction, and no major effect on monosynaptic spinal reflexes. Its effects are greatest on polysynaptic pathways. The overall effect of these actions is thought to reduce facilitation of spinal motor neurons. Its imidazoline chemical structure is related to that of the antihypertensive drug clonidine and other α_2-adrenergic agonists.

TUBOCURARINE CHLORIDE

Tubocuraranium, 7′,12′-dihydroxy-6,6′-dimethoxy-2,2′,2′-trimethyl-, chloride, hydrochloride, pentahydrate; (+)-Tubocurarine Dichloride; *d*-Tubocurarine Chloride



(+)-Tubocurarine chloride hydrochloride pentahydrate [6989-98-6] $C_{37}H_{41}ClN_2O_6.HCl.5H_2O$ (771.73); *anhydrous* [57-94-3] (681.65).

Preparation—Isolated from the stems and bark of the freshly gathered plant *Chondodendron tomentosum,* which is extracted with small portions of water.

Description—White or yellowish white to grayish white, odorless, crystalline powder; melts about 270°, with decomposition.

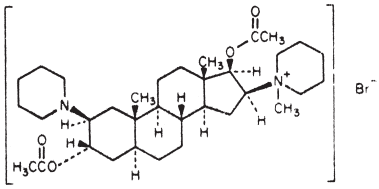
Solubility—1 g in 20 mL water or 45 mL alcohol; insoluble in chloroform or ether.

Comments—A competitive neuromuscular blocking agent; see the introductory statement for the actions, uses, side effects, and drug interactions.

It is not absorbed from the gut. After intravenous administration it rapidly disappears from the plasma, with a distribution half-life of about 12 min; however, its terminal plasma half-life is 1 to 3 hr. The duration of action of the first dose is 10 to 30 min, but a residual effect lasting several hours has been shown. Subsequent doses may have a longer action. It is both excreted into urine (43%) and degraded in the liver and kidneys, and either renal failure or hepatic failure can prolong the half-life.

VECURONIUM BROMIDE

Piperidinium, 1-[(2β,3α,5α,16β,17β)-3,17-bis(acetyloxy)-2-(1-piperidinyl)androstan-16-yl]-1-methyl-, bromide, diacetate



[50700-72-6] $C_{34}H_{57}BrN_2O_4$ (637.74).

Preparation—See *J Med Chem* 1973; 16:1116.

Description—White crystals; melts about 230°.

Solubility—Soluble in water.

Comments—It retains the competitive neuromuscular blocking activity of pancuronium but is devoid of some of the side effects and, consequently, has clinical advantages over pancuronium. It does not release histamine significantly, cause ganglionic blockade, or interfere with neuronal reuptake of norepinephrine, hence, has negligible cardiovascular side effects. The duration of action in adults is about 15 to 30 min for doses that cause less than 100% paralysis. Partial recovery sufficient to permit breathing may take even less time. Consequently, it may be used for relatively short surgical procedures and endotracheal intubation in adults. Recovery time is slightly longer in young children and more than twice as long in infants. When doses are repeated after only 25% of recovery of muscle function, accumulation apparently does not occur.

It is excreted mostly into the bile, and the degree of paralysis and duration of action are increased in liver failure. Ten to 25% is excreted into urine, and renal failure may prolong the duration of action by as much as 32%.

CENTRALLY ACTING MUSCLE RELAXANTS

The cell bodies of the somatic motor nerves lie within the spinal cord and, hence, within the CNS. The activity of motor neurons is affected not only by facilitatory and inhibitory modulation through feedback from contralateral and ipsilateral stretch and other receptors but also from centers in the brain. Spasticity can arise from musculoskeletal injury, which may cause aberrant afferent impulse traffic into the spinal cord, from injury to, or disease of, the motor nerves or related interneurons within the cord or sensory neurons in the sensory ganglia and from disorders in the brain that alter the flow of suprasegmental impulses to the motor neurons. Involuntary movement, such as is seen in palsies, chorea, or parkinsonism, mostly is the result of impairment of feedback control within the brain.

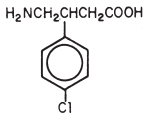
When the disorder is musculoskeletal or is within the spinal cord, the selectivity of drugs is relatively low, because the collective neurons involved in the reflex arcs are not sufficiently qualitatively different from the motor and sensory neurons in chemical sensitivity to permit a selective depression of the hyperactive influences on the motor neuron. However, some selectivity is achieved when interneurons are involved, simply because a small effect on each converging interneuron may summate to cause a moderate decrease in interneuronal input to the motor neuron. Because the interneurons are involved in the fine tuning of neuronal activity, their influences are balanced critically and hence are more susceptible to pharmacological action than the motor neuron itself. Consequently, most central relaxants are *interneuron depressants,* which, however, will manifest variable depressant actions throughout the CNS. Interestingly, many antianxiety and some sedative drugs possess muscle relaxant activity, probably because of the high sensitivity of the critically balanced interneurons to perturbation.

In tolerated doses, the centrally acting muscle relaxants are erratic, owing to their limited selectivity. Orally, they are usually ineffective (the tolerated doses being much too low); intravenously, they have some established value in treating acute muscle spasms resulting from trauma or inflammation. Motor dysfunctions that accrue to spinal cord or brain disorders are affected little.

The central relaxant effects and uses of certain benzodiazepines, such as diazepam, differ from those of interneuron depressants.

BACLOFEN

Butanoic acid, 4-amino-3-(4-chlorophenyl)-, Lioresal



β-(Aminomethyl)-*p*-chlorohydrocinnamic acid [1134-47-0] $C_{10}H_{12}ClNO_2$ (213.67).

Preparation—Synthesis by hydrogenation of β-cyano-*p*-chlorohydrocinnamic acid in acidified ethanol in the presence of platinic oxide catalyst is described in Swiss Pat 449,046 (*CA* 1968; 69:106273f).

Description—Crystalline powder; melts about 207° (190°?); pK_a 3.85, 9.25.

Solubility—Slightly soluble in water; poorly soluble in organic solvents.

Comments—Its muscle relaxant actions result from an action within the spinal cord, where both monosynaptic and polysynaptic reflexes are inhibited by the drug. It is an analog of γ-aminobutyric acid (GABA), an inhibitory neurotransmitter within the CNS. Part of the action of baclofen is likely attributable to its agonist properties at the $GABA_B$ receptor, which is coupled to a G-protein-activated K^+ channel. However, the precise mechanism of its muscle relaxant properties is unknown. Its sedative and ataxic actions are consistent with such an action in the brain.

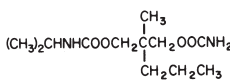
It is used in the relief of painful spasticity in *multiple sclerosis,* for which it is more effective than diazepam. Some residual ambulatory function must be present; the drug will not make nonambulatory patients ambulatory. Although spasticity may be lessened, the gait and posture of some patients may be worsened, because of the unmasking of incoordination. It also may afford some relief in patients with *spinal cord disease* and *traumatic transverse myelopathies*. It is not as effective as carbamazepine in the treatment of neuralgias but is an important substitute when needed. It has been reported to be of value in tardive dyskinesia. It is useful in the management of *external urinary sphincter hypertonicity* and *detrussor–external sphincter dyssynergia*. It is not indicated in musculoskeletal spastic disorders.

Sedation is the most frequent adverse effect, although it is less frequent and severe than with diazepam. Its use in combination with other CNS depressants or ethanol should be avoided, if possible. Weakness may occur, but it is less handicapping than with dantrolene. Other common side effects include dizziness, insomnia, pruritus, and rashes. The drug is contraindicated when a hypersensitivity exists. Less frequent side effects include hypotension and mental confusion. Abrupt withdrawal has been reported to result in anxiety, tachycardia, and even visual hallucinations; therefore, dosage must be discontinued gradually. In patients with epilepsy, it may increase the frequency of seizures. Overdoses may cause seizures, coma, loss of brainstem reflexes and respiratory depression. It is teratogenic, and this risk must be considered in pregnancy. It also has been found to cause ovarian cysts and enlarged or hemorrhagic adrenal glands in experimental animals.

It is absorbed rapidly, orally; absorption time is approximately 2 hr. More than 80% of the drug is excreted in the urine. The elimination half-life is 3 to 4 hr.

CARISOPRODOL

1,3-propanediol, 2-methyl-2-propyl-, carbamate isopropylcarbamate; Carisprodate; Isobamate; Soma



[78-44-4] $C_{12}H_{24}N_2O_4$ (260.33).

Preparation—Synthesis of the drug, which is an isopropyl meprobamate, is described in US Pat 2,937,119.

Description—White, crystalline powder; melts about 93°.

Solubility—1 g in about 3300 mL water; 2.5 mL of acetone or alcohol; soluble in many common organic solvents.

Comments—A sedative drug with muscle relaxant properties that result from reticulospinal depression. It is used to treat muscle spasm of local origin, such as results from strains, sprains, and lumbago. Part of its action may result from analgesia, sedation, and alleviation of anxiety. Onset of relief takes about 30 min; duration of action is 4 to 6 hr.

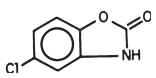
Adverse effects of the first dose may include sedation, diplopia, extreme weakness, ataxia, transient quadriplegia, tachycardia, postural hypotension, syncope, mydriasis, temporary loss of vision, dizziness, confusion, irritability, agitation, depression, disorientation, and dysarthria. Usually these subside within a few hours, but they may continue in milder form throughout treatment. Nausea and vomiting, hiccough, and epigastric distress also may occur. Sedation may occur throughout treatment. The patient should be advised not to operate a motor vehicle or machinery or attempt activities requiring alertness, judgment, or complex mentation. Addiction may occur; withdrawal signs and symptoms are abdominal cramps, chills, nausea, headache, and insomnia. Pregnant or lactating mothers should not use the drug. Hypersensitivity occasionally occurs, in part attributable to tartrazine in some products; manifestations may be smarting of the eyes, asthmatic episodes, pruritus, rash, fixed drug eruption, eosinophilia, fever, angioneurotic edema, hypotension, or anaphylaxis. It is contraindicated in acute intermittent porphyria.

The drug is metabolized mostly in the liver; the elimination half-life is usually about 8 hr.

CHLORPHENESIN CARBAMATE—see RPS-20, page 1338.

CHLORZOXAZONE

2(3*H*)-Benzoxazolone-, 5-chloro-, Parafon Forte



5-Chloro-2-benzoxazolol [95-25-0] $C_7H_4ClNO_2$ (169.58)

Preparation—From 2-amino-5-chlorobenzoxazole (US Pat 2,895,877).

Description—White, crystalline powder; melts about 192°.

Solubility—Sparingly soluble in water; freely soluble in aqueous solutions of alkali hydroxides or ammonia.

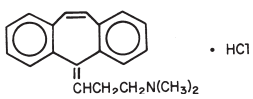
Comments—Inhibits polysynaptic reflexes within the spinal cord and subcortical regions of the brain. It is used to decrease muscle tone and tension and thus to relieve spasm and pain associated with musculoskeletal disorders such as fibrositis, bursitis, spondylitis, sprains, and muscle injury. It is of little use in spasticity resulting from lesions involving motor neurons or in dyskinetic movement disorders. It also exerts sedative actions, which aid in providing relief.

Adverse effects are infrequent and generally mild. CNS effects include drowsiness, vertigo, lightheadedness, headache, malaise, and occasional stimulation. Manifestations of hypersensitivity are rash, petechiae, ecchymosis, and, rarely, angioneurotic edema or anaphylaxis. Liver damage possibly occurs, so that it is wise to avoid the drug if there is a history of liver disease. Nausea and vomiting are relatively frequent, and diarrhea and GI bleeding also can occur, so the drug is contraindicated in peptic ulcer. Ethanol or other CNS depressants should not be taken concomitantly.

Absorption time is 3 to 4 hr. The elimination half-life is about 60 min. More than 90% of the drug is glucuronidated in the liver.

CYCLOBENZAPRINE HYDROCHLORIDE

1-Propanamine, 3-(5*H*-dibenzo[*a,d*]cyclohepten-5-ylidene)-*N,N*-dimethyl-, hydrochloride; Flexeril



N,N-Dimethyl-5*H*-dibenzo[*a,d*]cycloheptene-$\Delta^{5,\gamma}$-propylamine hydrochloride [6302-23-9 $C_{20}H_{21}N.HCl$ (311.85).

Preparation—Cyclobenzaprine may be synthesized by Grignard addition of α-dimethylaminopropylmagnesium chloride to 10,11- dihydro-5*H*-dibenzo[*a,d*]cycloheptene-5-one, followed by elimination of water from the resulting tertiary carbinol (Villani et al, *J Med Pharm Chem* 1962; 5: 373; see also Winthrop et al, *J Org Chem* 1962; 27:230).

Description—White, crystalline powder; melts about 217°; pK_a 8.47 (cyclobenzaprine base).

Solubility—Freely soluble in water or alcohol.

Comments—Depresses suprasegmental (upper) motor neurons in the brainstem and, to some degree, spinal motor neurons to decrease reflex skeletal muscle activity and tonus. It inhibits both the alpha and gamma motor systems. It is used to diminish spasm and pain associated with *musculoskeletal disorders* and to increase the range of movement. The drug also has weak antimuscarinic activity.

Frequent side effects include sedation, dry mouth and dizziness. Weakness, fatigue, insomnia, unpleasant taste and other paresthesias, blurred vision, tachycardia, nausea, and dyspepsia are less frequent. Rarely, there may be headache, nervousness, confusion, disorientation, tremors, ataxia, depression or euphoria, hallucinations, dyspnea, sweating, constipation, urinary difficulty and retention, dysarthria, and various allergic reactions (eg, rash, urticaria, and facial edema). The drug should be used with care in the presence of monoamine oxidase inhibitors (MAOIs) or CNS depressants (including ethanol) and when antimuscarinic drugs also are being given. It is contraindicated in narrow-angle glaucoma, when there is prostatic hypertrophy, after myocardial infarction, or during congestive heart failure, heart block, conduction disturbances, tachydysrhythmias, and thyrotoxicosis.

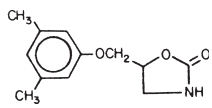
It is absorbed erratically. The onset of action is about 1 hr. It is highly bound to plasma albumin. It is biotransformed and conjugated to glucuronides in the liver. The elimination half-life is 1 to 3 days. Very little is excreted unchanged into the urine, but some is excreted into milk.

DIAZEPAM—page 1489.

MEPROBAMATE—page 1492.

METAXALONE

2-Oxazolidinone, 5-[(3,5-dimethylphenoxy)methyl]-, Skelaxin



[1665-48-1] $C_{12}H_{15}NO_3$ (221.26)

Preparation—Described in *J Am Chem Soc* 1960; 82:1166; US Pat 3,062,827.

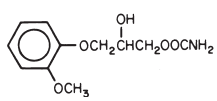
Description—White, crystalline powder; melts about 123°.

Solubility—Very slightly soluble in water; soluble in alcohol; freely soluble in chloroform.

Comments—Reputed to have muscle relaxant properties with a CNS focus of action. Marketed for relief of acute muscle spasm resulting from various injuries or strains, but its efficacy is in serious question, and there seems to be no reason to use the drug in lieu of drugs that obviously are more effective. Furthermore, its toxicity is greater than that of more efficacious drugs. Toxic effects include anorexia, nausea, vomiting, vertigo, drowsiness, nervousness, mental confusion, dry mouth, urinary retention, pruritus, dermatitis; rarely leukopenia, anemia, and jaundice; and possible pyuria, albuminuria, and nephrolithiasis. It may exacerbate grand mal epilepsy. It should not be used when there is anemia, liver or renal disease, or in persons with a history of such disease. Peak blood levels occur in about 2 hr; the duration of action is 4 to 6 hr. Elimination is by hepatic metabolism; the half-life is 2 to 3 hr.

METHOCARBAMOL

1,2-Propanediol, 3-(2-methoxyphenoxy)-, 1-carbamate; Robaxin



3-(*o*-Methoxyphenoxy)-1,2-propanediol 1-carbamate [532-03-6] $C_{11}H_{15}NO_5$ (241.24).

Preparation—3-(*o*-Methoxyphenoxy)-1,2-propanediol participates in a transesterification reaction with ethyl carbonate in the presence of an alkaline catalyst to eliminate ethanol and produce the cyclic carbonate of the starting diol. Subsequent treatment with ammonia ruptures the cyclic carbonate ring and forms the primary carbamate of the starting compound. US Pat 2,770,649.

Description—Fine, white powder; odorless or with a slight characteristic odor; melts between 93° and 97°.

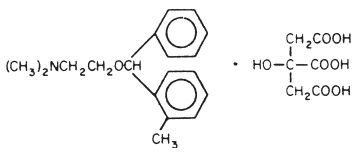
Solubility—1 g in 40 mL water; freely soluble in alcohol; sparingly soluble in chloroform.

Comments—A *centrally acting muscle relaxant*. After parenteral administration, its action is prompt and intense enough to *facilitate orthopedic procedures*. It is used in the *treatment of muscle spasm* resulting from injury, musculoskeletal disorders, tetanus, and other disorders. It has been used with limited success in the treatment of *paralysis agitans, cerebral palsy, multiple sclerosis,* and *cerebrovascular accidents* (with spastic manifestations). Side effects by the oral route include drowsiness, vertigo, headache, fever, rash, itching, urticaria, GI upsets and, rarely, syncope. After parenteral administration there also may be flushing, headache, muscular incoordination, nystagmus, diplopia, hypotension, bradycardia, and metallic taste. These effects are minimized if the injection is given slowly at a rate less than 300 mg/min and no more than 200 mg/injection. Extravasated injections are locally irritating and may cause sloughing or thrombophlebitis. The vehicle for commercial solutions, 50% polyethylene glycol 300, causes uremia in persons with renal dysfunction, and parenteral administration is contraindicated in the presence of renal disease. It should be avoided in pregnancy and in nursing mothers.

It is erratic by the oral route, probably owing to first-pass metabolism. Peak concentration occurs in about 30 min. Most of the drug is metabolized, with an elimination half-life of 1 to 2 hr.

ORPHENADRINE CITRATE

Ethaneamine, *N,N*-Dimethyl-2-[(2-methylphenyl)phenylmethoxy]-, 2-hydroxy-1,2-3-propanetricarboxylate (1:1); Norflex



[4682-36-4] $C_{18}H_{23}NO.C_6H_8O_7$ (461.51).

Preparation—From 2-methylbenzhydrol and 2-(dimethylamino) ethanol; the base is converted to the salt with citric acid (US Pat 2,991,225).

Description—White, crystalline powder; melts about 136°.

Solubility—About 1 g in 70 mL water or 400 mL alcohol.

Comments—Orphenadrine, a methyl analog of the antihistamine diphenhydramine, has weak antihistaminic and mild antimuscarinic activities. The drug reduces voluntary muscle spasm by a central effect. Indications for the citrate are as an adjunct for relief of discomfort associated with acute painful musculoskeletal conditions, by a mode of action not clearly defined but that may be related to the analgesic properties of the compound. It does not directly relax tense skeletal muscles in man. It sometimes induces mild excitement and also a mild euphoria in fatigued or depressed patients. Peripheral atropine-like actions are weak, but blurred vision, dry skin, and dry mouth may occur. Other side effects include nausea, vertigo, rash, headache, dizziness, drowsiness, constipation, increased intraocular pressure, weakness, mental confusion, and occasional hallucinations. It is contraindicated in patients with acute-angle closure glaucoma or myasthenia gravis. It should be used cautiously in patients with GI obstruction, urinary retention, urinary tract obstruction, or tachycardia; propoxyphene appears to interact to increase mental confusion, anxiety, and tremors. The manufacturer's recommendation of a longer interval between doses is based on the retarding effect of the plasticized matrix in which the citrate is compounded in the tablet dosage form. The citrate may be given parenterally.

PROPRANOLOL HYDROCHLORIDE—page 1403.
QUININE SULFATE—page 1667.

ANTIPARKINSON DRUGS

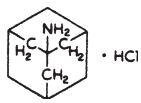
Some kinds of spasticity and involuntary movement arise from disorders within discrete nervous structures that contain neurons predominately of one or two transmitter types. These disorders may be controlled more selectively by drugs directed at the particular neurotransmitters. Parkinsonism (paralysis agitans) is an example of a disorder that lends itself to such specific treatment; the antiparkinson drugs are not interneuron depressants.

The disorder in parkinsonism lies mostly within the substantia nigra and corpus striatum. The cells in the substantia nigra, which connect to the corpus striatum, are mostly dopaminergic and inhibitory; in parkinsonism, the substantia nigra is deficient in dopamine. Striatal neurons that feed back upon the nigral cells are cholinergic and excitatory. Therefore, intervention with either dopaminergic or antimuscarinic drugs is capable of enhancing nigrostriatal activity and improving the condition. Dopaminergic intervention is the more effective, especially against the rigidity. L-Dopa and amantadine exert dopaminergic influences. Used alone, the antimuscarinic drugs are second- or third-order drugs, showing efficacy in fewer than 25% of patients, but they often are used effectively in combination with L-dopa or amantadine.

The antimuscarinic drugs can suppress the extrapyramidal effects of the antipsychotic drugs (phenothiazines, reserpine, etc), but since they mask the tardive dyskinesias, they should not be used chronically with such drugs.

AMANTADINE HYDROCHLORIDE

Tricyclo[3.3.1.1^{3,7}]decan-1-amine, hydrochloride; Symmetrel



1-Adamantanamine hydrochloride [665-66-7] $C_{10}H_{17}N.HCl$ (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* 6:760, 1963.

Description—White crystals; decompose over 360°; pK_a 10.4, (amino group).

Solubility—1 g in 3 mL water or 5 mL alcohol.

Comments—Possesses both antiparkinsonism and antiviral activity, having been introduced as an antiviral agent. Its use in the *prophylaxis of A_2 influenza virus infection (Asian flu)* is less well established and is discussed in Chapter 88.

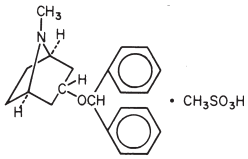
In the brain, it appears to block the reuptake of dopamine at dopaminergic nerve terminals, thus increasing the concentration of dopamine at the synapses. This facilitates the function of the remaining nigrostriatal neuronal pathways in patients with parkinsonism. It is inferior to levodopa but somewhat superior to the antimuscarinic drugs. Patients sometimes are improved dramatically, but the usual response is moderate to mediocre. Even when the response is excellent, usually after 6 to 8 weeks of continuous treatment, the efficacy gradually wanes, and control may be lost between months 2 and 18. Such tolerance is minimal if the drug is used for periods of only 2 to 3 weeks separated by intervals of several weeks. Consequently, many physicians administer the drug only for short periods, when the patient requires additional treatment. In combination with levodopa, better control is maintained than with either agent alone.

It may cause hyperexcitability, tremors, anxiety, ataxia, slurring of speech, insomnia, drowsiness, lethargy, psychic depression, vertigo, and postural hypotension. Less frequently, it may induce dry mouth, constipation, abdominal pain, nausea, vomiting, headache, dizziness, dyspnea, fatigue, and urinary retention. Dermatitis, pruritus, and livedo reticularis occasionally occur. Edema, which may precipitate cardiac congestion, is not infrequent. Confusion and visual hallucinations are seen, especially if the recommended dose is exceeded. Alkaline phosphatase in the blood may be elevated. It exaggerates the peripheral effects of the antimuscarinic drugs used during treatment. The drug is contraindicated in epileptics. There are indications that the drug may increase the incidence of measles. Medicated persons should avoid driving or other tasks in which safety depends upon alertness.

Orally, it is absorbed rapidly and completely. Over 90% is excreted in the urine unchanged. The elimination half-life is 10 to 37 hr; the half-life is pH-dependent, being increased at higher urine pH. It also is increased in renal impairment. It crosses the placental barrier and also is excreted into milk.

BENZTROPINE MESYLATE

8-Azabicyclo[3.2.1]octane, *endo*-3-(diphenylmethoxy)-, methanesulfonate; Benztropine Methanesulfonate; Cogentin



3α-(Diphenylmethoxy)-1α*H*,5α*H*-tropane methanesulfonate [132-17-2] $C_{21}H_{25}NO.CH_4O_3S$ (403.54).

Preparation—Bromodiphenylmethane, formed by bromination of diphenylmethane, is condensed with tropine, using the sodium alkoxide derivative of tropine. After purification, the benztropine base thus obtained is dissolved in a suitable organic solvent and precipitated by reaction with methanesulfonic acid.

Description—White, crystalline powder; colorless; slightly hygroscopic; melts between 141° and 145°; pK_a 10.

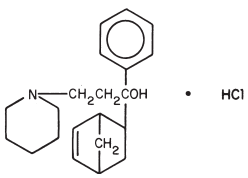
Solubility—Very soluble in water; freely soluble in alcohol; very slightly soluble in ether.

Comments—The structure of benztropine resembles both atropine and antihistaminics of the diphenhydramine type. It is thus an antimuscarinic drug of potency one-quarter that of atropine sulfate and an antihistaminic of potency equal to that of pyrilamine maleate. It also possesses local anesthetic properties. However, only its central actions to suppress tremor and rigidity are employed therapeutically. These actions are similar to those of atropine, but unlike atropine, it possesses sedative and other effects similar to those of diphenhydramine. Since some patients, particularly the elderly, often are excited by other antiparkinson drugs, the sedative property is of special value. It is used mainly in the treatment of *paralysis agitans* (parkinsonism; see the introductory statement) to control tremor and rigidity and also to relieve sialorrhea, oculogyric crises, mask-like facies, and pain secondary to muscle spasm. It also is used to treat extrapyramidal dyskinesia, but not tardive dyskinesia, resulting from the use of tranquilizers, such as reserpine or chlorpromazine. It may be used alone or in combination with other drugs.

Side effects include dry mouth, mydriasis, blurred vision, nausea, and nervousness, and less frequently, they may include vomiting, mental confusion, ataxia, sedation or excitement, hallucinations, paralysis of some muscle groups, dysphagia, hyperpyrexia, rash, and difficulty in urination. As with any antimuscarinic drug, it must be used cautiously in the presence of bladder neck obstruction or glaucoma.

BIPERIDEN HYDROCHLORIDE

1-Piperidinepropanol, α-bicyclo[2.2.1]hept-5-en-2-yl-α-phenyl-, hydrochloride; Akineton



α-5-Norbornen-2-yl-α-phenyl-1-piperidinepropanol [1235-82-1] $C_{21}H_{29}NO.HCl$ (347.93).

Preparation—Acetophenone undergoes a Mannich condensation with formaldehyde and piperidine hydrochloride and the resulting 3-piperidinopropiophenone is grignardized in benzene with 5-chloro-2-norbornene to yield the tertiary carbinol biperiden, which is extracted with methanol. Saturation of the solution with dry HCl yields the salt. US Pat 2,789,110.

Description—White, odorless, crystalline powder; decomposes about 275°; somewhat light-sensitive.

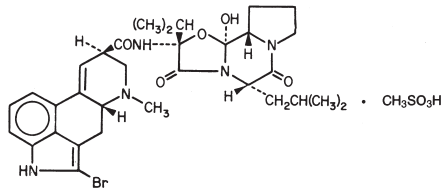
Solubility—Slightly soluble in water, alcohol, chloroform, or ether; sparingly soluble in methanol.

Comments—Exerts *antimuscarinic* and *antiparkinson* actions similar to those of trihexyphenidyl, of which biperiden is a congener. In the treatment of *paralysis agitans* (parkinsonism) it reduces tremor, akinesia, muscle rigidity, drooling, and sweating. It may also decrease the incidence and severity of oculogyric crises. It sometimes is of value in lessening spasticity in certain disorders of the pyramidal tract, particularly drug-induced extrapyramidal dyskinesia. The IV form (ie, the lactate) is employed for the management of severe drug-induced extrapyramidal dyskinesia.

Untoward effects result from the antimuscarinic properties and include dry mouth, blurring of vision, urinary retention, and heat stroke in hot weather. These effects usually are of low intensity and often do not result in intolerance. Less frequently, there occur drowsiness, dizziness, headache, dysuria, gastric irritation, and rash and, rarely, confusion, disorientation, hallucinations, or psychotic episodes. The patient should be monitored carefully if glaucoma or urinary bladder neck obstruction exist.

BROMOCRIPTINE MESYLATE

Ergotaman-3′,6′,18-trione methanesulfonate; Parlodel



2-Bromoergocryptine monomethanesulfonate (salt) [22260-51-1] $C_{32}H_{40}BrN_5O_5.CH_3SO_3H$ (750.70).

Preparation—From *N*-bromosuccinimide and α-ergocryptine (US Pat 3,752,814).

Description—Yellowish white, crystalline powder; melts about 194° with decomposition; pK_a 4.90.

Solubility—Soluble in water or chloroform; very soluble in benzene or hexane; poorly soluble in most organic solvents.

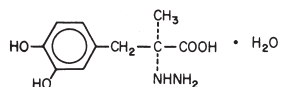
Comments—The 2-bromo derivative of α-ergocryptine. Like all of the ergot alkaloids, it has dopamine-like agonist activity. In the treatment of *parkinsonism* it is used to supplement levodopa, when refractoriness to that agent develops. It also decreases the secretion of prolactin, presumably by its dopaminergic actions in the median eminence; some authorities consider dopamine to be the prolactin release- inhibiting hormone. It is used to treat *galactorrhea* and associated *amenorrhea* and male and female prolactin-induced infertility. Approximately 4 weeks are required for an effect to peak. It is used to *shrink prolactinomas* prior to surgery. The drug also is used to *suppress postpartum lactation*. It decreases growth hormone secretion in *acromegaly* and is used to treat that disorder, mostly as an adjunct to radiotherapy or surgery; used alone, only a low percentage of remissions occur. It also has been used in the management of senile depression and related disorders.

The incidence of adverse effects seems to differ according to the particular clinical disorder, even when the same dosage regimen is used. When it is used to treat galactorrhea/amenorrhea/female infertility, nearly 70% of recipients have adverse effects, whereas only about 23% have adverse effects when the drug is used to suppress physiological lactation. Adverse effect–related discontinuation of treatment occurs in 3 to 7% of cases. In parkinsonism, the incidence is complicated by the concomitant administration of levodopa. Nausea is the most frequent side effect (51%) in galactorrhea but occurs in only 7% of postpartum patients. The incidences of other side effects are headache, 10–18%; dizziness, 8–16%; postural hypotension, up to 28%; vomiting, 3–5%; fatigue, 1–7%; diarrhea, 0.4–3%; nasal congestion, up to 5%. Other, less-frequent side effects (mostly in parkinsonism) are occasional syncope, urinary frequency and incontinence, dyskinesias, visual disturbances, paresthesias, anxiety, nightmares, anorexia, depression, convulsions, cutaneous vasoconstriction, mottling of the skin and Raynaud's phenomenon, muscle cramps, ataxia, erythromyalgia, and rashes. There may be elevations in BUN, alkaline phosphatase, urate, CPK, SGOT, SGPT, and GPT, which usually are transient. It is teratogenic and also may induce spontaneous abortions. The drug is contraindicated in angina pectoris, peripheral vascular disease, pregnancy, and if sensitivity to ergot alkaloids exists. Since it has been reported to cause delusions and hallucinations in postschizophrenics, it also should be withheld in patients with a history of psychoses.

Although about 28% of an oral dose is absorbed from the gut, only 6% reaches the systemic circulation, because of first-pass metabolism. One to 2 hr are required for onset of action; action persists for 6 to 14 hr.

CARBIDOPA

Benzenepropanoic acid, *(S)*-α-hydrazino-3,4-dihydroxy-α-methyl-, monohydrate, Lodosyn; ing of Sinemet



(−)-L-α-Hydrazino-3,4-dihydroxy-α-methylhydrocinnamic acid monohydrate [38821-49-7] $C_{10}H_{14}N_2O_4.H_2O$ (244.25); *anhydrous* [28860-95-9] (226.23).

Preparation—Condensation of 1-(4′-hydroxy-3′-methoxyphenyl)-2-propanone with aqueous hydrazine and potassium cyanide forms the corresponding hydrazinenitrile, which is hydrolyzed first with HCl to convert the nitrile to amide and then refluxed with HBr to convert the amide to carboxyl and the methoxy group to OH, yielding the DL-form of carbidopa (Sletzinger et al, *J Med Chem* 6:101, 1963). To obtain the L-form, one method involves acylation of the aforementioned hydrazinenitrile and resolution with 1-menthoxyacetyl chloride, producing crystals that on hydrolysis yield the levorotatory compound (Karady et al, *J Org Chem* 36:1946, 1949, 1971).

Description—White to creamy white powder; odorless or practically odorless, melts about 205° with decomposition; pK_a 2.3, 7.3.

Solubility—Slightly soluble in water; practically insoluble in alcohol, chloroform, or ether; freely soluble in 3*N* hydrochloric acid.

Comments—An inhibitor of L-aromatic amino acid decarboxylase, often called dopa-decarboxylase. It has no direct therapeutic actions of its own but, rather, is used only to *protect levodopa* and L-*5-hydroxytryptophan,* both of which are decarboxylated by aromatic amino acid decarboxylase. Levodopa is 95% decarboxylated in the periphery.

It does not enter the CNS in concentrations sufficient to inhibit aromatic amino acid decarboxylase, so its action is limited to the periphery, which is precisely what is desired. It is essential that levodopa and 5-hydroxytryptophan be decarboxylated in the brain to their respective biogenic amine products, dopamine and serotonin (5-hydroxytryptamine), which are the active agents. But in the periphery it is not desirable that these amino acids be decarboxylated, since decarboxylation not only lowers the concentration of aromatic amino acid available to the brain but also raises the concentrations of the amine products in the periphery, which give rise to some of the untoward effects of the aromatic amino acids. When it is given concomitantly with levodopa, only about 25% as much levodopa is needed; the onset of response is more rapid; pyridoxine no longer suppresses the efficacy; dietary control no longer is necessary; and certain side effects, such as nausea, vomiting, and natriuresis, are diminished. The combination permits smoother control of parkinsonism than with levodopa alone.

The side effects that result from the levodopa-derived amines in the brain (psychic disturbances, dyskinesias) or the static hypotension and cardiac arrhythmias are not affected. Indeed, they may occur sooner and be more serious if the dose of levodopa is not reduced sufficiently.

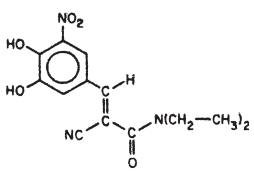
In the approved doses, it does not appear to cause adverse effects, even though the production in the periphery of dopamine and serotonin, which have natural physiological roles in the periphery, may be diminished. Therefore, side effects, precautions, and contraindications of a combination of levodopa and carbidopa are those of levodopa (see this page).

The drug may be given with levodopa from the outset of levodopa therapy or added after levodopa therapy is in progress. Since inhibition of peripheral dopa decarboxylase approximately quadruples the availability of levodopa to the brain, it is advisable to reduce ongoing levodopa dosage when adding this drug. Consequently, levodopa first should be discontinued for at least 8 hr and then reinstituted at 20% to 25% of the previous effective dose. Although it is available in a single-entity preparation to add to levodopa, it is simpler to employ a fixed-dose combination of the two. Fixed-dose ratios of 1:10 and 2.5:10 are available. Carbidopa saturates dopa decarboxylase in daily doses of about 70 to 100 mg. Some dosage schedules for the fixed-dose combination fail to provide a sufficient amount of this drug, and there may be persistence of some of the peripheral adverse effects of levodopa. This is especially the case when the daily dose of levodopa is less than 700 mg. Therefore, there is a place for single-entity preparation in the correction of such shortfalls of this drug. The approved dosage limit for it is 200 mg a day.

DIPHENHYDRAMINE—pages 1545 and 1548.

ENTACAPONE

Cinnamamide, (*E*)-α-cyano-*N,N*-diethyl-3,4-dihydroxy-5-nitro-; Comtan



[130929-57-6] $C_{14}H_{15}N_3O_5$ (305.29).

Preparation—From 3,4-dihydroxy-5-nitrobenzaldehyde and N,N-diethylcyanoacetamide heated in absolute ethanol with a catalytic amount of piperidine acetate. US Pat 5,446,194(1995).

Description—Crystals from acetic acid-HCl; melts about 153-156°; pK_a - 4.5.

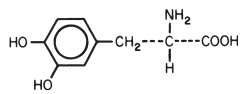
Comments—A selective and reversible inhibitor of catechol-*O*-methyltransferase (COMT). In mammals, COMT is distributed throughout various organs with the highest activities in the liver and kidney. COMT also occurs in the heart, lung, smooth and skeletal muscles, intestinal tract, reproductive organs, various glands, adipose tissue, skin, blood cells, and neuronal tissues, especially in glial cells. COMT catalyzes the transfer of the methyl group of *S*-adenosyl-L-methionine to the phenolic group of substrates that contain a catechol structure. Physiological substrates of COMT include copa, catecholamines (dopamine, norepinephrine, and epinephrine) and their hydroxylated metabolites. In the presence of a decarboxylase inhibitor, COMT becomes the major metabolizing enzyme for levodopa, catalyzing the metabolism to 3-methoxy-4-hydroxy-L-phenylalanine (3-OMD) in the brain and periphery.

The mechanism of action of entacapone is believed to be through its ability to inhibit COMT and alter the plasma pharmacokinetics of levodopa. When it is given in conjunction with levodopa and an aromatic amino acid decarboxylase inhibitor, such as carbidopa, plasma levels of levodopa are greater and more sustained than after administration of levodopa and an aromatic amino acid decarboxylase inhibitor alone. It is believed that at a given frequency of levodopa administration, these more sustained plasma levels of levodopa result in more constant dopaminergec stimulation in the brain, leading to greater effects on the signs and symptoms of Parkinson's disease. The higher levodopa levels also lead to increased levodopa adverse effects, something requiring a decrease in the dose of levodopa.

HYOSCYAMINE SULFATE—page 1408.

LEVODOPA

L-Tyrosine, 3-hydroxy-, L-Dopa; ing of Sinemet



(−)-3-(3,4-Dihydroxyphenyl)-alanine [59-92-7] $C_9H_{11}NO_4$ (197.19).

Preparation—By indirect resolution of DL-3-(3,4-dihydroxyphenyl)alanine (DL-dopa). One method first converts this to DL-*N*-acetyl-3-methoxy-4-acetoxyphenylalanine and then resolves the latter with the aid of α-phenethylamine. Hydrolysis of the desired enantiomer with aqueous HBr yields levodopa. The starting DL-dopa may be synthesized commencing with vanillin and glycine.

Description—Fine, white to off-white, crystalline powder; oxidized by atmospheric oxygen in the presence of moisture and darkens; melts about 280° with decomposition; pK_a 2.3, 8.7, 9.7, 13.4.

Solubility—1 g in 10 mL 0.1*N* HCl, 250 mL water, about 555 mL alcohol, or 1000 mL chloroform.

Comments—The single most important drug in the treatment of incapacitating *paralysis agitans* (parkinsonism). The neurochemical basis was indicated in the introductory statement. It also is effective in nonincapacitating parkinsonism, but its cost and side effects are such that its use is not warranted in many patients. Approximately 65% to 80% of patients are improved, some quite dramatically. The greatest effects are on rigidity and hypokinesia. Sialorrhea, dysphagia, seborrhea, postural instability, speech difficulties, and glabellar reflexes usually are suppressed and may be abolished. Tremor and akinesia respond only erratically and require prolonged treatment, up to 6 months, before improvement ensues. All forms of parkinsonism respond; the idiopathic form responds best, but the postencephalitic form responds to lower doses. Paradoxically, the postencephalitic patient may experience more severe adverse effects, including exacerbation of oculogyric crises, than patients with idiopathic or other forms of the disease. Consequently, postencephalitic patients require a conservative dosage regimen that increases the dose quite slowly. Levodopa also is used to treat the parkinsonism-like neurological syndrome of *manganese intoxication,* in which there is also a deficiency of dopamine in the basal ganglia.

It is 40% to 70% absorbed orally. Less than 1% penetrates into the brain. There and throughout the body, it is 99% decarboxylated to dopamine. Concurrent carbidopa (above) administration prevents peripheral decarboxylation and enhances availability to the brain. Peak concentrations of dopamine in the brain occur 1 to 2 hr after administration. The plasma half-life of levodopa alone is 0.5 to 1 hr; in combination with carbidopa it is 1.2 to 2.3 hr.

Nearly every patient experiences untoward effects, but only 5% find it desirable or necessary to discontinue medication. Nausea will occur in virtually all, and anorexia, vomiting, flatulence, epigastric pain, and dry mouth in most patients. Peptic ulceration and GI bleeding sometimes occur. With a slow increase in dosage, the GI side effects are less severe, and tolerance tends to develop. If nausea and

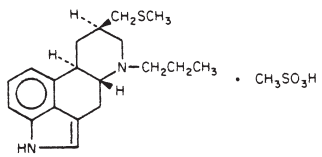
vomiting are intolerable, they may be managed with non-phenothiazine-, non- pyridoxine-containing antiemetics. The second most common type of side effect is the appearance of abnormal involuntary movements, which usually start with the face and tongue and gradually move downward to involve the arms, hands, and trunk. These dyskinesias are most severe 1 to 2 hr after administration. These effects are not seen immediately but progress slowly over a year's time. Eventually, nearly 75% of patients will show some such movements; however, most patients accept such movements as the price of increased mobility. The involuntary movements can be decreased by lowering the dose or by use of haloperidol or pyridoxine, but these recourses also abolish the therapeutic response to this drug. Hypotension occurs in about 75%, and orthostatic hypotension in about 30% of recipients, but vertigo and syncope are uncommon. Cardiac arrhythmias occur occasionally. After 2 or 3 months, tolerance develops. Increased myocardial contractility, tachycardia, and atrial fibrillation may occur. Behavioral changes frequently accompany treatment. Increased CNS excitability, with nervousness, anxiety, insomnia, vivid dreams, tremor, and flushing occurs. Paranoid ideation, delusions, hallucinations (often olfactory), delirium, and loss of judgment sometimes occur. Easy sexual arousal and loss of sexual inhibitions are common; in part this is the result of the emergence of normal desire long suppressed by physical incapacity. Serum glutamic oxaloacetate transaminase and glutamic pyruvate transaminase may be elevated somewhat early during therapy, but they usually subside later. Transient granulocytopenia may occur; agranulocytosis no longer seems to be an adverse effect, since the dextro form was removed from the preparations. Dental caries is accelerated, and fillings often fall out, perhaps because the buffering effect of sialorrhea is diminished. Other miscellaneous side effects include increased pain when pain-producing pathology or headache exists, sweating, alopecia, cough, hoarseness, urinary frequency, incontinence or retention, nocturia, mydriasis, blurred vision, Horner's syndrome, fever, hot flashes, and loss or gain in weight. A mild natriuresis occurs, probably as the result of the action of dopamine formed in the kidney. Thrombocytopenia occurs rarely after long-term treatment.

Pyridoxine antagonizes levodopa, possibly by promoting premature decarboxylation (as a coenzyme to dopa decarboxylase) before levodopa has penetrated into the brain. Some antagonism occurs with even as little as a Recommended Dietary Allowance, so patients should not take multivitamin supplements containing pyridoxine. To what extent some of the side effects of the CNS are attributable to pyridoxine deficiency is not known. Carbidopa prevents antagonism by pyridoxine. Methyldopa and reserpine, which interfere with catecholamine synthesis and storage, exacerbate the parkinson syndrome and, hence, antagonize levodopa. Tricyclic antidepressants and MAOIs given concomitantly evoke hypertensive crises and may precipitate many of the adverse side effects of the CNS, because they increase the local concentrations of dopamine formed from levodopa. Such drugs should be discontinued 2 weeks prior to taking levodopa. Antacids decrease gastric emptying time and thereby promote absorption, thus increasing efficacy in some patients. Levodopa is synergized by antimuscarinics.

Levodopa is contraindicated when there is evidence of uncompensated endocrine, renal, hepatic, pulmonary, or cardiovascular disease; narrow-angle glaucoma; blood dyscrasia; or hypersensitivity to the drug. It should be used cautiously in diabetes, hyperthyroidism, wide-angle glaucoma, epilepsy, and hypotension or when antihypertensives are being used. The drug should be discontinued 24 hr prior to anesthesia. Levodopa is a precursor of melanin and may activate latent malignant melanoma; it should be withheld from persons with a history of malignant melanoma or suspicious skin lesions.

PERGOLIDE MESYLATE

Ergoline-, [8-(methylthio) methyl]-6-propyl-, methanesulfonate salt, Permax



[66104-23-2]$C_{19}H_{26}S.CH_4O_3S$(410.59).

Preparation—See US Pat 4,166,182.

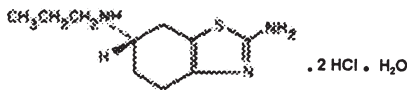
Description—White solid; melts at 207°. Log P at 25° (CHC_3/water) 6.14 at pH 2.2; 119.6 at pH 4.

Solubility—Sparingly soluble in DMF or ethanol; slightly soluble in water, 0.01 *N* HCl, chloroform acetonitrile, methylene chloride, absolute alcohol; very slightly soluble in acetone; practically insoluble in dilute NaOH, HCl or ether.

Comments—Has actions and uses like those of bromocriptine and is indicated as an adjunct to levodopa/carbidopa for the management of Parkinson's disease. It has both D_1- and D_2-dopaminergic activity. Side effects include nausea and vomiting, postural hypotension, premature ventricular contractions, confusion and hallucinations, dyskinesias, elevated SGOT, sedation, hallucinations, xerostomia and, rarely, reversible pleural fibrosis. It is likely that other side effects like those of bromocriptine eventually will be reported. The duration of action exceeds 24 hr.

PRAMIPEXOLE DIHYDROCHLORIDE

2,6-Benzothiazolediamine, (*S*)-4,5,6,7-tetrahydro-N^6-propyl-, dihydrochloride; Mirapex



(*S*)-2-Amino-4,5,6,7-tetrahydro-6-(propylamino)benzothiazole, dihydrochloride monohydrate [104632-26-0 (free base)] $C_{10}H_{17}N_3S.HCl.H_2O$ (302.27).

Preparation—Butanal and 2,6-diamino-4,5,6,7-tetrahydrobenzothiazole are heated in DMF and the imine reduced with sodium borohydride; water is added and acidified tp pH 1, extracted with ethyl acetate, which is discarded. The aqueous phase is made alkaline with potassium carbonate, extracted with ethyl acetate, dried, concentrated and the salt precipitated with ethereal HCl. *J Med Chem*, 1987; 30: 494. See also US Pat 4,886,812.

Description—White to off-white crystals from methanol; melts at 286–88°; $[\alpha]_D^{20}$ -67.2° (c = 1, MeOH). ***Note***: The bulk drug is stable but the tablets are susceptible to photo-degradation and should be protected from light.

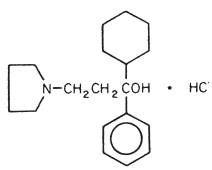
Solubility—About 20% in water, 8% in methanol or 0.5% in ethanol. Insoluble in chlorinated hydrocarbons.

Comments—A nonergot dopamine agonist with high relative in vitro specificity and full intrinsic activity at the D_2 subfamily of dopamine receptors, binding with higher affinity to D_3 than to D_2 to D_4 receptor subtypes. The relevance of D_3 receptor binding in Parkinson's disease is unknown.

The precise mechanism of its action as a treatment for Parkinson's disease is unknown, although it is believed to be related to its ability to stimulate dopamine receptors in the striatum. This is supported by electrophysiologic studies in animals that have demonstrated that it influences striatal neuronal firing rates via activation of dopamine receptors in the striatum and the substantia nigra, the site of neurons that send projections to the striatum.

PROCYCLIDINE HYDROCHLORIDE

1-pyrrolidinepropanol, α-cyclohexyl-α-phenyl-, hydrochloride; Kemadrin



[1508-76-5] $C_{19}H_{29}NO.HCl$ (323.91)

Preparation—From the cyclohexyl Grignard reagent and 3-(1-pyrrolidinyl)propiophenone; the resulting base then is converted to the hydrochloride.

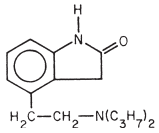
Description—White, crystalline powder melts about 226°.

Solubility—About 1 g in 33 mL water; more soluble in alcohol.

Comments—An antimuscarinic drug used mostly as a substitute for trihexyphenidyl in the treatment of parkinsonism when the latter drug fails to control symptoms. Sometimes it is used in combination with other drugs. The side effects, precautions, and contraindications are those of trihexyphenidyl.

ROPINIROLE HYDROCHLORIDE

2*(H)*-Indol-2-one, 4-[2-(dipropylamino)ethyl]-1,3-dihydro-, monohydrochloride; Requip



[91374-20-8] $C_{16}H_{24}N_2O.HCl$ (296.84).

Preparation—The acid chloride of 2-(2-methyl-3-nitrophenyl)acetic acid is prepared with thionyl chloride, then treated with dipropylamine to form the amide. The carbonyl group is reduced with borane in THF and then reacted with diethyl oxalate and sodium in alcohol in a Claisen-type reaction to produce the ethyl ester of 3-[[2-(dipropylamino)ethyl]-6-nitrophenyl]pyruvic acid. Hydrolysis and decarboxylation of the acid with peroxide and base removes the ethoxycarbonyl group and forms 2-[2-(dipropylamino)ethyl]-6-nitrophenylacetic acid. Cyclization to the product is effected by catalytic reduction of the nitro group, using palladium/hydrogen to give the amine, which through loss of water forms the lactam (indolone). Heating with HCl forms the title substance.

Description—White to pale yellowish green powder melting about 245°.

Solubility—About 130 mg/mL of water.

Comments—A dopamine receptor antagonist. This nonergot derivative displays high-affinity specificity for dopamine D_2 receptors.

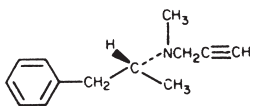
It has been approved for the management of symptoms associated with mild-to-severe Parkinson's disease. The precise mechanism of action has not been elucidated clearly. Unlike levodopa, which is thought to act by elevating synaptic concentrations of dopamine, ropinirole is presumed to be effective by direct activation of postsynaptic dopamine receptors in the corpus striatum.

In several double-blind controlled trials, ropinirole was found to be effective in improving daily activities of patients with parkinsonian syndrome and reduce their motor manifestations such as bradykinesia, tremor, rigidity, and postural instability. In addition, it was reported to reduce the off-time of patients with advanced symptoms who were experiencing the deteriorating response to levodopa treatment.

Patients receiving dopamine agonists should be counseled to avoid rapid transitions in posture due to increased likelihood for development of orthostatic hypotension. Patients receiving ropirinole are also at increased risk for hallucinations. This particular adverse effect is greater in the geriatric population.

SELEGILINE HYDROCHLORIDE

Benzeneethanamine, *N*,α-dimethyl-*N*-2-propynyl-, hydrochloride; Deprenyl; L-Deprenyl; Eldepryl



[14611-52-0] $C_{13}H_{17}N.HCl$ (223.78).

Preparation—By reacting propargyl bromide with L-(*N*,α-dimethyl)- phenethylamine and distilling the extracted oil. US Pat 3,496,195.

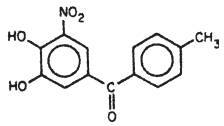
Description—Oil, boiling point 92° to 93° at 0.8 mm; η_D^{20} 1.518; $t\alpha_D$ −11.2. The HCl salt melts about 141°.

Solubility—Freely soluble in water, chloroform, or methanol.

Comments—An inhibitor of monoamine oxidase B, which enzyme is selective for dopamine over norepinephrine and epinephrine. As such, selegiline is an approved adjunct to levodopa for the treatment of parkinsonism. The drug decreases the effective dose of levodopa and smooths out dose-related fluctuations in efficacy, effects that should rouse only mild interest. However, recent reports indicate that it slows the progress of idiopathic parkinsonism and increases the lifespan of the afflicted. The drug is converted to amphetamine and methamphetamine in the body, which metabolites possibly account for some of the antiparkinson activity. Dyskinesias have been reported to occur in about one-third of users, but this high incidence of adverse effects is undoubtedly the result of failure to reduce the dose of levodopa to which the drug was added. Dry mouth, nausea, and dizziness occur in 10–20% of cases. Side effects of low incidence are postural hypotension, unpleasant taste, circumoral paresthesias, hallucinations, depression, and paranoia.

TOLCAPONE

Methanone, (3,4-dihydroxy-5-nitrophenyl)(4-methyphenyl)-; Tasmar



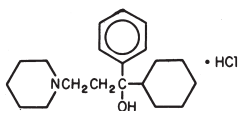
3,4-Dihydroxy-4′-methyl-5-nitrobenzophenone [134308-13-7] $C_{14}H_{11}NO_5$ (273.25).

Preparation—*Drugs of the Future* 16:719, 1991.

Description—Yellow, odorless, non-hygroscopic crystals from methylene chloride; melts about 147°.

TRIHEXYPHENIDYL HYDROCHLORIDE

1-Piperidinepropanol, α-cyclohexyl-α-phenyl-, hydrochloride; Artane; Benzhexol Hydrochloride



α-Cyclohexyl-α-phenyl-1-piperidinepropanol hydrochloride [52-49-3] $C_{20}H_{31}NO.HCl$ (337.93).

Preparation—From a Mannich reaction of acetophenone, piperidine, and formaldehyde. The piperidinopropiophenone formed is treated as for *Procyclidine*.

Description—White or slightly off-white, crystalline powder; no more than a very faint odor; melts between 247° and 253° with slight decomposition.

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

Comments—Has weak *antimuscarinic* and *antispasmodic* activity. In the treatment of parkinsonism it is preferred to levodopa in patients with mild-to-moderate nonincapacitating symptoms, and most neurologists prefer to begin treatment of all patients with it. It is effective in all forms of the disease, although not uniformly. It is most effective against rigidity, but it also is useful in the relief of akinesia, tremor, sialorrhea, and oculogyria. Tolerance may develop, but not necessarily. It also is useful in the treatment of *drug-induced extrapyramidal dyskinesias*.

The adverse effects mostly derive from its antimuscarinic actions, but they are much less troublesome than with atropine. The most frequent are dry mouth, blurred vision, tachycardia, constipation, dry skin, nervousness, headache, sedation, and muscle weakness. Some of these effects subside after continued administration. Sometimes insomnia may occur. Urinary retention is infrequent, but it does occur. Occasionally, vomiting, severe tinnitus, vertigo, suppurative parotitis, or rash occur and may require discontinuation of medication. With large doses, inability to concentrate, impaired memory, disorientation, and confusion may occur, and if the dose is not reduced, they are followed by agitation, excitement, delirium, visual hallucinations, and psychoses. Elderly patients or persons with arteriosclerosis especially are susceptible to the adverse central effects. It should be used cautiously in persons with cardiovascular or liver pathology, glaucoma, bladder neck obstruction, prostatitis, hyperthyroidism, or arteriosclerosis and in elderly patients. Trihexyphenidyl may interact with CNS-active antihypertensive drugs, ethanol and other CNS depressants, tricyclic antidepressants, MAOIs, other antimuscarinic drugs, dopamine agonists, dopamine antagonists, phenothiazine, and procainamide. When it is used in combination with levodopa, bromocriptine, or amantadine, the doses of both drugs in combination may need reduction.

ACKNOWLEDGMENT—The author acknowledges the tremendous efforts of H Steve White, PhD in previous editions of this work.

CHAPTER 75

Diuretic Drugs

Cynthia A Burman, BS, PharmD

Diuretics are drugs that reduce the volume of extracellular fluid, enhance the urinary excretion of sodium chloride, and, secondarily, increase the volume of urine excreted by the kidneys. They are used primarily to prevent and alleviate edema and ascites. These conditions occur in diseases of the heart, kidneys, and liver. Consequently, diuretics are used in the treatment of edema associated with chronic congestive heart failure, acute pulmonary edema, edema of pregnancy, brain edema, and cirrhosis associated with ascites. They also are used in hypertension, diabetes insipidus, renal calculi, hypercalcemia, acute and chronic renal failure, and the nephrotic syndrome.[1]

Some diuretics have highly specialized uses in glaucoma, hyperkalemia, bromide intoxication, anginal syndrome, epilepsy, migraine, and premenstrual depression, conditions in which edema is not present or at least not definitely established. In addition, diuretics sometimes are used to maintain adequate urine volume, as in the case of some severe traumatic injuries, or to reduce the concentration of a noxious agent in the urine, to minimize renal damage.

The formation of urine from the blood, in simplest terms, consists of glomerular filtration and selective tubular reabsorption and secretion. In healthy individuals, the filtration rate amounts to 180L/day.[1] As the glomerular filtrate passes through the tubules, substances essential to the blood and tissues—water, glucose, salts, and amino acids—are reabsorbed.

Other substances in the glomerular filtrate, such as urea, are not absorbed as readily by the tubules. Thus, it is thought that in the renal tubule there is a specific mechanism for the transport of each ionic species, the capacities of which are quite different. For example, the capacity of the renal tubule to reabsorb sulfate ion is limited. The tubular capacity for the reabsorption of phosphate is such that a sufficient amount is reabsorbed to maintain the normal extracellular level, and any excess is excreted. On the other hand, much larger amounts of bicarbonate ion and chloride ion can be reabsorbed.

Under normal circumstances the glomerular filtration rate is about 100 mL/min. About 99 mL of the fluid is returned to the blood, and only 1 mL is excreted as urine. It follows, therefore, that drugs may increase the rate of urine formation by:

1. Increasing glomerular filtration
2. Decreasing tubular reabsorption

Increasing glomerular filtration is not an efficient mechanism and usually causes only a moderate increase in urine formation. If, for example, the percentage of fluid reabsorbed by the renal tubules is assumed to remain constant, glomerular filtration rate would have to be increased twofold to double the urinary output. On the other hand, a 1% decrease in the tubular reabsorption of water, induced either by the administration of excessive quantities of electrolytes or nonelectrolytes (osmotic diuretics) or by agents that alter selective reabsorption of substances in the renal tubules, would double the urinary output.

Most diuretics block sodium and/or chloride reabsorption in the renal tubules.[2] This results in natriuresis and diuresis. However, the mechanism(s) by which diuretics block the reabsorption and the site of action varies; they may act at the proximal tubule, loop of Henle, distal tubule, collecting tubule, or combinations of these sites.

Osmotic diuretics are thought to produce diuresis by multiple mechanisms. Mannitol, the most widely used osmotic diuretic, is freely filtered at the glomerulus and is not reabsorbed by the renal tubules. Because of its osmotic action in the proximal tubule and thick ascending limb, mannitol prevents the reabsorption of water and impairs sodium and chloride reabsorption by lowering the concentration in the tubular fluid.[2] *Carbonic anhydrase inhibitors* act on the proximal convolution and possibly the collecting tubule to inhibit cytoplasmic and brush border carbonic anhydrase. This enzyme catalyzes the reaction $CO_2 + OH^- \rightarrow HCO_3^-$ The overall inhibition of carbonic anhydrase decreases bicarbonate reabsorption and passive forces favoring chloride reabsorption. The excess chloride (with accompanying sodium) subsequently is reabsorbed in the loop of Henle. The net effect is bicarbonate is excreted with both sodium and potassium, but the total diuretic effect is minimal.[2] After several days of continuous administration, a mild hyperchloremic acidosis develops, which decreases the diuretic effect.

Thiazide diuretics act mainly to block sodium and chloride reabsorption at the distal convoluted tubule, connecting tubule, and early collecting duct.[2] At sufficient concentrations thiazides have mild inhibitory activity toward carbonic anhydrase. The resulting natriuresis is accompanied by increased excretion of potassium (particularly in short-term treatment), bicarbonate, chloride, and water. However, glomerular filtration rate actually may be reduced by these drugs, causing a problem in patients with diminished renal reserve. The antihypertensive action of the thiazides may be attributable to:

A depletion of sodium and subsequent reduction in plasma volume
A decrease in peripheral resistance

Thiazides are useful in blunting the sodium retention that occurs with vasodilators.

Potassium-sparing diuretics interfere with sodium absorption in the distal tubules and collecting ducts, thereby promoting sodium excretion while conserving potassium. Aldosterone stimulates the exchange of sodium for potassium and hydrogen. Therefore, spironolactone, a competitive inhibitor of aldosterone, blocks sodium reabsorption through a different mechanism than triamterene and amiloride. Triamterene and amiloride interfere directly with electrolyte transport. These agents are not potent diuretics when used alone, but there main use is to correct potassium and/or magnesium deficiency.

Potassium-sparing diuretics are often with a thiazide diuretic. The onset of diuresis with combination therapy is much more rapid than with spironolactone alone (4 to 7 days).

Loop, or high-ceiling, diuretics act mainly on the medullary and cortical portions of the thick ascending loop of Henle and cause a peak diuresis far greater than that that occurs with other diuretics. At the thick ascending limb of the loop of Henle 20% to 30% of filtered sodium is reabsorbed and a maximally effective dose of a loop diuretic can cause excretion of 20% to 25% of filtered sodium.[3] The thick ascending limb is also important for urinary concentration ability. Loop diuretics reduce the osmotic gradient in the renal medulla that in turn impairs both the concentrating and diluting capacities of the kidney.[2] Although initially increasing renal blood flow, the reduction in extracellular fluid volume that is caused by the diuresis can result in a decrease in renal blood flow.

Contraindications and adverse effects resulting from diuretic therapy usually are due to electrolyte imbalance induced by these agents. Many commonly employed diuretics can produce acute and chronic sodium depletion, hypokalemia, hyperglycemia, and hyperuricemia, as well as alterations in chloride, magnesium, and calcium balance. Osmotic diuretics must be used with caution because they can produce a marked increase in vascular blood volume in patients with acute renal failure.[2] Hypersensitivity to diuretic agents sometimes occurs. Also, blood dyscrasias, pancreatitis (thiazides), decreased glucose tolerance (thiazides at doses higher than clinically useful), and ototoxicity (chronic high dose loop diuretics) occasionally are encountered during diuretic therapy.

Concurrent administration of diuretic agents and other drugs result in some of the most frequently encountered drug interactions. A common example is the prescribing of a cardiac glycoside and a diuretic; the diuretic-induced hypokalemia potentiates the cardiotoxicity of the glycoside. The adverse interaction can be minimized either by increasing potassium intake (potassium supplements, diet, or potassium-sparing diuretic) or by administering the diuretic intermittently (allows homeostatic mechanisms to correct imbalance). Other examples of adverse interactions include:

- More-intensive skeletal muscle blockade in patients on certain muscle relaxants and hypokalemia-inducing diuretics
- Orthostatic hypotension induced by concurrent administration of centrally acting antihypertensives and a diuretic
- Increased incidence of ototoxicity when patients on aminoglycoside antibiotics are given diuretics reported to cause ototoxicity (chronic high dose loop diuretics)
- Hyperkalemia when potassium salts are administered with potassium sparing diuretics
- Disruption of uricosuric therapy by administration of a diuretic that increases plasma uric acid levels (thiazides)
- An increased anticoagulant effect induced by displacement of warfarin from protein binding sites

Thoughtful management of these interactions will not only result in improved patient response, but also will spare the patient unnecessary inconvenience and expense.

Agents employed clinically as diuretics may be divided into two groups: (1) osmotic diuretics and (2) renal tubule–inhibiting diuretics. In this presentation a third category, miscellaneous renal agents, is provided for probenecid, an agent that is not a diuretic but inhibits renal tubule reabsorption of uric acid and blocks the renal excretion of a number of substances.

OSMOTIC DIURETICS

The capacity of the renal tubule to reabsorb various electrolytes and nonelectrolytes is limited and, as previously mentioned, varies for each ionic species. If large amounts of these substances are administered to an individual, their concentration in the body fluids and, subsequently, in the glomerular filtrate exceeds the reabsorption capacity of the tubule, and the excess appears in the urine accompanied by an increased volume of water.

Traditionally, substances that increase urine formation in this manner are called osmotic diuretics. Osmotic agents may have multiple sites of action; nevertheless, their major component is a decrease in medullary solute content resulting in less water reabsorption from the thin descending limb of Henle and collecting duct and less sodium chloride reabsorption in the proximal tubule and thick ascending limb of Henle.

The major toxic effect of osmotic diuretics is related to the amount of solute administered and its effect on the volume and distribution of body fluids. For example, following its administration, mannitol is distributed throughout the extracellular fluid; consequently, the administration of hypertonic solutions sufficient to make a significant contribution to extracellular osmolarity will be accompanied by a significant expansion of extracellular fluid volume, largely at the expense of intracellular fluid volume. In edematous states accompanied by diminished cardiac reserve, the use of mannitol introduces a risk that far outweighs any advantages. Also, a variety of signs and symptoms suggestive of hypersensitivity reactions have accompanied the use of some osmotic diuretics.

This group of diuretics includes osmotic electrolytes (potassium and sodium salts), osmotic nonelectrolytes (urea, glycerin, and mannitol), and acid-forming salts (ammonium chloride). Osmotic diuretics are highly effective treatments for cerebral edema and are used primarily for this purpose.

AMMONIUM CHLORIDE

Muriate of Ammonia; Sal Ammoniac

Ammonium chloride [12125-02-9] NH_4Cl (53.49).

Preparation—By the following processes: (1) the ammoniacal liquid obtained from the destructive distillation of coal is neutralized with HCl and the crude product subsequently is purified, (2) the vapors of ammonia from synthetic processes are absorbed in HCl, and (3) as a by-product in the Solvay process for sodium bicarbonate.

Description—Colorless crystals, or a white, fine or coarse crystalline powder; cool, saline taste; somewhat hygroscopic; when dissolved in water the temperature of the solution is lowered; pH (1 in 20 solution) between 4.6 and 6.

Solubility—1 g in 3 mL water, 100 mL alcohol, or 8 mL glycerin.

Comments—A *diuretic, systemic acidifier,* and *expectorant.* Ammonium chloride is a combination of a labile cation and a fixed anion. When the ammonium ion is converted to urea, the liberated hydrogen ion reacts with bicarbonate and other body buffers. The end result is that chloride ion displaces bicarbonate ion; the latter is converted to CO_2 Thus, the chloride load to the kidneys is increased, and an appreciable amount escapes reabsorption along with an equivalent amount of cation (predominantly sodium) and an isoosmotic quantity of water. This is the basic mechanism by which ammonium chloride brings about a net loss of extracellular fluid and promotes the mobilization of edema fluid.

Ammonium chloride has limited value when used alone for its diuretic effects. It occasionally is combined with a xanthine for short-term relief from temporary water-related weight gain, bloating, or edema associated with menstrual periods.

The fact that ammonium chloride causes systemic acidosis makes the salt of some value in the treatment of alkalosis. It also renders the urine acidic and is prescribed for this purpose in conjunction with methenamine. In the rare instances when it is desired to produce an acidosis, ammonium chloride may be used. An example is in the treatment of lead poisoning when an acidosis is desired to hasten the excretion of lead or to treat alkalosis from excessive use of alkalinizing drugs.

GLYCERIN

1,2,3-Propanetriol; Glycerol; Ophthalgan; Osmoglyn

[56-81-5] $C_3H_8O_3$ (92.09)

Preparation—Obtained in the production of soaps and fatty acids through hydrolysis or by hydration of propylene.

Description—Syrupy liquid with a sweet warm taste; hygroscopic.

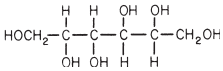
Solubility—Completely miscible with water or alcohol; insoluble in most nonpolar solvents.

Comments—*An oral osmotic agent for reducing intraocular pressure.*

GLUCOSE—pages 1885–1886
GLUCOSE, LIQUID—page 1886.

MANNITOL

Mannite; Manna Sugar; Osmitrol



D-Mannitol [69-65-8] $C_6H_{14}O_6$ (182.17).

Preparation—May be extracted from manna and other natural sources with hot alcohol or other selective solvents. Commercially, it is produced by catalytic or electrolytic reduction of certain monosaccharides such as mannose and glucose. Manufacture is somewhat complicated by the need for separation of stereoisomers.

Description—White, crystalline powder or free-flowing granules; odorless and with a sweetish taste; density about 1.52 at 20°; melts between 165° and 168°; pK_a (19°) 3.4.

Solubility—1 g in about 5.5 mL water; slightly soluble in pyridine; very slightly soluble in alcohol; soluble in alkaline solutions; practically insoluble in ether.

Comments—A *diuretic* and a *diagnostic agent for kidney function.* The intravenous administration of hypertonic solutions of mannitol is used to promote an *osmotic diuresis.* It is not absorbed significantly from the gastrointestinal (GI) tract, and if given orally, mannitol causes osmotic diarrhea.

Mannitol is a useful adjunct in the treatment of acute renal failure before irreversible renal failure becomes established. However, to be effective, there must be sufficient renal blood flow and glomerular filtration for mannitol to reach the kidneys. It also is used to reduce intracranial pressure, treat cerebral edema, reduce intraocular pressure when elevated pressure is not amenable to other therapy, and promote urinary excretion of toxic substances.

When administered parenterally, mannitol is distributed in the extracellular space. Only 7% to 10% is metabolized to glycogen, and the rest is excreted in the urine. Plasma half-life after a single IV dose is 15 min with normal renal function. In severe renal insufficiency, mannitol excretion is reduced greatly; retained mannitol may increase extracellular tonicity, expand extracellular fluid volume, and induce hyponatremia. It is superior to dextrose in that it is metabolized only slightly in the body and is reabsorbed only slightly by the renal tubule. Although it requires a larger volume, it produces fewer side effects than urea and is equally effective.

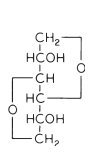
Side effects mostly are due to fluid and electrolyte imbalance. Significant accumulation of mannitol can occur because of rapid administration of large doses or inadequate renal output, leading to an expanded extracellular fluid volume. Isolated cases of adverse reactions (such as pulmonary congestion, fluid and electrolyte imbalances, acidosis, electrolyte loss, dryness of the mouth; thirst, osmotic nephrosis, marked diuresis, urinary retention, edema, headache, blurred vision, convulsions, nausea, vomiting, rhinitis, diarrhea, arm pain, thrombophlebitis, chills, dizziness, urticaria, dehydration, hypotension, hypertension, and anginal-like chest pains) have been reported during or following mannitol infusion.

Since only a negligible amount of mannitol, which appears in the glomerular filtrate, is reabsorbed by the renal tubule, it has been employed for the measurement of *glomerular filtration rate.*

Mannitol and Sodium Chloride Injection—A sterile solution of mannitol and sodium chloride in water for injection. It contains no bacteriostatic agents. pH between 4.5 and 7. *Uses*: See *Mannitol.*

ISOSORBIDE

D-Glucitol, 1,4:3,6-dianhydro-, Ismotic



[652-67-5] $C_6H_{14}O_4$ (146.14).

Preparation—By acid dehydration of sorbitol.

Description—White, crystals melting about 63°; usually supplied as an aqueous solution of approximately 75% concentration.

Solubility—Completely miscible with water; insoluble in most nonpolar organic solvents.

Comments—Used for short-term reduction of intraocular pressure.

UREA

Carbonyldiamide; Ureaphil

$CO(NH_2)_2$

Carbamide [57-13-6] CH_4N_2O (60.06).

Preparation—A product of the metabolism of proteins, it is excreted in human urine in average amounts of 30 g/day. In 1828, Wöhler obtained it on evaporating a solution containing potassium cyanate and ammonium sulfate, the ammonium cyanate first produced isomerizing to urea—reputedly the first synthesis of an organic compound from inorganic material.

A large-scale process for preparing urea is by heating calcium cyanamide with water under pressure:

$$CaNCN + 3H_2O \rightarrow CO(NH_2)_2 + Ca(OH)_2$$

Description—Colorless to white, prismatic crystals or a white, crystalline powder; almost odorless with a cooling, saline taste; may gradually develop a slight odor of ammonia, especially in the presence of moisture; melts between 132° and 135°; aqueous solutions are neutral to litmus but, on standing or heating, decompose into NH_3 and CO_2; pK_a (21°) 0.1.

Solubility—1 g in 1.5 mL water, 10 mL alcohol, 20 mL anhydrous alcohol, 6 mL methanol, or 2 mL glycerol; practically insoluble in chloroform or ether.

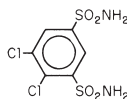
Comments—Used to reduce intracranial and intraocular pressure.

RENAL TUBULE–INHIBITING DIURETICS

The most powerful and consistently effective diuretics are those that depress tubular mechanisms responsible for the active reabsorptive transport of certain ions. Drugs that induce diuresis in this way may be divided into five groups: carbonic anhydrase inhibitors, benzothiadiazine and related derivatives, potassium-sparing diuretics, loop diuretics, and other renal tubular-inhibiting diuretics. The mechanisms, uses, and limitations of these several groups of diuretics are discussed in the introductory statement to the respective section.

DICHLORPHENAMIDE

1,3-Benzenedisulfonamide, 4,5-dichloro-, Daranide



4,5-Dichloro-*m*-benzenedisulfonamide [120-97-8] $C_6H_6Cl_2N_2O_4S_2$ (305.15).

Preparation—*o*-Chlorophenol is reacted with chlorosulfonic acid to produce 5-chloro-4-hydroxy-1,3-benzenedisulfonyl chloride, which is treated with PCl_5 to replace the 4-hydroxy with chlorine. Ammonolysis of the sulfonyl chloride yields the disulfonamide.

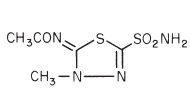
Description—White or nearly white, crystalline powder, with not more than a slight characteristic odor; melts between 236.5° and 240°.

Solubility—Very slightly soluble in water; freely soluble in 1 *N* NaOH; soluble in alcohol; slightly soluble in ether.

Comments—Used for primary, and the acute phase of secondary, glaucoma.

METHAZOLAMIDE

Acetamide, *N*-[5-(aminosulfonyl)-3-methyl-1,3,4-thiadiazol-2(3*H*)-ylidene]-,



N-(4-Methyl-2-sulfamoyl-Δ^2-1,3,4-thiadiazolin-5-ylidene)acetamide [554-57-4] $C_5H_8N_4O_3S_2$ (238.26).

Preparation—2-Acetamido-5-mercapto-1,3,4-thiadiazole, prepared as described under *Acetazolamide,* is treated with *p*-chlorobenzyl chloride to produce the *p*-chlorobenzylmercapto derivative, which, on treatment with methyl bromide in the presence of sodium methylate, undergoes methylation and rearrangement to yield the acetylimino thiadiazoline derivative. This is oxidized with chlorine water to the 2-sulfonyl chloride, which yields methazolamide on amidation with ammonia.

Description—White or faintly yellow, crystalline powder with a slight odor; melts about 213°; pK_a 7.30.

Solubility—Weakly acidic; slightly soluble in water, alcohol or acetone; soluble in dimethylformamide.

Comments—Chemically related to *Acetazolamide.*

Carbonic Anhydrase Inhibitors

Carbonic anhydrase is an ubiquitous enzyme responsible for the catalytic reversible hydration of carbon dioxide and dehydration of carbonic acid, a process critical to the transport of carbon dioxide in the erythrocyte and its exchange in the parenchyma of the lungs. This enzyme also is found in the renal cortex, gastric mucosa, pancreas, eye, and central nervous system (CNS).

The renal tubular cells also contain substantial amounts of carbonic anhydrase, and the CO_2 produced metabolically in the cells of the renal tubule is converted immediately to carbonic acid by the enzyme. Urine is normally acidified by secretion of hydrogen ions derived from carbonic acid formed in the proximal tubular cells in exchange for sodium ions in the lumen of the tubule.

When carbonic anhydrase is inhibited, via adenyl cyclase stimulation, pH of the urine increases because the number of hydrogen ions available for exchange with sodium is decreased; the excess sodium ions retained in the tubule combine with bicarbonate and are excreted by the kidney with an increased volume of water and a loss of potassium. The diuretic effect is self-limiting when it is administered for longer than 48 hr, since the subsequent metabolic acidosis prevents further diuretic action by the carbonic anhydrase inhibitor.

Although carbonic anhydrase inhibitors were developed originally as diuretics, their major usefulness is in glaucoma. Inhibition of carbonic anhydrase in the ciliary body of the eye markedly reduces secretion of aqueous humor; oral or parenteral administration of carbonic anhydrase inhibitors decreases intraocular pressure in most patients with this ocular defect.

These agents also have been used in some cases of absence and generalized tonic-clonic epilepsy refractory to anticonvulsants. The anticonvulsant effects of the carbonic anhydrase inhibitors may be due to the metabolic acidosis caused by these agents.

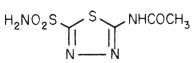
Adverse reactions to carbonic anhydrase inhibitors are seldom serious and are reversed rapidly, since the drug is excreted rapidly. The most frequent adverse effects include paresthesia, particularly tingling in the extremities; loss of appetite; polyuria; some drowsiness; and confusion. During long-term systemic therapy, an acidotic state may supervene; this can be corrected by administration of bicarbonate. Transient myopia has been reported.

Other occasional reactions include urticaria, melena, flaccid paralysis, and convulsions. Drowsiness may impair ability to drive or perform other tasks requiring alertness; patients should be advised of this. Like other sulfonamide derivatives, the sulfonamide-type carbonic anhydrase agents may produce fever, rash, crystalluria, renal calculus, bone-marrow depression, thrombocytopenic purpura, hemolytic anemia, leukopenia, pancytopenia, and agranulocytosis. At the first signs of such reactions the drug should be discontinued and appropriate therapy instituted.

The safe use of these agents during pregnancy has not been established. These agents are contraindicated in patients with idiopathic renal hyperchloremic acidosis, renal failure, a known depletion of sodium and/or potassium, or Addison's disease and patients known to be sensitive to this class of drugs. Moreover, long-term therapy is contraindicated in patients with chronic, noncongestive, angle-closure glaucoma.

ACETAZOLAMIDE

Acetamide, *N*-[5-(aminosulfonyl)-1,3,4-thiadiazol-2-yl]-, Diamox



[59-66-5] $C_4H_6N_4O_3S_2$ (222.24).

Preparation—Hydrazine hydrate is reacted with a two-molar quantity of ammonium thiocyanate to produce 1,2-bis(thiocarbamoyl) hydrazine, which yields, through loss of ammonia and rearrangement, 5-amino-2-mercapto-1,3,4-thiadiazole. This is acetylated and then oxidized to the 2-sulfonyl chloride with chlorine. The final step is amidation with ammonia.

Description—White to faintly yellowish white, crystalline, odorless powder; pK_a; 7.2, 9.0.

Solubility—Very slightly soluble in water; sparingly soluble in hot water (90° to 100°); slightly soluble in alcohol.

Comments—A *carbonic anhydrase inhibitor* effective for adjunctive treatment of *edema due to congestive heart failure, drug-induced edema, absence* and other *centrencephalic epilepsies,* chronic simple (open-angle) *glaucoma,* secondary glaucoma and *preoperatively in acute angle-closure glaucoma* when it is desired to lower intraocular pressure prior to surgery.

It also is used in the prevention and amelioration of symptoms associated with acute mountain (high altitude) sickness. When used orally in tablet form to lower intraocular pressure, it has a rapid onset of action (1–1½ hr), reaches peak effect in 2 to 4 hr and the effect persists for 8 to 12 hr. When sustained-release capsules are employed, onset of action is approximately 2 hr, peak effect varies from 8 to 12 hr and the effects persist for 18 to 24 hr. It particularly is useful where careful following of blood electrolytes is not possible, as in outpatients. It has low toxicity. For additional information on adverse effects and precautions, see introductory statement.

ACETAZOLAMIDE SODIUM

Acetamide, *N*-[5-(aminosulfonyl)-1,3,4-thiadiazol-2-yl]-, monosodium salt; Diamox Sodium

[1424-27-7] $C_4H_5N_4NaO_3S_2$ (244.22); prepared from acetazolamide with the aid of NaOH. It is suitable for parenteral use. For the structure of the base, see *Acetazolamide.*

Preparation—Acetazolamide is dissolved in aqueous NaOH solution containing an equimolar quantity of NaOH, whereupon the acidic H of the—SO_2NH_2 group is replaced by Na. The solid sodium compound then may be produced by various drying or crystallization techniques.

Description—White solid, with the characteristic appearance of freeze-dried products; pH (freshly prepared solution, 1 in 10) between 9 and 10.

Comments—See *Acetazolamide.*

Benzothiadiazine and Related Diuretics

The benzothiadiazine diuretics occurred from efforts to develop more-potent carbonic anhydrase inhibitors. This resulted in the introduction of the prototype thiazide, chlorothiazide, in 1958, a widely used, reliable, well-tolerated, orally effective diuretic.

The thiazide diuretics increase urinary excretion of sodium and water by inhibiting sodium reabsorption on the distal convoluted tubule, connecting tubule, and early collecting duct. They also increase excretion of chloride, potassium, and, to a lesser extent, bicarbonate ions. The latter effect is due to their slight carbonic anhydrase–inhibitory action, although this action is usually of minor diuretic consequence. Because of their site of action, they interfere with the dilution, but not the concentration, of urine.

The thiazide drugs also decrease the glomerular filtration rate. This effect does not appear to contribute to the diuretic action of these drugs and may explain their diminished efficacy in the presence of impaired kidney function.

The thiazide drugs are frequently employed in the treatment of hypertension and can add to the effectiveness of other antihypertensive drugs and reverse the fluid retention caused by some of these agents. Although the precise mechanism of their antihypertensive action is unknown, it may be due to an altered sodium balance. Since the thiazides induce only a limited (10%) reduction in blood pressure, they are useful either in mild cases of hypertension or as adjunctive therapy to other drugs.

Thiazide diuretics are effective as adjunctive therapy in *edema* associated with *congestive heart failure, hepatic cirrhosis,* and *corticosteroid* and *estrogen therapy,* as well as edema

due to *various forms of renal dysfunction (nephrotic syndrome, acute glomerulonephritis,* and *chronic renal failure)* if estimated creatinine clearance is > 40°mL/min. Thiazide diuretics also have been used successfully (alone or in combination with amiloride and/or allopurinol) to prevent the formation and recurrence of calcium stones in *hypercalciuric* and *normal calciuric patients*.

Thiazide diuretics are contraindicated in anuria, patients hypersensitive to these and other sulfonamide drugs and in otherwise healthy pregnant women with or without mild edema. Diuretics can decrease placental perfusion. Thiazides are excreted into breast milk; therefore, use by nursing mothers is not recommended. These drugs should be used with caution in patients with renal disease, since they may precipitate azotemia. They also should be used with caution in patients with impaired liver function, diabetes, gout, or a history of lupus erythematosus.

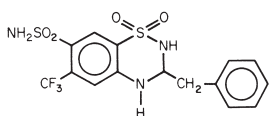
Adverse effects have been observed as follows: *GI* (anorexia, gastric irritation, nausea, vomiting, cramping, diarrhea, constipation, jaundice, pancreatitis, sialadenitis), *CNS* (dizziness, vertigo, paresthesias, headache, xanthopsia), *hematological* (leukopenia, agranulocytosis, thrombocytopenia, aplastic anemia), *cardiovascular* (orthostatic hypotension), *hypersensitivity* (purpura, photosensitivity, rash, urticaria, necrotizing angiitis, fever, respiratory distress, anaphylactic reactions), and *other* (hyperglycemia, glycosuria, hyperuricemia, muscle spasm, weakness, restlessness, transient blurred vision).

Periodic serum electrolyte determinations should be done on all patients to detect electrolyte imbalance such as hyponatremia, hypochloremic alkalosis, and hypokalemia. Finally, in higher doses, thiazides may increase total cholesterol, triglycerides, and low-density lipoproteins (LDLs).

Thiazides are involved in several clinically important drug interactions. They interact with adrenal corticosteroids to enhance hypokalemia, with vitamin D and calcium to induce hypercalcemia, with diazoxide to cause hyperglycemia, with indomethacin to decrease the natriuretic and/or antihypertensive effect, and with digitalis glycosides to produce digitalis toxicity. Moreover, the thiazides increase lithium levels and the neuromuscular blocking effect of tubocurarine but decrease the anticoagulant effect of the oral anticoagulants.

BENDROFLUMETHIAZIDE

2*H*-1,2,4-Benzothidiazine-7-sulfonamide, 3,4-dihydro-3-(phenylmethyl)-6-(trifluoromethyl)- 1,1-dioxide; Naturetin



[73-48-3] $C_{15}H_{14}F_3N_3O_4S_2$ (421.41).

Preparation—One method consists of cyclization of 4-amino-6-trifluoromethyl-*m*-benzenedisulfonamide through condensation with phenylacetaldehyde (*J Am Chem Soc* 1959; 81:4807).

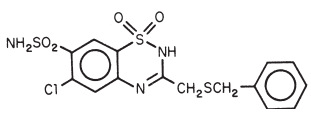
Description—White to cream-colored, finely divided, crystalline powder that is odorless or has a slight, characteristic floral odor; melts about 220°. pK_a 8.5.

Solubility—1 g in 23 mL alcohol or 200 mL ether; practically insoluble in water, chloroform, or benzene.

Comments—A potent, orally effective thiazide diuretic.

BENZTHIAZIDE

2*H*-1,2,4-benzothiadiazine-7-sulfonamide, 6-chloro-3-[[(phenylmethyl)thio]methyl]- 1,1-dioxide; Aquatag, Proaqua; Exna; Hydrex



3-[(Benzylthio)methyl]-6-chloro-2*H*-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide [91-33-8] $C_{15}H_{14}ClN_3O_4S_3$ (431.93).

Preparation—4-Amino-6-chloro-*m*-benzenedisulfonamide is reacted with chloroacetic anhydride to give 2,3′-dichloro-4′,6′-disulfamoylacetanilide, which is then condensed and cyclized with benzyl mercaptan in the presence of sodium hydroxide (US Pat 3,111,517).

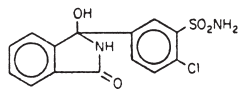
Description—Fine, white, crystalline powder with both a characteristic odor and taste; stable in both light and air; melts about 240°.

Solubility—1 g in 41,000 mL water, 480 mL alcohol, 24,000 mL chloroform, or 2900 mL ether; soluble in alkaline solutions.

Comments—A diuretic and antihypertensive similar to the thiazides.

CHLORTHALIDONE

Benzenesulfonamide, 2-chloro-5-(2,3-dihydro-1-hydroxy-3-oxo-1*H*-isoindol-1-yl)-, Hygroton; Hylidone; Combipres



2-Chloro-5-(1-hydroxy-3-oxo-1-isoindolinyl)benzenesulfonamide [77-36-1] $C_{14}H_{11}ClN_2O_4S$ (338.76).

Preparation—3-Amino-4-chlorobenzophenone-2-carboxylic acid is diazotized, and the resulting diazonium chloride is reacted in the cold with sulfur dioxide in the presence of cupric chloride to form 4-chloro-2′-carboxybenzophenone-3-sulfonyl chloride (1). Heating 1 with thionyl chloride yields 3-chloro-3-(3′-chlorosulfonyl-4′-chlorophenyl)phthalide, which is reacted with ammonia. Removal of the solvent and treatment of the residue with HCl yields chlorthalidone (US Pat 3,055,904).

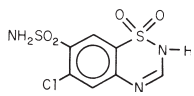
Description—White to yellowish white, crystalline powder; melts with decomposition above 215°; pK_a 9.4.

Solubility—Practically insoluble in water (12 mg/100 mL at 20°), chloroform, or ether; slightly soluble in alcohol; soluble in methanol. Soluble in alkali carbonates or basic solutions.

Comments—An orally effective nonthiazide diuretic.

CHLOROTHIAZIDE

2*H*-1,2,4-Benzothiadiazine-7-sulfonamide, 6-chloro-, 1,1-dioxide; Diachlor; Diuril



[58-94-6] $C_7H_6ClN_3O_4S_2$ (295.72).

Preparation—3-Chloroaniline is acylated with chlorosulfonic acid to produce the 4,6-disulfonyl chloride, which is amidated with ammonia to give the 4,6-disulfonamide. Heating the latter with formic acid results in cyclization through double condensation.

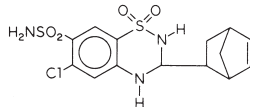
Description—White or practically white, odorless, crystalline powder; melts about 340°, with decomposition. pK_a 6.7, 9.5.

Solubility—Very slightly soluble in water (0.4 g/L at pH4, 0.65 g/L at pH 7); freely soluble in dimethylformamide or dimethyl sulfoxide; slightly soluble in methanol or pyridine; practically insoluble in ether, benzene, or chloroform. Soluble in alkaline solutions but decomposes on heating or standing.

Comments—The prototype benzothiadiazine diuretic, with the therapeutic indications, warnings, precautions, drug interactions, and adverse reactions described above. Diuretic effects are apparent within 2 hr after oral administration, reach peak activity in 4 hr, and persist for about 6 to 12 hr; after intravenous administration, effects are apparent in 15 min, reach a peak in 30 min, and persist for about 2 hr. Refractoriness to the drug is relatively uncommon, even after prolonged periods of continuous administration. For information on drug interactions of benzothiazides, see above.

CYCLOTHIAZIDE

2*H*-1,2,4-Benzothiadiazine-7-sulfonamide, 3-bicyclo[2.2.1]hept-5-en-2-yl-6-chloro-3,4-dihydro-, 1,1-dioxide; Anhydron



6-Chloro-3,4-dihydro-3-(5-norbornen-2-yl)-2*H*-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide [2259-96-3] $C_{14}H_{16}ClN_3O_4S_2$ (389.87).

Preparation—The process is analogous to that for *Chlorothiazide,* except that 5-norbornene-2-carboxaldehyde is employed in the cyclization step instead of formic acid (US Pat 3,275,625).

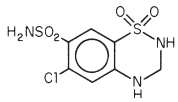
Description—White to nearly white, practically odorless powder; melts within a range of 4° between 217° and 225°.

Solubility—1 g in 70 mL alcohol or 30 mL methanol; practically insoluble in water, chloroform or ether.

Comments—An orally effective diuretic and antihypertensive.

HYDROCHLOROTHIAZIDE

2*H*-1,2,4-Benzothiadiazine-7-sulfonamide-, 6-chloro-3,4-dihydro-, 1, 1-dioxide



[58-93-5] $C_7H_8ClN_3O_4S_2$ (297.75).

Preparation—The process is identical with that for *Chlorothiazide,* except that formaldehyde is employed in the final cyclization step instead of formic acid.

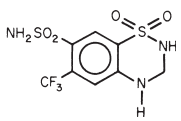
Description—White, or practically white, odorless, crystalline powder; melts about 268° with decomposition; pK_{a1} 7.9; pK_{a2} 9.2.

Solubility—Slightly soluble in water; freely soluble in sodium hydroxide solution or dimethylformamide; sparingly soluble in methanol; insoluble in ether or chloroform.

Comments—A drug similar to *Chlorothiazide.*

HYDROFLUMETHIAZIDE

2*H*-1,2,4-Benzothiadiazine-7-sulfonamide, 3,4-dihydro, 6-(trifluoromethyl)-, 1,1-dioxide



[135-09-1] $C_8H_8F_3N_3O_4S_2$ (331.28).

Preparation—4-Amino-6-(trifluoromethyl)-*m*-benzenedisulfonamide is heated with formaldehyde in a sulfuric acid environment, thus effecting concomitant condensation and cyclization to hydroflumethiazide (US Pat 3,254,076).

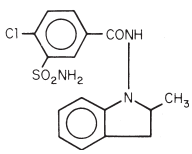
Description—White to cream-colored, finely divided, crystalline powder; odorless; melts between 270° and 275°; pH (1 in 100 dispersion in water) between 4.5 and 7.5; pK_1 8.9, pK_2 10.7.

Solubility—1 g in >5000 mL water, 39 mL alcohol, >5000 mL chloroform, or 2500 mL ether.

Comments—A potent, oral thiazide diuretic.

INDAPAMIDE

Benzamide, 3-(aminosulfonyl)-4-chloro-*N*-(2,3-dihydro-2-methyl-1*H*-indol-1-yl)- Lozol



4-Chloro-*N*-(2-methyl-1-indolinyl)-3-sulfamoylbenzamide [26807-65-8] $C_{16}H_{16}ClN_3O_3S$ (365.84).

Preparation—*p*-Chlorotoluene is sulfonated and converted to the sulfonamide yielding 3-chloro-4-sulfamoylbenzoic acid. This acid is reacted with thionyl chloride to form the carbonyl chloride and treated with 2-methylindole (skatole) to give the product (US Pat 3,565,911).

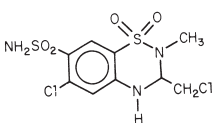
Description—White to yellow orthogonal crystals melting about 161°; weak acid, pK_a = 8.8.

Solubility—Soluble in aqueous solutions of strong bases.

Comments—An oral diuretic and antihypertensive related to the indolines.

METHYCLOTHIAZIDE

2*H*-1,2,4-Benzothiadiazine-7-sulfonamide, 6-chloro-3-(chloromethyl)-3,4-dihydro-2-methyl-, 1,1-dioxide



[135-07-9] $C_9H_{11}Cl_2N_3O_4S_2$ (360.23).

Preparation—By a process analogous to that for *Chlorothiazide,* 4-amino-6-chloro-N^3-methyl-*m*-benzenedisulfonamide is cyclized through condensation with monochloroacetaldehyde or an acetal thereof (US Pat 3,163,644).

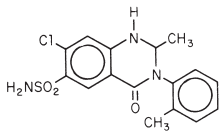
Description—White or practically white, crystalline powder; odorless or has a slight odor and is tasteless; chars slightly below 220° and decomposes at 220°; pK_a (extrapolated from water-acetone) 9.4.

Solubility—1 g in >10,000 mL water, 92.5 mL alcohol, >10,000 mL chloroform, or 2700 mL ether; freely soluble in acetone.

Comments—A thiazide diuretic.

METOLAZONE

6-Quinazolinesulfonamide, 7-chloro-1,2,3,4-tetrahydro-2-methyl-3-(2-methylphenyl)-4-oxo-, Diulo; Mykrox; Zaroxolyn



[17560-51-9] $C_{16}H_{16}ClN_3O_3S$ (365.83).

Preparation—5-Chloro-*o*-toluidine is converted through a series of reactions into *N*-(*o*-tolyl)-2-amino-4-chloro-5-sulfamoylbenzamide, which undergoes ring closure through reaction with acetaldehyde (US Pat 3,360,518; *J Med Chem* 1970; 13:886).

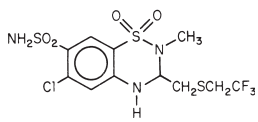
Description—Colorless, odorless, tasteless, crystalline powder; light-sensitive; pK_a 9.72; melts between 253° and 259°.

Solubility—Sparingly soluble in water or alcohol, more soluble in plasma, blood, alkali, and organic solvents.

Comments—A quinazoline-derived nonthiazide diuretic.

POLYTHIAZIDE

2*H*-1,2,4-Benzothiadiazine-7-sulfonamide, 6-chloro-3,4-dihydro-2-methyl-3-[[(2,2,2-trifluoroethyl)thio]methyl]-, 1,1-dioxide; Renese



[346-18-9] $C_{11}H_{13}ClF_3N_3O_4S_3$ (439.87).

Preparation—6-Amino-4-chloro-*N*′-methyl-*m*-benzenedisulfonamide is condensed with the dimethyl acetal of 2,2,2-trifluoroethylmercaptoacetaldehyde. The crude polythiazide, which precipitates when the reaction mixture is added to cold water, is recrystallized from 2-propanol (US Pat 3,009,911).

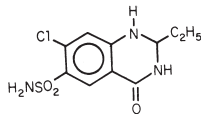
Description—White, crystalline powder with a characteristic odor; melts between 207° and 217°, with decomposition; pK_a 9.1.

Solubility—1 g in >1000 mL water, 150 mL alcohol, 175 mL chloroform or >1000 mL ether; soluble in acetone; soluble in aqueous alkali carbonates or hydroxides with increasing decomposition as pH increases.

Comments—A thiazide diuretic.

QUINETHAZONE

6-Quinazolinesulfonamide, 7-chloro-2-ethyl-1,2,3,4-tetrahydro-4-oxo



[73-49-4] $C_{10}H_{12}ClN_3O_3S$ (289.74).

Preparation—4′-Chloro-*o*-acetotoluidide is subjected to chlorosulfonation and subsequent amination to form 2-amino-4-chloro-5-sulfamoylbenzamide. Refluxing with an acidulated alcholic solution of the diethylacetal of propionaldehyde effects the required condensation cyclization to yield quinethazone (US Pat 2,976,289; *J Am Chem Soc* 1960; 82:2731).

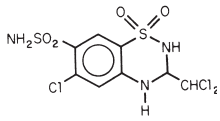
Description—White to yellowish white, odorless, crystalline powder with a bitter taste; discolors in the presence of strong light and alkaline materials; melts between 250° and 252°.

Solubility—1 g in 500 mL alcohol; freely soluble in solutions of alkali hydroxides and carbonates; very slightly soluble in water.

Comments—A quinazoline derivative with 6-thiazide-like effect.

TRICHLORMETHIAZIDE

2*H*-1,2,4-Benzothiadiazine-7-sulfonamide, 6-chloro-3-(dichloromethyl)-3,4-dihydro-, 1,1-dioxide; Metahydrin; Naqua



[133-67-5] $C_8H_8Cl_3N_3O_4S_2$ (380.65).

Preparation—By reacting 4-amino-6-chloro-*m*-benzenedisulfonamide with dichloroacetaldehyde, or an acetal thereof, in a suitable condensation environment (US Pats 3,163,645 and 3,264,292).

Description—White, crystalline powder that is odorless or has a slight characteristic odor; light-sensitive, but stable in air and heat; melts about 274° with decomposition.

Solubility—1 g in 1100 mL water, 48 mL alcohol, 5000 mL chloroform, or 1400 mL ether.

Comments—An orally long-acting thiazide.

Potassium-Sparing Diuretics

The potassium-sparing diuretics include *spironolactone, triamterene,* and *amiloride.* The effects of these agents on urinary electrolyte composition are similar in that they cause a mild natruresis and decrease potassium and hydrogen ion excretion. Despite this similarity, these agents actually compose two groups with respect to mechanism of action.

Spironolactone, the prototype agent of the so-called *aldosterone antagonists,* is a specific competitive inhibitor of aldosterone at the receptor site level; hence, it is effective only when aldosterone is present. The other two potassium-sparing diuretics, triamterene and amiloride, exert their effect independent of the presence or absence of aldosterone.

Triamterene, on the peritubular side, inhibits the potential in the collecting duct and not on the distal tubule. Amiloride, on the other hand, inhibits the potential in both the collecting duct and the distal tubule. In addition, amiloride also decreases sodium transport in the proximal tubule. The potassium-sparing action common to all three of these agents is due to alteration of passive forces controlling movement of these ions.

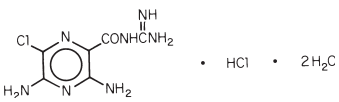
The potassium-sparing agents are used in the management of *edema* associated with *congestive heart failure, hepatic cirrhosis with ascites, the nephrotic syndrome,* and *idiopathic edema* Because these diuretics have little antihypertensive action of their own they are used mainly in combination with other drugs in the management of hypertension and to correct hypokalemia often caused by other diuretic agents. Spironolactone also is used in *primary hyperaldosteronism*.

Potassium-sparing diuretics are contraindicated in patients with anuria, acute renal insufficiency, impaired renal function, or hyperkalemia. Adverse reactions include diarrhea, nausea, vomiting, weakness, headache, erythematous rash, and urticaria. Gynecomastia and carcinoma of the breast have been reported after spironolactone; however, no causal relationship between the latter and the drug has been established.

These drugs can cause life-threatening hyperkalemia in patients using potassium-containing *salt substitutes* or in those with renal impairment. Serum potassium levels should be monitored in diabetics, the elderly, and patients with renal failure.

AMILORIDE HYDROCHLORIDE

Pyrazinecarboxamide, 3,5-diamino-*N*-(aminoiminomethyl)-6-chloro-, monohydrochloride, dihydrate; Midamor



N-Amidino-3,5-diamino-6-chloropyrazinecarboxamide hydrochloride, dihydrate [2016-88-8] $C_6H_8ClN_7O.HCl.H_2O$ (302.12).

Preparation—Pyrazine-2,3-dicarboxamide is converted to 3-amino-2-carboxamide through a Hoffman degradation using one equivalent of NaOBr, the carboxamide forming the ethyl ester by ethanolysis, followed by reaction with sulfuryl chloride. This latter treatment forms the 5,6-dichloro derivative. As the 5-chloro is activated by the *p*- carboxyl it is readily converted to the amine with ammonia. Finally, the ester group is condensed with guanidine to yield the product (Belg Pat 639,386 [*CA* 1965; 62:14698f]).

Description—Odorless, pale yellowish-green powder melting about 240°; pK_a 8.7.

Solubility—Soluble 1 g in 200 mL water or 350 mL alcohol; practically insoluble in chloroform or ether.

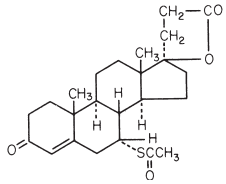
Comments—A potassium-conserving drug with natriuretic, diuretic, and antihypertensive activity. It is approved only for concurrent use with other thiazide diuretics or other kaliuretic-diuretic agents in the management of congestive heart failure or hypertension. It is used to restore normal serum potassium levels in patients who develop hypokalemia and in patients who would be exposed to a particular risk if hypokalemia were to develop.

Its effect on electrolyte excretion is first observed 2 hr after drug administration, reaches a peak between 6 and 10 hr, and lasts about 24 hr. Peak plasma levels are reached in 3 to 4 hr and plasma half-life varies from 6 to 9 hr. The drug is not metabolized by the liver and is excreted unchanged in the urine. It is contraindicated in patients with hyperkalemia or those taking potassium supplements or other potassium-sparing drugs, anuria, acute or chronic renal insufficiency, and diabetic nephropathy. It should be used with extreme care in patients with diabetes.

Amiloride usually is well-tolerated, and serious side effects are infrequent, although minor adverse effects occur in 20% of the users. Adverse effects include headache, nausea, anorexia, diarrhea, and vomiting (3–8%). Other adverse effects such as dizziness, encephalopathy, abdominal pain, constipation, weakness, muscle cramps, decreased libido, cough, and impotence occur less frequently. Amiloride alone has little effect on electrolytes other than potassium; however, electrolyte disturbances may occur when it is combined with other diuretics. Serum potassium levels should be monitored.

SPIRONOLACTONE

(7α, 17α)-Pregn-4-ene-21-carboxylic acid, 7-(acetylthio)-17-hydroxy-3-oxo γ-lactone; Aldactone



17-Hydroxy-7α-mercapto-3-oxo-17α-pregn-4-ene-21-carboxylic acid γ-lactone acetate [52-01-7] $C_{24}H_{32}O_4S$ (416.57).

Preparation—By treating dehydroepiandrosterone (prepared from cholesterol or sitosterol) with acetylene to form the 17α-ethynyl-17β-hydroxy derivative, which is carbonated to the 17α-propiolic acid. Reduction of the unsaturated acid in alkaline solution yields the saturated acid, which cyclizes to the lactone on acidification. Bromination to the 5,6-dibromo compound, followed by oxidation of the 3-hydroxyl group to the ketone, then dehydrobromination to the 7α-hydroxyl derivative, produces spironolactone when esterified with thiolacetic acid.

Description—Light, cream-colored to light tan, crystalline powder; faint to mild mercaptan-like odor; stable in air; melts between 198° and 207°, with decomposition.

Solubility—Practically insoluble in water; freely soluble in benzene and chloroform; soluble in alcohol; slightly soluble in fixed oils.

Comments—A synthetic steroid that acts as a competitive antagonist of the potent, endogeneous mineralocorticosteroid, aldosterone. It has a slower onset of action than triamterene or amiloride, but its natriuretic effect is slightly greater during long-term therapy.

It is indicated in the treatment of *essential hypertension, edema* associated with *congestive heart failure, hepatic cirrhosis* with ascites, the *nephrotic syndrome,* and *idiopathic edema*, *hypokalemia*, and in the diagnosis of *primary aldosteronism* By blocking the sodium-retaining effects of aldosterone on the distal convoluted tubule, it corrects one of the most important mechanisms responsible for the production of edema, but spironolactone is effective only in the presence of aldosterone.

Its onset of diuretic action is gradual (24–48 hr), reaches a peak in 48 to 72 hr, and lasts for 48 to 72 hr. It is a relatively weak diuretic and usually is employed as an adjunct to other diuretics, such as the thi-

azides. When used in this combined manner, it enhances the excretion of sodium and decreases the excretion of potassium.

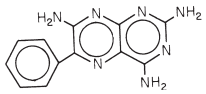
Further increase in diuresis may be obtained by the use of a glucocorticoid with this drug in combination with another diuretic. It is metabolized rapidly after oral administration. The metabolites are excreted largely in the urine, but also in bile. The primary metabolite, canrenone, reaches peak plasma levels 2 to 4 hr after oral administration of the drug.

The half-life of canrenone, following multiple doses of the drug is 13 to 24 hr. Both this drug and canrenone are more than 90% bound to plasma proteins. It has been shown to be a tumorigen in chronic toxicity studies in rats; 500 mg/kg induced hepatocytomegaly, hyperplastic liver nodules, and hepatocellular carcinoma.

It is contraindicated in acute renal insufficiency, anuria, significant impairment of renal excretory function, and hyperkalemia. Patients on digoxin should be monitored closely. Concurrent use elevates digoxin plasma levels and may induce digoxin toxicity. Similarly, concurrent use with lithium increases the risk of lithium toxicity. Side effects include hyponatremia, hyperkalemia, and drowsiness. Other adverse effects include headache, diarrhea, rashes, urticaria, mental confusion, drug fever, ataxia, gynecomastia, decreased libido in the male, and mild androgenic effects, such as hirsutism, irregular menses, and deepening of the voice in the female.

TRIAMTERENE

2,4,7-Pteridinetriamine, 6-phenyl-, Dyrenium



2,4,7-Triamino-6-phenylpteridine [396-01-0] $C_{12}H_{11}N_7$ (253.27).

Preparation—5-Nitroso-2,4,6-triaminopyrimidine is refluxed with phenylacetonitrile in the presence of sodium methoxide (US Pat 3,081,230; *J Org Chem* 1963; 28:1191).

Description—Yellow, odorless, crystalline powder; stable to temperature and light; pK_a 6.2.

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

Comments—Inhibits reabsorption of sodium ions in exchange for potassium and hydrogen ions at that segment of the distal tubule under the control of adrenal mineralocorticoids. The effect is unrelated to the level of aldosterone secretion. After oral administration, 30% to 70% is absorbed, and 50% to 67% is bound to plasma protein. Diuresis appears within 2 hr after administration, reaches a peak in 6 to 8 hr, and lasts for 12 to 16 hr.

It is metabolized primarily by the liver (hydroxytriamterene sulfate, an active metabolite), and about 3% to 5% is excreted unchanged in the urine. It also is used in combination with hydrochlorothiazide in treatment of edema associated with *congestive heart failure, cirrhosis,* and the *nephrotic syndrome.* It also is indicated in steroid-induced edema, idiopathic edema, edema due to secondary hyperaldosteronism, and in edematous patients unresponsive to other therapy. It directly inhibits the reabsorption of sodium and chloride independent of aldosterone.

Although it promotes the excretion of sodium and chloride, it is believed to conserve potassium by reducing the transport of this ion from the tubular cell to the tubular lumen.

It is contraindicated in patients with hyperkalemia or those taking potassium supplements or other potassium-sparing drugs, anuria, acute or chronic renal insufficiency, and diabetic nephropathy. Patients receiving long-term triamterene treatment should be monitored for electrolyte imbalances. Side effects are usually mild and include nausea, vomiting, GI disturbances, weakness, headache, dry mouth, and rash.

Loop Diuretics

The loop, or high-ceiling, diuretics, ethacrynic acid, furosemide, and bumetanide, are the most potent currently available diuretic agents. Although differences do exist between these agents, they are similar in that their most important action is in the medullary and cortical portions of the thick ascending limb of the loop of Henle. Loop diuretics inhibit active chloride, and possibly sodium, transport in the ascending thick limb of Henle.

The loop diuretics have a much greater diuretic effect than the thiazides and are effective even in the presence of electrolyte and acid-base disturbances. Excess amounts of the potent diuretics can lead to serious water and electrolyte depletion; thus, careful medical monitoring is required. The time of onset and duration of action of the loop diuretics are shorter than those with the thiazides.

Despite their similar actions, there are some essential differences between the loop diuretics. Furosemide usually is preferred to ethacrynic acid for a number of reasons:

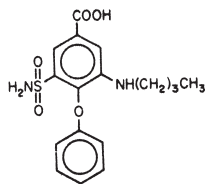
1. It has a broader dose-response curve.
2. It is less ototoxic.
3. It causes fewer gastrointestinal side effects.
4. It is more convenient for intravenous use.
5. It may be less likely to cause alkalosis.

Considerable controversy persists concerning the loop diuretic antihypertensive effectiveness compared with that of the thiazides. Studies have suggested that the loop diuretics are not more effective than the thiazides in the management of uncomplicated mild-to-moderate hypertension in most patients. There is little controversy relative to the superiority of the loop diuretics in hypertension associated with renal insufficiency. Moreover, the loop diuretics *increase* renal blood flow, whereas the thiazides tend to *decrease* renal blood flow and further compromise renal function.

Many of the adverse effects are similar for both the thiazides and loop diuretics, and the management of these effects are the same. However, because of the much greater potency of the loop diuretics, compared with the thiazides, close monitoring is warranted to avoid severe electrolyte imbalances.

BUMETANIDE

Benzoic acid, 3-(aminosulfonyl)-5-(butylamino)-4-phenoxy-, Bumex



3-(Butylamino)-4-phenoxy-5-sulfamoylbenzoic acid [28395-03-1] $C_{17}H_{20}N_2O_5S$ (364.41).

Preparation—3-Chloro-5-(chlorosulfonyl)benzoic acid is nitrated in the 3-position with nitric/sulfuric acid, treated with ammonia to form the sulfonamide, then with sodium phenoxide to form the phenyl ether (replacing the active ring halogen), the nitro group reduced with acid bisulfite to the amine and a butylamino group generated by reductive coupling of the ring amino group with butyraldehyde in the presence of Pd and H_2 This latter step also produces the butyl ester of the carboxylic acid function, which subsequently is saponified with base and the free acid generated with HCl (*J Med Chem* 1971; 14:432).

Description—White crystals melting about 230°; pK_{a1} 0.3; pK_{a2} 4.0; pK_{a3} 10.

Solubility—1 gm in 30 mL alcohol or 10,000 mL water.

Comments—A metanilamide derivative that is a potent *loop diuretic* with efficacy and biochemical effects similar to those of furosemide. Orally, it is effective in patients with *chronic congestive heart failure, chronic renal failure, chronic hepatic disease,* and the *nephrotic syndrome.*

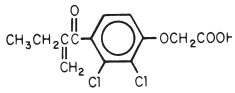
Orally, 1 mg is equivalent to 40 mg of furosemide. It is 95% protein bound and the volume of distribution is 12 to 35 L. Approximately 45% of an oral dose is excreted unchanged. The half-life is 1 to 1.5 hrs and is prolonged in patients with renal failure. Onset of diuresis is observed within 30 to 60 mins following oral administration, reaches a peak in 1 to 2 hr and persists for 4 to 6 hrs. Diuresis starts within minutes following intravenous administration and reaches maximum levels in 15 to 30 mins. It inhibits both chloride and sodium reabsorption in the ascending limb of the loop of Henle; it is somewhat more chloruretic than natriuretic.

Bumetanide causes dilation of renal vasculature and increases renal blood flow. Since fluid and electrolyte changes are similar to those for furosemide, the same precautions apply (see this page). It also may cause azotemia, hyperuricemia, and rarely, impaired glucose tolerance.

Nausea, dizziness, muscle cramps, hypotension, and headache have been reported. Thrombocytopenia has occurred rarely. Reported drug interactions are similar to those for furosemide.

ETHACRYNIC ACID

Acetic acid, [2,3-dichloro-4-(2-methylene-1-oxobutyl)phenoxy]-, Edecrin



[2,3-Dichloro-4-(2-methylenebutyryl)phenoxy]acetic acid [58-54-8] $C_{13}H_{12}Cl_2O_4$ (303.14).

Caution—Use care in handling, since it irritates the skin, eyes, and mucous membranes.

Preparation—2,3-Dichlorophenoxyacetic acid is subjected to a Friedel-Crafts reaction with butyryl chloride to form the 4-butyryl derivative. This undergoes a Mannich reaction with formaldehyde and dimethylamine, the product decomposing thermally to introduce the methylene group (*J Med Pharm Chem* 1962; 5:660).

Description—White or practically white, crystalline powder that is odorless or practically odorless and has a bitter taste; relatively stable in light and at room temperature; nonhygroscopic; melts between 121° and 125°; pK_a 3.5.

Solubility—1 g in 1.6 mL alcohol, 3.5 mL ether, or 6 mL chloroform; very slightly soluble in water.

Comments—An aryloxyacetic acid derivative that is a potent, short-acting diuretic. Maximum water and sodium diuresis is similar to that with furosemide but greatly exceeds that with the thiazides. It is useful especially in patients who require an agent with greater diuretic potential than those commonly employed. It is also useful in patients with a documented sulfa allergy. It is used in the treatment of *edema* caused by *congestive heart failure, cirrhosis of the liver,* and *renal disease,* including the nephrotic syndrome.

It also is recommended for the short-term management of ascites due to malignancy, idiopathic edema, and lymphedema. In addition, it is useful for the short-term management of hospitalized pediatric patients with congenital heart disease or the nephrotic syndrome. It has also been used as adjunctive therapy for acute pulmonary edema. It exerts its action on the cortical ascending (thick) loop of Henle and on the proximal and distal tubule, where it affects both the concentrating and diluting mechanisms of the kidney.

It causes the excretion of virtually an isoosmotic urine by preventing sodium reabsorption from the loop of Henle. Initially chloride excretion exceeds that of sodium. With prolonged administration, chloride excretion declines. Ethacrynic acid is almost 100% bioavailable following oral administration. After oral administration, diuresis begins within 30 mins, reaches a peak in 2 hrs, and persists for 6 to 8 hrs. After intravenous administration, diuresis begins within 5 mins, reaches a peak in 15 to 30 mins, and lasts about 2 hrs. Approximately 95% of the drug is bound to plasma proteins. Plasma half-life is about 1 hr. It can be used with additive effect with diuretics having different sites of action.

Adverse reactions include anorexia, malaise, abdominal discomfort, dysphagia, nausea, vomiting, diarrhea, hyperuricemia, and acute gout have been reported. Blood dyscrasias (agranulocytosis, severe neutropenia, and thrombocytopenia) have been reported rarely. Patients should have determinations of blood urea nitrogen, serum carbon dioxide, and electrolytes and white blood cell counts made frequently.

ETHACRYNATE SODIUM

Acetic acid, [2,3-dichloro-4-(2-methylene-1-oxobutyl)phenoxy]-, sodium salt; Edecrin Sodium

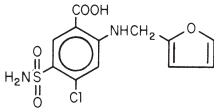
Sodium [2,3-dichloro-4-(2-methylenebutyryl)phenoxy]acetate [6500-81-8] $C_{13}H_{11}Cl_2NaO_4$ (325.12).

Preparation—A sterile, cryodesiccated powder prepared by the neutralization of ethacrynic acid with NaOH.

Comments—See *Ethacrynic Acid.*

FUROSEMIDE

Benzoic acid, 5-(aminosulfonyl)-4-chloro-2-[(2-furanylmethyl)amino]-, Lasix



4-Chloro-*N*-furfuryl-5-sulfamoylanthranilic acid [54-31-9] $C_{12}H_{11}ClN_2O_5S$ (330.74).

Preparation—2,4-Dichlorobenzoic acid is heated with chlorosulfonic acid, and the resulting 5-chlorosulfonyl derivative is reacted with concentrated ammonia to convert it to the 5-sulfamoyl analogue (I). Refluxing I with furfurylamine in large excess or in the presence of sodium bicarbonate yields crude furosemide, which is recrystallized from aqueous ethanol (US Pat 3,058,882).

Description—Fine, white to off-white, crystalline powder; odorless and practically tasteless; unstable in light but stable in air; melts between 203° and 205° with decomposition; pK_a 3.9 (acid).

Solubility—Practically insoluble in water; freely soluble in acetone or solutions of alkali hydroxides; sparingly soluble in alcohol; slightly soluble in ether; very slightly soluble in chloroform.

Comments—A *diuretic* chemically related to the sulfonamide diuretics. It is characterized by high efficacy, rapid onset of action, comparatively short duration of action, and a tenfold ratio between minimum and maximum diuretic dose. Moreover, it is slightly more potent than the organomercurial agents, is orally effective, and its diuretic action is independent of alterations in body acid-base balance. It acts not only on the proximal and distal tubules but also on the ascending limb of the loop of Henle.

It is indicated for the treatment of *edema* associated with *congestive heart failure, cirrhosis of the liver,* and *renal disease,* including the *nephrotic syndrome.* It is indicated particularly when a greater diuretic potential is needed than that produced by commonly employed diuretic agents. It is thought to decrease peripheral resistance in hypertensive patients and dilate the veins in patients with congestive heart failure (*TIPS* 1987; 8:254).

It is given by both oral and parenteral routes of administration; parenteral administration should be reserved for those cases in which oral therapy is not practical. Orally, the diuretic effect begins within 1 hr, reaches a peak in 1 or 2 hr and persists for 6 to 8 hr. Administered intravenously, the diuretic effect begins within 5 mins, reaches a peak in 30 min, and persists for 2 hrs.

Clinical pharmacokinetic studies carried out after a single intravenous dose of 0.5, 1.0, or 1.5 mg/kg indicate that peak diuresis occurs between 20 and 60 min after injection. Apparent volume of distribution of the drug averages 11.4% of the body weight and is independent of the dose. Mean plasma half-life in these studies was 29.5 min, with a clearance rate of 162 mL/min.

Renal excretion was found to be the main route of elimination and averaged 92% of the administered dose, with a mean renal clearance of 149 mL/min. Since this exceeds the glomerular filtration rate, it is thought that tubular secretion of this drug occurs, despite the fact that 95% of it is bound to plasma protein. The bioavailability of furosemide is considerably less than with other loop diuretics.

Like the other diuretics, furosemide is known to be involved in a number of drug interactions. It increases the toxicity of lithium, digitalis, anticoagulants, and theophylline. It decreases the arterial responsiveness of norepinephrine and antagonizes the skeletal muscle relaxant effects of tubocurarine and may potentiate the action of succinylcholine. Concomitant administration of indomethacin may reduce the natriuretic and antihypertensive effects of the drug. This effect also may occur with other nonsteroidal anti-inflammatory drugs such as ibuprofen or naproxen. Metolazone acts synergistically with this to stimulate profound diuresis in patients resistant to it.

It is contraindicated in anuria, in hepatic coma, and in patients known to be sensitive to the drug. Adverse effects that may result from therapy include reduction of renal, cerebral, and cardiac blood flow; potassium loss with resultant cardiac and neuromuscular abnormalities; elevation of blood uric acid and blood sugar levels; allergic reactions; rare cases of exfoliative dermatitis; pruritus; and blood dyscrasias (thrombocytopenia and leukopenia). Paresthesia, blurring of vision, postural hypotension, nausea, vomiting, or diarrhea may occur. In addition, cases of reversible deafness and tinnitus have been reported. Ototoxicity is associated with rapid injection, severe renal impairment, with doses several times the usual dose, and with concurrent use with other ototoxic drugs.

Diuresis induced by the drug also has been accompanied by weakness, fatigue, light-headedness or dizziness, muscle cramps, thirst, and urinary frequency. Excessive therapy can lead to profound diuresis with water and electrolyte depletion. Patients on this drug should be tested at frequent intervals for blood urea nitrogen, sodium, potassium, chloride, and carbon dioxide concentrations. The drug should not be used in cirrhotic patients, unless they do not respond to other therapy.

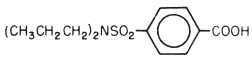
Other Renal Tubule–Inhibiting Diuretics

THEOBROMINE—see RPS-19, page 1050.

MISCELLANEOUS RENAL AGENT

PROBENECID

Benzoic acid, 4-[(dipropylamino)sulfonyl]-, Benemid



[57-66-9] $C_{13}H_{19}NO_4S$ (285.36).

Preparation—Oxidation of the methyl group of *p*-toluenesulfonyl chloride produces *p*-carboxybenzenesulfonic acid. This acid is then converted into the corresponding sulfonyl chloride by treatment with chlorosulfonic acid, which is condensed with di-*n*-propylamine (US Pat 2,608,507).

Description—White or nearly white, fine, crystalline powder; practically odorless; melts between 198° and 200°; pK_a 5.8.

Solubility—Soluble in alcohol, chloroform, or acetone; practically insoluble in water. Soluble in dilute aqueous alkali.

Comments—An agent that blocks both renal and CSF transport of weak acids. With respect to the inward renal transport, it is an effective *uricosuric* agent for the treatment of gout and gouty arthritis. It inhibits tubular reabsorption of urate at the proximal convoluted tubule, thus increasing urinary excretion of uric acid and decreasing serum uric acid levels. With regard to outward renal transport probenecid blocks secretion of weak organic acids at the proximal and distal tubules and is effective as an adjuvant therapy with penicillin G, O, or V, or with ampicillin, methicillin, oxacillin, cloxacillin, or nafcillin for elevation and prolongation of penicillin plasma levels by whatever route the antibiotic is given.

It inhibits the renal excretion and may increase the plasma levels of methotrexate, sulfonamides, sulfonylureas, naproxen, indomethacin, rifampin, aminosalicylic acid, dapsone, clofibrate, or pantothenic acid. Patients concurrently taking any of these agents should be monitored closely and the dosage regimen adjusted appropriately.

It is absorbed rapidly and completely after oral administration. Plasma levels of 100 to 200 μg/mL are necessary for an adequate uricosuric effect, whereas plasma levels of only 40 to 60 μg/mL produce maximal inhibition of penicillin excretion. Plasma levels of 25 μg/mL are reached 30 min after a single 1-g oral dose; plasma levels reach a peak in 2 to 4 hr and remain above 30 μg/mL for 8 hr. Following a single 2-g oral dose, peak plasma levels of 150 to 200 μg/mL are reached in 4 hr, and levels of 50 μg/mL are sustained for 8 hr; the plasma half-life ranges from 4 to 17 hr. At a plasma concentration of 14 μg/mL, about 17% of the drug is bound to plasma protein.

It is contraindicated in hypersensitive individuals, children under 2 years, and persons with known blood dyscrasias or uric acid stones. Therapy should not be started until an acute gouty attack has subsided. Exacerbation of gout following therapy may occur; in such cases, colchicine or other appropriate therapy is advisable. The drug should not be given with methotrexate, since plasma levels of the latter agent have been reported to be increased. Use of salicylates also is contraindicated because these substances antagonize the drug's uricosuric action. Patients who require a mild analgesic should be advised to use acetaminophen rather than salicylates. Probenecid is devoid of analgesic activity.

It is tolerated well, but an occasional patient may experience headache, anorexia, nausea, vomiting, urinary frequency, hypersensitivity reactions, sore gums, flushing, dizziness, and anemia. In gouty patients, exacerbation of gout and uric acid stones with or without hematuria, renal colic, and costovertebral pain have been observed. Nephrotic syndrome, hepatic necrosis, and aplastic anemia occur rarely. Hemolytic anemia, which in some cases could be related to genetic deficiencies of red blood cell glucose 6-phosphate dehydrogenase, has been reported.

REFERENCES

1. *Am J Med Sci* 2000; 319:51.
2. *Am J Med Sci* 2000; 319:38
3. *Kidney Int* 1979; 16:187.

CHAPTER 76

Uterine and Antimigraine Drugs

John E Hoover, BSc Pharm, RPh

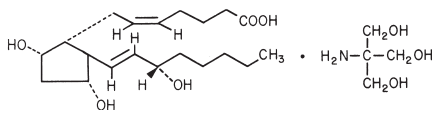
OXYTOCICS

Drugs that stimulate the smooth muscle of the uterus are known as oxytocics. Three chemical types of oxytocics are principally used clinically: (1) the oxytocic fraction (oxytocin) of the posterior pituitary extract, (2) certain ergot alkaloids (ergonovine), and (3) certain prostaglandins (dinoprostone). However, a number of other agents possess mild to intense oxytocic actions. Some of these (eg, hydrastis and quinine) have been used formerly but are now archaic. The main clinical uses of the oxytocics include (1) induction of abortion, (2) evacuation of the uterus in situations of incomplete abortions, (3) induction and augmentation of labor, and (4) involution of the uterus to normal during puerperium.

The response of the uterus to oxytocics depends on estrogenic and progestational hormonal influences. Progesterone hyperpolarizes the uterine smooth muscle and, thus, diminishes its responsiveness and coordination, while estrogen increases myometrial excitability. Consequently, and fortunately, during the first two terms of pregnancy, oxytocics generally are incapable of inducing labor. Late in the third term, as the progesterone levels decline and the estrogen influence increases, uterine responsiveness rises sharply in advance of pelvic relaxation, cervical dilatation, and the coordination of uterine contractions necessary for proper delivery of the fetus. The premature induction of labor by oxytocics can result in harm to both mother and infant and may result in stillbirth if premature separation of the placenta, placental vasoconstriction, or umbilical strangulation occur. Therefore, only under rare circumstances should oxytocics be used to induce labor; indeed, they generally are withheld during labor until the cervix is dilated and presentation of the fetus has occurred (ie, until the third stage of labor). The oxytocic then is given to hasten the delivery of the placenta and to diminish uterine bleeding by contractile compression of the blood sinuses and vasoconstriction. Oxytocics also may be employed during the puerperium to aid in the involution of the uterus to normal. Oxytocin promotes and facilitates the normal phasic contractions that are characteristic of normal delivery. The ergot alkaloids induce prolonged contractions or contracture, which may be detrimental to safe delivery, and hence, they are employed mainly in the third stage of labor to diminish bleeding. Prostaglandins, notably PGE_2 and PGF_2, promote normal-type phasic contractions. However, the effects of the prostaglandins are not so dependent on the estrogen-progesterone balance as those of oxytocin, so prostaglandins can induce labor considerably in advance of term and, hence, can be used to induce abortion.

CARBOPROST TROMETHAMINE

Prosta-5,13-dien-1-oic acid (5*Z*,9α,11α,13*E*,15*S*)-9,11,15-trihydroxy-15-methyl-, compound with 2-amino-2-(hydroxymethyl)-1,3-propanediol (1:1); Hemabate



(15*S*)-15-Methylprostaglandin F_α tromethamine [58551-69-2] $C_{21}H_{36}O_5.C_4H_{11}NO_3$ (489.65)

Preparation—By a series of complex alterations on a prostaglandin precursor. See US Pat 3,728,382.

Comments—Dinoprost-like, with a longer duration of action.

DIHYDROERGOTAMINE MESYLATE

Ergotaman-3′,6′,18-trione, (5′α)-9,10-dihydro-12′-dihydroxy-2′-methyl-5′-(phenylmethyl)-, monomethanesulfonate (salt); DHE 45; Migranal

Dihydroergotamine monomethanesulfonate [6190-39-2] $C_{33}H_{37}N_5O_5 \cdot CH_4O_3S$ (679.79).

Preparation—Dihydroergotamine, prepared by catalytic hydrogenation of ergotamine, is reacted with an equimolar portion of methanesulfonic acid in a suitable solvent.

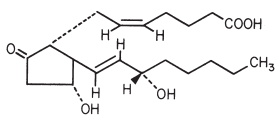
Description—White, yellowish, or faintly red powder; pH (1 in 1000 solution) between 4.4 and 5.4.

Solubility—1 g in 125 mL water, 90 mL alcohol, 175 mL chloroform, or 2600 mL ether.

Comments—A smooth muscle stimulant with somewhat weaker actions than ergotamine.

DINOPROSTONE

Prosta-5,13-dien-1-oic acid, (5*Z*,11α,13*E*,15*S*)-11,15-dihydroxy-9-oxo-, Cervidil; PGE_2; Prepidil; Prostin E_2



Prostaglandin E_2 [363-24-6] $C_{20}H_{32}O_5$ (352.47).

Preparation—The limited availability of the prostaglandins from natural sources has spurred efforts to synthesize them, and total synthesis of prostaglandins F_2 (dinoprost) and E_2 (dinoprostone) has been achieved. The complex syntheses are described in articles in *J Am Chem Soc* 1969; 91:5675; 1586, 1970; 92:397; 1972; 94:2123, 4342.

Description—Colorless crystals or white to off-white crystalline solid; melts between 66° and 68°.

Solubility—1 g in about 1000 mL water; soluble in alcohol.

Comments—It is one of a family of over 30 natural, partially cyclic, alkenoic acids, called prostaglandins, derived from arachidonic acid. They are involved in the regulation of endocrine, reproductive, secretory, digestive, nervous, cardiovascular, respiratory, renal, and hemostatic systems. Certain prostaglandins are involved in the cyclical changes in uterine tone and activity and the changes consequent to pregnancy. Furthermore, prostaglandins in semen stimulate the myometrium and fallopian tubes in a way that facilitates the transport of sperm to the ovum. Not all prostaglandins have the same actions; some are vasodilators and others vasoconstrictors, etc. Some prostaglandins, eg, prostaglandins E_2 (PGE_2, dinoprostone), are oxytocic and also induce cervical softening. Unlike oxytocin, they are oxytocic even in the second trimester of pregnancy and, hence, can be used as an early abortifacient. Dinoprostone is used to terminate pregnancy from the 12th week through the second trimester (80–90% effective), to evacuate the uterus in intrauterine fetal death or missed abortion up to 28 weeks after conception, and to manage benign hydatidiform mole. It also is used to induce labor in midtrimester and later, contract the postpartum uterus and, hence, decrease hemorrhage and ripen the cervix prior to curettage or abortion procedures.

Endovaginally, it may be absorbed sufficiently into the bloodstream to cause systemic side effects; some of the effects attributed to the drug possibly may be the result of hormonal changes and of release of substances from the fetoplacental unit or hydatidiform mole consequent to sloughing and movement or to movement itself. Adverse effects include the following: nausea and vomiting (67%), transient fever (50%; PGE_2 is the mediator of pyrogens), diarrhea (40%), headache (10%), chills and shivering (10%), hypotension (10%), backache, arthralgia, flushing, vertigo, vaginal pain, chest pain, dyspnea, endometritis, faintness, syncope, vulvovaginitis, asthenia, muscle cramps and myalgia, tightness in the chest, breast tenderness, blurred vision, cough, rash, stiff neck, dehydration, tremor, paresthesias, impaired hearing, urinary retention, pharyngitis, laryngitis, sweating, wheezing, tachycardia, skin discoloration, vaginismus, tension, and convulsions (rare). Also, it is not fetotoxic, and near the end of the second trimester a live fetus may be presented. Caution should be exercised when there is asthma or chronic obstructive pulmonary disease, hypotension, hypertension, other cardiovascular disease, renal or hepatic disease, anemia, jaundice, diabetes, a past history of epilepsy, endocervical disease, vaginitis, or cervicitis. It is contraindicated in acute pelvic inflammatory disease and when there is hypersensitivity to the drug.

ERGONOVINE MALEATE

Ergoline-8-carboxamide, [8β(*S*)]-9,10-didehydro-*N*-(2-hydroxy-1-methylethyl)-6-methyl-, (*Z*)-2-butenedioate (1:1) (salt); Ergometrine Maleate

9,10-Didehydro-*N*-[(*S*)-2-hydroxy-1-methylethyl)-6-methyl-ergoline-8β-carboxamine maleate (1:1) (salt) [129-51-1] $C_{19}H_{23}N_3O_2.C_4H_4O_4$ (441.48).

Preparation—May be prepared from the natural alkaloid ergonovine by dissolving the latter in a suitable solvent and reacting it with an equimolar portion of maleic acid.

Ergonovine alkaloid also is prepared synthetically from isolysergic acid obtained by alkaline hydrolysis of ergot alkaloids. One of the methods of synthesis involves the following steps: (1) conversion of the acid to its methyl ester by reaction with diazomethane; (2) hydrazinolysis of the ester to lysergic acid hydrazide; (3) condensation of the hydrazide with nitrous acid to form the azide; (4) metathesis of the azide with D-2-amino-1-propanol to form the amide; and (5) isomerization of the amide to the normal form by treatment with acetic or phosphoric acid.

Description—White to grayish white or faintly yellow, odorless, microcrystalline powder; affected by light.

Solubility—1 g in about 36 mL water or about 120 mL alcohol; insoluble in ether or chloroform.

Comments—Ergonovine is the most valued of the ergot alkaloids for obstetrical use. It is a powerful uterine stimulant and is active after either oral or parenteral administration. It is less toxic than the other natural alkaloids of ergot and is much less prone to cause gangrene. It is given after the delivery of the placenta for the purpose of inducing prolonged, nonphasic contractions of the uterus, to reduce postpartum bleeding. It also may be administered during the puerperium to promote involution of the uterus. In incomplete abortion, it may be used to accelerate the expulsion of the uterine contents. It constricts the cerebral vessels and, hence, is used in the treatment of migraine headache, but it is inferior for this purpose and not recommended. It constricts coronary arteries; in variant angina pectoris the arteries respond to otherwise ineffective doses, so low doses may be used in the diagnosis of variant angina pectoris.

It may cause nausea and vomiting, especially when given intravenously. Like other oxytocics, occasionally it evokes severe hypertensive episodes, especially in hypertensive or toxemic patients or when regional anesthetics containing vasoconstrictors have been used. Such hypertensive episodes can be suppressed by chlorpromazine. Hypersensitivity, including anaphylactic shock, has been reported.

It is contraindicated before the fetus has been presented and should not be used to induce or augment labor. In addition, ergonovine should not be used in persons with known allergy to ergot alkaloids, in uterine sepsis, toxemia of pregnancy, peripheral vascular disease, coronary insufficiency, or kidney or liver disease. It should be used cautiously if there is cardiac disease or hypertension. The actions are antagonized by hypocalcemia, and calcium gluconate can be used judiciously to improve the response.

When used properly, there is little problem with adverse side effects; however, high doses administered by the IV route can cause nausea and vomiting, headaches, tinnitus, dyspnea, muscle cramps, nasal congestion, diarrhea, and a foul taste.

METHYLERGONOVINE MALEATE

Ergoline-8-carboxamide, [8β(*S*)]-9,10-didehydro-*N*-[1-(hydroxymethyl)propyl]-6-methyl-, (*Z*)-2-butenedioate (1:1) (salt); Methergine; Methylergometrine Maleate

9,10-Didehydro-*N*-[(*S*)-1-(hydroxymethyl)propyl]-6-methyl-ergoline-8β-carboxamide maleate (1:1) (salt) [7054-07-1] [57432-61-8] $C_{20}H_{25}N_3O_2 \cdot C_4H_4O_4$ (455.51).

Preparation—Synthesized by the method described above for ergonovine except that in step (4), D-2-amino-1-butanol is employed. The base, dissolved in a suitable solvent, yields the maleate by reaction with an equimolar quantity of maleic acid.

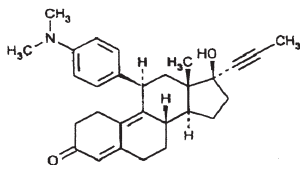
Description—White to pinkish tan, microcrystalline powder; odorless and a bitter taste; must be protected from light and heat; pH (1 in 5000 solution) between 4.4 and 5.2.

Solubility—1 g in 100 mL water, 175 mL alcohol, 1900 mL chloroform, or 8400 mL ether.

Comments—Has actions similar to those of ergonovine.

MIFEPRISTONE

11β,17β-Estra-4,9-dien-3-one, 11-[4-(diethylamino)phenyl]-17-hydroxy-17-(1-propynyl)-; Mifeprex



[84371-65-3] $C_{29}H_{35}NO_2$ (429.59).

Preparation—In a multi-step synthesis from 3,3-ethylenedioxy)estra-5(10),9(11)-diene-17-one.[1,2]

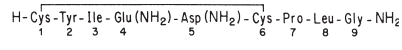
Description—Yellow powder melting about 150°; $[\alpha]_D^{20} = 139°$ (c = 0.5, $CHCl_3$)[1]; melting range[3] 191–196°.

Solubility—Very soluble in methanol, chloroform, or acetone, poorly soluble in water, hexane, or isopropyl ether.

Comments—Its antiprogestational activity results from competition interaction with progesterone at progesterone-receptor sites. Based on studies with various oral doses in several animal species (mouse, rat, rabbit, and monkey), the compound inhibits the activity of endogenous or exogenous progesterone. The termination of pregnancy results.

OXYTOCIN

Alpha-Hypophamine; Pitocin



[50-56-6] $C_{43}H_{66}N_{12}O_{12}S_2$ (1007.19).

Preparation—Obtained from the posterior lobe of the pituitary of healthy hogs or cattle; from either source it has the same amino acid

1. *Drugs of the Future* 1994; 9:755.
2. US Pat 4,386,085 (1982).
3. Danco Labs LLC, FDA label information.

composition. Synthesis was achieved by du Vigneaud and is beyond the scope of this text (see *J Am Chem Soc* 1954; 76:3107). Commercial preparation is described in US Pat 3,076,797.

Description—White powder; $[\alpha]_D^{22} - 26.2°$ (c = 0.53).

Solubility—Soluble in water, 1-butanol or 2-butanol.

Comments—See *Posterior Pituitary*. Natural, endogenous oxytocin is involved in normal parturition. The hormone stimulates guanyl cyclase in myometrial tissue, which promotes inward movement of sodium ion and the consequent increase in both the frequency and strength of contractions. The contractions that are induced are normal phasic contractions. It does not appear to initiate activity not already latent.

Hence, the drug is not very active until close to term, and it is less likely than ergonovine to cause harm to the fetus and mother. Nevertheless, unless the cervix is dilated, oxytocin can cause injury. Oxytocin is used antepartum when an early vaginal delivery is desired. It is the drug of choice for the induction and maintenance of labor once the pregnancy is at term. It is used more frequently when there is prolonged uterine inertia than when labor is only somewhat sluggish. It may be used to assist an ongoing abortion. It cannot induce an abortion except in high doses (20–30 units) and usually not until after the 20th week of pregnancy. It may be used to control postpartum hemorrhage and promote uterine involution, but the appropriate ergot alkaloids are preferred. It induces contraction of the myoepithelial cells around the breast alveoli, thus squeezing milk into the larger ducts and increasing flow through the nipple, and it is used occasionally in the treatment of breast engorgement or to increase milk flow to the infant.

It has a weak antidiuretic hormone-like activity, and during prolonged infusion it can cause water intoxication with convulsions and coma, especially in patients with toxemia of pregnancy. For infusion, saline, rather than dextrose, lessens this danger. The drug also occasionally induces a hypertensive episode, which may cause subarachnoid hemorrhage or fetal death. Pelvic hematomas and allergic reactions may occur in the mother, and cardiac arrhythmias and jaundice in the fetus. The drug is contraindicated in toxemia, abruptio placentae, undilated cervix, overdistended uterus, abnormal presentation, and renal or cardiovascular disease.

Extreme care must be used when combining it with another oxytocic drug.

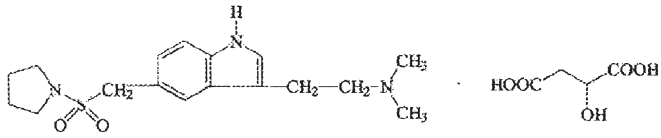
ANTIMIGRAINE DRUGS

As many as 20 million persons suffer the excruciating pain associated with migraine headaches. Migraines are distinct from other types of headaches and can cause 4 to 72 hr of severe unilateral pain accompanied by nausea and sensitivity to light or noise. Although the precise mechanisms leading to migraines are unknown, they appear to relate to hereditary and environmental (eg, some foods, food additives, stress, and fatigue) factors. Because 70% of migraine sufferers are female, monthly hormonal changes also have been implicated. Although there are theories as to the cause of migraines, most experts believe the associated pain is due to dilation of cerebral blood vessels. One possible explanation is that release of neuropeptides from the neurons of the trigeminal ganglia is prompted by initial serotonin-induced vasoconstriction and inflames the cerebral blood vessels, which causes their persistent and painful vasodilation.

The four principal phases of a migraine attack include the prodrome (sensitivity to light and sound, mood changes, fatigue, etc.), aura (partial blindness, flashes, dizziness, and tinnitus), headache (persists for several hours and in extreme cases for days), and postdrome (listless, weak, and irritable). The most frequent medications employed to treat migraine problems are those drugs to relieve the symptoms of an acute attack. These typically are most effective when administered in the early phases of the migraine and include the effective and popular *triptan* compounds (eg, sumatriptan, naratriptan, and zolmitriptan), the ergotamines with and without caffeine, nonsteroidal anti-inflammatory agents (NSAIDs), and narcotic analgesics. For sufferers who experience more than two or three migraines per month, prophylactic treatment is recommended. These drugs typically are used daily for the prevention, or reduced incidence and severity, of migraines. The only medications FDA-approved for prophylactic treatment of migraines are β-adrenergic blockers (see propranolol and timolol, Chapter 72), ergotamines, dihydroergotamine, and methysergide. Other agents also reported to prevent migraines, but not FDA- labeled, are calcium channel blockers (Chapter 68), monoamine oxidase inhibitors (MAOIs) (Chapter 82), NSAIDs (Chapter 83), tricyclic antidepressants (Chapter 82), and valproic acid (Chapter 81).

ALMOTRIPTAN MALATE

Pyrrolidine, 1-[[[3-[2-(dimethylamino)ethyl]-1*H*-indol-5-yl]methyl]sulfonyl]-, hydroxybutanedioate (1:1); Axert



[181183-52-8] $C_{17}H_{25}N_3O_2S.C_4H_6O_5$ (469.56).

Preparation—One method involves the reaction of p-nitrobenzenesulfonyl chloride with pyrrolidine to form the sulfonamide. The nitro group is diazotized and the diazonium salt catalytically reduced to the hydrazine (I). The intermediate(I) is involved in all of the reported syntheses. In one scheme, I is reacted with 4-chlorobutyraldehyde dimethyl acetal and HCl to form 3-(2-aminoethyl)-5-(1-pyrrolidinyl)-1*H*-indole. The primary amino group is converted to dimethylamino with formaldehyde and sodium borohydride. Reaction with malic acid forms the salt. *Drugs of the Future* 1999; 24:367. See also US Pat 5,565,447.

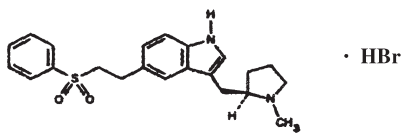
Description—White to off-white crystals; melts about 170°.

Solubility—Soluble in water.

Comments—Binds with high affinity to 5-HT_{1D}, 5-HT_{1B}, 5-HT_{1F} receptors. It has weak affinity for 5-HT_{1A} and 5-HT_7 receptors, but has no significant affinity or pharmacological activity at 5-HT_2, 5-HT_3, 5-HT_4, 5-HT_6; alpha or beta adrenergic; adenosine (A_1, A_2); angiotensin (AT_1, AT_2); dopamine (D_1, D_2); endothelin (ET_A, ET_B); or tachykinin (NK_1, NK_2, NK_3) binding sites.

ELETRIPTAN HYDROBROMIDE

Indole, 3-[[(*R*)-1-methyl-2-pyrrolidinyl]methyl]-5-[2-(phenylsulfonylethyl]-, monohydrobromide; Relpax



[177834-92-3] $C_{22}H_{26}N_2O_2S.HBr$ (463.40).

Preparation—A multi-step synthesis starting with 1-(benzyloxycarbonyl)-2-pyrrolecarboxylic acid . *Drugs of the Future* 1997; 22:221.

Description—White to off-white powder.

Solubility—Soluble in water.

ERGOTAMINE TARTRATE

Ergotaman-3′,6′,18-trione, 12′-hydroxy-2′-methyl-5′-(phenylmethyl)-, (5′α)-*R*-(*R,*R**)-2,3-dihydroxybutanedioate (2:1) (salt); ing of Cafergot; Ergomar**

Ergotamine tartrate (2:1) (salt) [379-79-3] $(C_{33}N_{35}N_5O_5)_2.C_4H_6O_6$ (1313.43).

Description—Colorless crystals or a white to yellowish white, crystalline powder, usually containing solvent of crystallization; these crystals lose the solvent of crystallization in a high vacuum; melts about 180° with decomposition.

Solubility—1 g in about 500 mL water or about 500 mL alcohol; slightly more soluble in the presence of a slight excess of tartaric acid.

Comments—It possesses the characteristic actions of ergot alkaloids. It is the drug of choice in the treatment of migraine, cluster, and other vascular headaches, and it affords relief in about 90% of cases. It contracts the painfully dilated cerebral vessels in these disorders. The drug is most effective if given early in the course of the attack. It usually is administered sublingually or by oral inhalation. When combined

with caffeine, ergotamine is given orally or rectally. However, recently a semisynthetic derivative of ergotamine, dihydroergotamine, also became available in the US as an intranasal preparation (Migranal). Ergotamine also exerts oxytocic actions, but stimulates uterine contractions much less effectively than ergonovine. There is no acceptable evidence that ergotamine is of benefit in menopausal disorders. The use of ergotamine to treat cardiovascular disorders could be dangerous.

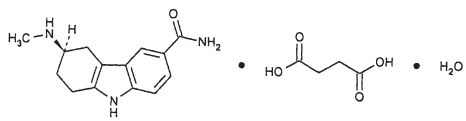
Many of the ergotamine-containing products are combinations. Caffeine (100 mg) frequently is included in these combination products and may enhance the relief of vascular headaches by ergotamine by increasing its gastrointestinal (GI) absorption or by causing cerebral vasoconstriction of its own. Some products contain belladonna alkaloids in marginally effective amounts, with the unsupported rationale that the alkaloids correct some hypothetical autonomic imbalance. Products containing pentobarbital also are promoted with faulty rationale; if an antianxiety drug is justified, a benzodiazepine should be used.

Peak plasma levels after oral administration occur within 0.5 to 3 hr, but the pharmacokinetics after sublingual, oral, inhalation, or rectal applications are not well studied.

Adverse effects are most common after large doses or accumulation of small doses. They include nausea, vomiting, epigastric distress, diarrhea, muscle weakness, precordial distress and pain (indicative of coronary spasm), coldness of the skin (from vasoconstriction), bradycardia or tachycardia, paresthesias in the extremities, myalgia (especially in the thigh and neck muscles), localized edema (mostly in the face and extremities), itching, and dermatitis. Occasionally, hypertensive episodes occur. With continued administration, severe vasoconstriction, endarteritis, and gangrene may result. With combinations, the potential adverse effects of the other components also must be kept in mind. It is contraindicated in pregnancy, peripheral vascular disease, coronary insufficiency or angina pectoris, thrombophlebitis, peptic ulcer, kidney disease, liver disease, sepsis, malnutrition and when there is a history of hypersensitivity to ergot alkaloids.

FROVATRIPTAN SUCCINATE

1*H*-Carbazole-6-carboxamide, (+)-*R*-2,3,4,9-tetrahydro-3-(methylamino)-, butanedioate (1:1), monohydrate; Frova



[158930-17-7] $C_{14}H_{17}N_3O.C_4H_6O_4.H_2O$ (379.41).

Preparation—Either of two methods in a six-step synthesis starting with *p*-hydrazinobenzamide and *N*-(4-oxocyclohexyl)phthalimide. *Drugs of the Future*, 1997; 22: 725.

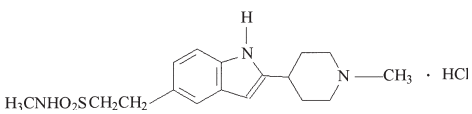
Description—White crystals melting about 220°. $[\alpha]_D^{25}$ +25.4° (c = 0.063, MeOH).

Solubility—Soluble in water.

METHYSERGIDE MALEATE—see RPS 20, page 1356.

NARATRIPTAN HYDROCHLORIDE

1*H*-Indole-5-ethanesulfonamide, *N*-methyl-3-(1-methyl-4-piperidinyl)-, monohydrochloride; Amerge



[143388-64-1] $C_{17}H_{25}N_3O_2S.HCl$ (371.93)

Preparation—One method involves refluxing 1-methyl-4-piperidone and 5-bromo-(1*H*)-indole in alcoholic alkali to yield 3-[(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-5-bromoindole. The pyridine ring is further reduced to piperidine catalytically, and the resulting indole is treated with *N*-methylallylsulfonamide to displace the bromine in the 5-position; the alkene produced is again reduced catalytically to form the product. *Drugs of the Future,* 1996; 21(5):476. US Pat 4,977,841.

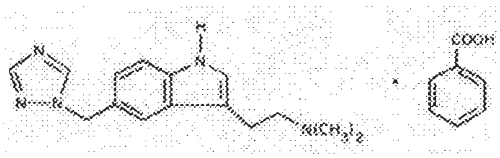
Description—White crystals melting about 157°.

Solubility—Readily soluble in water.

Comments—Binds with high affinity to 5-HT_{1D} and 5-HT_{1B} and has no significant affinity or pharmacological activity at 5-HT_{2-4} receptor subtypes or at adrenergic α1, α2, or β; dopaminergic D1 or D2; muscarinic; or benzodiazepine receptors. The therapeutic activity in migraine generally is attributed to its agonist activity at 5-$HT_{1D/1B}$ receptors. Two current theories have been proposed to explain the efficacy of 5-$HT_{1D/1B}$ receptor agonists in migraine. One theory suggests that activation of 5-$HT_{1D/1B}$ receptors located on intracranial blood vessels, including those on the arteriovenous anastomoses, leads to vasoconstriction, which is correlated with the relief of migraine headache. The other hypothesis suggests that activation of 5-$HT_{1D/1B}$ receptors on sensory nerve endings in the trigeminal system results in the inhibition of proinflammatory neuropeptide disease.

RIZATRIPTAN BENZOATE

1*H*-Indole-3-ethanamine, *N,N*-dimethyl-5-(1*H*-1,2,4-triazol-1-ylmethyl)-, monobenzoate; Maxalt



[145202-66-0] $C_{15}H_{19}N_5O_2.C_7H_6O_2$ (391.48).

Preparation—Several methods; one of which starts with p-nitrobenzyl bromide and 4-amino-1,2,4-triazole to 1-(p-nitrobenzyl)-3-amino-1,2,4-triazolium bromide, I. Deamination of I by diazotization and warming forms 1-(p-nitrobenzyl)-1,2,4-triazole; the nitro group is catalytically reduced to the amine which is diazotized and treated with sodium sulfite to form the hydrazine derivative which is converted to the product with *N*-(4,4-dimethoxybutyl)diethylamine, which is converted to the benzoate salt. *J Med Chem*, 1995; 38:1799 and *Tetra Lett*, 1994, 35, 6981. See also US Pat 5,298,520.

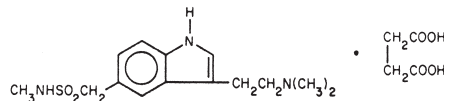
Description—Off-white crystalline solid melting about 180° (benzoate); free base melts about 121°.

Solubility—About 42 mg/mL (expressed as free base) at 25°.

Comments—Binds with high affinity to human cloned 5-HT_{1B} and 5-HT_{1D} receptors. It has weak affinity for other 5-HT_1 receptor subtypes (5-HT_{1A}, 5-HT_{1E}, 5-HT_{1F}) and the 5-HT_7 receptor, but has no significant activity at 5-HT_2, 5-HT_3, alpha- and beta-adrenergic, dopaminergic, histaminergic, muscarinic, or benzodiazepine receptors.

SUMATRIPTAN SUCCINATE

1*H*-Indole-5-methanesulfonamide, 3-[2-(dimethylamino)ethyl]-*N*-methyl-, butanedioate; Imitrex



[103628-84-4] $C_{14}H_{21}N_3O_2S.C_4H_6O_4$ (413.49).

Preparation—Ger Pat 3,320,521.

Description—White crystalline powder; melts about 165°.

Solubility—Soluble in water or chloroform; sparingly soluble in methanol; practically insoluble in hydrocarbon solvents.

Comments—A serotonin agonist at the 5HT-1 receptor, used for treatment of migraine headaches. It is thought to relieve migraines by selectively constricting the large intracranial blood vessels of the carotid circulation. This action is thought to be therapeutically advantageous because it helps to relieve the inflammation around sensory nerves caused by vasodilation of intracranial vessels during migraine episodes. Sumatriptan does not cross the blood-brain barrier; also, it neither decreases cerebral blood flow nor has any direct analgesic action. When sumatriptan is administered subcutaneously, it is rapidly absorbed and reaches peak concentrations in 5 to 20 min. The drug is inactivated by hepatic metabolism and following oral administration only 15% reaches the systemic circulation because of first-pass clearance by the liver. The mean $t_{1/2}$ after subcutaneous administration is approximately 2 hr.

Sumatriptan is not recommended for prophylactic use. In clinical trials, 70% of the patients receiving this drug reported relief from migraine headache pain, compared with 22% receiving placebo. In addition, 33% of the patients treated with sumatriptan remained pain-free for 24 hr, compared with 11% of the patients receiving placebo. In one trial it was observed that 30 min after subcutaneous injection of 6 mg of sumatrip-

tan, 50% of the patients received relief from migraine pain, and within 2 hr of treatment, 90% of the migraine suffers experienced diminished pain (Study Group, *N Engl J Med* 1991; 325: 316). This serotonin agonist also is more effective than placebo in relieving migraine-associated nausea, vomiting, phonophobia, and photophobia. In addition, sumatriptan has been reported to relieve pain associated with cluster headaches within 15 min of a subcutaneous administration in 70% of the patients.

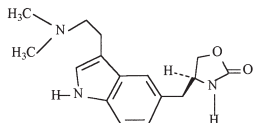
In general, sumatriptan appears to be more effective than previously available drugs for treatment of acute attacks of migraine and cluster headaches. The auto-injected, subcutaneous formulation appears to be faster acting and more effective than tablets; however, neither form is recommended for prophylactic use. Recently, an intranasal product (Imitrex spray) became available in the US and was found to be more effective than the oral form, but less effective than the injection form, for relieving migraines.

If given intravenously, it can cause a transient increase in blood pressure and occasionally constriction of coronary arteries. Consequently, sumatriptan is not recommended for patients with ischemic heart disease or uncontrolled hypertension. In addition, the manufacturer recommends caution when using it in patients with cardiac risk factors such as men over 40 years, postmenopausal women, diabetes, obesity, smoking, and high cholesterol.

Subcutaneous injection of sumatriptan can cause localized pain and redness. Other side effects of injected sumatriptan include tingling, flushing, burning of the skin, nausea, and a sense of tightness and thoracic pressure. The most frequent complaints with oral sumatriptan are nausea and vomiting. Sumatriptan should not be used until 24 hr after administering an ergotamine, and ergotamine preparations should not be used until 6 hr after sumatriptan. In addition, sumatriptan should not be used within 2 weeks of an MAOI and should be used with caution in persons using selective serotonin uptake inhibitors.

ZOLMITRIPTAN

2-Oxazolidinone, (*S*)-4[[3-[2-(dimethylamino)ethyl-1*H*-indol-5-yl]-methyl]-, Zomig



[139264-17-8] $C_{16}H_{21}N_3O_2$ (287.36)

Preparation—By a multistep synthesis starting with 4-(*p*-nitrophenyl)alanine, conversion to the methyl ester with thionyl chloride and methanol; reduction to the alcohol with sodium borohydride; closure of the oxazolidinone ring with phosgene and alkali; catalytic reduction of the nitro group to an amine with subsequent diazotization and treatment with stannous chloride to form the hydrazine derivative. The latter compound with 4,4-dimethoxybutyronitrile yields the Schiff base, which is cyclized to the 3-cyanoindole, which is reductively animated with diethylamine to form the product. *Drugs of the Future* 1997; 22: 260; *J Med Chem* 1995; 38:3566. US Pat 5,466,699.

Description—White crystals melting about 141° $[\alpha]_D^{22}$ − 5.79° (c = 0.5, MeOH); maleate, mp 152°; succinate, mp 123°; benzoate, mp 91°; HCl, mp 119° $[\alpha]_D^{23}$ − 9.35° (c = 0.31, water) (mps approx).

Solubility—Soluble in water at pH 7, about 20 mg/mL.

Comments—Like sumatriptan, but readily crosses the blood-brain barrier. It may be effective with patients who do not respond to sumatriptan.

ACKNOWLEDGMENT—The author acknowledges the tremendous efforts of Glen R. Hanson, DDS, PhD in previous editions of this work.

CHAPTER 77

Hormones and Hormone Antagonists

Charles Ruchalski, PharmD
Michael A Mancano, PharmD

Hormones are substances secreted directly into the blood by endocrine glands. This chapter focuses on hormones that regulate growth, reproduction, and intermediary metabolism. The synthesis and secretion of many hormones are controlled by other hormones or changes in the concentration of essential chemicals or electrolytes in the blood. The interrelationships between the peptide hormones of the hypothalamus, the trophic hormones of the anterior pituitary, and peripheral endocrine glands are elegant examples of feedback regulation. Drugs and disease can modify hormone secretion as well as specific hormone effects at target organs. Some of the hormones affect nearly all the tissues of the body; the action of others is restricted to but a few tissues or organs.

Chemically, the hormones represent a very diverse group of compounds. Some, such as epinephrine and thyroxine, are relatively simple amino acid derivatives. Several groups of hormones, such as those produced by the adrenal cortex and the gonads, are steroids, while the pituitary, parathyroid, and pancreatic hormones are polypeptides or proteins; the molecular weights of the latter range from about 1000 to 30,000 or more.

ADMINISTRATION—A few of the hormones can be administered orally with full effect (eg, thyroid and certain steroid hormones). There is usually some loss due to destruction of the hormone in the digestive tract, its elimination from the circulation, or inactivation while it is in transit through the liver immediately after absorption. Some hormones must be administered by injection, either subcutaneously or intramuscularly, because they are inactivated in the digestive tract. The intramuscular injection usually is chosen, and it gives rapid absorption if the hormone is in aqueous solution or slower absorption if the hormone is in oil. Suspensions of crystals of differing size also have variable repository actions. Another technique is the implantation of compressed pellets of those hormones that are only slightly soluble in tissue fluid; these pellets are placed in the subcutaneous tissues and are absorbed during a period of a few months. Hormones entrained in degradable polymers, or even in silicones, can be used for slow-release forms. Still another form is the buccal tablet of very highly compressed steroid hormone that is held in the buccal area (usually anteriorly between the upper lip and gingiva). This avoids the disadvantage of the oral route, by which steroids must pass through the liver where they are largely inactivated. Some of the synthetic or semisynthetic hormones are structured so that they greatly diminish enzymatic destruction in the liver and hence are effective orally. Notable among these are the oral contraceptives. Some drugs, particularly insulin, may be delivered subcutaneously through a permanently implanted cannula, with the injection powered by a tiny attached programmable pump. Some peptide hormones are administered as a nasal spray to avoid inactivation in the digestive tract.

THE PITUITARY HORMONES

The pituitary gland consists of an anterior lobe *(adenohypophysis)* and posterior lobe *(neurohypophysis)* that are under the influence of hypothalamic hormones that control the secretion of specific trophic hormones that regulate peripheral endocrine gland secretions and target tissues. Some of the anterior pituitary hormones also are produced outside the adenohypophysis, and extrapituitary production plays a role in physiological functions of certain pituitary hormones. Hormones of the intermediate lobe of the pituitary of animals have melanocyte-stimulating properties that influence skin color changes, but they have not been identified as discrete hormones in humans. The anterior lobe of the pituitary has at least six separate hormones: growth hormone (somatotropin, GH), adrenocorticotropin (ACTH), thyroid-stimulating hormone (TSH), follicle-stimulating hormone (FSH), luteinizing hormone (LH), and prolactin (PRL). The links between hypothalamic hormones, pituitary hormones, and target glands are shown in Table 77-1.

1. **Somatropin** *(Growth Hormone, GH, Somatotropin, STH)*—This hormone causes an increase in weight and length of the body. The increase in length is especially prominent, due to the bone growth, but its effect is manifested in nearly all the tissues of the body. Human GH also possesses most of the activities of lactogenic hormone. For maximum action of growth hormone, all the essential and quasi-essential amino acids must be present in abundance. The effects of GH are mediated by several somatomedins, two of which are called insulin-like growth factors (I and II) and at least one of which is the sulfation factor. Human GH contains 191 amino acid residues and has a molecular weight of 22,000.

   In addition to its protein anabolic action, GH affects the metabolism of carbohydrates, fats, and steroids. These effects include (1) maintenance of a normal amount of muscle glycogen in hypophysectomized animals, (2) decreased responsiveness to insulin, and (3) increased concentration of nonesterified fatty acids in plasma and promotion of steroid-metabolizing cytochrome P-450s that differ in males and females. In turn, sex hormones regulate GH secretion. Human GH also exerts prominent effects on the kidney and electrolyte metabolism.

   Unlike corticotropin, insulin, and some of the other protein hormones, a considerable species difference has been observed in response to GH administration. GH prepared from simian or human pituitaries is active in both primate species, but GH from other sources is inactive in humans. Human GH is used to stimulate growth in hypopituitary dwarfs and other forms of retarded growth, and the nitrogen-sparing anabolic effect may suppress catabolism from burns and other severe trauma. Potential uses include the stimulation of hematopoiesis and postmenopausal and other bone mineralization, the treatment of renal failure, obesity, hyperlipidemia, immune disorders, aging, and hypothalamic hypofunction.

Table 77-1. Summary of Hypothalamic, Anterior Pituitary, and Target Organ Hormones

HYPOTHALAMIC HORMONE	PITUITARY HORMONE	TARGET ORGAN (HORMONE PRODUCT)
Stimulatory hormones		
GH-RH	Somatotropin, GH	Liver (IGF, somatomedins)
CRH	ACTH	Adrenal cortex (glucortiocoids, mineralocorticoids, androgens)
TRH	TSH	Thyroid (thyroxine, triiodothyronine)
GnRH	FSH, LH	Gonads (estrogen, progesterone, testosterone)
Inhibitory hormones		
Somatostatin	GH	Liver (IGF) Pancreas (insulin)
Dopamine	Prolactin	Breast (none)

2. **The Gonadotropic Hormones** (FSH and LH)—These two distinct hormones act both in concert and sequentially to control the menstrual cycle.
   a. *Follicle-stimulating Hormone (FSH)*—Human FSH is a two-subunit glycoprotein with a molecular weight of 32,000. It promotes maturation of the primordial follicle and in combination with small amounts of LH (see below) stimulates secretion of estrogen by the developing follicle. During the first 7 days of the menstrual cycle, estrogens suppress the release of FSH, as a result of negative feedback actions on both the anterior pituitary and hypothalamus. In days 9 to 18, estrogens have a positive feedback effect to increase FSH secretion; progesterone blocks the positive but not the negative feedback effect.
   b. *Luteinizing Hormone (LH)*—Human LH is also a two-subunit glycoprotein with a molecular weight of 32,000. The secretion of LH increases near the middle of the cycle. As noted above, small amounts of LH, acting with FSH, stimulate the secretion of estrogen by the ovarian follicle. As the amount of LH increases, ovulation occurs, and the corpus luteum begins to form.

   LH also acts upon the male gonads, specifically upon the interstitial cells of the testis, to produce testosterone. Because of this property, LH also is referred to sometimes as interstitial cell-stimulating hormone (ICSH).

   As with FSH, estrogens have a suppressant effect on LH secretion early and an augmenting effect later in the estrous cycle, but the time course of sensitivity is somewhat different from that with FSH. Progesterone similarly blocks the positive feedback effect. Androgens also suppress the secretion of LH.

   Other Gonadotropic Substances—Two are produced by the chorionic cells of the placenta of women and mares, respectively. The third is a gonadotropin (urofollitropin), which is a preparation of highly purified FSH extract from the urine of postmenopausal women. Follitropins alpha and beta are human FSH preparations of recombinant DNA origin. Human chorionic gonadotropin (HCG) is secreted into the maternal blood and is excreted in the urine, where it may be detected within 48 hr after the ovum is implanted. HCG maintains the secretion of the corpus luteum, enabling pregnancy to continue. Like LH, it will act upon gonadal interstitial cells. HCG is a glycoprotein of molecular weight 35,000.

   Uses of Gonadotropic Hormones—The follitropins or other preparations of FSH (urofollitropin or menotropins) are administered with HCG to induce ovulation and pregnancy in anovulatory women in whom infertility is functional and not caused by primary ovarian failure. The gonadotropins also are used to stimulate development of follicles in ovulatory patients undergoing assisted reproductive technologies (eg, in vitro fertilization). HCG also is used for stimulation of androgen secretion by testicular interstitial cells and for expediting the descent of the testes in boys and young men with cryptorchidism. However, HCG appears to induce ovulation only when a mature ovarian follicle is present. HCG is not effective in the treatment of obesity.
3. **Prolactin** (Prl; lactogenic hormone, mammotropin)—It is a protein of MW 20,000, which is derived from a prohormone of MW 50,000. In the last 50 *N*-terminal amino acids of prolactin, there is 24% identity with growth hormone in the amino acids and sequence. Human placental lactogen has an identity of 76%, which accounts for the greater growth hormone–like properties of the placental lactogen. A related hormone, placental lactogen (PL; chorionic somatomammotropin) is produced by the placenta. It now is recognized that Prl is a hormone with many different actions, perhaps more so than growth hormone, of which primitive prolactin appears to be the phylogenetic precursor. By itself, Prl does not cause breast development, but in concert with estrogens, progesterone, and permissive actions of hydrocortisone and insulin it is mammotropic. In the human, it also stimulates milk secretion by the mammary glands, but only after suitable priming by estrogens and progesterone. Other effects in humans include lipolysis, luteotropism, and luteolysis, promotion of growth and secretion, increase in testicular steroidogenesis and development of the male accessory sex organs, and involvement in the regulation of gonadotropin release.
4. **Thyrotropic Hormone** *(Thyrotropin, TSH)*—TSH obtained from beef pituitaries is a glycoprotein of molecular weight about 28,000. Thyrotropin sustains the activity of the thyroid gland, promoting increased uptake of inorganic iodine and release of organically bound iodine. In the absence of TSH, the thyroid gland atrophies, producing only small amounts of thyroid hormone. An excess of TSH causes hypertrophy and hyperplasia of the thyroid and a clinical picture resembling Graves' disease.
5. **Adrenal Corticotropic Hormone** *(Corticotropin, ACTH)*—It is a polypeptide containing 39 amino acid residues with a molecular weight of 4566. ACTH is produced not only by the adenohypophysis but also by the placenta. The hormones from pituitaries of various species of animals differ with respect to the sequence of amino acids 25 to 32, but these differences do not affect their biological actions. A synthetic polypeptide containing the first 23 amino acid residues of naturally occurring corticotropin has essentially all of the biological and clinical properties of corticotropin. Several peptides have been synthesized that are more potent than natural ACTH.

Physiological Effects—ACTH maintains and controls the functions of the adrenal cortex and thus indirectly affects carbohydrate, protein, and mineral metabolism. Since the known physiological actions of corticotropin are mediated through the adrenal cortex, its effects are similar to those of the adrenal cortical hormones, especially the glucocorticoids. ACTH also slightly enhances the adrenal cortical output of aldosterone and hence has a minor action on mineral metabolism. However, aldosterone secretion is mostly under the control of the renin-angiotensin system. Since the first 13 amino acids of ACTH are identical in sequence to those of α-MSH (melanocyte-stimulating hormone), ACTH causes some hyperpigmentation of the skin. ACTH also causes ketosis, fat mobilization (adipokinesis), hypoglycemia, and insulin resistance in high doses.

HYPOTHALAMIC REGULATION OF ANTERIOR PITUITARY SECRETION

RELEASING HORMONES AND INHIBITING FACTORS (*HYPOTHALAMIC HORMONES*)—The secretion of an anterior pituitary hormone is not constant but rather undergoes intrinsic cyclical variations and additionally is affected by noncyclical factors, such as stress and input from sensory nerves. The intrinsic cycles are determined mostly by what are called negative feedback loops, that is to say a hormone eventually suppresses its own release indirectly by suppressing the secretion of a specific releasing hormone from the median eminence of the hypothalamus. For each anterior pituitary hormone there is a distinct releasing hormone (except that LH and FSH share the same gonadotropin-releasing hormone). The specific hypothalamic releasing hormones include the following: CRH designating that for corticotropin, TRH for

thyrotropin, LH-RH/FSH-RH or gonadotropin-releasing hormone (GnRH) for luteinizing and follicle-stimulating hormones, and GH-RH for growth hormone. For growth hormone and prolactin, there are also specific release inhibitory factors (GH-RIH and dopamine respectively). These factors are secreted into the bloodstream of the pituitary portal system, by which route they reach the anterior hypophysis, where they evoke burst electrical activity. To be effective, releasing hormones must be released in pulses. Sustained-release and long-acting congeners (eg, leuprolide) down-regulate receptors and thus have inhibitory actions. GH-RIH, LHRH, and TRH are distributed widely in the brain and probably are also neurotransmitters; CRF also is produced in the periphery and is released during stress; GH-RIH (somatostatin) also is produced in the pancreas. There is also a pro-GH-RIH that is a stronger inhibitor of insulin release but weaker inhibitor of glucagon release than GH-RIH. Dopamine release by specific hypothalamic cells acts as a sustained or tonic inhibitor of prolactin secretion.

The negative feedback loop that goes from the anterior hypophysis to the hypothalamus is called the short negative feedback loop. There is also a long negative feedback loop that involves the appropriate target-gland hormone (cortisol for ACTH, thyroid hormone for TSH, estrogen for FSH, etc.). The target hormone not only feeds back negatively on the hypothalamus but also directly on the anterior hypophysis, which appears to be the main locus of feedback for some target-cell hormones. Negative feedback to the hypothalamus apparently elicits both a decrease in secretion of a releasing hormone and an increase in the secretion of the inhibitory factor. There is also a non-estrogen-mediated long negative feedback on FSH secretion; the factors involved are called inhibins. In the case of LH there is a long positive feedback loop in which secretion of estrogens favors secretion of GnRH. The noncyclical perturbations in anterior pituitary hormone output also are effected through the hypothalamic releasing and inhibiting factors.

The hypothalamic releasing hormones are relatively small polypeptides with molecular weights ranging up to 8000. In man, the prolactin-releasing factor may be both norepinephrine and vasoactive intestinal polypeptide (VIP). The simplest releasing factor is TRH, the structure of which is a cyclic tripeptide. Some releasing factors appear to function as neurotransmitters or neuromodulators elsewhere in the central nervous system (CNS) and autonomic nervous system.

The natural and synthetic hypothalamic releasing hormones are used for diagnostic tools to assess abnormalities of hypothalamic and pituitary function as well as for therapeutic uses. For example, if a hypothyroid patient responds to TRH with an increase in TSH, then the hypothyroidism may be a lesion in the hypothalamus or pituitary portal system rather than in the anterior hypophysis. In thyrotoxicosis, TRH fails to affect plasma TSH or thyroid hormone concentrations, so that TRH may distinguish between thyrotoxicosis and apparent hyperthyroid states. GnRH can distinguish between hypothalamic and pituitary defects in hypogonadotropic hypogonadism in men but is not reliable in women. GnRH can be used to treat infertility if the defect is in the hypothalamus; even when the defect appears to be at the anterior pituitary level, after a course of treatment anovulatory women frequently go on to secrete normal amounts of LH. GH-RH is used to accelerate growth in growth-retarded children. GH-RIH may be used to treat acromegaly, gigantism, and diabetes mellitus associated with excess GH secretion. Structural analogs of some releasing hormones are now available and are used as agonists and antagonists. Leuprolide, nafarelin, goserelin, and histrelin are GnRH analog agonists that induce pituitary suppression and are available for treating prostate cancer. Pulsatile administration of leuprolide is used to stimulate pituitary function and is available to treat infertility caused by hypothalamic hypogonadotropic hypogonadism in both sexes.

The releasing hormones and inhibiting factors are not only under the control of the various peripheral hormones but the brain as well, and the secretion of some has been demonstrated to be affected by neuropharmacological drugs. Thus drugs such as reserpine and methyldopa that decrease the release of dopamine and/or norepinephrine increase the output of lactogenic and growth hormones. Bromocriptine, lergotrile, and pergolide, potent dopaminergic agonists, suppress the output of these two hormones and consequently have been tried, successfully, in the treatment of galactorrhea, prolactin-secreting tumors with hypogonadism in men, hyperprolactinemia-associated infertility in women, and acromegaly.

ARGININE HYDROCHLORIDE—page 1270.
AMANTADINE HYDROCHLORIDE—page 1417.
BROMOCRIPTINE MESYLATE—page 1418.

CHORIOGONADOTROPIN ALFA

Choriogonadotropin Alfa; Ovidrel

APDVQDCPEC	TLQENPFFSQ	PGAPILQCMG	CCFSRAYPTP
LRSKKTMLVQ	KNVTSESTCC	VAKSYNRVTV	MGGFKVENHT
ACHCSTCYYH	KS		
SKEPLRPRCR	PINATLAVEK	EGCPVCITVN	TTICAGYCPT
MTRVLQGVLP	ALPQVVCNYR	DVRFESIRLP	GCPRGVNPVV
SYAVALSCQC	ALCRRSTTDC	GGPKDHPLTC	DDPRFQDSSS
SKAPPPSLPS	PSRLPGPSDT	PILPQ	

[177073-44-8] $C_{437}H_{682}N_{122}O_{134}S_{13}$ (10205.71)α-subunit; $C_{668}H_{1090}N_{196}O_{203}S_{13}$ (15531.93) β-subunit.

Preparation—The five major steps usually followed in the manufacture of recombinant human gonadotropins are:

1. Constructs of DNA, containing coding sequences of either α- or β-subunits of FSH or LH are prepared.
2. Chinese hamster ovary (CHO) cells are co-transfected with two DNA constructs.
3. Stable CHO cell lines containing integrated FSH or LH sequences are selected.
4. *Master* and *Working* Cell Banks are prepared for production in bioreactors.
5. FSH or LH in the harvested cell cultures are purified by chromatography.

Description—Consists of two non-covalently linked subunits (designated α and β, of 92 and 145 amino acid residues, respectively), with carbohydrate moieties linked to specific amino acids on each subunit. It is a sterile, lyophilized powder; pH of reconstituted solution is 6.5 to 7.5.

Solubility—Soluble in water.

Comments—A biosynthetic, recombinant DNA-derived hCG utilized as a component of infertility regimens (Assisted Reproductive Technologies) and for the induction of ovulation in infertile females.

CORTICOTROPIN

ACTH; Adrenocorticotropin; Acthar, ACTH, HP

The polypeptide hormone derived from the anterior lobe of the pituitary of mammals used for food by man, which increases rate of secretion of adrenal corticosteroids.

Preparation—Most commercial preparations of *corticotropin* are obtained from either hog or sheep pituitary glands, although beef and whale glands also have been used. Isolation of the hormonal principle(s) from swine and sheep pituitaries was reported in 1943 by Sayers et al. *J Biol Chem* 1943; 149:425, and by Li et al. *J Biol Chem* 1943; 149:413. A process of purification of the hormonal substance is described in US Pat 3,124,509.

Two types of preparations are available: short- and long-acting. The short-acting preparations consist of a lyophilized powder or a stable aqueous solution containing 1% phenol. The powder is dissolved in physiological saline or other suitable medium before injection. Short-acting preparations are administered either intramuscularly or intravenously.

Long-acting preparations (repository and gel) contain *the drug* incorporated in a gelatin menstruum designed to delay the rate of absorption and increase the period of effectiveness. Combination with zinc hydroxide suspension also delays the rate of absorption. These are injected intramuscularly.

It is standardized by the Sayers assay. The clinical effectiveness, however, varies with the mode of administration. The difference is evident particularly in comparisons of short-acting preparations injected intramuscularly with long-acting preparations similarly administered. For this reason, gel preparations are labeled in terms of *clinical units* to conform more nearly to their expected physiological potency. Fourteen

USP Units in gelatin medium possess the approximate clinical efficacy of 40 USP Units of aqueous solution by intermittent intramuscular injection.

Description—White or practically white, soluble, amorphous solid with the characteristic appearance of substances prepared by freeze-drying; pH (of the liquid form or after reconstitution from the solid state) between 3 and 7.

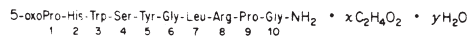
Comments—Stimulates the adrenal gland to produce hydrocortisone, desoxycorticosterone, and androgens. It is used as a diagnostic drug to assess the functional capacity of the adrenal gland. After injection, a rise in plasma cortisol or urinary 17-hydroxycorticosterone indicates a functional gland. This is at present the most important clinical use of this agent. This drug has been promoted as a therapeutic agent in a wide variety of glucocorticoid-responsive disorders. In general, with the exception of primary adrenal insufficiency, it is effective in all of the conditions for which glucocorticoids are found useful, but it is ineffective when applied locally. The continued administration of large amounts of the hormone may result in one or more of the manifestations of Cushing's syndrome, may exacerbate the symptoms of latent or frank diabetes, and, because of its anti-inflammatory action, may mask symptoms of infection. The need for adequate medical supervision during its use, therefore, cannot be overemphasized. They occur frequently when the dosage exceeds 40 Units a day.

Abrupt cessation of corticotropin injections may be followed by withdrawal effects that take the form of symptoms of adrenal insufficiency. These result from pituitary inhibition that occurs during treatment with corticotropin and may be minimized or eliminated by gradually reducing the amount injected. Corticotropin causes some side effects not caused by glucocorticoids, namely, hypersensitivity, salt and water retention, and androgenic effects (acne, hirsutism, and amenorrhea) in women. It is contraindicated if there is osteoporosis, systemic mycosis, corneal herpes, or scleroderma.

ENTACAPONE—page 1419.

GONADORELIN ACETATE

Luteinizing hormone–releasing factor acetate (salt) hydrate; LH-RH; Lutrepulse



[52699-48-6] $C_{55}H_{75}N_{17}O_{13}.xC_2H_4O_2.yH_2O$

Preparation—By synthesis or from the hypothalamus, *Science* 1973; 179:34.

Description—Faint-yellow powder.

Solubility—1 g in 25 mL water, 50 mL methanol, or 25 mL 1% acetic acid.

Comments—Identical to natural GnRH. Gonadorelin is used in the treatment of primary hypothalamic amenorrhea. Gonadorelin hydrochloride (Factrel, *Ayerst)* is a related preparation and is used as a diagnostic agent to determine whether hypogonadism is the result of a defect in anterior pituitary release of LH or in hypothalamic release of LH-RH. If gonadorelin evokes a rise in LH levels, the disturbance is in the hypothalamus; if it does not, the disturbance is in the anterior pituitary. Administered in pulsatile fashion, it evokes secretion of both FSH and LH. However, if plasma levels remain high for periods longer than a few hours, preceptor down-regulation occurs. LH receptors are affected more than FSH receptors. By careful selection of dose regimen it is thus possible to increase or decrease male or female fertility, in the latter instance without marked changes in estrogen secretion.

Local swelling, itching, or pain and occasional rash at the injection site may occur after subcutaneous injection. Headache, nausea, lightheadedness, abdominal discomfort, and rare flushing may occur. It does not cause multiple births.

LEUPROLIDE—page 1577.
LEVODOPA/CARBIDOPA—pages 1418 and 1419.

MENOTROPINS

Pergonal

Menotropins [9002-68-6]; an extract of postmenopausal urine containing the follicle-stimulating hormone (FSH) and luteinizing hormone (LH) in a 1:1 ratio.

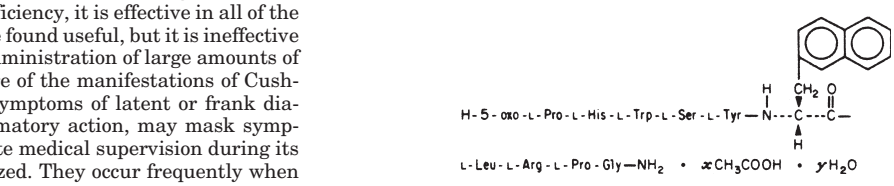
Comments—Has the gonadotropic activities of FSH and LH It is used to induce ovulation in women with infertility consequent to insufficient endogenous production of gonadotropins. HCG is given following menotropins. Clinical experience is that about 75% of anovulatory women ovulate after treatment, and 25% become pregnant after two courses of treatment. Multiple gestation occurs in about 15% to 30% of completed pregnancies. The hyperstimulation syndrome occurs in 1% to 2% of cases.

It also is used concomitantly with HCG for >3 months to induce spermatogenesis in men with hypogonadotropic hypogonadism.

Side effects include ovarian enlargement, flatulence, abdominal discomfort, oliguria, weight gain, ascites, pleural effusion, hypotension, and hypercoagulability; these are all evidence of hyperstimulation. Other adverse reactions include arterial thromboembolism, hypersensitivity, and febrile reactions. Birth defects occurred in 5 of 287 pregnancies. Occasionally, ovarian rupture and intraperitoneal hemorrhage occur, and surgery is required.

NAFARELIN ACETATE

Luteinizing hormone-releasing factor (pig), 6-[3-(2-naphthadenyl)-D-alanine, acetate (salt), hydrate; Synarel



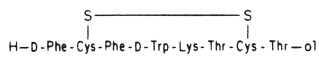
[86620-42-0] $C_{66}H_{83}N_{17}O_{13}.xC_2H_4O_2.yH_2O$.

Preparation—US Pat 4,234,571.

Comments—An agonist for LH-RH receptors. However, the duration of action is too long for pulsatile dosing, so the effect of repetitive administration is that of down-regulation of LH-RH receptors. It has been found to be effective in the treatment of endometriosis and central precocious puberty. In women, adverse effects are those of hypoestrogenemia, namely, hot flashes, vaginal dryness, decreased libido, and a moderate decrease in trabecular bone mineralization in the spine in about 67% of patients. In men, weight gain, hot flashes, decreased libido, and decreased drive and initiative occur. These effects disappear after discontinuation of the drug. It is absorbed rapidly by the intranasal but not sublingual route. Intranasal bioavailability is about 21%. The drug is metabolized to at least six metabolites. The half-life is about 2 hr.

OCTREOTIDE

L-Cysteinamide, [*R*-(*R,*R**)]-D-phenylalanyl-L-cysteinyl-L-phenyl-alanyl-D-tryptophyl-L-threonyl-*N*-[2-hydroxy-1-(hydroxy-methyl)propyl]-, cyclic (2 → 7)-disulfide; Sandostatin, Sandostatin LAR**



[83150-76-9] $C_{49}H_{66}N_{10}O_{10}S_2$ (1019.24).

Preparation—US Pat 4,395,403.

Comments—An analog of somatostatin that differs in that it inhibits growth hormone secretion in lower doses than affect insulin secretion, it is long acting (2-hr half-life), there is no rebound hypersecretion after discontinuation, and it is orally effective. It is approved for symptomatic treatment of carcinoid tumors and profuse diarrhea associated with vasoactive intestinal peptide tumors (lipomas, vipomas). In light of octreotide's short half-life a depot injection (Sandostatin LAR) was formulated for chronic use of carcinoid tumors and vipomas and can be administered every 4 weeks. However, patients should be stabilized on subcutaneous octreotide for 2 weeks prior to switching to the long-acting intramuscular depot injection.

The drug is tolerated well. During the first few days of treatment there are flatulence, loose stools, diarrhea, and abdominal pains. A mild steatorrhea occurs in some patients and may persist during treatment or disappear in a few days. Malabsorption does not occur. There may be a moderate decrease in postprandial glucose tolerance, but no complications have been recorded.

PERGOLIDE MESYLATE—page 1420.
PRAMIPEXOLE—page 1420.
ROPINIROLE—page 1421.

SOMATREM AND SOMATROPIN

***N*-L-Methionylsomatotropin (human); Protropin**

[82030-87-3] $C_{995}H_{1537}N_{263}O_{301}S_8$ (22,256.21)

SOMATROPIN

Genotropin, Humatrope, Nutropin

Growth hormone, human; somatotropin (human) [12629-01-5] $C_{990}H_{1528}N_{262}O_{300}S_7$ (21,500.00)

Preparation—A single polypeptide chain of 191 amino acids once obtained from the anterior lobe of the human pituitary gland. See US Pat 3,118,815.

Comments—Both somatrem and somatropin products are from recombinant DNA–directed syntheses. Somatropin is identical to human pituitary–derived somatropin. Somatrem (Protropin) is identical to natural growth hormone except it contains an additional methionine on the *N*-terminus of the molecule. However, the effects and potencies are identical; therefore, both peptides are considered together. Somatropin from pituitary extracts was discontinued because of reports that its use was sometimes the cause of Creutzfeldt-Jakob disease. For description, actions, and uses see *Growth Hormone*.

Intramuscular administration of the hormone is preferred to subcutaneous injection because the hormone causes lipodystrophy or lipoatrophy at the cutaneous injection site. Pain and swelling usually occur on injection, so sites should be rotated. Hypercalciuria occurs frequently but usually regresses in 2 to 3 months. Hyperglycemia and frank diabetes mellitus due to insulin resistance may occur. Myalgia and early morning headaches are relatively frequent. Antibodies to the hormone may be found in 30% to 40% of recipients given somatrem, but patients rarely fail to respond to therapy. Approximately 2% of patients receiving somatropin developed antibodies, but growth responses have not been limited in such patients. Occasionally, somatotropin causes hypothyroidism. If the epiphyses are closed, the hormone should not be used because continued stimulation of growth of the phalanges and jawbone, but not other bones, can cause abnormal body proportions. Available products are exceedingly expensive.

THE POSTERIOR PITUITARY (NEUROHYPOPHYSIS)

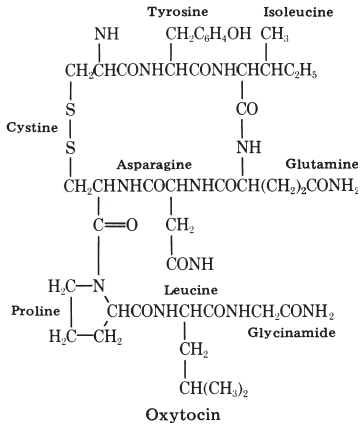
The posterior pituitary contains two peptide hormones, oxytocin and vasopressin. Neither is made in the posterior pituitary, but rather they are synthesized in neurons in the hypothalamus. Oxytocin is synthesized in the paraventricular nucleus, and vasopressin in the supraoptic nucleus. The axons of the hormone-secreting nerve cells pass from the hypothalamus to the internal infundibular zone of the posterior pituitary (hence the name neurohypophysis). The hormones flow down the axons as granules or vesicles composed of a hormone and a carrier protein called neurophysin. Their release at the nerve terminals is effected by nerve impulses. Thus, the control of release is actually in the appropriate hypothalamic nuclei.

Human and most mammalian vasopressin is Cys-Tyr-Phe-Gln-Asn-Cys-Pro-Arg-GlyNH_2, called arginine vasopressin. An exception is pigs whose vasopressin called lypressin contains lysine at position 8. Vasopressin possesses antidiuretic hormone (ADH) and vasopressor activities. The ADH activity decreases urine flow by increasing the resorption of water from the distal convoluted tubules and collecting ducts of the kidney. The effect is a decrease in the osmolarity of the extracellular fluid.

When there is a defect in the hypothalamic-pituitary secretion of ADH, diabetes insipidus results in a watery diuresis. Vasopressin is used mainly for its antidiuretic effects in this disease rather than for its vasoconstrictor actions, from which the name vasopressin is derived. However, not only does vasopressin stimulate vascular smooth muscle, but also it increases bowel motility, and it has been used to treat bowel stasis and to expel gas postsurgically. The vasoconstrictor and bowel spastic actions have special usefulness in arresting hemorrhage from peptic ulcers. The smooth muscle stimulant effects occur with higher doses than are necessary to affect renal function. Vasopressin also has weak oxytocic activity. Vasopressin has a brief half-life (less than 20 min).

Oxytocin stimulates the contraction of smooth muscle in the uterus and alveoli of the lactating breast. At coitus, uterine stimulation by oxytocin causes peristaltic activity that assists the migration of spermatozoa. During parturition, the hormone enhances the uterine contractions. The uses of oxytocin in labor and breast engorgement are described in Chapter 76. Neither vasopressin nor oxytocin survives the acid and enzymes of the gastrointestinal (GI) tract, so they must be given parenterally or intranasally.

Each of the octapeptides has been synthesized. Oxytocin has the structure

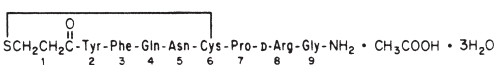


Oxytocin

The structure of vasopressin from human, monkey, dog, cat, ox, camel, rabbit, and rat pituitaries is identical with that of oxytocin, except that the isoleucine and leucine residues are replaced by residues of phenylalanine and arginine, respectively. The successful synthesis of the naturally occurring posterior lobe hormones has provided the impetus for the synthesis of a number of analogs of both oxytocin and vasopressin. Thus, substances in which one or more of the amino acids of the native hormones have been replaced by others or that contain fewer or additional amino acid residues have been prepared, and their pharmacological properties explored. One of these was the compound vasotocin, containing the pentapeptide ring of oxytocin and the tripeptide side chain of vasopressin. This substance possesses the biological properties of both neurohypophyseal hormones, although in lesser degree. Synthetic analogs of oxytocin and vasopressin, in which one or more of the amino acids of the native hormones have been replaced, are named by using numbers to denote the alterations represented in the synthetic. A synthetic vasopressin in which the moiety at position 8 is arginine is named simply 8-arginine vasopressin.

DESMOPRESSIN ACETATE

Vasopressin, 1-(3-mercaptopropionic acid)-8-D-arginine, monoacetate (salt), trihydrate; DDVAP; Stimate



[62357-86-2] $C_{48}H_{68}N_{14}O_{14}S_2.3H_2O$ (1183.22).

Preparation—A synthetic analog of 8-arginine vasopressin in which the amino group has been removed from the *N*-terminal cysteine and L-arginine at position 8 has been replaced by the D-enantiomer. *Helv Chim Acta* 1966; 49:695.

Description—White fluffy powder; pK_a (gly-NH_2) 4.8.

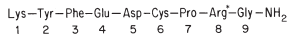
Solubility—Soluble in alcohol or water.

Comments—Used in the treatment of central *(neurogenic)* diabetes insipidus. It also is used to test the ability of the kidney to concentrate urine. Since the hormone can raise the plasma levels of Factor VIII (antihemophilic factor), it is sometimes used to treat Factor VIII bleeding disorders and to increase Factor VIII levels prior to surgery. It may be used alone or as an adjunct for some refractory cases of primary nocturnal enuresis.

Headache, mild hypertension, nasal congestion, mild abdominal cramping, water intoxication, and vulval pain sometimes occur. Chlorpropamide and clofibrate potentiate, and glyburide inhibits, antidiuretic action.

VASOPRESSIN

Beta-Hypophamine; Pitressin



(*in pig vasopressin, Arg is Lys)

8-L-Lysine (or arginine) vasopressin: Lysine form-[50-57-7] $C_{46}H_{65}N_{13}O_{12}S_2$ (1056.22); Arginine form-[113-79-1] $C_{46}H_{65}N_{15}O_{12}S_2$ (1084.23).

Comments—Its actions are discussed on page _____. It is employed for its antidiuretic effect in central diabetes insipidus and to dispel gas shadows in bowel roentgenography and pyelography. It should not be used as a pressor agent.

Untoward effects related to overdosage include water intoxication (with headache, nausea and vomiting, confusion, lethargy, coma, and convulsions), especially when patients drink excessive amounts of water or are given intravenous fluids, and stimulation of vascular, uterine, and intestinal smooth muscle, which may result in pallor, hypertension, coronary constriction (with anginal chest pain, electrocardiographic changes, and occasional myocardial infarction), uterine cramps, menorrhagia, and nausea, vomiting, diarrhea, and abdominal cramps. Hypersensitivity occasionally occurs; manifestations include urticaria, neurodermatitis, flushing, fever, wheezing, dyspnea, and rare anaphylactic shock. Large doses are oxytocic and also cause milk ejection. Alcohol, heparin, demeclocycline, lithium, and large doses of epinephrine antagonize it; carbamazepine, chlorpropamide, clofibrate, glucocorticoids, and urea potentiate it.

The plasma half-life is 10 to 20 min. However, the effect of an intramuscular injection lasts from 2 to 8 hr. From 10% to 15% is excreted unchanged. Vasopressin tannate is also available as a longer-acting preparation.

THE ADRENOCORTICAL STEROIDS

The steroid hormone products of the adrenal cortex are grouped into two classes: the corticosteroids (glucocorticoids and mineralocorticoids), which have 21 carbons, and the androgens, which have 19. Adrenal corticosteroids differ in their relative glucocorticoid (carbohydrate-regulating) and mineralocorticoid (electrolyte-regulating) activities. In humans hydrocortisone (cortisol) is the main glucocorticoid and aldosterone is the main mineralocorticoid. The cortex, or outer portion, of the adrenal gland is one of the endocrine structures most vital for normal metabolic function. While it is possible for life to continue in the complete absence of adrenal cortical function, serious metabolic derangements ensue, and the capacity of the organism to respond to physiological or environmental stress is lost completely.

PHYSIOLOGICAL ACTIONS—Adrenocortical steroids have diverse effects that include alterations in carbohydrate, protein, and lipid metabolism; maintenance of fluid and electrolyte balance; and preservation of normal function of the cardiovascular system, the immune system, the kidney, skeletal muscle, the endocrine system, and the nervous system. One of the major pharmacological uses of this class of drugs is based on their anti-inflammatory and immunosuppressive actions. A protective role for cortisol is apparent in the physiological response to severe stress that can increase daily production over 10-fold. Furthermore, many immune mediators associated with the inflammatory response can lead to decreased vascular tone and cardiovascular collapse if unopposed by adrenal corticosteroids. The relative or complete absence of adrenocortical function, known as Addison's disease, is accompanied by loss of sodium chloride and water, retention of potassium, lowering of blood-glucose and liver-glycogen levels, increased sensitivity to insulin, nitrogen retention, and lymphocytosis. The disturbances in electrolyte metabolism are the cause of morbidity and mortality in most cases of severe adrenal insufficiency. All of these disorders may be corrected by administration of adrenal cortical extract or the pure adrenal cortical steroids now available.

In its biosynthesis of the steroid hormones, the adrenal cortex uses cholesterol, which is present in large amounts in the gland; during periods of secretory activity it also consumes large quantities of ascorbic acid, which is likewise present in high concentration. The synthesis and secretion of the glucocorticoids (essentially hydrocortisone) takes place in the zona fasciculata. Corticotropin (ACTH) is the primary stimulus to hydrocortisone secretion. ACTH is released in response to the hypothalamic hormone CRH (see page _____). Glucocorticoid secretion, then, is regulated through suprahypothalamic and hypothalamic nuclei, which integrate responses to sensory, emotional, and chemical inputs, including the glucocorticoids themselves, and the basophilic cells of the adenohypophysis, release from which is suppressed by circulating glucocorticoids. Physical (injury, surgery, etc.) and emotional stress and hypoglycemia increase secretion. Synthesis in the zona fasciculata can be altered by drugs that inhibit specific enzymes involved. CRH, ACTH, and glucocorticoid release follows a circadian rhythm such that blood concentrations of hydrocortisone are highest between 6 and 8 AM and lowest around midnight.

The synthesis and release of the mineralocorticoid aldosterone takes place in the zona glomerulosa. ACTH has only a slight effect on secretion. Rather, angiotensins II and III are the primary stimulants, although hyperkalemia is also an important stimulus. The production of the angiotensins is under renal, CNS, and sympathetic nervous system control. In the kidney, the macula densa around the juxtaglomerular distal tubules monitors Na^+ and Cl^- concentrations and luminal osmolarity. Low Na^+ concentration and osmolarity or high Cl^- causes signals to be sent to the juxtaglomerular (JG) cells in the afferent arterioles, which then release renin. Renin secretion also is increased by low blood pressure at the JG cells and by sympathetic impulses, which work through β_1-adrenoreceptors. Renin then cleaves angiotensin I from angiotensinogen, both locally and in the blood. Angiotensin I is converted to angiotensin II by a converting enzyme (CE or kininase II), mainly in the lung. (Angiotensin III is a metabolite of II.) Thus, a variety of electrolyte, emotional, cardiovascular, and drug factors can affect aldosterone secretion indirectly.

STRUCTURE-ACTIVITY RELATIONSHIP—Clinical experience has indicated that the anti-inflammatory activity of adrenal cortical steroids in man correlates well with their glucocorticoid activity. The undesirable side effects of sodium retention and edema are associated with mineralocorticoid activity. Synthetic steroids possessing higher glucocorticoid and lower mineralocorticoid activity than cortisone or cortisol have been prepared and marketed. A comparison of some commonly used systemic corticosteroids is included in Table 77-2.

All adrenal corticoids require the 3-keto group and 4,5 unsaturation. Additional unsaturation in Ring A enhances the anti-inflammatory properties while at the same time reducing the sodium-retaining effect. The presence of oxygen at position 11 is necessary for significant glucocorticoid activity; the 11β-hydroxy group is more potent than the 11-keto group; the 11-keto group is converted to the active β-hydroxy group in the body. The 17α-hydroxy group also is important to glucocorticoid activity. Introduction of either a methyl or hydroxyl group at position 16 markedly reduces mineralocorticoid activity but only slightly decreases glucocorticoid and anti-inflammatory activity. The 9α-fluoro group enhances both glucocorticoid and mineralocorticoid activities, but the effects of substituents at the 6 and 16 positions override this effect.

BIOLOGICAL ACTIVITY—The glucocorticoids appear to affect all cells, although not all in the same way. Clinical interest primarily focuses on their anti-inflammatory and immunosuppressant effects. They prevent release of various lytic enzymes that extend tissue damage during inflammation and generate leukotactic substances. Glucocorticoids decrease phagocytosis by macrophages. Anti-inflammatory effects include the retardation of the migration of polymorphonuclear leukocytes, suppression of repair and granulation, reduction in the erythrocyte sedimentation rate, decreased fibrinogenesis, and diminished elaboration of C-reactive protein. Glucocorticoids suppress the production of cytokines (eg, IL-1,IL-6, interferon gamma, TNF-alpha, and others) by inflammatory cells (eg, monocytes, macrophages, and lymphocytes) that recruit eosinophils. They also decrease lipid eicosanoid and prostaglandin production by inhibiting the

Table 77-2. Major Adrenal Corticosteroids[a]

DRUG	RELATIVE ACTIVITY			DOSAGE FORM
	ANTI-INFLAM	TOPICAL	NA + RET	
Short- to medium-acting glucocorticoids				
Hydrocortisone (Cortisol)	1	1	1	Oral, Inj, Top
Cortisone	0.8	0	0.8	Oral, Inj, Top
Prednisone	4	0	0.3	Oral
Prednisolone	5	4	0.3	Oral, Inj, Top
Methylprednisolone	5	5	0	Oral, Inj, Top
Intermediate-acting glucocorticoids				
Triamcinolone	5	5–100	0	Oral, Inj, Top
Fluprednisolone	15	7	0	Oral
Long-acting glucocorticoids				
Betamethasone	25–40	10	0	Oral, Inj, Top
Dexamethasone	30	10–40	0	Oral, Inj, Top
Mineralocorticoids				
Fludrocortisone	10	10	250	Oral, Inj, Top
Desoxycorticosterone acetate	0	0	20	Inj, pellets

[a]Legend: Relative activity, potency relative to hydrocortisone; anti-inflammatory, anti-inflam; sodium retention, Na + Ret; Injection, Inj; topical, Top.

production of cytokines that induce cyclooxygenase-II in inflammatory cells. The immunosuppressant effects may be partly the result of the suppression of phagocytosis, gene expression of cytokines and a decrease in the number of eosinophils and lymphocytes, suppression of delayed hypersensitivity reactions, decrease in tissue reaction to antigen-antibody interactions, and reduction in plasma immunoglobulins.

Effects on carbohydrate, fat, and protein metabolism are responsible for both beneficial and untoward effects. These hormones increase hepatic gluconeogenesis and glycogen deposition, both lipolysis and lipogenesis (but increase fat deposition at only a few specialized sites), and protein catabolism in various tissues (especially skeletal muscle).

In addition to the above-mentioned changes brought about by glucocorticoids are the so-called permissive effects. In these, the steroids do not themselves cause change but physiological amounts are required for certain organs or structures to respond to stimuli. For example, neither the kidney can respond to a water load nor the arterioles to epinephrine in the absence of adequate levels of glucocorticoids.

Once a glucocorticoid hormone has permeated a cell membrane, it combines with a cytosolic glucocorticoid receptor that is inactive because it is bound to some specific proteins, including some heat shock proteins that prevent them from reaching the nucleus and binding to DNA. The glucocorticoid-receptor complex undergoes conformational changes that allow dissociation from the heat shock proteins and other immunomodulatory proteins, then it is translocated to the cell nucleus, where it attaches to glucocorticoid receptor elements in the DNA. The result is an enhancement or reduction of the gene transcription that leads to an increased or decreased synthesis of certain proteins. Other transcription factors also interact at the same DNA binding sites. The protein produced is determined, in part, by the glucocorticoid receptor, of which there is more than one kind within the cell. There are estimated to be from 10 to 100 glucocorticoid target genes per cell, but not all of them are expressed in every cell. Tissue selectivity for different steroid hormones seems to be considerably determined by steroid-metabolizing enzymes that differentially alter intracellular steroids that upon transport to the nucleus bind to specific hormone response elements in the DNA.

Mineralocorticoids act on the distal tubules and collecting ducts of the kidney to increase the expression of genes that encode for proteins that enhance reabsorption of Na^+ from the tubular fluid. The effects on electrolytes are associated with an increase in the number of open Na^+ and K^+ channels in the luminal membrane tubular cells, and they increase the activity of basolateral membrane Na^+/K^+-activated ATPase. The net result is a return of Na^+ to the systemic circulation in exchange for K^+. Similar electrolyte effects are promoted by mineralocorticoids in other tissues (eg, colon, salivary glands, and sweat glands).

Glucocorticoids also inhibit membrane lipid peroxidation, which possibly contributes to the salutary effects in brain edema; the effect appears to be one of decreasing the activity of membrane-bound, superoxide radical-generating mixed-function enzymes. Possibly related is an action to block phospholipase-A2, which prevents the release of arachidonic acid from membrane phospholipids and its subsequent conversion to eicosanoids. This inhibitory effect results from the production of an inhibitory protein, lipocortin, in leukocytes.

The primary effects of mineralocorticoids are on cortical collecting tubule cells in the kidney to increase sodium reabsorption and potassium secretion. Thus, elevated aldosterone titers cause sodium retention and potassium depletion with accompanying volume expansion and weight gain, hypertension, and metabolic alkalosis.

SIDE EFFECTS—Certain side effects may appear during the first week of treatment with glucocorticoids; they include euphoria and a rare paradoxical suicidal depression, psychoses (especially with high doses), hypertension (rare), anorexia, occasional hyperglycemia, colonic ulceration (rare), increased susceptibility to infections (especially viral infections, fungal infections, tuberculosis), and acne. After 7 to 10 days of treatment, the pituitary release of ACTH is suppressed, and the adrenal secretion of cortisol is temporarily inadequate once glucocorticoid administration ceases. In the case of a medical emergency, the depressed pituitary-adrenal response may make the patient unable to respond to stress. Additional exogenous corticosteroid is given in a dosage and for a duration appropriate for the severity of the stress. Consequently, patients on high-dose or long-term treatment should carry identification stating that they are under treatment with corticosteroids. Withdrawal of corticosteroids should be slow.

From the first week through the first year of therapy, additional side effects may appear, namely, fat redistribution to the nape of the neck *(buffalo hump)* and lower abdomen, diabetes mellitus and hyperglycemia, *moon face* and other edematous states, and renal potassium loss (from mineralocorticoid activity), alkalosis, additional infections (including tuberculosis), papilledema, glaucoma, posterior subcapsular cataracts, diplopia, 6th nerve palsies, osteoporosis, myopathy, ecchymoses and purpura, and cutaneous striae. After prolonged suppression of the anterior pituitary secretion of ACTH, there may be a permanent defect in pituitary-adrenal function. Continuous or repetitive use of glucocorticoids may cause painless joint destruction, especially if the drug is given intra-articularly. After prolonged glucocorticoid therapy, additional untoward effects include bone fractures and vertebral collapse (from marked osteoporosis), hyperlipidemia, and possible premature atherosclerosis.

Adverse effects of glucocorticoids applied to the skin include stinging or burning sensations, itching, irritation, dryness, scaliness, vasoconstriction, folliculitis, acne, bacterial or yeast infections, hypopigmentation, atrophy, and striae. Systemic effects also can occur, especially if occlusive dressings are used. Topical ophthalmological glucocorticoids not only may cause serious exacerbations of viral, fungal, and bacterial infections of the eye but also glaucoma. From all of the above, it can be seen that glucocorticoids are drugs that have numerous and potentially serious side effects.

Because the mineralocorticoids are used mainly in physiological doses for replacement therapy, untoward effects are usually infrequent and mild. Sodium and water retention (with *moon face*), potassium loss, alkalosis, and hypertension can occur with excessive doses.

DRUG INTERACTIONS—Glucocorticoids decrease the hypoglycemic activity of insulin and oral hypoglycemics, so that a change in dose of the antidiabetic drugs may be necessitated. In high doses, glucocorticoids also decrease the response to somatotropin. The usual doses of mineralocorticoids and large doses of some glucocorticoids cause hypokalemia and may exaggerate the hypokalemic effects of thiazide and high-ceiling diuretics. In combination with amphotericin B they also may cause hypokalemia. Glucocorticoids appear to enhance the ulcerogenic effects of nonsteroidal anti-inflammatory drugs (NSAIDs). They decrease the plasma levels of salicylates, and salicylism may occur on discontinuing steroids. Glucocorticoids may increase or decrease the effects of prothrombopenic anticoagulants. Estrogens, phenobarbital, phenytoin, and rifampin increase the metabolic clearance of adrenal corticosteroids and hence necessitate dose adjustments.

PRECAUTIONS AND CONTRAINDICATIONS—Both glucocorticoids and mineralocorticoids must be used cautiously in congestive heart failure, hypertension, liver failure, renal failure, or nephrolithiasis. When glucocorticoids are used in persons with emotional instability or psychotic tendencies, hyperlipidemia, diabetes mellitus, hypothyroidism, myasthenia gravis, osteoporosis, peptic ulcer, ulcerative colitis, chronic infections (especially tuberculosis or a positive test), or a history of herpetic infections, patients should be monitored frequently for untoward effects. Topical application to the eye is absolutely contraindicated in the presence of ophthalmological infections.

PHARMACOKINETICS—Most corticosteroids are absorbed rapidly and completely from the GI tract. Some corticosteroids (hydrocortisone and some inhaled congeners including beclomethasone and budesonide) are rapidly inactivated by metabolism as they pass through the liver. Thus, some corticosteroids must be given parenterally for systemic effects. Esterification with large hydrophobic organic acids decreases solubility and therefore slows systemic absorption from sites of injection. Esterification with water-soluble acids, such as phosphoric or succinic, increases the rate of absorption from injection sites and even may permit intravenous administration. All of the glucocorticoids are absorbed from the skin, but some slowly enough that metabolic destruction can limit systemic accumulation. Many glucocorticoids also are metabolized in the skin. Fluorination at the 9-position and various substituents at the 17-position make glucocorticoids resistant to local destruction and hence make these derivatives more likely to cause systemic effects.

In the plasma, corticosteroids are bound to both corticosteroid-binding globulin (CBG, transcortin, α_1-macroglobulin) and albumin, which serve as transport vehicles. The extent of binding varies among the steroids. Various drugs and diseases can affect the concentration of transport proteins and their capacities. Corticoids cross the placental barrier and may cause congenital malformations. They also appear in breast milk and may suppress growth of the infant. The action of a steroid-receptor complex at the genes long outlasts significant plasma concentrations of the steroid, so that the plasma half-life has little relevance to a dosage regimen. Instead, a parameter known as the biological half-life is the primary determinant of dosage intervals.

THERAPEUTIC USES—The adrenal corticosteroids are used for replacement therapy in adrenal insufficiency (eg, Addison's disease and congenital adrenal hyperplasia). In this use, toxic effects are infrequent, since the aim is to approximate the equivalent of physiological body concentrations. Both mineralocorticoids and glucocorticoids may be required. Glucocorticoids additionally are used to treat rheumatic, inflammatory, allergic, neoplastic, and other disorders; the effects are palliative only and do not eradicate the underlying disorders. It is necessary to use supraphysiological doses, so some untoward effects are unavoidable.

The anti-inflammatory actions of the glucocorticoids are employed in the treatment of noninfectious acute ocular inflammation and certain infectious inflammations, especially in combination with antibiotics. Glucocorticoids are of value in decreasing some cerebral edemas (eg, vasogenic). Their value in the treatment of bacterial meningitis probably accrues to decreased permeability of the blood-brain barrier plus inhibition of cytokine production, especially tumor necrosis factor (TNF-alpha).

In serious acute allergic disorders, systemic glucocorticoids may be indicated; they should not be used chronically in allergic disorders, except in acute flare-ups. However, potent topical corticosteroids are now regularly used by inhalation for chronic treatment of bronchial asthma and intranasally for chronic noninfectious rhinitis (see *Respiratory Drugs* in Chapter 69). Similarly, acute bronchial asthma, status asthmaticus, and some chronic obstructive pulmonary disease may require systemic glucocorticoids. These drugs suppress allergic and inflammatory manifestations of trichinosis.

Topical or systemic glucocorticoids often markedly improve certain skin diseases, such as pruritus, psoriasis, dermatitis herpetiformis, and eczema; pemphigus, erythema multiforme, exfoliative dermatitis, and mycosis fungoides usually require systemic treatment, which may be life-saving.

Probably the most widely known application of the anti-inflammatory actions of the glucocorticoids is in the treatment of the arthritic and rheumatic disorders. Immunosuppressant actions also may play a role in the treatment of such disorders. These disorders are systemic lupus erythematosus, polyarteritis nodosa, temporal arteritis, Wegener's granulomatosis, polymyositis, and polymyalgia rheumatica. Glucocorticoids may be indicated in severe cases of rheumatoid arthritis unresponsive to other treatment, Still's disease, mixed connective tissue disease, drug-induced lupoid syndromes, and psoriatic arthropathy.

Rheumatic or arthritic conditions in which glucocorticoids may or may not provide temporary relief but are not justified chronically because of a high toxicity/benefit ratio are osteoarthritis, systemic ankylosing spondylitis, gout fibrositis, and Reiter's syndrome. Even though the nephrotic syndrome is not inflammatory, it may respond to treatment, perhaps as the result of immunosuppression. Ulcerative colitis sometimes may respond dramatically. The beneficial effects in myasthenia gravis are probably immunosuppressant. Chronic multiple sclerosis does not respond, but acute relapses may. The incidence and severity of the respiratory distress syndrome in premature infants can be decreased by glucocorticoid treatment.

Glucocorticoids may be palliative in acute leukemia and also in chronic lymphocytic leukemia, and they are components of certain curative antineoplastic combinations. They suppress the associated autoimmune hemolytic anemia and the nonhemolytic anemia, granulocytopenia, and thrombocytopenia that result from encroachment on the bone marrow. The effects are only temporary, and the patient eventually becomes refractory to steroid therapy. Hodgkin's disease, lymphosarcoma, and multiple myeloma also may be suppressed temporarily.

In the treatment of endotoxin shock, massive doses of glucocorticoids suppress the vasculotoxic effects of the toxin. In all kinds of shock, massive doses decrease peripheral resistance, stimulate the heart, and decrease the amount of circulating myocardial depressant factor. To be optimally effective they must be given as boluses.

MODALITIES AND REGIMENS OF CORTICOSTEROID THERAPY—*Replacement Therapy*—Treatment of primary and secondary adrenal insufficiency requires replacement of both glucocorticoids and mineralocorticoids in sufficient doses to relieve the signs and symptoms of insufficiency. However, when the patient experiences an additional stress, supplements of glucocorticoids may be required. The dose and dose-interval vary from patient to patient, but the doses are small, and complications are infrequent and minimal; the most difficult challenge is in the adjustment of dosage in response to changes in stress.

CHRONIC LOW-DOSE SYSTEMIC THERAPY OF DISEASE—In mild inflammatory or collagen disorders, low doses of glucocorticoids often are sufficient to be palliative, and low-dose regimens are preferable, since adverse effects usually are of low intensity, provided that the therapeutic endpoint is only amelioration and not elimination of the morbidity. Although low-dose therapy may cause some suppression of pituitary-adrenal function, the suppression is readily reversible, and some reserve exists in the system. However, abrupt withdrawal of the drug may be followed not only by a return to the previous condition but also an acute exacerbation of the disease. Pituitary-adrenal suppression and consequent acute flare-up after withdrawal may be lessened by avoiding round-the-clock administration and, instead, giving the drug between 6 and 9 AM, so that plasma levels and, hence, pituitary-adrenal suppression are at a minimum during the early morning sleeping hours, when pituitary adrenal function is at its diurnal peak. Moreover, the selection of a steroid with a short biological half-life allows some drug-free time during the day, during which pituitary-adrenal recovery can occur.

CHRONIC HIGH-DOSE SYSTEMIC THERAPY—In serious chronic inflammatory or immunological disorders or in glucocorticoid-responsive neoplasia, large doses of glucocorticoids may be given for long periods of time. Consequently, side effects are frequent, and pituitary-adrenal suppression may be severe. The suppression may continue for weeks to months after cessation of treatment, so withdrawal must be tapered slowly to allow the pituitary-adrenal system to recover.

Abrupt withdrawal will result in adrenal insufficiency, which may be life-threatening, as well as an acute recrudescence of the original disorder. Pituitary-adrenal suppression and systemic side effects may be less severe if the dose is given in the morning, so that nocturnal pituitary-adrenal activity is less inhibited. Another device to minimize such adverse systemic effects is use of alternate-day therapy. Thus, twice the usual daily dose is given, but only every other day, which permits the hypothalamic-pituitary segment of the pituitary-adrenal negative feedback system and various undiseased target organs time to recover partially between doses. Only glucocorticoids with an intermediate duration of action (12–36 hr) should be used for alternate drug therapy.

INTENSIVE SHORT-TERM SYSTEMIC THERAPY—Massive doses of glucocorticoids may be required in certain acute conditions, such as bacteremic shock or status asthmaticus. The short duration of such treatment, sometimes no longer than 48 hr, is not enough to give rise to pituitary-adrenal suppression, serious immunosuppression, or opportunistic infections, although in septic shock, suprainfections may occur. Psychosis, GI bleeding, and hyperosmolar diabetic coma can occur in such short-term use.

LOCAL TREATMENT (TOPICAL APPLICATION)—Topical efficacy depends on the inherent glucocorticoid activity (or potency) of the steroid, the concentration in the preparation, permeability coefficient, the vehicle and excipients, and local metabolic processes. Except for serious conditions, low-potency glucocorticoids are preferred by many authorities, because adverse effects on the skin appear to be less severe than with high-potency agents, even if the latter are used at appropriately lower concentrations. Only hydrocortisone and its acetate are available for nonprescription topical use.

Drugs with a high lipid-water distribution coefficient penetrate well from absorbable or nonoleaginous vehicles and tend to remain longer in the skin than water-soluble agents, exerting a more extended local action but lesser systemic side effects, especially if the drug is metabolized rapidly systemically. However, it is desirable that the agents be metabolized in the skin, so that less is delivered to the systemic circulation. Steroids that have the 17-OH group substituted and/or that are fluorinated are metabolized poorly locally and hence may have a significant potential for systemic effects; for this reason, special caution is urged when such compounds are used in children.

Occlusive dressings may be used, especially for low-potency, poorly penetrant steroids. The stratum corneum under the dressing becomes macerated and more permeable. However, such dressings increase absorption into the bloodstream and hence favor systemic effects. The relative potency of several of the most commonly used topical corticosteroids are summarized in Table 77-3.

LOCAL TREATMENT (LOCAL INJECTION)—To achieve high, rapidly acting local concentrations of a glucocorticoid, it sometimes is injected as a very soluble derivative that rapidly generates the parent steroid. However, such soluble

Table 77-3. Potency Ranking of Some Commonly Used Topical Corticosteroids[a]

Super-potent
Group I
- Betamethasone dipropionate ointment or cream 0.05%
- Clobetasol propionate ointment or cream 0.05%
- Diflorasone diacetate ointment 0.05%

Potent
Group II
- Amcinonide ointment 0.1%
- Betamethasone dipropionate ointment 0.05%
- Desoximetasone cream, gel or ointment 0.25%
- Diflorasone diacetate ointment 0.05%
- Fluocinonide cream, gel or ointment 0.05%
- Halcinonide cream 0.1%

Group III
- Betamethasone benzoate gel 0.025%
- Betamethasone dipropionate cream 0.05%
- Betamethasone valerate ointment 0.1%
- Diflorasone diacetate cream 0.05%
- Mometasone furoate cream or ointment 0.1%
- Triamcinolone acetonide cream or ointment 0.5%

Mid-strength
Group IV
- Desoximetasone cream 0.05%
- Fluocinolone acetonide cream 0.2% or ointment 0.025%
- Flurandrenolide ointment 0.05%
- Hydrocortisone valerate ointment 0.2%
- Triamcinolone acetonide cream or ointment 0.1%

Group V
- Betamethasone benzoate cream 0.025%
- Betamethasone diproprionate lotion 0.02%
- Betamethasone valerate cream or lotion 0.1%
- Fluocinolone acetonide cream 0.025%
- Flurandrenolide cream 0.05%
- Hydrocortisone butyrate cream 0.1%
- Hydrocortisone valerate cream 0.2%
- Triamcinolone acetonide cream or lotion 0.1%

Mild
Group VI
- Alclometasone dipropionate cream or ointment 0.05%
- Desonide cream 0.05%
- Fluocinolone acetonide solution 0.01%

[a]Legend: Relative potency, Group I > II > III > IV > V > VI; topical activity of corticosteroids may vary considerably depending upon the vehicle, site of application, disease, individual patient, and whether or not an occlusive dressing is used. Approximate relative activity is based on vasoconstrictor assay and/or clinical effectiveness in psoriasis (preparations in each group are approximately equivalent).

forms also rapidly leave the region of injection. For this reason, insoluble derivatives may be included or injected alone, so that a sustained action in parallel with slow dissolution may be effected.

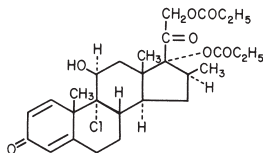
INHALATION AND INTRANASAL TREATMENT—Inhalers and nasal sprays are now available with glucocorticoids that possess high topical activity and low systemic bioavailability. These corticosteroids (beclomethasone, budesonide, fluticasone, and fluocinolide) have either low systemic absorption and/or high first-pass hepatic metabolism. These drugs are discussed in Chapter 69.

INHIBITORS OF BIOSYNTHESIS—Several drugs that interfere with the biosynthesis of adrenocorticoids are used clinically as *antiadrenal* drugs. Their mechanisms of action vary. Mitotane causes adrenocortical atrophy and a consequent decrease in the biosynthesis of all products of adrenocortical cells. Aminoglutethimide blocks the conversion of cholesterol to pregnenolone, and trilostane the dehydrogenation of the 3β-hydroxyl group of pregnenolone; hence, they both interrupt the biosynthesis of all active adrenal-derived steroids, including androgens and estrogens.

Mitotane blocks 11β-hydroxylation and hence the biosynthesis of aldosterone, cortisone, and hydroxycortisone. Mitotane and aminoglutethimide, especially, are used in the treatment of adrenal tumors, and aminoglutethimide also to suppress the production of androgens and estrogens in carcinoma of the breast. These two drugs are discussed in Chapter 86. Since blocking 11-hydroxylation leads to the homeostatic overflow of ACTH and the 11-deoxy precursors of cortisone and hydrocortisone, metyrapone is used diagnostically to ascertain the source of excess hydrocortisone in suspected adrenal carcinoma or autonomous adenoma by monitoring plasma ACTH and 11-deoxycorticoids. Metyrapone and trilostane are used in the management of Cushing's syndrome.

BECLOMETHASONE DIPROPIONATE

Pregna-1,4-diene-3,20-dione, (11β,16β)-9-chloro-11-hydroxy-16-methyl-17,21-bis(1-oxopropoxy)-, Beclovent; Beconase; Vanceril; Vancenase



[5534-09-8] $C_{26}H_{37}ClO_7$ (521.05).

Preparation—Synthesis of beclomethasone, a 9-chloro-16β-methyl derivative of prednisolone, and esters of beclomethasone, from steroid intermediates is described in British Pats 901,093 and 912,378 (*CA* 1963; 58:3488c and 1963; 59:14082b).

Description—White to cream-white powder; odorless.

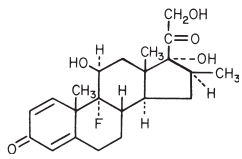
Solubility—Very slightly soluble in water; very soluble in chloroform; freely soluble in alcohol or acetone.

Comments—Has 500 times the topical anti-inflammatory activity of dexamethasone but is less active as a systemic glucocorticoid and is almost inactive by the oral route. The low systemic activity is the result of rapid deesterification and further metabolism in the liver. Also, it has a high lipid, but low water, solubility, so that it not only is absorbed well topically but also tends to remain at the site of application. Thus, it may be administered by oral inhalation with usually negligible systemic side effects. It is indicated for treatment of bronchial asthma. As long as 2 to 4 weeks may be required for the onset of a beneficial effect. It is also employed in the treatment of noninfectious rhinitis.

The most common side effects of the inhaled drug are dry mouth, hoarseness, sore throat, and pharyngeal or tracheal candidiasis. Usually, the effects on pituitary-adrenal function are negligible, but suppression of plasma cortisol levels occurs in a few percent of adult patients who receive higher doses. Adverse effects of intranasal administration include epistaxis, nasal irritation, sneezing, and nasopharyngeal candidiasis. Hypersensitivity or other adverse effects of the propellants (CHF_3 and CH_2F_2) and oleic acid (a dispersing agent) may occur; hypersensitivity absolutely contraindicates use of the aerosol. The plasma half-life is about 0.5 hr based on intravenous administration.

BETAMETHASONE

Prena-1,4-diene-3,20-dione, (11β,16β)-9-fluoro-11,17,21-trihydroxy-16-methyl-, Celestone



[378-44-9] $C_{22}H_{29}FO_5$ (392.47).

Preparation—Betamethasone is prepared from 16-dehydropregenolone (see *Progesterone,* page 1468) by treatment with methylmagnesium iodide to insert the 16β-methyl group, catalytic reduction of the remaining double bond, enol acylation at position 20, and reaction with peracetic acid followed by hydrolysis to the 16β-methyl-17α-hydroxy compound. Bromination and acetoxylation give the 3β-hydroxy-21- acetoxy derivative, which is oxidized to the 3-oxo compound with chromic acid. Dibromination at positions 1 and 4 followed by dehydrobromination with dimethylformamide to the 1,4-diene, then incubation with *Pestalotia foedans* (or a similar organism) results in the 11α-hydroxy derivative. Esterification at the 11-position with ethyl chloroformate, elimination of the ester function with acetic acid to form the 1,4,9(11)-triene, treatment with *N*-bromoacetamide and perchloric acid gives the 9α-bromo-11β-hydroxy compound. Abstraction of HBr with potassium acetate affords the 9β,11β,-epoxy derivative, which by treatment with HF in a halogenated hydrocarbon yields the 9α-fluoro-11β-hydroxy analog, betamethasone.

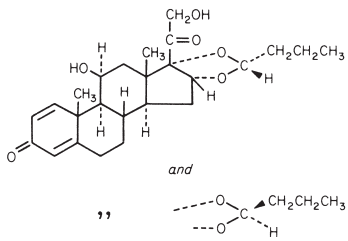
Description—White to practically white, odorless, crystalline powder; melts about 240° with some decomposition.

Solubility—1 g in 5300 mL water, 65 mL alcohol or 325 mL chloroform; very slightly soluble in ether.

Comments—An extremely potent glucocorticoid with actions, uses, and side effects typical of this class of steroids (see the introduction to this section). Its activity is 20 to 30 times that of cortisol. However, it only rarely induces sodium and water retention and potassium loss such as accompany treatment with cortisone and many other adrenal corticoids; on occasion, it even may increase sodium excretion and induce diuresis. In the usual doses, the incidence of characteristic adrenal corticoid untoward effects such as anorexia, protracted weight loss, vertigo, headache, and muscle weakness is quite low. The plasma half-life is about 6.5 hr, and the biological half-life, 36 to 54 hr. The volume of distribution is 1.8 L/kg.

BUDESONIDE

Pregna-1,4-diene-3,20-dione, [11β,16α(17*R*)]-16,17-butylidenebis(oxy)-11β,21-dihydroxy-, and 11β,16α(17*S*)]-isomer; Pulmicort; Rhinocort



[51333-22-3] [51372-29-3] [51372-28-2] $C_{25}H_{34}O_6$ (430.54).

Preparation—11β, 16α,17,21-Tetrahydroxypregna-1,4-diene-3,20-dione is converted to the 16,17-acetal with butyraldehyde. US Pat 3,929,768 (1973); *Arzneimittel-Forsch* 1979; 29:1607.

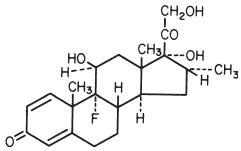
Description—Off-white crystals melting about 225° (decompn.). A mixture of *R* and *S* isomers (40–51% *S*-isomer), but not necessarily a racemic mixture.

Solubility—Practically insoluble in water or hydrocarbon solvents; sparingly soluble in alcohol; freely soluble in chloroform. Partition coefficient (octanol/water) at pH 4 is 1.6×10^3.

Comments—It is orally inhaled for maintenance treatment of asthma as well as intranasally for treatment of allergic rhinitis. The onset of action is within 24 hr, which is relatively rapid for an inhaled corticosteroid, but maximum benefit may not be achieved for 1 to 2 weeks or longer. The oral availability of inhaled drug is low (~10%) primarily because of extensive first-pass metabolism in the liver (half-life, 2 hr). It has higher topical activity than beclomethasone propionate. The most common side effects of the inhaled drug are dry mouth, hoarseness, sore throat, and pharyngeal or tracheal candidiasis.

DEXAMETHASONE

(11β-16α)-Pregna-1,4-diene-3,20-dione, 9-fluoro-11,17,21-trihydroxy-16-methyl-, Decadron



[50-02-2] $C_{22}H_{29}FO_5$ (392.47).

Preparation—In a manner quite similar to that for *Betamethasone,* the difference being that the 16-methyl group is inserted in the α-configuration.

Description—White to practically white, odorless, crystalline powder; stable in air; melts about 250° with some decomposition.

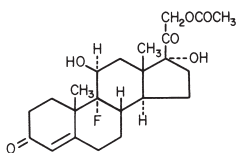
Solubility—1 g in 42 mL alcohol or 165 mL chloroform; sparingly soluble in acetone, dioxane, or methanol; very slightly soluble in ether; practically insoluble in water.

Comments—Possesses glucocorticoid activity, for which it is used clinically (see the introduction to this section). It especially is used as an anti-inflammatory and antiallergic drug. Topically, it is employed in the treatment of glucocorticoid-responsive dermatoses. Systemically, it decreases the incidence and severity of hearing loss consequent to bacterial meningitis. Its systemic glucocorticoid potency is about 25 times that of cortisone. It is capable of inducing all the usual side effects of adrenal corticoids, except that the mineralocorticoid-like side effects are less pronounced than with cortisone acetate.

Its effect to suppress pituitary-adrenocortical function is used for differential diagnostic purposes in Cushing's syndrome. The plasma half-life is 3 to 4 hr, and the biological half-life is 36 to 54 hr. The volume of distribution is 0.75 L/kg. It binds linearly to albumin but does not bind to transcortin.

FLUDROCORTISONE ACETATE

(11β)-Pregn-4-ene-3,20-dione, 21-(acetyloxy)-9-fluoro-11,17-dihydroxy-, Florinef Acetate



[514-36-3] $C_{23}H_{31}FO_6$ (422.49).

Preparation—One method starts with *Hydrocortisone Acetate,* which is first dehydrated to the 4,9-diene. The 9α-fluoro and 11β-hydroxy groups are inserted by a method similar to that used for *Betamethasone.*

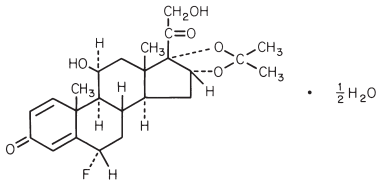
Description—Fine, white to pale-yellow powder that is odorless or practically odorless; hygroscopic; melts about 225° with some decomposition.

Solubility—Insoluble in water; soluble 1 g in 50 mL alcohol, 50 mL chloroform, or 250 mL ether.

Comments—A potent mineralocorticoid with considerable glucocorticoid activity. Its uses and side effects are those of mineralocorticoids, except that when used for replacement therapy in adrenal insufficiency it may not always be necessary to use a glucocorticoid concurrently, although usually hydrocortisone or cortisone are administered also. With the doses used for replacement therapy, glucocorticoid side effects of the drug alone are mild and infrequent. The plasma half-life is about 3.5 hr, and the biological half-life is 18 to 36 hr.

FLUNISOLIDE

Pregna-1,4-diene-3,20-dione, (6α,11β,16α)-6-fluoro-11,21-dihydroxy-16,17-[(1-methylethylidene)bis(oxy)]-, hemihydrate; AeroBid; Nasalide, Nasarel



[77326-96-6] $C_{24}H_{31}FO_6.1/2H_2O$ (443.51).

Preparation—See US Pat 3,124,571.

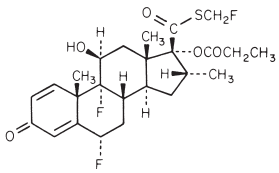
Description—White to creamy white crystalline powder melting about 245°.

Solubility—Soluble in acetone; sparingly soluble in chloroform; slightly soluble in methanol; practically insoluble in water.

Comments—A topical glucocorticoid for the treatment of noninfectious rhinitis and bronchial asthma. It has a high lipid/water- distribution coefficient, which favors both absorption into nasal and pulmonary tissue and retention at the site of application. By inhalation, about 40% is absorbed, which is considerably more than is absorbed of beclomethasone. The plasma half-life is about 1.8 hr, so absorbed steroid is destroyed rapidly enough so that pituitary-adrenocortical suppression does not occur with recommended doses. Dry mouth, hoarseness, sore throat, and pharyngeal, laryngeal, or tracheal candidiasis sometimes occur after continuous use. Occasional coughing, wheezing, and chest tightness are attributable to the vehicle and/or propellant.

FLUTICASONE PROPIONATE

Androsta-1,4-diene-17-carbothioic acid, (6α,11β,17α)-6,8-difluoro-11-hydroxy-16-methyl-3-oxo-17-(1-oxopropoxy)-, *S*-fluoromethyl ester; Cutivate; Flonase; Flovent



[80474-14-2] $C_{25}H_{31}F_3O_5S$ (500.57).

Preparation—US 4,335,121(1981); Neth Appl 8,100,707 (1981)

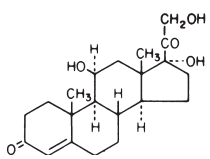
Description—White to off-white crystals melting about 272° (decomposition).

Solubility—Practically insoluble in water; freely soluble in DMSO or DMF; slightly soluble in ethyl alcohol or methanol.

Comments—It is similar to other potent inhaled corticosteroids that are useful in the maintenance treatment of chronic asthma and intranasally to treat allergic rhinitis. About 30% of the inhaled dose is absorbed from airways and is systemically available, with an elimination half-life of about 14 hr. The most common side effects include oral candidiasis and hoarseness. Higher doses of inhaled fluticasone can suppress the hypothalamic-pituitary-adrenal axis.

HYDROCORTISONE

(11β)-Pregn-4-ene-3,20-dione, 11,17,21-trihydroxy-, Compound F; Reichstein's "Substance M"; Cortef, Hydrocortone, Hytone



Cortisol [50-23-7] $C_{21}H_{30}O_5$ (362.47).

Preparation—The most attractive commercial synthesis involves the oxidation of 17α-21-dihydroxypregn-4-ene-3,20-dione, which is readily obtainable from diosgenin. Microbiological hydroxylation at the 11β-position is effected on the diacetate of the above compound employing organisms of the *Rhizopus, Aspergillus,* or *Streptomyces* species. Saponification then yields hydrocortisone.

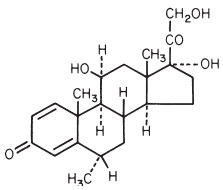
Description—White to practically white, odorless, crystalline powder; melts about 215°, with decomposition.

Solubility—1 g in 40 mL alcohol; very slightly soluble in water or ether; slightly soluble in chloroform.

Comments—The principal natural glucocorticoid in man and thus the prototype of all glucocorticoids (for actions, uses, and side effects of glucocorticoids, see the introduction to this section). Systemic side effects can result from topical application. Allergic bronchospasm after use in asthmatics has been reported. The plasma half-life is 1.5 to 3 hr, and the biological half-life is 8 to 12 hr. The volume of distribution is 0.3 to 0.5 L/kg, varying with the dose.

METHYLPREDNISOLONE

(6αa,11β)-Pregna-1,4-diene-3,20-dione, 11,17,21-trihydroxy-6-methyl-, Medrol;



[83-43-2] $C_{22}H_{30}O_5$ (374.48).

Preparation—*Progesterone* is converted to the 6α-methyl derivative in the same manner as indicated in the synthesis of *Medroxyprogesterone Acetate*. Incubation of the 6α-methyl compound with an ascomycetes, such as *Pestalotia,* forms the 11α-hydroxy derivative, which is oxidized to the 3,11-diketo compound with chromic acid. Further treatment with ethyl oxalate followed by bromination, rearrangement with sodium methoxide, and debromination with zinc dust gives the methyl ester of the 4,17(20)-diene-21-carboxylate. With pyrrolidine, lithium aluminum hydride reduction, and treatment with alkali, the 11β,21-dihydroxy-4,17(20)-diene is formed, which is converted to the 21-acetate and then oxidatively hydroxylated to 6α-methylhydrocortisone acetate. Saponification, followed by dehydrogenation with *Septomyxa affinis* gives the 1,4,17(20)-triene, which is again converted to the 21- acetate, oxidatively hydroxylated to yield the 17α-hydroxy derivative, and saponified to give methylprednisolone.

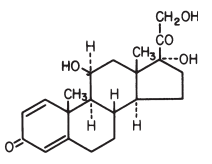
Description—White to practically white, odorless, crystalline powder; melts about 240° with some decomposition.

Solubility—1 g in 10,000 mL water, 100 mL alcohol, 800 mL chloroform, or 800 mL ether.

Comments—A glucocorticoid with actions, uses, and side effects typical of drugs of this class (see the introduction to this section). It induces considerably less retention of sodium and water than the parent prednisolone. Because it possesses only weak mineralocorticoid activity, it is not employed in the management of acute adrenal insufficiency. The plasma half-life is 3 to 4 hr, and the biological half-life is 18 to 36 hr. The volume of distribution is 0.7 L/kg. The drug does not bind to transcortin.

PREDNISOLONE

(11β)-Pregna-1,4-diene-3,20-dione, 11,17,21-trihydroxy-, Prelone



[50-24-8] $C_{21}H_{28}O_5$ (360.45); *sesquihydrate* [52438-85-4] (387.47); anhydrous or contains one and one-half molecules of water of hydration.

Preparation—From hydrocortisone by a microbiological process using *Corynebacterium simplex,* which selectively dehydrogenates cortisol at the 1 and 2 positions.

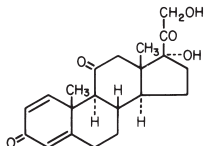
Description—White to practically white, odorless, crystalline powder; melts about 235° with some decomposition.

Solubility—1 g in 30 mL alcohol or 180 mL chloroform; very slightly soluble in water.

Comments—A glucocorticoid with the actions, uses, and side effects typical of drugs of this class (see the introduction to this section). It is four times as potent as, but relatively somewhat weaker than, hydrocortisone as a mineralocorticoid, although sodium retention and potassium depletion can occur. The plasma half-life is said to be about 3 hr, and the biological half-life is 18 to 36 hr. However, the pharmacokinetics are dose-dependent because of nonlinear protein binding. With high doses the plasma half-life may approach 1.7 hr. Except for its higher solubility, it may be considered equivalent to prednisone; it is the biologically active metabolite of *Prednisone*.

PREDNISONE

Pregna-1,4-diene-3,11,20-trione, 17,21-dihydroxy-, Deltasone, Orasone



[53-05-2] $C_{21}H_{26}O_5$ (358.43).

Preparation—As described for *Prednisolone* except that cortisone is used instead of hydrocortisone.

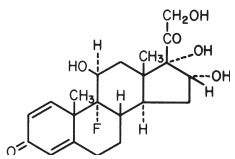
Description—White to practically white, odorless, crystalline powder; melts about 230°, with some decomposition.

Solubility—1 g in 150 mL alcohol or 200 mL chloroform; very slightly soluble in water.

Comments—The active form of the drug is its metabolite, prednisolone. It has three to five times the glucocorticoid activity of hydrocortisone but somewhat less of mineralocorticoid activity, although sodium retention and potassium depletion may occur. It cannot be used alone for replacement therapy in adrenal insufficiency. It is the glucocorticoid predominantly used in cancer chemotherapy, always in combination with other drugs. In pediatrics it is used widely to treat nephrosis, rheumatic carditis, leukemias, other tumors, and tuberculosis. The plasma half-life is 3 to 5 hr, but the biological half-life is 12 to 36 hr.

TRIAMCINOLONE

(11β,16α)-Pregna-1,4-diene-3,20-dione, 9-fluoro-11,16,17,21-tetrahydroxy-, Aristocort; Kenacort



[124-94-7] $C_{21}H_{27}FO_6$ (394.44).

Preparation—From hydrocortisone acetate via the 3,20-bisketal by treatment with thionyl chloride, refluxing with potassium hydroxide and acetylation to give 21-acetoxy-4,9,11(16)-pregnatriene-3,20-dione. Oxidation with osmium tetroxide to the 16α,17α-dihydroxy derivative and subsequent insertion of the 9α-fluoro and 11β-hydroxy groups as indicated for *Betamethasone* (page 1444) gives a product lacking only a double bond at the 1-position. This latter step is accomplished by incubation with *Nocardia corallina,* followed by saponification of the acetate to yield triamcinolone. Alternatively, the compound can be made from *Fludrocortisone* by enzymatically inserting the 16α-hydroxyl group and dehydrogenating as above at the 1,2-position.

Description—Fine, white or practically white, crystalline powder with not more than a slight odor; its polymorphic forms and/or solvates melt between 248 and 250°, 260 and 263°, or 269 and 271°.

Solubility—1 g in about 5000 mL water, 70 mL propylene glycol, or less than 20 mL dimethyl sulfoxide; slightly soluble in alcohol or chloroform.

Comments—A glucocorticoid with actions, uses, and side effects typical of drugs of this class (see the introduction to this section). It is 7 to 13 times more potent than hydrocortisone. It has been claimed that therapeutic doses of this drug are nearly devoid of mineralocorticoid and other side effects of hydrocortisone, but the mineralocorticoid actions vary from patient to patient. It appears that the drug may induce natriuresis, negative sodium balance with weight loss in most patients (along with headache, dizziness, and fatigue), and sodium retention with weight gain, moon face, etc. in others. Nearly every side effect seen with hydrocortisone has been observed with this drug, but the relative frequencies are lower; however, it does not increase appetite and thus differs from other glucocorticoids. By the oral route, more of it survives the first pass through the liver than does hydrocortisone, and blood levels are somewhat more predictable. The plasma half-life is about 5 hr, and the biological half-life is 18 to 36 hr. The volume of distribution is 1.4 to 2.1 L/kg, depending upon the dose.

THE PANCREATIC HORMONES

The larger portion of the pancreas consists of glandular tissue that contains acinar cells that secrete digestive enzymes. However, there also are isolated groups of pancreatic cells called the islet of Langerhans that are composed of four cell types, each of which produces a distinct polypeptide hormone: insulin in the beta (β) cell, glucagon in the alpha (α) cell, somatostatin in the delta (δ) cell, and pancreatic polypeptide in the PP or F cell. β cells make up 60% to 80% of the islet. Dysregulation of certain pancreatic cell function can lead to a disorder known as diabetes mellitus.

Diabetes mellitus is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, action or both. This condition affects approximately 17 million persons in the United States. Diabetes mellitus can be divided into 3 major types, Type 1, Type 2, and gestational diabetes.

Type 1 diabetes mellitus, (formerly known as juvenile diabetes or insulin dependent diabetes mellitus(IDDM) comprises about 10% of the diabetic population. It typically occurs during childhood and has an abrupt onset. Type 1 diabetes mellitus results from an autoimmune attack on the beta-cells of the pancreas and often times follows some environmental triggers such as certain viruses. There also may be some genetic component. Type 1 diabetes mellitus is associated with certain HLA phenotypes with detectable serum antibodies to islet cells. There is an absolute deficiency of insulin secretion from the β-cells of the pancreas and patients must be treated with exogenous insulin to sustain life.

Type 2 diabetes mellitus, formally known as non-insulin dependent diabetes mellitus (NIDDM), makes up approximately 90% of all cases of diabetes mellitus. Historically it was thought to occur mainly in adults greater than 40 years of age, however, the incidence has been increasing in younger patients due to physical inactivity and obesity. The onset is gradual and is often diagnosed at a routine physical examination with the patient unaware of any signs and symptoms. Type 2 diabetes mellitus may result from a deficiency of insulin secretion from the β-cells of the pancreas, peripheral insulin resistance, and/or persistent hepatic glucose production. There is a strong correlation to heredity and many Type 2 patients have central upper body obesity. Treatment of Type 2 diabetes mellitus can be accomplished by using diet and exercise, and if need be, using oral antidiabetic medication(s) or even insulin.

Typical signs and symptoms of diabetes mellitus are polyuria, polydipsia, and polyphagia. The increase in plasma glucose causes a marked glucosuria and an osmotic diuresis, resulting in dehydration. Hyperglycemia may also cause blurred vision, fatigue, nausea, and lead to increase incidence of various fungal and bacterial infections.

Complications of diabetes mellitus can be classified as acute and chronic. Hypoglycemia is an acute complication that occurs if there is excess insulin. The blood glucose concentration falls below a patient specific range and manifests by episodes of sweating, hunger, incoherence, palpitations, convulsions, coma and death. Severe cases of hypoglycemia can be treated with glucagon, which will increase blood glucose. Hyperglycemic crisis is an acute complication that occurs when the blood glucose concentration rises above a patient specific range. Type 1 patients are at risk for diabetic ketoacidosis, and Type 2 patients are at risk for hyperglycemic hyperosmolar non-ketotic syndrome.

Chronic complications can be classified as microvascular and macrovascular. Cardiovascular, cerebrovascular, and peripheral vascular diseases are examples of macrovascular complications all occurring at higher rates in the diabetic population. Examples of microvascular complications include peripheral and autonomic neuropathies, retinopathy, where it is the leading cause of blindness in the United States, and nephropathy, where it is responsible for 50% of all cases of dialysis. The results of the Diabetes Complications and Control Trial (DCCT) established that intensive treatment of diabetic patients can prevent or slow the progression of chronic complications.

Recent research and evidence has described a constellation of disorders comprising the metabolic syndrome (or Syndrome X). Hypertension, dyslipidemia, obesity and diabetes mellitus are the components of the metabolic syndrome and should be treated as a whole in order to prevent serious consequences to the cardiovascular system.

INSULIN—Insulin, a hormone secreted by the pancreas, was discovered more than 75 years ago and was initially extracted from beef and pork sources. These products were associated with immunologically mediated sequelae such as lipodystrophy and hypersensitivity reactions. The purity of animal derived insulins was improved over subsequent years. Finally Human insulin was introduced. This form of insulin is the most widely used insulin in therapeutic practice today. Current insulin preparations are available from two different species including pig, and human. Beef insulin, formally available in the United States has been removed from the market due to concerns regarding the transmission of Bovine Spongiform Encephalopathy (BSE) also known as "Mad Cow Disease." Human insulin is produced by recombinant DNA technology by inserting human genes into *Escherichia coli*. The recombinant products have the same physiological properties as insulin from beef or pork but are much less likely to cause allergic reactions and refractoriness.

Insulin is a protein containing 51 amino acids; it consists of A and B chains (containing 21 and 30 amino acids) linked by disulfide bonds. The 2 chains are produced along with C-peptide from a single proinsulin molecule. C-peptide can be measured clinically as an indicator of endogenous insulin production in diabetic patients It has a molecular weight of 6000. In aqueous solution, insulin polymerizes to form macromolecules of molecular weight 12,000 or 36,000, depending on pH and concentration. The isoelectric point of insulin is 5.3.

The physicochemical properties of human and porcine insulins differ slightly because of substitutions in a couple of amino acids. Porcine insulin differs from human insulin by only one carboxy-terminal amino acid of the B chain. The human insulin analogue Lispro inverts the amino acids at positions 28 (proline) with position 29 (lysine). Insulin Aspart differs from human insulin by the substitution of aspartic acid at amino acid position 28. The changes of amino acids in Insulin Lispro and Aspart result in quicker onset of action and activity that more closely mimics normal physiologic insulin secretion in response to meals.

Regular insulin is a clear solution that has the FDA indication to be administered subcutaneously, intramuscularly or intravenously. (Please note that this is currently the only insulin that can be administered IV). Lispro and Aspart are clear solutions that have been studied by the intravenous route, however do not have the indication for such use and should therefore be administered subcutaneously. Glargine is also clear solution, but must be given by the subcutaneous route because it depends on precipitation in order to exert its long-acting effect. All other currently available insulins are suspensions because regular insulin has been complexed with protamine (NPH) or Zinc (Lente and UltraLente) to extend their actions. These solutions should never be given intravenously.

PHYSIOLOGY AND ACTIONS—Insulin is the hormone that facilitates the uptake of glucose into skeletal muscle and adipose tissue by increasing the number of glucose transporters (specifically the GLUT1 and GLUT4 subtypes) that facilitate glucose diffusion in these target cells. In response to insulin, vesicles containing GLUT-4 move to the plasma membrane, where they dock, forming complexes. The vesicles fuse with the plasma membrane, increasing the number of GLUT-4 molecules in the membrane and thus the rate of glucose transport into cells. Insulin also decreases hepatic gluconeogenesis and increases glycogenesis. As previously stated, when the supply of, or response to, insulin is inadequate, a disease known as diabetes mellitus occurs.

Although attention focuses on the intervention of insulin in glucose metabolism, it also has independent actions to stimulate lipogenesis and promote the synthesis of many proteins important for cell growth and differentiation. Other actions include the suppression of synthesis of some proteins that regulate catabolic states that promote hepatic gluconeogenesis.

Insulin binds to the α-subunit of the insulin receptors. This evokes tyrosine kinase activity in the β-subunit and autophosphorylation of the receptor and also the translocation of glucose transporters to the plasma membrane. Phosphatidyl-inositol system coupling also occurs; inositol phosphates mediate recruitment of intracellular calcium, and inositol phosphate glycans and diacylglycerol mediate the activation of receptor-contained threonine and serine kinases and gene transcription. Furthermore, phosphodiesterase activity is increased, which decreases cAMP, and guanylate cyclase activity is increased. Inward potassium and magnesium transports are stimulated. Intracellular enzyme activities are altered variously by phosphorylation, dephosphorylation, and changes in protein synthesis. Overall, protein, lipid, and DNA syntheses are increased, and cell growth is promoted. Down-regulation of the insulin receptors begins within minutes of receptor activation and becomes maximal within a few hours.

In Type 1 diabetes mellitus, insulin injections must be spaced throughout the day, usually being given before meals. During the night, when no insulin is available, the blood sugar rises and is usually at its highest point before the morning dose. This erratic behavior of the level of blood sugar can be controlled more adequately by the use of insoluble insulins, which are absorbed more slowly and thus can exert a continuous, even action over a period as long as 24 hr (see below). Several different types of continuous infusion pumps for insulin are available that are easy to program for pulse injections at times of increased insulin demand. Devices for the nasal inhalation of insulin, and dry-powder for oral inhalation of insulin are under investigation but none are currently on the market.

The major insulin preparations are summarized in Table 77-4. The different insulin preparations are categorized according to their onset and duration of action.

PREPARATIONS—*Crystalline Zinc Insulin*—By addition of appropriate amounts of zinc salts, insulin may be crystallized. This achieves a superior degree of purification in order to minimize possible allergic sensitivity reactions to earlier insulin products. The speed and duration of action of the zinc insulins depends on the crystal size. The microcrystalline form (regular insulin) dissolves promptly and hence, by the subcutaneous route, has an onset of action of 0.5 hours, a peak of 2 to 4 hours, and duration of action of 4 to 6 hours.

Zinc insulins of larger crystal size have slow-release properties that depend on crystal size. Thus Insulin Zinc Suspension (Lente) has a duration of 12 to 18 hours, and Extended Insulin Zinc Suspension (UltraLente) has a duration of 18 to 36 hours.

Crystalline Protamine Zinc Insulin—Insulin or zinc insulin may be combined with protamine to yield complexes of larger molecular weight.

Neutral Protamine Hagedorn insulin (NPH) is injected as a suspension. It goes into solution slowly, and this limits the rate of absorption. It has a duration of action of about 12 to 16 hours.

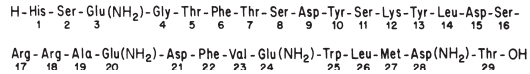
Proinsulin—This is the single-chain protein precursor of insulin. The removal of the C-peptide moiety leaves insulin. When administered exogenously, its metabolic effects differ somewhat from those of insulin in that it mostly suppresses hepatic glucose output and has only a slight action to stimulate peripheral glucose uptake. Therefore, it has a much lower probability of causing severe hypoglycemia. The locus of action especially lends itself to the treatment of Type 2 diabetes mellitus. The pharmacokinetics permit once-a-day dosage. A recombinant human product is undergoing clinical trials.

Glucagon (Hyperglycemic Factor; Hgf)—In addition to insulin, the pancreas also produces a substance that exerts an effect on blood sugar opposite to that of insulin. This HGF, or glucagon, is produced by the α-cells of the Islets of Langerhans. It plays an important role in the physiological regulation of blood sugar, and defects in the control of glucagon secretion are a factor in certain types of diabetes mellitus.

Somatostatin (Gh-Rif)—Somatostatin also is produced in the pancreas, where it inhibits release of both insulin and glucagon; it is involved in the physiological regulation of the secretion of these hormones. In diabetes mellitus, the persistence of glucagon output contributes to hyperglycemia and ketoacidosis; administration of somatostatin improves the metabolic condition by suppressing glucagon blood levels. Unfortunately, the half-life of somatostatin is very short, so that longer-lived congeners with separate activities to treat diabetes, acromegaly, peptic ucler, and other disorders are being developed.

GLUCAGON

Glucagon (pig)



Glucagon [16941-32-5] $C_{153}H_{225}N_{43}O_{49}S$ (3482.78); a polypeptide occurring in the pancreas glands of domestic mammals used for food by man, which has the property of increasing the blood glucose concentration. It is employed as the hydrochloride.

Description—Fine, white or faintly colored, crystalline powder; practically odorless and tasteless.

Solubility—Soluble in dilute alkali or acid solutions; insoluble in most organic solvents.

Comments—Stimulates the hepatic adenylate cyclase system and hence promotes the breakdown of liver glycogen. The end result is the release of glucose and an elevation of blood glucose. Stimulation of adenylate cyclase in the heart causes positive inotropy and in intestinal muscle, relaxation. After parenteral injection the glucose response is quite prompt. The action lasts but 45 to 90 minutes. It is used primarily to terminate hypoglycemic coma, such as may occur from an overdose of insulin. It is dubious that it offers any compelling advantage over intravenous dextrose for this purpose, except when it is difficult to give an intravenous infusion. Its value in idiopathic hypoglycemia, islet cell car-

Table 77-4. Summary of Major Insulin Preparations

TYPE OF INSULIN	ONSET (HOURS)	PEAK (HOURS)	DURATION (HOURS)	APPEARANCE
Rapid-acting				
Aspart	<¼	1–2	2–4	Clear
Lispro	<½	1–3	2–4	Clear
Short-acting				
Regular	<½–1	2–4	4–6	Clear
Intermediate-acting				
Lente	1–2	6–14	12–18	Cloudy
NPH	1–2	6–14	10–16	Cloudy
Long-acting				
Glargine	1–2	2–20	20–24+	Clear
Ultralente	4–10	8–30	18–36+	Cloudy

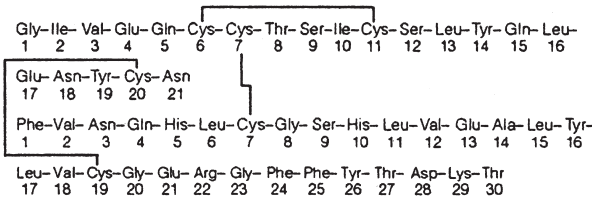
cinoma, and glycogen storage disease has not yet been determined fully. However, it can be used to diagnose glycogen storage disease and to determine pancreatic β-cell secretory reserve; in the latter test, the amount of C-peptide that appears in the plasma quantifies the reserve. It must be used cautiously in islet cell carcinoma, because it stimulates the release of insulin and may cause hypoglycemia. Even in the diabetic patient it may cause rebound hypoglycemia, mostly, however, because of the persistence of insulin levels from the overdose for which glucagon was administered. It is used as an adjunct in hypotonic radiography of the GI tract, to relax the smooth muscle. Side effects include dizziness, nausea, vomiting, hypotension, and rebound hypoglycemia, especially after intravenous administration. Occasional allergy causes dyspnea or rash.

INSULIN INJECTION

Rapid-Acting Insulins

INSULIN ASPART

Insulin Aspart; NovoLog



28^{B}-L-Aspartic acid-insulin (human) [11609423-6] $C_{256}H_{381}N_{65}O_{79}S_6$ (5825.54).

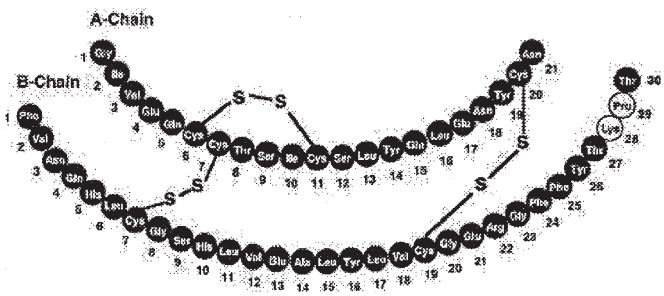
Preparation—Using a recombiant technology utilizing Brewer's yeast (*Saccharomyces cerevisiae*).

Description—It is homologous with human insulin with the exception of a single substitution of proline by aspartic acid in position B28.

Comments—A rapid-acting insulin that can be injected 5 to 10 minutes prior to a meal. It has an onset within 15 minutes as well as a much shorter peak (0.5–1.5 hr) and duration (2–4 hr) than regular insulin injection. It is therefore associated with greater reductions in postprandial blood glucose concentrations. Because of its short duration of action, it is most commonly used in regimens that contain an intermediate-acting or long-acting insulin.

INSULIN LISPRO

Insulin(human), 28B-L-lysine-29B-L-proline-, Humalog



[133107-64-9]

Preparation—US Pat 5,514,646 (1966).

Description—A Lys(B28), Pro(B29) human insulin analog created when the amino acids at positions 28 and 29 on the insulin B-chain are reversed. This type of analog is less prone to dimerization or self association to higher molecular weight forms, thus possessing a more rapid onset of activity while retaining the biological activity of native human insulin.

Comments—A rapid-acting insulin that can be injected immediately prior to a meal. It has an onset of action within 15 minutes. It has a much shorter peak (0.5–1.5 hours) and duration (2–4 hours) than regular insulin injection. It is therefore associated with greater reductions in postprandial blood glucose concentrations. Because of its short duration of action, it is most commonly used in regimens that contain an intermediate-acting or long-acting insulin.

Short-Acting Insulins

REGULAR INSULIN

Humulin R and Novolin R

A sterile, acidified or neutral solution of insulin. The solution has a potency of 100, or 500 USP Insulin Units in each mL.

Description—When containing in each mL not more than 100 USP Units, it is a colorless or almost colorless liquid; that containing 500 Units may be straw-colored; substantially free from turbidity and from insoluble matter; contains from 0.1% to 0.25% (*w*/*v*) of either phenol or cresol and 1.4% to 1.8% (*w*/*v*) of glycerin; pH, determined potentiometrically, between 2.5 and 3.5 for acidified injection, and 7.0 and 7.8 for neutral injection.

Comments—Regular insulin is a short-acting insulin that is injected prior to a meal. It has an onset of action of about 30 to 60 minutes. It has a relatively short peak (3–4 hours) and duration (6–8 hours). It is commonly used in regimens that contain an intermediate-acting or long-acting insulin in order to attain better control of blood glucose concentrations. It is an insulin that may be administered by the intravenous route (IV).

Intermediate-Acting Insulins

ISOPHANE INSULIN SUSPENSION (NEUTRAL PROTAMINE HAGEDORN)

Humulin N and Novolin N

NPH Insulin

A sterile suspension of zinc-insulin crystals and protamine sulfate in buffered water for injection, combined in a manner such that the solid phase of the suspension consists of crystals composed of insulin, protamine, and zinc. The protamine sulfate is prepared from the sperm or from the mature testes of fish belonging to the genera *Oncorhynchus* Suckley or *Salmo* Linné (Fam *Salmonidae*).

Each mL is prepared from sufficient insulin to provide 100 USP Insulin Units of insulin activity.

Description—White suspension of rod-shaped crystals approximately 30 μm in length and free from large aggregates of crystals following moderate agitation; contains either (1) 1.4% to 1.8% (*w*/*v*) glycerin, 0.15% to 0.17% (*w*/*v*) metacresol, and 0.06% to 0.07% (*w*/*v*) phenol or (2) 1.4% to 1.8% (*w*/*v*) glycerin and 0.20% to 0.25% (*w*/*v*) phenol; contains 0.15% to 0.25% (*w*/*v*) dibasic sodium phosphate; contains also 0.01 to 0.04 mg of zinc and 0.3 to 0.6 mg of protamine for each 100 USP Insulin Units; when examined microscopically, the insoluble matter in the suspension is crystalline and contains not more than traces of amorphous material; pH between 7.1 and 7.4, determined potentiometrically.

Comments—An intermediate-acting insulin that is typically injected twice daily. It has an onset of action of 1 to 2 hours, a peak of 6 to 14 hours and a duration of action of approximately 10 to 16 hours. There may be occasional hypersensitivity to the protamine component. It is never given intravenously.

INSULIN ZINC SUSPENSION

Lente

A sterile suspension of insulin in buffered water for injection, modified by the addition of zinc chloride in a manner such that the solid phase of the suspension consists of a mixture of crystalline and amorphous insulin in a ratio of approximately 7 parts of crystals to 3 parts of amorphous material. Each mL is prepared from sufficient insulin to provide 100 USP Insulin Units of insulin activity.

Description—Almost colorless suspension of a mixture of characteristic crystals predominantly 10 to 40 μm in maximum dimension and many particles that have no uniform shape and do not exceed 2 μm in maximum dimensions; contains 0.15% to 0.17% (*w*/*v*) sodium acetate, 0.65% to 0.75% (*w*/*v*) sodium chloride, and 0.09% to 0.11% (*w*/*v*) methylparaben; contains also, for each 100 USP Insulin Units, 0.12 to 0.25 mg of zinc of which 20% to 65% is in the supernatant liquid; pH between 7.2 and 7.5.

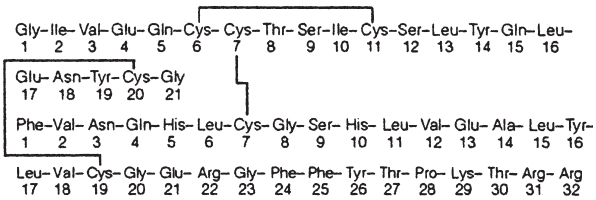
Comments—An intermediate-acting insulin that is typically injected twice daily. It has an onset of action of 1 to 2 hours, a peak of 6 to 14 hours and a duration of action of approximately 10 to 16 hours. It is never given intravenously.

A theoretical advantage of Lente insulin is its freedom from foreign proteins, such as protamine, to which certain patients are sensitive (however the most commonly used intermediate-acting insulin remains NPH).

Long-Acting Insulins

INSULIN GLARGINE

Insulin (human), 21^{A}-glycine-30^{B}a-L-arginine-30^{B}b-L-arginine-, Lantus



[160336-95-1] $C_{267}H_{404}N_{72}O_{78}S_6$ (6062.89).

Preparation—By a recombinant DNA procedure using a nonpathogenic strain of *E coli* (K_{12}).

Description—Differs from human insulin in that asparagine, at position A21 is replaced by glycine.

Comments—A long-acting insulin that has a pKa of 4.0. When administered by the subcutaneous route, the clear solution precipitates, releases slowly, and thus provides a sustained duration of action. It has an onset of action of approximately 2 hours, is lacking an appreciable peak of action, and has a duration of action of 24 hours. It is the only true 24-hour insulin available. This insulin most closely mimics the human bodies' production of a basal insulin concentration throughout the day. It is a clear solution, but must never be given IV. It must be administered subcutaneously. It must never be administered in the same syringe as other insulins.

EXTENDED INSULIN ZINC SUSPENSION

Ultra-Lente

A sterile suspension of insulin in buffered water for injection, modified by the addition of zinc chloride in a manner such that the solid phase of the suspension is predominantly crystalline. In its preparation, sufficient insulin is used to provide 100 USP Insulin Units for each mL of the suspension.

Description—Almost colorless suspension of a mixture of characteristic crystals the maximum dimension of which is predominantly 10 to 40 μm; contains, for each 100 USP Units of insulin, 0.12 to 0.25 mg of zinc (of which 20–65% is in the supernatant liquid) and not more than 0.70 mg of nitrogen; contains also 0.15% to 0.17% (*w*/*v*) sodium acetate, 0.65% to 0.75% (*w*/*v*) sodium chloride, and 0.09% to 0.11% (*w*/*v*) methylparaben; pH, between 7.2 and 7.5.

Comments—The crystals in this form are of sufficient size to have a slow rate of dissolution. It is a long-acting insulin with an onset of action of 4 to 8 hr, a peak at 10 to 30 hr, and duration usually in excess of 36 hr (Although this has been very variable in clinical practice). A theoretical advantage is that it is free of protamine and other foreign proteins so the incidence of allergic reactions is possibly minimized.

COMBINATION INSULIN PRODUCTS

Insulin 70/30: 70% NPH and 30% Regular (Humulin 70/30, Novolin 70/30)
Insulin 50/50: 50% NPH and 50% Regular (Humulin 50/50)
Insulin 75/25: 75% Insulin Lispro Protamine (Intermediate-acting) and 25% Lispro (Humalog Mix 75/25)

ORAL ANTIDIABETIC DRUGS

As discussed previously, patients with Type 2 diabetes mellitus have a defect in insulin secretion from the pancreas, inappropriate hepatic glucose production, tissue insulin resistance, or a combination of any of these as a major cause of the glucose dysregulation. In Type 2 diabetic patients, as the fasting plasma glucose concentration rises, insulin secretion from the pancreas decreases progressively. Also the rate of basal hepatic glucose output is excessive. Defects in insulin receptor function and glucose transport contribute to tissue insulin resistance. Drugs that improve insulin secretion, decrease hepatic glucose production and improve insulin sensitivity at the tissue receptors are therefore effective in treating type 2 diabetes mellitus.

Sulfonylureas

The sulfonylurea drugs have been available in the United States since 1954 and have been the mainstay of oral antidiabetic therapy for many years. They are classified as either first-generation (Acetohexamide, Chlorpropamide, Tolbutamide, and Tolazamide) or second-generation (Glyburide, Glipizide, and Glimeperide) based on their pharmacokinetic profiles. Second generation sulfonylureas tend to be prescribed more frequently based on their tolerability and dosing schedule.

The sulfonylureas exert their blood glucose lowering actions by stimulating insulin release from β- cells in the pancreatic islets. They bind to the sulfonylurea receptor found on the surface of the pancreatic β-cells. This interaction leads to a closure of voltage dependent potassium adenosinetriphosphate channels, which leads to decreased potassium influx and β-cell membrane depolarization. This depolarization opens a voltage-gated calcium channel that results in calcium influx and the secretion of insulin. Some functional β-cells must be present for an effect on blood glucose. Although this is the primary mechanism of action, the possibility that sulfonylureas decrease hepatic glucose production as well as a decrease in tissue insulin resistance has arisen. Typical reduction in fasting plasma glucose is 50–60 mg/dl, and decrease in HgA1c by 1% to 2%.

There are two types of drug failure with regard to the sulfonylurea agents. First is primary failure, which is when the patient does not respond to a properly titrated course of therapy. Secondary failure describes a tolerance that may develop during chronic treatment such that a blood glucose lowering response in not seen. It also could be due to a failure to follow diet and exercise regimens or certain stressful situations that worsen the appearance of glycemic control.

In the past there were concerns about the adverse cardiac effects from the use of sulfonylureas. The results of the UKPDS trial showed that there was no link between the use of sulfonylureas and increased incidence of coronary artery disease in patients with Type 2 diabetes mellitus, which refutes the results from an earlier study by the University Group Diabetes Program.

α-Glucosidase Inhibitors

Dietary carbohydrates require enzymatic degradation by α-glucosidase to monosaccharides within the gastrointestinal tract in order to be able to be absorbed. The α-glucosidase inhibitors (Acarbose and Miglitol) are a unique class of drugs that act on this enzyme in the brush border of the proximal small intestine epithelium. By competitively inhibiting the enzyme α-glucosidase, these agents result in a delay of intestinal carbohydrate absorption. These agents should be taken at the beginning of each meal in order to exert their pharmacologic actions. They seem to be useful when there is consistent postprandial hyperglycemic episodes. Typical reduction in postprandial plasma glucose is 25-50 mg/dl, and decrease in HgA1c by 0.5% to 1%.

The widespread use of these agents is limited because of the occurrence of gastrointestinal side effects such as abdominal pain, flatulence, and diarrhea. Increase liver enzymes have been reported with high doses of Acarbose. When used as monotherapy, these agents do not cause hypoglycemia, however the incidence rises when combined with insulin or other insulin secretagogues. Because of the nature of the mechanism of action, it is imperative to treat episodes of hypoglycemia with a source of sucrose as opposed to more complex carbohydrates.

Biguanides

Metformin, a biguanide that has been in clinical use for more than 40 years, was introduced in the United States in 1995. It is chemically related to an earlier Biguanide, Phenformin, which was removed from the market in the 1970s due to an association with lactic acidosis. Metformin, however, differs structurally from Phenformin and rarely causes lactic acidosis in diabetic patients. The decrease incidence of lactic acidosis has to due in part by the strict contraindications to its use. All of the following are contraindications to the use of metformin: serum creatinine in males ≥1.5 mg/dl and females ≥1.4 mg/dl,

abnormal creatinine clearance, active liver disease, active alcoholics, conditions that may cause significant hypoxemia, patients with CHF requiring pharmacologic therapy, and concurrent use of IV contrast dyes for imaging tests (Metformin must be discontinued before the test and not restarted until 48 hours after the test as long as renal function seems adequate).

Metformin exerts its blood glucose lowering effect primarily by the inhibition of basal hepatic glucose production. In addition, metformin may lower blood glucose secondarily by increasing tissue sensitivity to insulin. Typical reduction in fasting plasma glucose is 50 to 70 mg/dl, and decrease in HgA1c by 1.5% to 2%.

Since metformin lacks any insulin secretagogue activity, it does not cause hypoglycemia when used as monotherapy. Based on the results of the UKPDS trial in which metformin showed significant improvement in glucose control in overweight diabetic patients, it should be considered the drug of choice in obese Type 2 diabetic patients unless contraindicated.

Meglitinides

The meglitinides, Repaglinide and Nateglinide, are structurally different from the sulfonylureas; however, they exert their blood glucose lowering action by the same mechanism. They bind to a different portion of the sulfonylurea receptor found on the surface of the pancreatic β-cells. This interaction leads to a closure of voltage-dependent potassium adenosinetriphosphate channels, which leads to decreased potassium influx and β-cell membrane depolarization. This depolarization opens a voltage-gated calcium channel that results in calcium influx and the secretion of insulin. They are insulin secretagogues, like the sulfonylureas, but result in a much more rapid, and short-lived release of insulin. These agents are particularly useful in patients who demonstrate consistent postprandial hyperglycemia. Typical reduction in fasting plasma glucose is 50–60 mg/dl, and decrease in HgA1c by 1% to 2%.

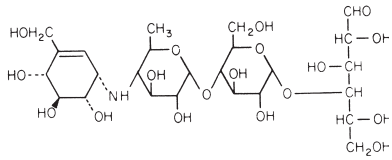
Thiazolidinediones

The thiazolidinediones, Pioglitazone and Rosiglitazone, are chemically related to Troglitazone, which was removed from the market because of rare idiosyncratic hepatocellular injury. Pioglitazone and Rosiglitazone have a unique mechanism of action, binding to a novel receptor known as the peroxisome proliferator activated receptor γ (PPARγ). When activated, the receptor binds with response elements on DNA, altering transcription of a variety of genes that regulate carbohydrate and lipid metabolism. The primary effect is decreasing tissue insulin resistance thereby stimulating glucose uptake by peripheral tissues. Secondarily, thiazolidinediones may decrease hepatic glucose production, and this may aid in the overall blood glucose reduction. These agents do not stimulate the β-cells of the pancreas to secrete insulin; however, they may enhance the responsiveness and efficacy of the β-cells. Historically not thought of as first line therapy for Type 2 diabetic patients, preliminary data suggest that these agents may actually prolong β-cell survival, and should be considered earlier in therapy. Typical reduction in fasting plasma glucose is 50–60 mg/dl, and decrease in HgA1c by 1% to 2%.

Pioglitazone and Rosiglitazone appear to be safer with regard to hepatic injury, possibly due to the strict guidelines for monitoring liver function in these patients. Patients who are prescribed Pioglitazone or Rosiglitazone need to have baseline LFTs performed, and repeated monitoring every 2 months for the first year of therapy, then quarterly thereafter. If at any time the LFTs are >2.5 times the upper limit of normal, these medications should be discontinued. Other side effects include edema, weight gain, and certain lipid abnormalities. Due to the edema that may occur when using Thiazolidinediones, there is a precaution for use in patients with congestive heart failure.

ACARBOSE

Glucose, *O*-4,6-dideoxy-4-[[[1*S*-(1α,4α,5β,6α)]-4,5,6-trihydroxy-3-(hydroxymethyl)-2-cyclohexen-1-yl]amino]-α-D-glucopyranosyl-(1→4)-*O*-α-D-glucopyranosyl-(1→4)-, Precose



[56180-94-0] $C_{25}H_{43}NO_{18}$(645.61).

Preparation—An oligosaccharide obtained through fermentation processes involving *Actinoplanes utahensis*. US Pat 4,062,950(1975); *Carbohydrate Res* 1989; 189:309.

Description—Amorphous powder.

Solubility—Soluble in water; pK_a is 5.1.

Comments—Acarbose is an oral antidiabetic agent in the α-glucosidase class that is used to treat Type 2 diabetes mellitus. It is indicated as monotherapy or in combination with sulfonylureas. It is not bound to plasma proteins. It is primarily metabolized within the GI tract by intestinal bacteria. The metabolites are excreted in the urine. Side effects include gastrointestinal disturbances and rash. Since Acarbose is not an insulin secretagogue, there is no risk for hypoglycemia when used as monotherapy, however the risk increases when used in combination with other insulin secretagogues.

Acarbose is dosed initially at 25 mg three times a day and the maintenance dose is 50 mg three times a day (if patient weighs <60 kg) or 100 mg three times a day (if patient weighs >60 kg). Drug interactions are mainly with drugs that may bind Acarbose in the GI tract (Example: digestive enzymes and charcoal).

ACETOHEXAMIDE

Benzensulfonamide, 4-acetyl-*N*-[[cyclohexylamino]carbonyl]-, Dymelor

[968-81-0] $C_{15}H_{20}N_2O_4S$ (324.39).

Preparation—*p*-Acetylbenzenesulfonamide in acetone is treated with anhydrous potassium carbonate and the resulting potassium salt of the sulfonamideis reacted with cyclohexyl isocyanate. After removal of the solvent, the residual potassium salt of acetohexamide is acidified to precipitate the product. US Pat 3,320,312 (1967).

Description—White, practically odorless, crystalline powder melting about 183°.

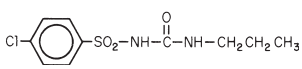
Solubility—1 g in 230 mL of alcohol or 210 mL of chloroform; practically insoluble in water or ether.

Comments—A first generation sulfonylurea oral hypoglycemic agent that stimulates the β-cells of the pancreas to secrete insulin. It is indication to treat Type 2 diabetes mellitus as monotherapy or in combination with other oral anti-diabetic agents (Metformin, Thiazolidinediones, or α-glucosidase inhibitors), except the meglitinides. It is extensively bound to plasma proteins. It is metabolized in the liver to an inactive metabolite and is excreted through the kidneys. Side effects include hypoglycemia, weight gain, gastrointestinal disturbances, skin rash, and insulin resistance.

Acetohexamide is dosed 250 to 1500 mg once daily. See Table 77-5 for a list of possible drug interactions.

CHLORPROPAMIDE

Benzenesulfonamide, 4-chloro-*N*-[(propylamino)carbonyl]-, Diabinese



1-[(*p*-Chlorophenyl)sulfonyl]-3-propylurea [94-20-2] $C_{10}H_{13}Cl\text{-}N_2O_3S$ (276.74).

Preparation—*p*-Chlorobenzenesulfonamide undergoes addition to propyl isocyanate by warming a solution of equimolar quantities of the two reactants.

Description—White, crystalline powder, with a slight odor; melts between 125° and 129°.

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

Comments—A first generation sulfonylurea oral hypoglycemic agent that stimulates the β-cells of the pancreas to secrete insulin.

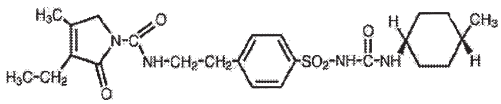
It is indicated to treat Type 2 diabetes mellitus as monotherapy or in combination with other oral anti-diabetic agents (metformin, thiazo-

lidinediones, or α-glucosidase inhibitors), except the meglitinides. Chlorpropamide is highly bound to plasma proteins, is metabolized 80% hepatically, and cleared renally. It has a long half-life (25–60 hr) and duration of action (about 24–48 hr).

Side effects include hypoglycemia, weight gain, gastrointestinal disturbances, skin rash and insulin resistance. In addition, chlorpropamide may increase the endogenous release of vasopressin (ADH) and thus causes water retention with resultant hyponatremia and hypoosmolality with symptoms similar to SIADH and should be avoided in the elderly who are at increased risk. There have been reports of a disulfiram reaction when taking concomitantly with alcohol. Chlorpropamide is dosed 250 mg to 500 mg once daily. See Table 77-5 for a list of possible drug interactions.

GLIMEPERIDE

Urea, 1-[[*p*-[2-(3-ethyl-4-methyl-2-oxo-3-pyrroline-1-carboxamido)ethyl]phenyl]sulfonyl]-3-(4-methylcyclohexyl)-, Amaryl



[93479-97-1] $C_{24}H_{34}N_4O_5S$ (490.62).

Preparation—US Pat 4,379,785 (1983).

Description—White to yellowish-white crystalline, practically odorless powder melting about 207°.

Comments—A second-generation sulfonylurea oral hypoglycemic agent that stimulates the β-cells of the pancreas to secrete insulin.

It is indicated to treat Type 2 diabetes mellitus as monotherapy or in combination with other oral anti-diabetic agents (metformin, thiazolidinediones, or α-glucosidase inhibitors), except the meglitinides.

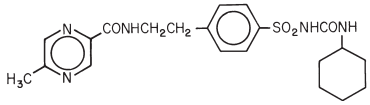
Glimeperide is highly protein bound, but principally nonionic which may make for less propensity to be displaced from proteins by other highly protein bound drugs. It is metabolized hepatically and cleared renally. It has a half-life of 9 hours and duration of action of about 24 hours.

Side effects include hypoglycemia, weight gain, gastrointestinal disturbances, skin rash, and insulin resistance.

Glimeperide is dosed 1 to 8 mg once daily. See Table 77-5 for a list of possible drug interactions.

GLIPIZIDE

Pyrazinecarboxamide, *N*-[2-[4-[[[(cyclohexylamino)carbonyl]amino]sulfonyl]phenyl]ethyl]-5-methyl-, Glucotrol, Glucotrol XL



[29094-61-9] $C_{21}H_{27}N_5O_4S$ (445.54).

Preparation—By the condensation of 4-[2-(5-methyl-2-pyrazinecarboxamido)ethyl]benzenesulfonamide and cyclohexyl isocyanate; *Arzneimittel-Forsch* 1971; 21:200.

Description—White, odorless powder; pK_a 5.9; melts about 205°.

Solubility—Insoluble in water or polar solvents; freely soluble in dimethylformamide or fixed alkalies.

Comments—A second- generation sulfonylurea oral hypoglycemic agent that stimulates the β-cells of the pancreas to secrete insulin.

Table 77-5. Drug Interactions with Sulfonylureas

ADDED DRUG	MECHANISM
Highly protein bound drugs	Displacement of sulfonylureas
β-Blockers	Increase blood glucose concentrations
Corticosteroids	
Diazoxide	
Nicotinic acid	
Sympathomimetics	
Thiazide diuretics	
Charcoal	Decrease absorption

*This list is not all-inclusive. See Facts and Comparisons for a comprehensive list of medications that could possibly interact with sulfonylureas.

It is indicated to treat Type 2 diabetes mellitus as monotherapy or in combination with other oral anti-diabetic agents (Metformin, Thiazolidinediones, or α-glucosidase inhibitors), except the meglitinides..

Glipizide is highly protein bound, but principally nonionic which may make for less propensity to be displaced from proteins by other highly protein bound drugs. It is metabolized hepatically and cleared renally. It has a half-life of 2 to 4 hours and duration of action of about 12 to 24 hours.

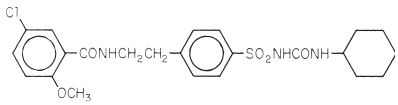
Food delays the absorbtion but not affect the peak concentrations of Glipizide.

Side effects include hypoglycemia, weight gain, gastrointestinal disturbances, skin rash, and insulin resistance.

Glipizide is dosed 5 to 40 mg once daily. It is available in an extended-release formulation. See Table 77-5 for a list of possible drug interactions.

GLYBURIDE

Benzamide, 5-chloro-*N*-[2-[4-[[[(cyclohexylamino)carbonyl]amino]sulfonyl]phenyl]ethyl]-2-methoxy-, DiaBeta; Glynase Pres Tab; Micronase



Glybenclamide [10238-21-8] $C_{23}H_{28}ClN_3S$ (494.00).

Preparation—See *Arzneimittel-Forsch* 1966; 16:640; *CA* 66: 65289h.

Description—White to off-white crystalline powder; melts about 170°; pK_a 5.3.

Solubility—Sparingly soluble in water or ether; 1 g dissolves in 330 mL of alcohol or 36 mL of chloroform.

Comments—A second-generation sulfonylurea oral hypoglycemic agent that stimulates the β-cells of the pancreas to secrete insulin.

It is indicated to treat Type 2 diabetes mellitus as monotherapy or in combination with other oral anti-diabetic agents (metformin, thiazolidinediones, or α-glucosidase inhibitors), except the meglitinides.

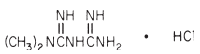
Glyburide is about 97% is bound to plasma albumin as a weak-acid anion and, hence, is susceptible to displacement by many weak acid drugs. It is metabolized hepatically and eliminated in both the urine and feces equally. The half-life is approximately 5 hr, and the duration of action is 12 to 24 hours.

Side effects include hypoglycemia, weight gain, gastrointestinal disturbances, skin rash, and insulin resistance. In addition, glyburide has been associated with a disulfiram reaction if taken concomitantly with alcohol, cholestatic jaundice, and eosinophilia.

Glyburide is dosed 2.5 mg to 20 mg once daily. It is available in a micronized formulation that is dosed 1.5 mg to 12 mg once daily. See Table 77-5 for a list of possible drug interactions.

METFORMIN HYDROCHLORIDE

Imidodicarbonimidic diamide, *N,N*-dimethyl-, monohydrochloride; Glucophage;Glucophage XR; Metiguanide



[657-24-9] $C_4H_{11}N_5.HCl$(165.67).

Preparation—By the reaction of dimethylamine hydrochloride with dicyandiamide to yield the base; *J Am Chem Soc* 1959; 81:2220, 3728.

Description—White crystals melting about 230°

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

Comments—An oral antidiabetic agent of the Biguanide class that is used in the management of Type 2 diabetes mellitus. It is indicated as monotherapy or as an adjunct to diet or other oral antidiabetic agents (sulfonylureas, thiazolidinediones, α-glucosidase inhibitors or meglitinides) and insulin. In Type 2 diabetic patients, metformin may decrease insulin requirements. Metformin does not bind to plasma proteins to any appreciable extent. It is not metabolized by the liver and is excreted primarily by the kidneys through the process of glomerular filtration and proximal tubular secretion.

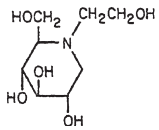
Side effects include gastrointestinal disturbances that can happen in up to 30% of patients started on metformin and are a primary reason for patients not continuing therapy. This can be minimized by taking metformin after a meal and by slow careful dose titration. Since metformin is not an insulin secretagogue, there is no risk for hypoglycemia when used as monotherapy. This is not true when metformin is used in combination with insulin or other insulin secretagogues. Other side effects include vitamin b-12 deficiency (clinical implications are unknown), mi-

nor rash, and the rare complication of lactic acidosis. (Please see contraindications in the Biguanide description section). Unlike certain other oral antidiabetic medications, metformin has neutral or even beneficial effects on serum lipids. In studies, metformin was shown to reduce triglycerides and LDL-cholesterol levels.

Metformin is dosed 500 mg to 1000 mg twice daily. Maximum dose is 2550 mg daily. Blood glucose lowering as well as an improvement in HgA1c levels are not seen until a dose of 1000 to 1500 mg a day are achieved. It is available as an extended-release product. Metformin is available in combination products with glyburide (Glucovance), glipizide (Metaglip) and Rosiglitazone (Avandamet) which have been shown to be very effective in reducing blood glucose concentrations.

MIGLITOL

Piperidinetriol, 1-(2-hydroxyethyl)-2-(hydroxymethyl)-[2*R*-(2α,3β,4α,5β)]-, Glyset



[72432-03-2] $C_8H_{17}NO_5$ (207.22).

Preparation—One method involves the of nojirimycin, a natural product obtainable from the leaves of the mulberry tree (*M elba, M bombycis, or M nigra*).

Nojirimycin retains the configuration of D-glucose with the ether linkage replaced by a secondary amino group. The hydrogen atom on carbon-1 is removed by regioselective oxidation with *Gluconobacter oxydans* to form 1-deoxynojirimycin. The amine hydrogen atom is replaced by a hydroxyethyl group to form the product.

US Pat 4,639,436(1987) and www.wiley-vch.de/books/biotech/pdf/v08b_regi.pdf.

Description—Crystals from ethanol melting about 114°.

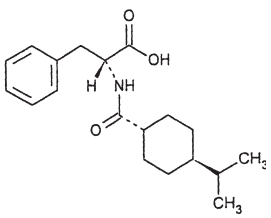
Solubility—Soluble in water; pK_a 5.9.

Comments—Miglitol is an oral antidiabetic agent in the α-glucosidase class that is used to treat Type 2 diabetes mellitus. It is indicated as monotherapy or in combination with sulfonylureas. It is not bound to plasma proteins, is not metabolized, and is excreted unchanged in the urine. Side effects include gastrointestinal disturbances and rash. Since miglitol is not an insulin secretagogue, there is no risk for hypoglycemia when used as monotherapy, however the risk increases when used in combination with other insulin secretagogues.

Miglitol is dosed initially at 25 mg three times a day and a maintenance dose of 50 mg to 100 mg three times a day. Drug interactions are mainly with drugs that may bind Miglitol in the GI tract (Example: digestive enzymes and charcoal).

NATEGLINIDE

D-Phenylalanine, *N*-[[*trans*-4-(1-methylethyl)cyclohexyl]carbonyl]-, Starlix



[105816-04-4] $C_{19}H_{27}NO_3$ (317.42).

Preparation—4-Isopropylbenzoic acid is catalytically reduced to the cyclohexyl derivative yielding a mixture of both *cis* and *trans* isomers. The cyclohexanecarboxylic acid is converted to the acyl chloride and then the methyl ester. At this point the racemic mixture is resolved using chiral HPLC and the trans-ester saponified to the acid, converted back to the acyl halide, which then is coupled with phenylalanine to form the product. US Pat 4,816,484 (1989) and *J Med Chem* 1989; 32:1436.

Description—White crystals from methanol melting about 130°. $[\alpha]^{20}_D$ −9.4°, (c=1, methanol).

Solubility—Freely soluble in methanol, ethanol or chloroform; soluble in ether;

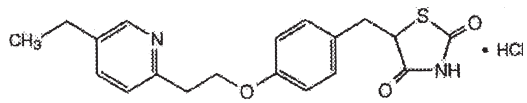
Comments—Nateglinide is an oral antidiabetic agent of the meglitinide class that is used to treat Type 2 diabetes mellitus. It is approved for use as monotherapy, or in combination with Metformin

It is extensively protein bound (98%). It is metabolized by the cytochrome P450 2C9 and 3A4 and is primarily excreted through both urine and feces.

Side effects include hypoglycemia, upper respiratory tract infection, and gastrointestinal disturbances. Nateglinide is dosed as 60 mg to 120 mg three times a day. Drug interactions involving the CYP 450 system are lacking.

PIOGLITAZONE

(±)-2,4-Thiazolidinone, 5-[[4[2-(5-ethyl-2-pyridinyl)ethoxy]phenyl]methyl]-, monohydrochloride; Actos



[112529-15-4] $C_{19}H_{20}N_2O_3S.HCl$ (392.90). US Pat 4,687,777 (1987).

Description—White, odorless crystalline powder melting about 193°.

Solubility—Soluble in DMF; slightly soluble in absolute ethanol; very slightly soluble in acetone or acetonitrile; practically insoluble in water; insoluble in ether.

Comments—Pioglitazone is an oral antidiabetic agent of the Thiazolidinediones class that is used to treat Type 2 diabetes mellitus. It is indicated as monotherapy or in combination with insulin or other oral antidiabetic agents (sulfonylureas, metformin, meglitinides, α-glucosidase inhibitors).

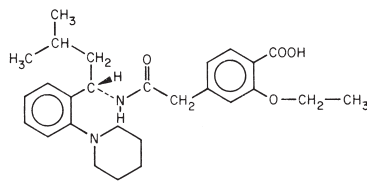
It is highly protein bound (>99%). It is metabolized by cytochrome P450 2C8, 3A4, and 1A1. It is excreted through both the urine and feces.

Side effects include headache, edema, and weight gain, and increased liver function tests. Pioglitazone appears safer than Troglitazone with respect to hepatic injury. (Please see LFT monitoring parameters in the Thiazolidinedione description section). Since Pioglitazone is not an insulin secretagogue, there is no risk for hypoglycemia when used as monotherapy. The risk is greater when used in combination with other insulin secretagogues. Pioglitazone may have a neutral or beneficial effect on lipids. In studies, Pioglitazone decreased triglycerides and LDL-cholesterol levels.

Pioglitazone is dosed as 15 to 45 mg once daily. The maximum benefit of Pioglitazone may take from 8 to 12 weeks. Since Pioglitazone is metabolized by CYP450 3A4, combining medications that inhibit or induce this pathway should be done cautiously. Pioglitazone has the possibly of decreasing the effect of oral contraceptives.

REPAGLINIDE

***p*-Toluic acid, (+)-2-ethoxy-α-[[(*S*)-α-isobutyl-*o*-piperidinobenzyl]carbamoyl]-, Prandin**



[135062-02-1] $C_{27}H_{36}N_2O_4$ (452.59).

Preparation—See Int Pat Appl WO 93 00,337 (1993).

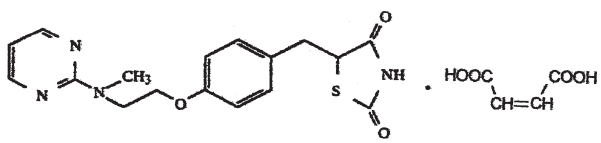
Description—White powder melting about 129°.

Comments—Repaglinide is an oral antidiabetic agent in the meglitinide class used in the treatment of Type 2 diabetes mellitus. It is indicated as monotherapy or in combination with metformin. It is bound to plasma proteins > 98%. It is metabolized by cytochrome P450 3A4 and is excreted through the feces and urine. Side effects include hypoglycemia, upper respiratory tract infection and gastrointestinal disturbances.

Repaglinide is dosed as 0.5 mg to 4 mg taken with meals. Since Repaglinide is metabolized by CYP450 3A4, combining medications that inhibit or induce this pathway should be done cautiously.

ROSIGLITAZONE MALEATE

2,4-Thiazolidinedione, (±)-5-[[4-[2-(methyl-2-pyridylamino)-ethoxy)phenylmethyll]-, maleate salt (1:); Avandia



[155141-29-0] [122320-73-4](base) $C_{18}H_{19}N_3O_3S.C_4H_4O_4$ (473.50).

Preparation—*J Med Chem* 1994; 37:3977 and US Pat 5,002,953 (1991).

Description—(Base) Crystals from methanol melting about 154°; (maleate) white to off-white solid melting about 122°. pK_{a1}6.1; pK_{a2} 6.8.

Solubility—Readily soluble in methanol or aqueous solutions buffered to pH 2.3–2.5. Solubility decreases with increase in pH.

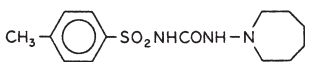
Comments—Rosiglitazone is an oral antidiabetic agent of the Thiazolidindione class that is used to treat Type 2 diabetes mellitus. It is indicated as monotherapy or in combination with insulin or other oral antidiabetic agents (sulfonylureas, metformin, meglitinides, α-glucosidase inhibitors). When added to regimens containing insulin, rosiglitazone may decrease the insulin requirements. It is highly protein bound (>99%). It is metabolized by cytochrome P450 2C8 and 2C9 and is excreted through both the urine and feces.

Side effects include headache, edema, and weight gain, and increased liver function tests. Rosiglitazone appears safer than troglitazone with respect to hepatic injury. (Please see LFT monitoring parameters in the thiazolinidione description section.) Since rosiglitazone is not an insulin secretagogue, there is no risk for hypoglycemia when used as monotherapy. The risk is greater when used in combination with other insulin secretagogues. Rosiglitazone is available in a combination product with metformin (Avandamet).

Rosiglitazone is dosed as 4 to 8 mg once daily. The maximum benefit of rosiglitazone may take from 8 to 12 weeks. There are no significant drug interactions seen with rosiglitazone

TOLAZAMIDE

Benzenesulfonamide, *N*-[[(hexahydro-1*H*-azepin-1-yl)amino]carbonyl]-4-methyl-, Tolinase



[1156-19-0] $C_{14}H_{21}N_3O_3S$ (311.40).

Preparation—Methyl *p*-toluenesulfonylcarbamate undergoes an ammonolysis type of reaction with 1-aminohexamethylenetetramine. US 3,063,903 (1962).

Description—White to off-white crystalline powder; odorless or slight odor; melts between 161° and 169°.

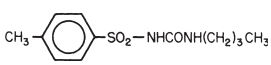
Solubility—Very slightly soluble in water; freely soluble in chloroform; soluble in acetone; slightly soluble in alcohol.

Comments—A first generation sulfonylurea oral hypoglycemic agent that stimulates the β-cells of the pancreas to secrete insulin. It is indication to treat Type 2 diabetes mellitus as monotherapy or in combination with other oral anti-diabetic agents (metformin, thiazolidinediones, or α-glucosidase inhibitors), except the meglitinides. It is extensively bound to plasma proteins. It is metabolized in the liver to an inactive metabolite and is excreted through the kidneys. Side effects include hypoglycemia, weight gain, gastrointestinal disturbances, skin rash, and insulin resistance.

Tolazamide is dosed as 100 to 1000 mg daily. See Table 77-5 for a list of possible drug interactions.

TOLBUTAMIDE

Benzenesulfonamide, *N*-[(butylamino)carbonyl]-4-methyl-, Orinase



1-Butyl-3-(*p*-tolylsulfonyl)urea [64-77-7] $C_{12}H_{18}N_2O_3S$ (270.35).

Preparation—Toluene is treated with chlorosulfonic acid and the resulting *p*-toluenesulfonyl chloride is converted into *p*-toluenesulfonamide by interaction with ammonia. Condensation of the sulfonamide with ethyl chloroformate in the presence of pyridine or another suitable basic catalyst produces ethyl *N*-*p*-toluenesulfonylcarbamate. Aminolysis with butylamine in ethylene glycol monomethyl ether solutions yields tolbutamide.

Description—White, or practically white, crystalline powder; slightly bitter and practically odorless; melting range is 126° to 132°.

Solubility—Practically insoluble in water, soluble in alcohol or chloroform.

Comments—A first generation sulfonylurea oral hypoglycemic agent that stimulates the β-cells of the pancreas to secrete insulin. It is indication to treat Type 2 diabetes mellitus as monotherapy or in combination with other oral anti-diabetic agents (metformin, thiazolidinediones, or α-glucosidase inhibitors), except the meglitinides. It is extensively bound to plasma proteins. It is metabolized in the liver to an inactive metabolite and is excreted through the kidneys. Side effects include hypoglycemia, weight gain, gastrointestinal disturbances, skin rash and insulin resistance.

Tolbutamide is dosed as 500 to 3000 mg once daily. See Table 77-5 for a list of possible drug interactions.

COMBINATION ORAL ANTIDIABETIC AGENTS

GLUCOVANCE—(Glyburide and Metformin)
METAGLIP—(Metformin and Glipizide)
AVANDAMET—(Rosiglitazone and Metformin)

THE PARATHYROID HORMONE AND CALCITONIN

Spontaneous atrophy or injury (as at thyroidectomy) of the parathyroid glands is followed by a decrease in the concentration of serum calcium and an increase in serum phosphorus. These changes can be reversed by the parenteral administration of suitably prepared extracts of the parathyroids of domestic animals. The active principle of the parathyroid gland is a protein of molecular weight 9500. Active amino-terminal and carboxyl-terminal fragments of lower molecular weight (3800 and 6900, respectively) are found in plasma. These products possess 1/4 to 1/2 the specific calcium-mobilizing activity of parathyroid hormone (PTH).

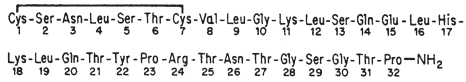
Various cancers produce an active peptide homologous to the amino end of PTH, which is called parathyroid hormone–like peptide (PTH-LH) and causes hypercalcemia, bone destruction, and pain. PTH-LH also is found in lactating mammary tissue and plays a role in the mobilization of calcium to milk.

Secretion of PTH is stimulated by a fall in the free Ca^{2+} concentration of the plasma. The hormone then acts to restore Ca^{2+} concentration by (1) increasing reabsorption of calcium and the excretion of phosphate and decreasing the absorption of bicarbonate by the kidney; (2) increasing resorption of bone, with release of Ca^{2+}; and (3) increasing absorption of calcium and phosphate from the GI tract. The GI effects are mediated by 1α,25-dihydroxycholecalciferol (calcitriol), a metabolite of vitamin D_3 that may be considered a hormone; PTH is a trophin for renal synthesis of calcitriol. The metabolite also promotes the action of vitamin D_3 on bone. Vitamin D_2 (calciferol) and dihydrotachysterol can simulate the hypercalcemic effect of PTH; these compounds, moreover, are active orally. Overdosage with any of these compounds can lead to dangerously high calcium concentrations in the blood, with attendant complications, such as calcification of kidneys and blood vessels.

The thyroid gland produces a hormone, thyrocalcitonin, that reduces serum calcium concentration. A small amount of calcitonin also is produced in the parathyroid gland as well as the thymus, but the main source is the thyroid gland. The biological function of calcitonin is to prevent excessive hypercalcemia from parathyroid hormone activity. It has an effect to decrease osteoclastic activity, thus inhibiting the movement of bone salts from bone to the blood. It decreases the renal tubular secretion of calcium and probably inhibits calcium pumping in many types of cells. It also increases renal excretion of phosphate. It has very little effect on the absorption of calcium from the intestine. It plays a role in the homeostasis of blood calcium. When plasma calcium levels are elevated, thyrocalcitonin is released in increased quantities. Thus it tends to oppose parathyroid hormone but at different cell targets. The molecular weight of monomeric thyrocalcitonin is 3500. It is a polypeptide of 32 amino acid units. Despite only a 50% homology between human and salmon calcitonins, their biochemical actions are the same. However, salmon calcitonin is allergenic.

CALCITONIN

Calcitonin; Calcimar; Miacalcin



[47931-85-1] $C_{145}H_{240}O_{48}S_2$ (3431.88).

A polypeptide hormone secreted by the parafollicular cells of the thyroid gland in mammals and by the ultimobranchial gland of birds and fish, isolated from various of these sources, all apparently containing 32

amino acid residues but differing in the linear sequence. Human and salmon calcitonin differ at 18 positions. Both human and salmon calcitonins are available as synthetic products. The source of the product is indicated in the labeling.

Description—White, fluffy powder; lyophilized.

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

Comments—Does not have much effect on normal plasma calcium, and patients with calcitonin-producing tumors of the thyroid medulla often do not manifest disturbances of calcium metabolism. It appears to act only in hypercalcemia, such as that caused by hyperparathyroidism, various carcinomas, and multiple myeloma. It normalizes plasma calcium and causes a favorable change in bone structure in Paget's disease; 3 to 12 months of treatment may be required to restore plasma electrolyte, alkaline phosphatase, and hydroxyproline to normal. Human calcitonin is less potent than salmon calcitonin because it is more rapidly degraded. Used alone against osteoporosis the hormone has a variable effect that may be related to the formation of antibodies. In combination with calcitriol and calcium it may be effective against senile and postmenopausal osteoporosis.

Side effects are mild nausea, vomiting, diarrhea, facial flushing, and malaise. Rashes may occur with salmon calcitonin. Inflammation and pain at the injection site sometimes occur. Diuresis at the onset of treatment often occurs.

The half-life of human calcitonin is about 1 hr; that of salmon calcitonin is considerably longer, but the exact figure is unknown. The duration of action is 6 to 8 hr.

AGENTS AFFECTING BONE MINERALIZATION

The two hormones that serve as the principal regulators of calcium and phosphate homeostasis in bone and the extracellular fluid are PTH and vitamin D, which acts as a prohormone because it must be metabolized to the biologically active calciferol and calcitriol. Other hormones that are considered secondary regulators include calcitonin, prolactin, growth hormone, insulin, thyroid hormone, and sex hormones. However, the most important agents used therapeutically are calcitonin, glucocorticoids, estrogen, and the bisphosphonates (nonhormonal analogs of pyrophosphate). Bone undergoes a continuous remodeling process involving resorption and formation, so alterations in the balance of controlling factors can lead to increased resorption, resulting in osteoporosis.

The principal effects of calcitonin are to lower serum calcium by effects on bone and kidney. Calcitonin inhibits osteoclastic bone resorption and reduces renal reabsorption of calcium and phosphate plus other ions, namely sodium, potassium, and magnesium. Prolonged use of glucocorticoids inhibit collagen synthesis in bone and antagonize vitamin D actions on intestinal calcium absorption and renal excretion; the result is an increased incidence of osteoporosis in adults and stunted growth in children. Estrogens can prevent accelerated bone loss during the immediate postmenopausal period and transiently increase bone in these patients. Estrogen receptors are present in bone and have some direct effects on bone remodeling that involves the osteoclasts that resorb bone and osteoblasts that are responsible for bone formation but are influenced by osteoclasts.

Treatment of postmenopausal osteoporosis is an important area of new drug development because estrogen replacement therapy is associated with increased cardiovascular problems as well as the potential increased risk of endometrial and breast cancer in some patients. Parenteral salmon calcitonin causes nausea, flushing, and formation of antibodies that may lead to resistance to the drug. A potential improvement is the availability of salmon calcitonin as a nasal spray that has little toxicity other than nasal irritation, but it appears to be less potent than the bisphosphonates.

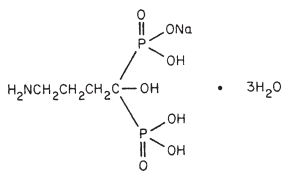
New-drug developments include the selective estrogen- receptor modulators (SERMs) such as raloxifene plus new-generation bisphosphonates (alendronate) and slow-release formations of fluoride. Raloxifene represents a new class of synthetic estrogen analogs that have selectivity for the signal transduction that occurs at estrogen receptors; raloxifene has an agonist effect on bone and an antagonist effect on both the breast and the uterus. Alendronate has improved efficacy over etidronate for increasing bone mass and decreasing bone fractures in patients with osteoporosis. Unlike bisphosphonates and calcitonin, which decrease bone resorption, sodium fluoride stimulates osteoblast proliferation and increases bone formation. However, too much fluoride can increase bone fragility. Slow-release sodium fluoride has been successful in maintaining serum fluoride concentrations in the therapeutic range associated with increased formation of normal bone, and clinical trials have demonstrated increased bone mass in women with severe postmenopausal osteoporosis. Plain sodium fluoride can cause moderately serious GI effects, including bleeding, but the slow-release form has only minor GI toxicity.

BISPHOSPHONATES—This group of agents are analogs of pyrophosphate in which the P-O-P bond is replaced by a nonhydrolyzable P-C-P bond. The bisphosphonates have the ability to retard formation and dissolution of hydroxyapatite crystals within bone and other sites, although the exact mechanism by which they selectively inhibit bone resorption is unclear. The first bisphosphonate available for clinical use was etidronate, but several new analogs are now available including pamidronate, alendronate, tiludronate, and risedronate. The limitations of etidronate include the lack of efficacy in increasing bone mass and reducing fractures in patients with osteoporosis for more than 2 years, plus it has potential toxicity of a mineralization defect called osteomalacia with higher doses. Alendronate is absorbed poorly and must be given on an empty stomach but has a greater efficacy in increasing bone density and reducing fractures over at least 5 years of continuous therapy. Pamidronate can cause an acute flulike illness and must be given by the intravenous route because it causes gastric irritation. The bisphosphonates are useful in treating hypercalcemia associated with malignancy, osteoporosis, and syndromes of ectopic calcification. They also are used to manage Paget's disease, which is a localized disease characterized by uncontrolled osteoclastic bone resorption with secondary increases in bone formation. Tiludronate and risedronate are available for oral treatment of Paget's disease. A summary of the comparative features of bisphosphonates is included in Table 77-6.

Other agents used to treat hypercalcemia include gallium nitrate and plicamycin, which have toxicity problems. Gallium nitrate inhibits bone resorption but has potential nephrotoxicity. Therapy with plicamycin is associated with sudden thrombocytopenia followed by hemorrhage as well as hepatic and renal toxicity. Chronic hypercalcemia of sarcoidosis, vitamin D intoxication, and certain cancers may be treated with glucocorticoids.

ALENDRONATE SODIUM

Phosphonic acid, (4-amino-1-hydroxybutylidene)bis-, monosodium salt, trihydrate; Fosamax; Onclast



[121268-17-5] $C_4H_{12}NNaO_7P_2.3H_2O$ (325.12).

Preparation—Orthophosphorous acid is heated with 4-aminobutyric acid in an atmosphere of nitrogen and phosphorous trichloride is added to the melt. Finally, water is added, the solution is decolorized with charcoal, and diluted with methanol to precipitate the free acid which is treated with one equivalent of sodium hydroxide. US Pat 4,705,651 (1987).

Description—(Acid) White crystalline, nonhygroscopic powder melting about 234° (decomposition). pK_1 2.27; pK_2 8.73; pK_3 10.5; pK_4 11.6 (in 0.1*M* KCl).

Solubility—(salt) Very soluble in water.

Comments—The first oral bisphophonate to be approved for the treatment and prevention of osteoporosis in postmenopausal women. It is more potent than etidronate and also is used to treat Paget's disease. Alendronate is a highly selective inhibitor of bone resorption (100–500

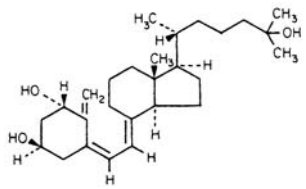
Table 77-6. Major Features of Bisphosphonates

BISPHOSPHONATES	COMMENTS
Etidronate	Less potent inhibitor of bone resorption; causes mineralization defects
Pamidronate	Only IV administration; causes acute flulike illness
Alendronate	Useful in treatment of osteoporosis; may cause esophageal ulcers
Tiludronate	Similar to etidronate but does not cause mineralization defects
Risedronate	More potent inhibitor than etidronate of bone resorption; may cause flulike syndrome and arthralgia

× more potent), while etidronate has the disadvantage of secondarily reducing bone formation that is coupled to resorption. The drug should be taken at least 30 min before food, beverage, or other medication. The mean oral bioavailability is 0.7%, which can be decreased by food. It is not metabolized and is eliminated from the systemic circulation by renal excretion. Several GI adverse effects may occur that include flatulence, acid regurgitation, dysphagia, and gastritis. Other effects include headache, musculoskeletal pain, and rash. Upper GI side effects including esophagitis and gastritis may be increased with higher doses used to treat Paget's disease.

CALCITRIOL

(1α,3β,5*Z*,7*E*)-9,10-Secocholesta-5,7,10(19)-triene-1,3,25-triol; Dihydrotachysterol; DHT; Calcijex; Rocaltrol; Topitrol



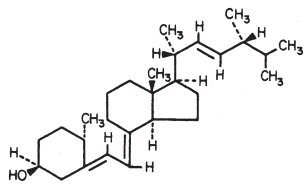
[3222-06-3] $C_{27}H_{44}O_3$ (416.65).

Preparation—Stereospecific synthesis from *d*-carvone in Lednicer D, Mitscher LA. *The Organic Chemistry of Drugs,* vol 3. New York: Wiley, 1984, pp 103–106; Baggiolini et al. *J Am Chem Soc* 1982; 104:2945.

Description—White crystals melting about 114°. Sensitive to air and light.

DIHYDROTACHYSTEROL

9,10-Secoergosta-5,7,22-trien-3-ol, (3β,5*E*,7*E*,10α,22*E*)-, Dihydrotachysterol; DHT



9,10-Secoergosta-5,7,22-trien-3β-ol [67-96-9] $C_{28}H_{46}O$ (398.67).

Preparation—Calciferol (activated ergosterol) is dissolved in a suitable organic solvent and subjected to catalytic hydrogenation until the proper amount of hydrogen has reacted.

Description—Colorless or white crystals, or a white, crystalline powder; odorless; melts between 123.5° and 129° for one form, or about 113° for the other form.

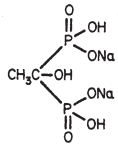
Solubility—Practically insoluble in water; soluble in alcohol; freely soluble in ether or chloroform; sparingly soluble in vegetable oils.

Comments—Chemically closely related to vitamin D_2 (calciferol) and consequently classified frequently as a D vitamin. However, it possesses very weak antirachitic activity, being only about 1/400 as potent as calciferol in this respect, mainly because its effects on calcium absorption from the intestine are quite weak. But it has potent calcemic activity (ie, raises plasma calcium concentration) and is similar to parathyroid hormone in this action. Consequently, it long has been used in lieu of parathyroid hormone in the treatment of idiopathic and postoperative tetanies, hypocalcemia, and hypoparathyroidism. The drug should not be used in the presence of renal insufficiency or hyperphosphatemia. Extreme care must be used to prevent overdosage.

Adverse effects result mainly from hypercalcemia. They include anorexia, nausea, vomiting, diarrhea, languor, osteoporosis, weight loss, metastatic calcification, renal damage, anemia, band keratitis, and convulsions. In severe hypercalcemia there may be headache, vertigo, tinnitus, abdominal cramps, polyuria, thirst, ataxia, albuminuria, and xanthemia.

ETIDRONATE DISODIUM

Phosphonic acid, (1-hydroxyethylidene)bis-, disodium salt; Didronel



$C_2H_6Na_2O_7P_2$ (249.99).

Preparation—Etidronic acid may be prepared in various ways, as by passing gaseous phosphorus trichloride into acetic acid at about 75°, by reaction of the same substances in a lower aliphatic tertiary amine such as tributylamine, or by reaction of an anhydrous mixture of phosphorous acid, acetic anhydride, and acetic acid.

Description—White powder.

Solubility—Very soluble in water.

Comments—This first-generation bisphosphonate is approved for treatment of Paget's disease but is a less potent inhibitor of bone resorption than new analogs. It is adsorbed onto hydroxyapatite (bone crystal), where it interferes with resorption of the crystals in osteoclasia and, in higher concentration, with osteoblastosis. In Paget's disease (osteitis deformans), for which it mainly is used, it slows the rate of turnover of bone, decreases excessive osteoclastic and osteoblastic cellular activities, and diminishes hydroxyproline levels in blood and urine and brings the elevated serum alkaline phosphate down toward normal. Usually several months of treatment are required to effect a considerable improvement. It also is used in the prophylaxis or slowing of heterotopic ossification (eg, after hip replacement or vertebral injury) and to suppress hypercalcemia of malignancy.

In high doses or after prolonged use, increased bone pain, decreased mineralization, and increased bone fractures may occur as the result of inhibition of osteoid formation. Even with the usual dosage, there may be occasional nausea, vomiting, diarrhea, and abdominal cramps, which can be lessened by dividing the dose into two or more portions.

It is 50% absorbed by the oral route. Various constituents in food and antacids, especially calcium, impair absorption. The distribution half-life is 5 to 7 hr; the elimination half-life is about 24 hr. The drug is eliminated entirely by renal excretion. Therefore, it should be used cautiously in renal failure. Urine hydroxyproline levels and serum alkaline phosphatase activity should be monitored periodically during treatment.

GALLIUM NITRATE

Nitric acid, gallium salt, nonahydrate: Ganite

$Ga(NO_3).9H_2O$[135886-70-3] $GaN_3O_9 \cdot 9H_2O$ (417.87).

Preparation—By dissolution of gallium metal or gallium oxide in nitric acid.

Description—White, deliquescent crystals; decomposes about 110°; forms Ga_2O_3 at 200°.

Solubility—Very soluble in water; soluble in anhydrous alcohol.

Comments—To treat cancer-related hypercalcemia unresponsive to adequate hydration. It inhibits calcium resorption from bone, possibly by reducing increased bone turnover. The precise mechanism has not been determined. The plasma half-life is 72 to 115 hr with a prolonged intravenous infusion, and the major route of elimination is renal excretion.

Adverse effects include nephrotoxicity, transient hypophosphatemia, anemia, and leukopenia. It should not be used with other nephrotoxic drugs.

THE THYROID HORMONES

The thyroid gland modulates the energy metabolism and certain nonenergetic metabolic functions of the body. In the absence of the thyroid gland the basal metabolic rate is less than 55% of normal, and growth and development are impaired. In the presence of a hyperactive gland the metabolic rate may be up to 160% of normal; the excitability of irritable tissues is increased, and tachycardia, nervousness, etc. result. Thyroid *hormone* is used

clinically mainly to replenish the corporal hormone supply in conditions of thyroid insufficiency (hypothyroidism), such as may result from a natural thyroid or pituitary pathology or from thyroid surgery. The *hormone* rarely is administered to increase the metabolic rate and organic activity above normal, and such iatrogenic hyperthyroidism may indeed be dangerous.

The mediator by which the thyroid gland stimulates the tissues to a higher activity and rate of metabolism is called the thyroid hormone, but there are actually four active substances, all iodinated thyronines, released by the gland. Thyroxine (L-3,5,3′,5′-tetraiodothyronine, or T_4 is found in the greatest amount in blood (about 75% of the thyroid hormone content of the plasma), and the moderately less active L-3,3′-diiodothyronine is present in the next greatest amount (25%). L-3,5,3′-Triiodothyronine (liothyronine, or T_3, which is 3 to 10 times as active as thyroxine, and L-3,3′,5′-triiodothyronine make up less than 3% of the plasma thyroid hormone content. But since the triiodothyronines disappear more rapidly from blood than thyroxine, they probably constitute a somewhat larger proportion of the glandular secretion; in the thyroid gland they account for about 1/5 of the hormone content and as much as 40% of its hormone activity. Furthermore, in the tissues, some thyroxine is converted to liothyronine and perhaps as much as 1/2 to 2/3 of the body liothyronine is derived from thyroxine. Liothyronine regulates TRH release in the hypothalamus and is probably the principal hormone involved in the long negative-feedback-loop regulation of TSH (thyroid-stimulating hormone, or thyrotropin) release.

The thyroid gland concentrates iodide ion from the plasma and converts it to free iodine, which then reacts with tyrosine moieties within the substance of the gland eventually to produce the thyroid hormones. The glandular accumulation of iodine and the conversion to the intermediate 3,5- diiodotyrosine are under the control of the thyrotropic hormone. Iodine deficiency results in a compensatory increase in the size of the thyroid gland in a usually fruitless homeostatic attempt to manufacture more hormone. Iodine administration corrects this type of goiter and permits the normal production of the thyroid hormones. The incorporation of sodium iodide into table salt helps protect against iodine-deficiency thyroid disorders. In children under 14 years, iodine supplementation corrects endemic cretinism.

In the colloid of the thyroid gland these thyronine derivatives are bound to a globulin, thyroglobulin, which formerly was thought to be the thyroid hormone. About 90% of the thyroid hormone content of the gland is in the thyroglobulin complex. The molecular weight of thyroglobulin is 650,000. Before thyroxine and liothyronine can be released into the bloodstream, the thyroglobulin must be assimilated by the thyroid follicular cells, within which the globulin is split by proteases to release the hormones. In the blood, the hormones are bound mainly to an albumin; the complex is dissociable, so the hormones are free to pass into the body cells.

The thyroid hormones interact with nuclear receptors to increase RNA polymerase and also to increase the number of initiation sites for the polymerase. The result is an increase in transcription for a number of proteins, and the synthesis thereof is increased. Thyroid hormone also has a regulatory action on tRNA. The synthesized proteins in turn regulate various enzymes and enzyme complexes, so that oxidative phosphorylation in the mitochondria may become partially uncoupled, membrane ATPase activity is increased, adenylate cyclase activity is enhanced, etc. There also are some direct actions on cellular functions, such as stimulation of autocrine growth factors and amino acid transport systems and inhibition of some zinc-dependent dehydrogenases, prostaglandin dehydrogenases, etc. The uses and adverse effects of the thyroid hormones are indicated in the monograph on *Thyroid*. Thyroid hormones lower plasma lipid concentrations. However, because of their effect to increase the metabolic rate, they are not used clinically to lower blood lipids. The lipid-lowering action is possessed also by the dextro isomers of thyroid hormones, but the dextro forms have only a very weak effect on the metabolic rate. Consequently, dextrothyroxine is employed to lower blood lipids.

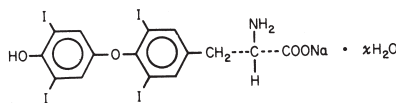
Table 77-7. Thyroid Hormone Products

PREPARATION	COMPOSITION (RATIO OF T_4/T_3)	COMMENTS
Crude hormone		
Thyroid	2–5	Powdered extract from domestic animals
Thyroglobulin	2.5	Extracted from hog thyroid glands
Thyroid strong	3.1	Desiccated thyroid with higher iodine content, 50% stronger than thyroid
Synthetic hormone		
Levothyroxine	Pure T_4	Longer half-life (6–7 days)
Liothyronine	Pure T_3	Short half-life (<2 days), potency 4× > T4
Liotrix	4	Mixture of pure T4 and T3

A summary of the thyroid hormone products is shown in Table 77-7.

LEVOTHYROXINE SODIUM

***l*-Tyrosine, *O*-(4-hydroxy-3,5-diiodophenyl)-3,5-diiodo-, monosodium salt, hydrate; Levothroid; Levoxyl, Synthroid, Unithroid**

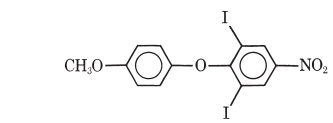


Monosodium L-thyroxine hydrate [25416-65-3] $C_{15}H_{10}I_4NNaO_4 \cdot xH_2O$; *anhydrous* [55-03-8] (798.86); the sodium salt of the levo isomer of thyroxine, an active physiological principle obtained from the thyroid gland of domesticated animals used for food by man, or prepared synthetically. It contains 61.6% to 65.5% of iodine, corresponding to 97% to 103% of levothyroxine sodium.

Preparation—L-Thyroxine is dissolved in dilute NaOH solution, and the resulting sodium salt is precipitated by saturating the solution with NaCl.

Thyroxine may be prepared from thyroid glands or by synthesis. Preparation from the glands (fresh or desiccated) involves extraction with dilute sodium hydroxide followed by acidification with hydrochloric acid, whereupon a very crude form of thyroxine is precipitated. Purification involves repeated solubilization by means of sodium hydroxide and reprecipitation with acid, these operations being conducted under increasingly refined conditions and with the aid of auxiliary operations designed to enhance the purity of the final precipitate of thyroxine.

The key compound in the synthesis of thyroxine is 3,5-diiodo-4- (*p*-methoxyphenoxy)nitrobenzene (I), which is readily formed by condensing *p*-methoxyphenol with 3,4,5-triiodonitrobenzene under the influence of anhydrous potassium carbonate. A series of subsequent operations involves (a) reduction of nitro to amino; (b) replacement of amino by cyano by treatment with cuprous cyanide and butyl nitrite;



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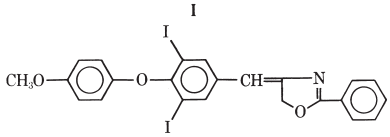
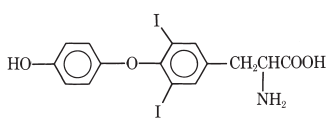


II



(c) hydration of cyano to carboxyl, and (d) reduction of carboxyl to formyl. The resulting aldehyde may be converted into thyroxine in various ways. One involves condensation with 2-phenyl-2-oxazolin-5-one to produce II, which is then simultaneously hydrogenated, demethylated, and reductively cleaved by hydrogen iodide in the presence of phospho-

rus and acetic anhydride to give the DL-form of 3-[4-(4-hydroxyphenoxy)-3,5-diiodophenyl]alanine (III), which is resolved, and the isolated L-enantiomorph is iodinated with ammoniacal potassium triiodide solution at the 3,5-positions on the phenoxy ring to give levothyroxine. Neutralization of this acid with NaOH yields the salt.

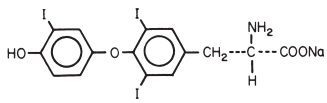
Description—Light yellow to buff-colored, odorless, tasteless, hygroscopic powder; stable in dry air but may assume a slight pink color upon exposure to light; pH (saturated solution) about 8.9.

Solubility—1 g in about 700 mL water or about 300 mL alcohol; insoluble in acetone, chloroform, or ether; soluble in solutions of alkali hydroxides.

Comments—Has the actions, uses, side effects, and limitations of thyroid. The sodium salt lends itself to intravenous administration in the treatment of myxedemic coma, although the more rapidly acting liothyronine is preferred. Approximately 50% of an oral dose is absorbed. The plasma half-life is about 9 to 10 days in hypothyroid, 6 to 7 days in euthyroid and 3 to 4 days in hyperthyroid persons, but the time for the intensity of its effect to fall to 1/2 of its initial value is 9 to 12 days, and some residual effects may be apparent for several weeks after the last dose. Although the *l*-form is twice as active as the racemic mixture, it offers no particular therapeutic advantage over the *dl*-form, and it has the disadvantage of being more expensive.

LIOTHYRONINE SODIUM

L-Tyrosine, *O*-(4-hydroxy-3-iodophenyl)-3-5-diiodo-, monosodium salt; Cytomel, Triostat, Liothyronine Sodium



Monosodium L-3-[4-(4-hydroxy-3-iodophenoxy)-3,5-diiodophenyl]alanine [55-06-1] $C_{15}H_{11}I_3NNaO_4$ (672.96).

Preparation—3,5-Diiodo-L-thyronine, the L-enantiomorph of compound (III) in the thyroxine synthesis described under *Levothyroxine Sodium,* is dissolved in methanol and iodinated only at the 3-position by treatment with ammonia and iodine at room temperature. The liothyronine (acid) is then liberated by acidifying the reaction mixture. It is purified and neutralized with NaOH to give the salt.

Description—Light-tan, odorless, crystalline powder.

Solubility—Very slightly soluble in water; slightly soluble in alcohol; practically insoluble in most other organic solvents.

Comments—Four times more potent than *Levothyroxine Sodium*. The actions and uses are those of *Thyroid* and *Levothyroxine Sodium*. It also has been used to reduce goiter, but it is less effective than Levothyroxine in suppressing TSH release. Because of the lesser pituitary suppression and the wide fluctuation in plasma levels, which negate monitoring, it is not the agent of choice for maintenance, especially after ablative radioiodine treatment. It is the treatment of choice to treat myxedemic coma, because of the rapid onset of action. It may be used to suppress goiter preparatory to surgery.

It has a rapid onset of action. The peak effect occurs in 1 to 3 days, and the offset of action is about 3 days. The prompt onset and rapid offset (compared with levothyroxine) are considered to be an advantage over thyroid or levothyroxine. The time for the intensity of its effect to fall to 1/2 of its initial value is 4 to 10 days. Liothyronine is absorbed erratically from the GI tract, and 30 to 40% may be recovered from the stools. Liothyronine is only loosely bound to plasma proteins and hence does not elevate the plasma protein-bound iodine (PBI) significantly. It crosses the blood-brain barrier and hence is not recommended for use in children.

THYROID

Desiccated Thyroid, Armour Thyroid, Thyroid USP

The cleaned, dried, and powdered thyroid gland previously deprived of connective tissue and fat. It is obtained from domesticated animals that are used for food by man.

Thyroid contains 0.17% to 0.23% of iodine (I) in thyroid combination and is free from iodine in inorganic or any form of combination other than that peculiar to the thyroid gland. A desiccated thyroid of a higher iodine content may be brought to this standard by admixture with a desiccated thyroid of a lower iodine content or with lactose, sodium chloride, starch, sucrose, or dextrose.

Description—Yellowish to buff-colored, amorphous powder, with a slight characteristic, meat-like odor and a saline taste.

Comments—Essential for normal metabolism and development. The congenital absence of thyroid hormone results in a condition known as cretinism. In childhood or adult life, absence of thyroid hormone causes myxedema. These conditions are characterized by an abnormally low basal metabolic rate. The primary therapeutic use is in their treatment.

These preparations may be used to suppress the secretion of thyrotropin in simple nonendemic goiter (hence decreases thyroid size) and chronic lymphocytic thyroiditis (Hashimoto's disease). These hormones do not decrease hyperthyroid exophthalmus. The use of them in the diagnosis of hyperthyroidism is outlined under *Liothyronine Sodium*.

In the absence of hypothyroidism, these hormones do not improve skin conditions, mental depression, fatigue, lethargy, obesity, irritability, nervousness, menstrual irregularities, and other endocrine and reproductive disorders, and there is danger that untoward effects may be produced.

Untoward effects of overdoses of these hormones include tachycardia, arrhythmias, angina pectoris, hypertension, insomnia, nervousness, hyperkinesis, tremors, diaphoresis, hot skin, GI disturbances, and hypoadrenocorticism. Even with physiological doses, it may be advisable to administer glucocorticoids concurrently. It may cause allergic reactions.

It has a very slow onset of action. A given dose does not exert its maximum effect for several days and will continue to have some degree of action for 2 to 3 months. Therefore, caution must be exercised in judging the dose, in that cumulative effects must be anticipated.

ANTITHYROID DRUGS

A number of linear and heterocyclic derivatives of thiourea inhibit the production of thyroid hormone by the thyroid gland. The mechanism of action is that of preventing iodination of tyrosine and the coupling between iodotyrosines. They also inhibit the conversion of thyroxine to liothyronine in the periphery. The decline in thyroid hormone output and the resultant lowering of plasma levels of the thyroid hormones is sensed in the hypothalamus, which through the long-loop feedback and intermediation of the thyrotropin-releasing factor stimulates the adenohypophysis to produce more thyrotropic hormone. Consequently, the thyroid gland is stimulated to enlarge, even though the enlarged gland cannot produce more thyroid hormone. Because of the thyroid enlargement consequent to the use of the thiourea class of antithyroid compounds, such compounds are called goitrogens. The goitrogens are employed in the control of hyperthyroidism. An enlarged thyroid gland is very vascular and friable, which makes surgery difficult. Therefore, iodine (or a thyroid hormone), which reduces the size of the gland, is added to the regimen preparatory to thyroid surgery. Antithyroid drugs also decrease T-lymphocyte cytotoxicity and restore normal suppressor-cell activity and are thought thus to decrease thyroid autoimmunity in Grave's disease.

Several other classes of compounds also are antithyroid agents. Compounds such as thiocyanates and perchlorates competitively inhibit the iodine uptake mechanism. Large doses of iodine inhibit the enzyme tyrosine iodinase and thus interfere with the production of thyroid hormone. Therefore, iodine also may be used in the treatment of hyperthyroidism. Curiously, this action of iodine is not goitrogenic; in fact, iodine opposes the goitrogenic effects of certain antithyroid drugs. Radioiodine I-131 (^{131}I) is antithyroid by virtue of tissue destruction caused by radiation. Thyroid hormones are antigoitrogenic by the long-loop homeostatic feedback mechanism to reduce the hypothalamic release of thyrotropin-releasing factor.

METHIMAZOLE

2*H*-Imidazole-2-thione, 1,3-dihydro-1-methyl-, Tapazole

1-Methylimidazole-2-thiol [60-56-0] $C_4H_6N_2S$ (114.16).

Preparation—One method consists of cyclizing (methylamino)acetaldehyde diethyl acetal with thiocyanic acid via de-ethanolation. Details are provided in *J Am Chem Soc* 1949; 71:4000.

Description—White to pale buff, crystalline powder, with a faint characteristic odor; solutions are practically neutral to litmus; melting range 144 to 147°.

Solubility—1 g in 5 mL water, 5 mL alcohol, 4.5 mL chloroform, or 125 mL ether.

Comments—An antithyroid drug for the preparation of the hyperthyroid patient for surgery and for the total treatment of hyperthyroidism. It is approximately 10 times as potent as propylthiouracil and is more prompt in eliciting an antithyroid response. The drug also exhibits a more prolonged action than propylthiouracil; a single dose of 5

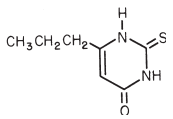
mg may inhibit the synthesis of thyroid hormone for 24 hr. The plasma half-life is 6 to 8.5 hr in hyperthyroid, but 8 to 18 hr in hypothyroid, patients; therefore, as the drug lowers the metabolic rate, its own metabolism is slowed, and accumulation will occur unless the dose is adjusted.

Approximately 6% of patients taking the drug experience some untoward effect. Thus, the incidence of untoward reactions is somewhat higher than with propylthiouracil but considerably lower than with other antithyroid drugs. Cross-sensitization to other thiouracils can occur. Three times as much of this drug crosses the placental barrier as propylthiouracil.

POTASSIUM IODIDE—page 1377.

PROPYLTHIOURACIL

4(1*H*)-Pyrimidinone, 2,3-dihydro-6-propyl-2-thioxo-, Propacil



6-Propyl-2-thiouracil [51-52-5] $C_7H_{10}N_2OS$ (170.23).

Preparation—By condensation of ethyl 3-oxocaproate with thiourea (*J Am Chem Soc* 1945; 67:2197).

Description—White, powdery, crystalline substance; starch-like in appearance and to the touch; bitter taste; melts about 220°.

Solubility—Slightly soluble in water; sparingly soluble in alcohol; slightly soluble in chloroform or ether; soluble in ammonia or alkali hydroxides.

Comments—Since the drug does not interfere with the release or use of stored thyroid hormone, the period that elapses between the beginning of medication and the manifestations of its antithyroid action depends upon the quantity of thyroid hormone stored in the gland. The marked hyperplasia of the thyroid gland that follows its administration is a result of a compensatory increase of thyrotropin release consequent to a reduction in the thyroid hormone titer of the blood. In the preparation of the hyperthyroid patient for surgery, when treatment with the drug has brought the basal metabolic rate to normal (euthyroidism) or nearly so, iodine is administered to reduce the marked vascularity and friability of the gland. In the total (medical) treatment of hyperthyroidism, the duration of treatment usually ranges from 6 months to 3 years, after which thyroid function may remain normal. However, at least half of patients so treated may be expected to have a recurrence 6 to 12 months after cessation of medication.

The most serious toxic actions are granulocytopenia, leukopenia, drug fever, and dermatitis. Joint pains and urticaria may occur. Cross-sensitivity to other thiouracils may occur. A small percentage of patients experience nausea, abdominal discomfort, headache, drowsiness, vertigo, paresthesias, and loss of taste sense. The overall incidence of untoward reactions to propylthiouracil is approximately 4%; the incidence of agranulocytosis approaches 0.5%. The drug passes the placental barrier and may affect the fetus, so that during pregnancy the lowest possible dose should be used. It also is secreted into milk, and the drug should be withheld from nursing mothers.

Only about 75% is absorbed by the oral route. There is considerable confusion about the elimination half-life, probably because redistribution has been confused with elimination and because of analytical difficulties. The elimination half-life is probably about 3 to 5 hr in hyperthyroid, 6 to 8 hr in euthyroid, and 24 to 34 hr in hypothyroid, persons; thus since the drug decreases the metabolic rate, the dose should be adjusted accordingly, to avoid accumulation.

THE GONADAL HORMONES AND INHIBITORS

Three main classes of steroid hormones are produced by gonadal tissues: estrogenic, progestational, and androgenic hormones. The ovary is the primary site for synthesis and secretion of estrogenic and progestational hormones in women. At puberty, the ovary begins a 30- to 40-year period of cyclic function called the menstrual cycle that is regulated by the pulsatile production of hypothalamic gonadotropin-releasing hormone (GnRH) that stimulates the release of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) from the anterior pituitary. In men and postmenopausal women, the principal source of estrogen is adipose tissue stroma, where the level of estrogens is regulated in part by the availability of androgenic precursors secreted from the adrenal cortex.

The most important androgenic hormone produced by the testes in men is testosterone, although the adrenal cortex also produces some androgenic hormones in both men and women. FSH and LH also regulate testosterone production by specific cells in the testis that control spermatogenesis and the development of primary and secondary sexual characteristics in men.

STRUCTURE—The natural estrogens are all steroids (see Chapter 26) containing 18 carbon atoms, oxygenated at carbons 3 and 17. Ring A of all the estrogens is aromatic and is formed from either androstenedione or testosterone precursors by a monooxygenase enzyme complex called aromatase that uses NADPH and molecular oxygen as cosubstrates.

Progesterone, the hormone of the corpus luteum, is a 21-carbon-atom steroid possessing, like adrenal cortical steroids, an α,β-unsaturated ketone component in Ring A. It differs from the latter in that its C17 does not carry a hydroxyl group.

The natural androgenic steroids are 19-carbon-atom compounds. They are characterized by a partly or completely saturated ring A and by either a hydroxyl or a keto group at C3 and C17. As with all other classes of steroids, stereoisomerism is of fundamental importance with the sex hormones; and the α- and β-configuration conventions are applied in drawing the structural formulas.

The Ovarian Hormones

The ovaries serve the dual purpose of secreting the female hormones and producing the ova that, after the menarche, are liberated normally at the rate of one every 4 weeks. The menstrual cycle can be described in terms of the development of both the ovarian follicles and changes in the endometrial lining of the uterus. The proliferative and secretory phases of the endometrial changes coincide with the follicular and luteal stages of the ovarian follicles, respectively. Estrogen predominates during endometrial proliferation and maturation of an ovarian follicle that is released at the time of ovulation. Both estrogen and progesterone are produced by the ruptured follicle that becomes the corpus luteum, which secretes estrogen and progesterone. Progesterone levels are greatest during the secretory phase of the endometrium and the luteal phase of the corpus luteum. Estrogen levels fall at the time of menstruation and are associated with bleeding and sloughing of the highly vascularized endometrium; if the released ovum or corpus luteum is not sustained by successful fertilization it regresses. During pregnancy the placenta produces large quantities of estrogen. The ovaries also secrete small amounts of androgens, adrenal steroids, and the nonsteroidal hormone relaxin (see below).

The ovarian production of hormones is regulated by the gonadotropic hormones of the anterior pituitary. However, the control of pituitary gonadotropin production is, in turn, modulated by the estrogens and progesterone, which in low plasma concentrations appear to stimulate, and at high concentrations inhibit, the production of FSH, LH, and LRH. Thus, a complex positive and negative feedback system subserves the cyclic phenomena of ovulation and menstruation. The exact details in this concert are not known completely for humans. It is known that in women ovulation can be prevented by estrogens as the result of suppression of FSH production. However, estrogen alone is not satisfactory for oral contraception, owing to what is termed *breakthrough* bleeding, except when high doses of estrogen are used. In large doses, progesterone also inhibits ovulation, presumably because of suppression of the pulsatile secretion of the hypothalamic GnRH. Furthermore, progesterone can favor infertility by antagonism of some estrogen actions, by maintaining the endometrium in a hypoproliferative and hyposecretory state that is unfavorable to implantation of the fertilized ovum. It now is known that some progestins have an antifertility effect at doses well below those necessary to suppress endometrial proliferation and secretion.

Intermenstrual bleeding occurs during continuous treatment with many progestins, and it was found desirable to add estrogens. Estrogen not only helped normalize cyclic bleeding but also contributed to the contraceptive effect. Progestins alone can be used for contraception, but their mechanism does not totally depend upon inhibition of ovulation that occurs in 70% to 80% of cycles by slowing the frequency of the GnRH pulse generator and blunting the LH surge. A thickening of the cervical mucus to decrease sperm penetration and endometrial changes that impair implantation are thought to contribute to their efficacy. Progestins alone avoid the drawbacks of estrogens, namely nausea, vomiting, headache, a tendency to venous thrombosis, and other untoward effects, but they are slightly less effective contraceptives than are the estrogens.

The luteinized granulosa cells of the corpus luteum also produce relaxin, a peptide with a tertiary structure similar to that of insulin and some growth factors. There are two chains linked through disulfide bonds. The molecular weight is about 6000. It relaxes the estrogen-primed symphysis pubis and increases the viscous pliability of the cervix, thus assisting the birth canal to prepare for parturition. It also increases glycogen synthesis and water uptake by the myometrium and decreases uterine contractility, which suggests a role during gestation. During the menstrual cycle, blood levels are high just following the LH surge and during menstruation. Much of its physiology remains to be learned. Relaxin also is found in the placenta and uterus.

Another relaxing peptide, lututrin, is produced in the ovary. Very little is known of its physiological functions. Relaxin and lututrin have been used to treat dysmenorrhea, premature labor, cervical dystocia, and scleroderma, but efficacy never has been proved.

NATURAL ESTROGENIC HORMONES AND CONGENERS

Natural estrogenic hormones are secreted by the ovarian follicles. They stimulate or regulate the growth and development of the uterus, the vaginal mucous membrane, and other structures such as mammary glands, subcutaneous fat, axillary and pubic hair, and certain elements in the skin. These latter comprise the secondary female sex characteristics. Therefore the estrogens also are called female sex hormones. Of the estrogens the most potent occurring naturally are β-estradiol and its two principal metabolic products, estrone and estriol, which also are estrogenic. Several other products of metabolic change occur in smaller amounts, but these are not offered as single substances for therapy. Estrogens are secreted throughout the period of activity of the ovaries, but at varying rates at different times of the menstrual cycle.

The naturally occurring estrogens can be prepared synthetically, but at greater cost than by extraction from natural materials or by simple chemical processing of natural estrogens as they occur in urine. An interesting improvement of the natural estrogen has been the synthetic modification of β- estradiol, the most potent natural estrogen, by the addition of a side chain, producing ethinyl estradiol. This has a very high activity when administered orally.

USES—Estrogens are used as substitution therapy when menopausal symptoms occur after cessation of ovarian function, following ovariectomy or x-ray or radium therapy, or in the natural menopause (also called the climacteric). There is general agreement that low-dose estrogen treatment will ameliorate the symptoms of vasomotor instability (hot flashes), prevent or reverse urogenital atrophy in menopausal women.

The beneficial effects of estrogen therapy on irritability, depression, anxiety, and insomnia are more unpredictable. Estrogen administration can alter high-density lipoproteins (HDLs) and low-density lipoproteins (LDLs), which improves the relative lipoprotein profile. However, any potential benefits of estrogen replacement therapy must be weighed against serious cardiovascular and breast cancer risk (see *Side Effects* below).

At this time estrogen replacement therapy can only be recommended for short-term management of menopausal symptoms.

Estrogens are used in young women in whom there is failure of steroidogenesis; treatment brings about acceleration of delayed development of the uterus, the appearance of secondary sex characteristics, and subtle biochemical and behavioral changes. Applied locally, the estrogens are useful in the treatment of atrophic or senile vaginitis, vulvovaginitis, or cervicitis resulting from hypoestrogenesis but not from other causes.

A number of menstrual irregularities may be treated with estrogens. Some of these, such as amenorrhea, may be the result of an asynchrony in the release of hypothalamic release factors and pituitary gonadotropin release. Estrogens used cyclically may regularize some of these conditions. They are of value in symptoms of premenstrual tension such as headache and electrolyte imbalance. In endometriosis, estrogens are effective for only a short time, endometrial hyperplasia eventually resulting. In dysmenorrhea and dysfunctional uterine bleeding, combined treatment with estrogens and progestogens is used, and normal withdrawal bleeding may follow the abrupt cessation of treatment.

Estrogens also are used to treat acne vulgaris and hirsutism. They may be used in the induction of parturition and in the postpartum period to reduce breast engorgement.

There is a choice of compounds for estrogenic therapy. A comparison of some major features of estrogenic agents is included in Table 77-8. Estrone is employed commonly by intramuscular injection, but considerable activity is lost if the oral route is used. Ethinyl estradiol is the most active of all oral estrogens, and its oral activity is nearly equal to its parenteral activity. Conjugated estrogens retain much of their activity on oral administration and are used extensively by this route. Estrogens also can be given by topical, intravaginal or with transdermal systems.

Synthetic or Nonsteroidal Estrogens

The best known is diethylstilbestrol, which possesses most of the therapeutic and untoward actions of the natural estrogenic hormones. Since nonsteroidal estrogens lose little activity after oral administration, they have advantages over the natural estrogens, but the comparative toxicities are not clear. Attempts to explain why such nonsteroidal compounds are estrogenically potent have been intriguing. There is a spatial resemblance between them and the true hormone estradiol. Others have focused attention on the closeness of the dimensions of the synthetics (especially length, width, and distance between OH groups) and those of estradiol. The synthetic estrogens combine with the same cytoplasmic receptors as natural estrogens and presumably also with the same nuclear receptor.

Table 77-8. Major Features of Estrogens

ESTROGENS	COMMENTS
Natural estrogens	
Estradiol	Low oral bioavailability due to extensive first-pass hepatic metabolism; oral, IM, topical, and transdermal forms
Conjugated estrogens	
Esterified estrogens	Mixture of sulfate esters of estrogenic substances from pregnant mares; predominantly estrone and equilin; used orally or topically
Synthetic estrogens	
Ethinyl estradiol	Slower metabolism; half-life = 13–27 hr
Mestranol	Metabolized to ethinyl estradiol
Nonsteroidal estrogens	
Diethylstilbesterol	Good oral absorption; slow inactivation

Synthetic estrogens have a greater bioavailability than natural ones. Regarding the latter it must be recalled that the oral doses of natural estrogens, with the possible exception of ethinyl estradiol (a derivative of a natural estrogen), may have to be five or more times that of the parenteral doses to secure similar results. This is the result of first-pass metabolism, excretion into bile, and destruction in the intestines. One disadvantage of some synthetic estrogenic compounds is that nausea follows the use of even the minimum effective dose in some women. It is most distressing in the first 2 weeks of use, after which tolerance develops. In such women the synthetic materials must be replaced by natural products. Whether the synthetic estrogens are more toxic than natural estrogens is not established unequivocally, but diethylstilbestrol differs significantly from natural compounds (see the introduction to this section and *Diethylstilbestrol*).

SIDE EFFECTS—Nausea and vomiting are frequent side effects of estrogens. These effects appear to be mainly of CNS origin. Estrogens may cause fluid retention and breast tenderness. They also may cause breast engorgement, in part by promoting the proliferation of the secretory acini and ducts. Headache and dizziness are more frequent with high doses and severe migraine may occur even with low doses. Malaise, irritability, and depression occasionally occur with small doses and frequently with large doses. The effect on libido is erratic, being increased in some and decreased in others.

Estrogens effect changes in the concentration of some of the clotting factors in blood, and therapeutic doses of semisynthetic and synthetic estrogens increase the incidence of thrombophlebitis and thromboembolism in both the superficial and deep veins. Pulmonary embolism, cerebral embolism with stroke, and mesenteric vascular occlusion occur. Coronary thrombosis also seems to be increased among users of estrogens.

Estrogens alter hepatic function, which may alter results of various tests of liver function as well as various synthetic and biotransformation processes. Effects of estrogen alone to decrease glucose tolerance are now believed to be related to their combined effects with progestins. 17-Alkyl derivatives, especially, occasionally cause cholestatic jaundice. The composition of the bile is altered, and there is a slightly increased incidence of gallstones after long-term use.

Acute porphyria may be precipitated. Changes in the concentration of blood proteins may occur; thyroxine- and glucocorticoid-binding proteins are increased, which may alter endocrine relationships. Aldosterone secretion is increased, which not only accounts for sodium retention but also for an abnormal incidence of hypertension among users of estrogens. Estrogen-induced hypertension is reversible.

Estrogens may induce changes in the skin, such as dermatitis, increased pigmentation (in combination with progestins, causes chloasma), a tendency to vaginal candidiasis, and spider angiomas. Photosensitization may occur, and protective measures are advisable. Although estrogens may improve acne, they only do so after a temporary worsening of the condition. Estrogens may cause a loss of scalp hair in some users and hypertrichosis in others. Allergic reactions include rashes, erythema multiforme, erythema nodosum, and cholestatic jaundice.

Recent data have shown the relationship of estrogen therapy to an increased risk of breast cancer for premenopausal women. Estrogens increase the risk of endometrial carcinoma by 4.5 to 13.9 times, and the incidence appears to depend on duration and dose. When diethylstilbestrol is taken during pregnancy, there is an increased likelihood of vaginal adenocarcinoma in the daughter after maturity; whether natural and semisynthetic estrogens are similarly fetotoxic is not known. There also is an increased likelihood of functional abnormalities in the reproductive tracts in both female and male offspring.

Hypercalcemia may occur, especially in men taking large doses for prostatic carcinoma.

In women, chronic use may cause spotting or breakthrough vaginal bleeding; after discontinuation, withdrawal bleeding usually occurs.

A discussion of the role of estrogens in the adverse effects of oral contraceptives is included under *Oral Contraceptives, Adverse Effects*.

PHARMACOKINETICS—Naturally occurring estrogens are not effective orally because they are destroyed almost totally in a single pass through the liver (first-pass effect). Oral effectiveness can be improved by administration of conjugated or esterified estrogens, by use of synthetic estrogens that are metabolized more slowly, or, in the case of estradiol, by preparation of the drug in a micronized form that is absorbed into the thoracic duct rather than into the portal circulation.

Estrogens are absorbed rapidly from intramuscular sites, mucous membranes, skin, and other sites of therapeutic application. The half-life of estradiol is 40 to 50 min, but other estrogens persist much longer. Estrogens circulate in both free and conjugated forms. These are bound in varying amounts to albumin and to a specific sex hormone–binding globulin (SSHBG).

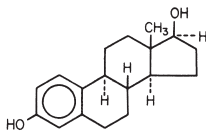
Estrogens are excreted primarily in the conjugated form in urine. Some free estrogen is secreted in bile, from which some is excreted in feces and most returns to the systemic circulation by the enterohepatic route. Estrogens are excreted in breast milk, so their use in nursing mothers is not recommended.

DRUG INTERACTIONS—Drugs that induce the hepatic microsomal mixed oxygenase system (eg, phenobarbital, phenytoin, and rifampin) will accelerate estrogen metabolism.

Estrogens antagonize oral anticoagulants and also interfere with tests of coagulation. They also interfere with tests of thyroid function.

ESTRADIOL

(17β)-Estra-1,3,5(10)-triene-3,17-diol, 17-Beta-estradiol; Estrace



Dihydrotheelin; [50-28-2] $C_{18}H_{24}O_2$ (273.39).

Preparation—Has been isolated from ovarian follicular fluid and from placental tissue and is the most potent of the natural estrogens. It is usually prepared through reduction of the 17-keto group of *Estrone*.

It is curious that the urine of stallions and of the males of other *Equidae* contains 3 to 5 times as much estradiol as that of the female of the species.

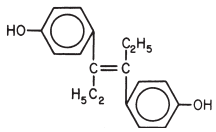
Description—White or creamy white, small crystals or a crystalline powder; odorless and stable in air; hygroscopic; melts about 175°.

Solubility—1 g in 28 mL alcohol, 435 mL chloroform, or 150 mL ether; practically insoluble in water.

Comments—A natural estrogen used for replacement mainly in the postmenopause but also in ovarian hypofunction and after ovariectomy. It has a high presystemic elimination rate, hence a low bioavailability by the oral route. However, a micronized preparation (*Estrace*) is absorbed rapidly enough to flood the pertinent liver enzyme sufficiently to make oral administration feasible. Transdermal systems also are used effectively for replacement. Intravaginal estradiol (cream and ring) work topically in atrophic vaginitis, but the action to correct kraurosis vulvae is probably partly systemic. Estradiol is considerably converted to estrone in the body. The half-life is about 1 hr. Employ the lowest effective dose for the shortest duration to control menopausal symptoms.

DIETHYLSTILBESTROL

Phenol, *(E)*-4,4′-(1,2-diethyl-1,2-ethenediyl)bis-, DES



α,α′-Diethyl-(*E*)-4,4′-stilbenediol [56-53-1] $C_{18}H_{20}O_2$ (268.35).

Preparation—A synthetic estrogen first synthesized by Dodds et al in 1938. As to be expected, the compound exists in two geometric isomeric

forms. The *cis*-isomer(*Z*), which has less than one-tenth the activity of the *trans*(*E*) and does not form readily, is unstable and tends to revert to the *trans*-isomer; hence the official product is *trans*- diethylstilbestrol.

Several methods of synthesis have been devised. That of Kharasch and Kleiman (*Medicinal Chemistry,* vol II, New York: Wiley, 1956) uses anethole hydrobromide as the starting material and is most convenient.

Description—White, odorless, crystalline powder; melts within a range of 4°, between 169° and 175°.

Solubility—Practically insoluble in water; soluble in alcohol, ether, chloroform, fatty oils, or dilute alkali hydroxides.

Comments—It is absorbed well orally. The rate of inactivation is slow. It can be administered orally in single daily doses, even with large doses.

Nausea and vomiting appear to be caused, in part, by local actions of the drug. Enteric coatings on tablets slow the rate of release and lessen the incidence and intensity of such local effects. It is advised to start with smaller doses for patients who tend to develop disagreeable symptoms such as nausea. It is contraindicated in pregnancy because of the danger of inducing a latent vaginal carcinoma in female offspring and structural abnormalities in the genitourinary tract in male offspring.

CONJUGATED ESTROGENS

Premarin

A mixture containing the sodium salts of the sulfate esters of the estrogenic substances, principally estrone and equilin, that are of the type excreted by pregnant mares. Conjugated estrogens contains 50% to 65% of sodium estrone sulfate, and 20% to 35% of sodium equilin sulfate, calculated on the basis of the total estrogens content.

Preparation—The urine of pregnant mares is subjected to a solvent extraction process. US Pats 2,565,115 and 2,720,483.

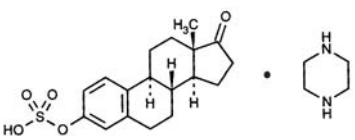
Description—Buff-colored powder; odorless or with a slight, characteristic odor.

Solubiltiy—Soluble in water.

Comments—Most commonly prescribed estrogen product, however it has fallen out of favor due to recent clinical trial data demonstrating increased risk of stroke, DVT/PE, CHD events and breast cancer. At this time therapy can only be recommended for short-term management of menopausal symptoms. Employ the lowest effective dose for the shortest duration as needed to control menopausal symptoms.

ESTROPIPATE

Estra-1,3,5(10)-triene-17-one, 3-(sulfooxy)-, compd with piperazine (1:1); Ogen; Ortho-Est



Piperazine estrone sulfate [7280-37-7] $C_{18}H_{22}O_5S.C_4H_{10}N_2$ (436.56).

Preparation—Estrone is treated with sulfur trioxide in DMF and excess piperazine is added which precipitates the product. US Pat 3,525,738 (1970), *Anal Profiles of Drug Subst* 5:375.

Description—Yellowish-white odorless, tasteless, crystalline powder melting about 190°, resolidifying and decomposing about 245°; racemic form melts about 251°.

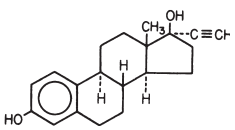
$$[\alpha]^{20}_{D} = +87.8° \text{ (c = 1, 0.4\% NaOH).}$$

Solubility—1 g in > 2000 mL water, alcohol, chloroform or ether.

Comments—Approved for the treatment of moderate-to-severe vasomotor menopausal symptoms. At this time therapy can only be recommended for short-term management of menopausal symptoms. Employ the lowest effective dose for the shortest duration as needed to control menopausal symptoms.

ETHINYL ESTRADIOL

(17α)-19-Norpregna-1,3,5(10)-trien-20-yne-3,17-diol, 17-Ethynylestradiol



[57-63-6] $C_{20}H_{24}O_2$ (296.41).

Preparation—By the Nef reaction, or a modification thereof, whereby estrone is caused to react with sodium acetylide in liquid ammonia. Hydrolysis of the sodoxy addition complex yields the desired carbinol. It also may be prepared by a typical Grignard reaction from estrone and ethynyl magnesium bromide.

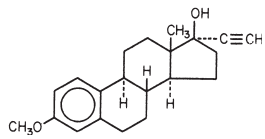
Description—White to creamy white, odorless, crystalline powder; melting range 180° to 186°; also exists in a polymorphic modification melting between 142° and 146°.

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

Comments—Has the actions, uses, and limitations of the other estrogens. It has an anovulatory effect at relatively low doses; it is the most widely used estrogen in oral contraceptive combinations. The ethinyl radical delays the decomposition of the estradiol molecule that occurs during absorption by the oral route. It is one of the most potent oral estrogens known.

MESTRANOL

(17α)-19-Norpregna-1,3,5(10)-trien-20-yn-17-ol, 3-methoxy-,



[72-33-3] $C_{21}H_{26}O_2$ (310.44).

Preparation—Estrone is converted to its 3-methoxy analog by reaction with methyl sulfate. The ethynyl group may then be introduced at position 17 either through reaction with sodium acetylide in liquid ammonia followed by hydrolysis of the sodoxy compound, or through grignardization with ethynyl bromide. US Pat 2,666,769.

Description—White to creamy white, odorless, crystalline powder; melts within a range of 4° between 146° and 154°.

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

Comments—This drug was incorporated with norethynodrel in the historically famous oral contraceptive, Norethynodrel with Mestranol, and it is now combined with several progestins in oral contraceptives. When suppression of the pituitary release of gonadotropins occurs with these preparations, it is likely that inhibition is more attributable to this drug than to the progestin. However, oral contraceptive preparations containing mestranol do not suppress ovulation in a large fraction of users, and the oral contraceptive effect cannot thus be correctly attributed to an anovulatory effect of the estrogen. It is an effective estrogen for the usual uses of estrogens, but it is not marketed as a single entity.

ANTIESTROGENS AND AROMATASE INHIBITORS

In a broad sense, antiestrogens are substances that suppress the effects of estrogens, regardless of mechanism. Androgens and progestins would thus qualify as incomplete antiestrogens, since they are antagonists to estrogens in some of their effects. With the advent of competitive antagonists of estrogens, the term *antiestrogen* has become restricted in use to apply only to such drugs. A number of estrogens have been found that reduce the intensity of response to other estrogens, behaving as agonists at some target organs and antagonists at other sites. Raloxifene is the first drug available in the new class of drugs called selective estrogen receptor modulators (SERMs). Raloxifene acts similarly to estrogen on bone, where it decreases bone resorption and increases bone mineral density; it also has estrogen-like effects on lipid (decrease in total and LDL cholesterol) metabolism. It is approved for prevention and treatment of postmenopausal osteoporosis. Raloxifene does not increase the incidence of uterine or breast tumors, which is consistent with the selective ability to act as an agonist at some but not all estrogen target tissues. Raloxifene is considered a second generation SERM. Studies with several estrogen target tissues have shown that some estrogenic drugs can promote selective gene transcription by activation of different estrogen-receptor elements upon transport of the drug-receptor complex to its nuclear binding site on DNA.

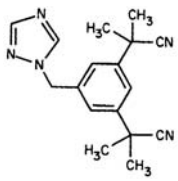
Tamoxifen is considered a first generation SERM because while it acts as an antagonist in bone, it demonstrated partial agonist activity in the uterus. The latter could be responsible for the increased incidence of uterine malignancies. Tamoxifen is indicated for primary and adjuvant therapy of breast cancer.

A closely related compound, clomiphene, has an even stronger antiestrogenic action in the hypothalamus but is sufficiently weak in the periphery so as not to interfere with the peripheral effects of endogenously released estrogens. By blocking the effects of endogenous estrogen to suppress adenohypophyseal release of gonadotropins, antiestrogens allow the anterior pituitary to produce more gonadotropins than normally. The ovaries are thus stimulated to a greater extent, and follicular development and maturation are enhanced. In cases of infertility resulting from failure to ovulate this effect may result in ovulation and the development of fertility.

Another approach to suppress the effects of endogenous estrogens is to decrease their synthesis. A new class of drugs for this purpose are the aromatase inhibitors. Aromatase is an enzyme complex that converts androgen precursors into estrogens. Inhibition of this enzyme complex decrease estrogen synthesis making these agents useful for the treatment of advanced breast cancer.

ANASTROZOLE

1,3-Benzenediacetonitrile, α,α,α′,α′-tetra-methyl-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 3,5-bis(bromomethyl)toluene, tetrabutylammonium bromide, dichloromethane and water is heated, then extracted with ethyl acetate and the extract evaporated to give 2,2′-(5-methyl-1,3-phenylene)diacetonitrile. To this latter compound is added iodomethane in DMF followed by sodium hydride in mineral oil to yield 2,2′-(5-bromomethyl-1,3-phenylene)diacetonitrile which is coupled with the sodio derivative of triazole using NBS and benzoyl peroxide to form the product, after suitable purification. US Pat 4,935,437 (1980).

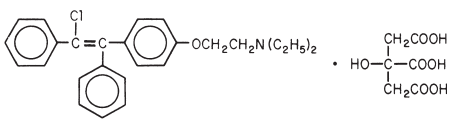
Description—Crystals from ethyl acetate/cyclohexane melting about 81°.

Solubility—About 0.5 mg/mL at 25°; freely soluble in methanol, acetone, ethanol or THF; very soluble in acetonitrile.

Comments—It is indicated as first-line treatment of postmenopausal woman with hormone receptor positive or hormone receptor unknown advanced or metastatic breast cancer. It is also indicated for treatment of advanced breast cancer following tamoxifen therapy.

CLOMIPHENE CITRATE

Ethanamine, 2-[4-(2-chloro-1,2-diphenylethenyl)phenoxy]-*N,N*-diethyl-, 2-hydroxy-1,2,3-propanetricarboxylate (1:1); Clomid; Milophene; Serophene



2-[*p*-(2-Chloro-1,2-diphenylvinyl)phenoxy]triethylamine citrate (1:1) [50-41-9] $C_{26}H_{28}ClNO.C_8H_8O_7$ (598.09).

Preparation—4-Hydroxybenzophenone is condensed with 2- (diethylamino)ethyl chloride in toluene in the presence of alkali. The 4-[2-(diethylamino)ethoxy]benzophenone thus formed is grignardized with benzyl chloride, and the tertiary carbinol thus produced is dehydrated to give 2-[*p*-(1,2-diphenylvinyl)phenoxy]triethylamine. This compound is chlorinated to yield clomiphene and then reacted with an equimolar quantity of citric acid. Clomiphene citrate is a mixture of (*E*)- and (*Z*)-geometric isomers containing 30.0 to 50.0% of the latter isomer.

Description—White to pale yellow powder, essentially odorless; not appreciably hygroscopic; melts about 118° with decomposition.

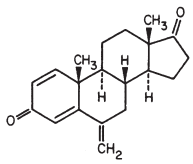
Solubility—Sparingly soluble in alcohol; slightly soluble in water or chloroform; insoluble in ether.

Comments—An antiestrogenic drug used to induce ovulation (increase fertility) in anovulatory and oligoovulatory women who have adequate endogenous estrogens and in whom the hypothalamic–anterior pituitary has a latent capacity to function. It blocks the negative feedback action of endogenous estrogens by blocking cytosolic estrogen receptors in the hypothalamus and diminishing their number. The result is an increase in the secretion of GnRH and, hence, in gonadotropins (FSH and LH). However, its effect is uneven, since it seems to be most effective in the late follicular, and not in the luteal, phase of the estrous cycle. The elevated LH levels bring about ovulation; sometimes more than one ovum is released, which may result in multiple pregnancies. In properly selected patients, 80% may be induced to ovulate, and successful pregnancy is achieved in 30% to 40%. The probability of multiple pregnancy is increased to eight times normal. This is about the same order of success as with human chorionic gonadotropin (HCG).

In addition to multiple pregnancy, the major side effect is cystic enlargement of the ovaries. Increased cyclic ovarian pain, breast enlargement, and hot flashes that resemble those of the menopause also occur. Nausea is frequent. Blurred vision and scintillating scotoma may occur, and they require discontinuation of the treatment.

EXEMESTANE

Androsta-1,4-diene-3,17-dione, 6-methylene-, Aromasin



[107868-30-4] $C_{20}H_{24}O_2$ (296.41).

Preparation—One method involves the 1,2-dehydrogenation of 6-methylene-

andros-4-ene-3,17-dione with selenium dioxide or dichlorodicyanobenzoquinone. US Pat 4,808,616 (1989).

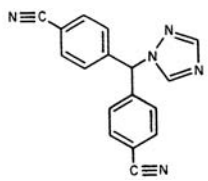
Description—White to slightly yellow powder melting about 190°.

Solubility—Freely soluble in dimethylformamide (DMF); soluble in methanol; practically insoluble in water.

Comments—It is indicated for the treatment of advanced breast cancer following tamoxifen therapy.

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—Imidazole and 4-(bromomethyl)benzonitrile in dichloromethane are stirred at room temperature, diluted with water, the organic layer separated and the solvent removed to form 4-[(1*H*-imidazole-1-yl)methyl]benzonitrile. This latter compound is treated with potassium *t*-butoxide and 4-fluorobenzonitrile in DMF to yield the product. US Pat 4,978,672 (1990).

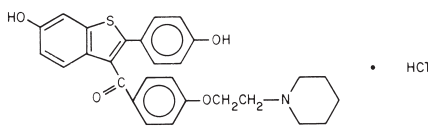
Description—Practically odorless, white to off-white powder melting about 185°.

Solubility—Freely soluble in dichloromethane; slightly soluble in ethanol; practically insoluble in water.

Comments—It is indicated as first-line treatment of postmenopausal woman with hormone receptor positive or hormone receptor unknown advanced or metastatic breast cancer. It is also indicated for treatment of advanced breast cancer following anti-estrogen therapy.

RALOXIFENE HYDROCHLORIDE

Methanone, [6-hydroxy-2-(4-hydroxyphenyl)benzo[*b*]thien-3-yl]-[4-[2-(1-piperidinyl)ethoxy]phenyl]-, hydrochloride; Evista



[82640-04-8] $C_{28}H_{27}NO_4S.HCl$ (510.05).

Preparation—Condensation of α-bromo-*p*-methoxyacetophenone with *m*-methoxythiophenol using polyphosphoric acid yields α-(*m*-methoxyphenylthio)-*p*-methoxy-acetophenone, which is cyclized by a Friedel-Crafts-type reaction to form 2-(*p*-methoxyphenyl)-6-methoxybenzothiazole. The methoxyphenyl group apparently shifts from the theoretical 3- to the 2-position on the thiazole ring. The two methyl ether groups are removed and the resulting phenols reacted with methanesufonyl chloride to form the sulfonate ester (I). Methyl paraben is alkylated with 1-(2-chloroethyl)piperidine to yield the piperidinoethyl ether; the ester is hydrolyzed to the acid and converted to the acyl halide (II). Compound I is then acylated with II (Friedel-Crafts), which attaches the carbonyl group to the 3-position of the thiazole ring, and finally the sulfonate esters are hydrolyzed to the free base of the title compound. *J Med Chem* 1984; 27:1057.

Description—Off-white to pale yellow crystals melting about 258°.

Solubility—Very soluble in water.

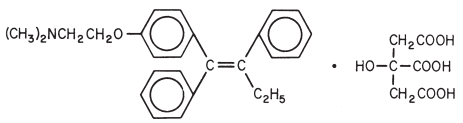
Comments—A selective estrogen receptor modulator (SERM) that is used in the prevention and treatment of osteoporosis in postmenopausal patients. It has estrogen-like effects on bone (in bone mineral density and decreases bone resorption) and on lipid (decrease in total and LDL cholesterol) metabolism; in addition, it is an estrogen antagonist and lacks estrogen-like effects in uterine and breast tissues.

Raloxifene is absorbed rapidly after oral administration, with about 60% of dose absorbed. However, absolute bioavailability is only 2% because the drug undergoes extensive first-pass metabolism in the liver to glucuronide conjugates and enterohepatic cycling that prolongs the elimination half-life to 27.7 hr. Cholestyramine may decrease absorption and enterohepatic cycling. The drug is >95% bound to plasma proteins and may be displaced by other drugs such as clofibrate, ibuprofen, and naproxen.

The most common side effects are hot flashes and leg cramps that seem to be dose-related. Other side effects may be observed such as insomnia, rash, and weight gain. The risk of developing venous thromboembolism seems to be similar to that with estrogen replacement therapy.

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 for palliative therapy of breast cancer in postmenopausal women. 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 vaginal bleeding and discharge, rashes, transient leukopenia, and thrombocytopenia. Increased bone and tumor pain may occur. Infrequent side effects are anorexia and hypercalcemia. There is an increased risk of uterine cancer. A few patients have developed retinal abnormalities.

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.

PROGESTINS AND ANTAGONISTS

Progesterone is the primary progestational substance produced by ovarian cells of the corpus luteum. It has a physiological action that is unique and distinct from that of estrogen. Progestins (progesterone and its derivatives) transform the proliferative endometrium into secretory endometrium. This alteration is part of the change that is essential to provide for the implantation of a fertilized ovum and for the continuing development of the placenta. This endometrial alteration requires the cooperation of an estrogen; in the absence of an estrogen, a progestin that is devoid of estrogenic activity will exert an atrophic effect on the endometrium.

Progestins also cause an increase in the viscosity of cervical secretions, which impedes the movement of sperm. Progestins in high doses suppress the pituitary release of luteinizing hormone and the hypothalamic release of GnRH, thus preventing ovulation.

Progestins also decrease uterine motility, which may contribute to a contraceptive effect. In addition, they antagonize the endometrial actions of estrogens, especially the natural estrogens. Progestins have the ability to stimulate development of the glandular portions of the mammae. They also exert some effects upon the capacity of tissues to retain water in the intercellular spaces. They also have a thermogenic action.

Progesterone is biotransformed in vivo, beginning with 5-α and 5-β reductions, to several active metabolites that affect the CNS in multiple ways and that may be responsible for some of the effects of progesterone described above. The metabolites decrease brain electrical activity, inhibit calcium entry into nerve terminals and norepinephrine release, and modify behavior. They also participate in the control of gonadotropin secretion. The metabolites appear to function both by modifying gene expression or by altering membrane permeability.

Progestins may be used cyclically in the treatment of infertility in which the uterus is not receptive to implantation; the progestin sustains the secretory endometrium during the third and fourth weeks of the menstrual cycle. They are used cyclically with estrogens in the treatment of secondary amenorrhea and dysfunctional uterine bleeding. They also may be used to lessen premenstrual tension, although they cause salt and water retention, which is a factor in this disorder.

The effect to suppress the release of LH and GnRH is used to prevent ovulation, not only with some oral contraceptives but also in the treatment of primary dysmenorrhea and endometriosis. In sexual infantilism in the female, progestins may be combined with estrogens to bring about genital development and maturation. Progestins may decrease breast size in mastodynia. In preeclampsia and toxemia of pregnancy due to hormonal imbalance, progestins plus estrogens may improve the condition, even though both types of hormone can cause salt and water retention, and estrogens can cause hypertension. They may be used in large doses as adjunctive treatment in endometrial carcinoma. They have been used in the past to prevent habitual abortion or treat threatened abortion.

The use of these agents during the first 4 months of pregnancy is not recommended because there is evidence that the fetus may be harmed; progestins may increase the risk of heart defects and deformed arms and legs in their children.

Untoward effects of progestins include nausea, vomiting, diarrhea, edema and weight gain, headache, fatigue, hirsutism, urticaria, ulcerative stomatitis, pruritus vulvae, and a tendency to galactorrhea and vaginal candidal infections. Some are locally irritating. Some have mild androgenic activity that may result in masculinization, especially in the female fetus. Others have a weak estrogenic component of activity. Some have both estrogenic and androgenic actions.

Progestins increase the cutaneous pigmenting effect of estrogens, thus favoring chloasma (melasma) when used in combination. It is probable that they increase the intensity of adverse effects of estrogens, especially headache and hypertension. There may be breakthrough bleeding when continuous high doses are used that suppress menstruation, yet there also may be decreased menstrual flow in many patients.

SUBCLASSES OF PROGESTINS—These agents can be grouped into three general categories, based on their structure: progesterone derivatives, 17α-ethinyl testosterone derivatives, and 19-nortestosterone derivatives. The most important differences between these synthetic agents are pharmacological changes in their activity profile. Table 77-9 provides a summary of several progestins that have been compared using various endpoints and target tissues, some of which may not apply to humans. In general, the 21-carbon compounds that are

Table 77-9. Major Features of Progestins

PROGESTINS	ACTIVITY PROFILE			
	PROGESTIN	ESTROGEN	ANTIESTROGEN	ANDROGEN
Progesterone and derivatives				
Progesterone	++++	0	+	0
Hydroxyprogesterone	+++	+	0	+
Megestrol acetate	+++	0	0	+
17α-Ethinyl testosterone derivatives				
Dimethisterone	+	0	+	0
19-Nortestosterone derivatives				
L-Norgestrel	+++	0	++	+++
Desogestrel	+++	0/+	+++	0/+
Norgestimate	+++	0	+++	0
Ethynodiol diacetate	++	+	+	++
Norethindrone acetate	+	+	+++	++
Norethindrone	+	+	+	++
Norethynodrel	+	+++	0	0

derivatives of progesterone closely reproduce the pharmacological actions of the natural hormone progesterone. The greatest variability in pharmacological actions of progestins is demonstrated by the 19-nortestosterone derivatives that vary in their relative androgenic (masculinizing effects), estrogenic, antiestrogenic, and progestational effects.

Most oral contraceptives contain both an estrogen and a progestogen. Certain progestins may be used alone.

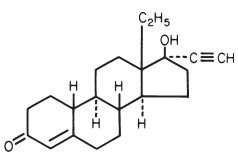
PROGESTERONE ANTAGONISTS

In addition to the widespread use of progestins in oral contraceptive agents, drugs that are classified as progesterone antagonists are receiving considerable attention in reproductive pharmacology. Since progesterone is essential for nidation and maintenance of early pregnancy, blockade of progesterone receptors or interference with progesterone synthesis prevents pregnancy and/or causes abortion early in gestation. Two such agents have been studied in some detail in experimental animals and humans.

Mifepristone (RU486) combines with progesterone receptors and acts as a progesterone antagonist. The drug is an abortifacient and acts as a contraceptive. The exact clinical status of mifepristone as an abortifacient remains to be established, but the potential availability of methods to produce safe, noninvasive abortions raises significant medical, social, and legal questions.

LEVONORGESTREL

(17α)-(−)-18,19-Dinorpregn-4-en-20-yn-3-one, 13-ethyl-17-hydroxy-,



[797-63-7] $C_{21}H_{28}O_2$ (312.45). This compound is the (−)-isomer of norgestrel, but the D-configurational isomer. A former designation as the *d*-enantiomer is incorrect.

Preparation—Refer to *Experiential* 1963; 19:394 for the (±)-form and US Pat 3,413,314 for both enantiomers.

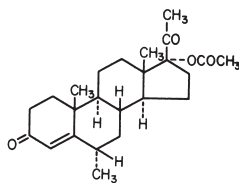
Description—White crystals melting about 240°.

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

Comments—The levo-isomer of norgestrel (see RPS-19, page 1097). It is the active form of norgestrel, hence it is twice as potent on a weight basis as norgestrel. Otherwise, the pharmacological properties of norgestrel and this drug are the same. It is used alone in subdermal implants and in combinations with ethinyl estradiol as an oral contraceptive.

MEDROXYPROGESTERONE ACETATE

(6α)-Pregn-4-ene-3,20-dione, 17-(acetyloxy)-6-methyl-, Cycrin, Depo-Provera, Provera



17-Hydroxy-6α-methylpregn-4-ene-3,20-dione acetate [71-58-9] $C_{24}H_{34}O_4$ (386.53).

Preparation—From 17α-hydroxyprogesterone by first forming the 3,21-bisethylene acetal with ethylene glycol, then treating with peracetic acid to give a mixture of the 5α,6α- and 5β,6β-epoxides. With methyl magnesium iodide the α-epoxide isomer yields the 5α-hydroxy-6β-methyl derivative, which dehydrates and epimerizes with hydrogen chloride in chloroform to the Δ^4-6α-methyl compound, medroxyprogesterone. Acylation with acetic anhydride and *p*-toluenesulfonic acid in acetic acid gives medroxyprogesterone acetate.

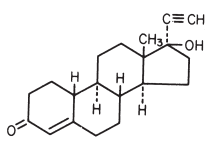
Description—White to off-white, odorless, crystalline powder; melts at about 205°; stable in air.

Solubility—Insoluble in water; freely soluble in chloroform; soluble in acetone or dioxane; sparingly soluble in alcohol or methanol; slightly soluble in ether.

Comments—Actions, uses, and side effects of the progestins in general. Its oral efficacy is an advantage over progesterone. The drug is teratogenic during the first 4 months of pregnancy and hence should not be used for threatened abortion. The long duration of action of intramuscular drug makes it popular in some countries. It is effective as a contraceptive when given IM at the recommended dose to women every 3 months. There is a black box warning stating "prolonged use may increase the loss of significant bone mineral density. Bone loss is greater with increasing duration of use and may not be completely reversible. Depo-Provera Contraceptive should be used as a long-term birth control method (eg, longer than 2 years) only if other birth control methods are inadequate. Gonadotropin secretion is inhibited, which prevents follicular maturation and ovulation and results in endometrial thinning. It has been found to be beneficial in some cases of sleep apnea. Aqueous suspensions administered intramuscularly have a duration of action of weeks to months.

NORETHINDRONE

(17α)-19-Norpregn-4-en-20-yn-3-one, 17-hydroxy-,; Micronor; Nor-Q.D.; Norlutin



[68-22-4] $C_{20}H_{26}O_2$ (298.42).

Preparation—The methyl ether of estrone is reacted with lithium metal in liquid ammonia to reduce ring A to the 4-ene state and the reduced compound is oxidized with chromic acid in aqueous acetic acid to form estr-4-ene-3,17-dione (I). To prevent the 3-keto group from participating in the ensuing ethynylation reaction, I is reacted with ethyl orthoformate in the presence of pyridine hydrochloride to form the 3-ethoxy-3,5-diene compound (II). Acetylene is passed into a solution of II in toluene, previously admixed with a solution of sodium in *tert*-amyl alcohol, to form the 17-ethynyl-17-hydroxy compound. Hydrolysis at the 3-ethoxy linkage by heating with dilute HCl is accompanied by rearrangement of the 3-hydroxy-3,5-diene compound to the 3-oxo-4-ene state. US Pat 2,744,122.

Description—White to creamy white, odorless, crystalline powder; melts about 205°; stable in air.

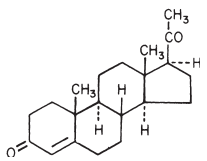
Solubility—Practically insoluble in water; sparingly soluble in alcohol; soluble in chloroform or dioxane; slightly soluble in ether.

Comments—In addition to its progestational actions, it has weak estrogenic actions, owing to biotransformation to an estrogenic metabolite. Among the progestational drugs, it ranks high in ability to postpone menstruation, and it is used for this purpose for both medical and social reasons. In high doses it prevents ovulation by suppressing pituitary gonadotropin output. In lower doses it suppresses the endometrium and decreases the fluidity of the cervical mucus. Consequently, the steroid is an important oral contraceptive. As an oral contraceptive, it is used alone or combined with an estrogen, especially *Mestranol* and *Ethinyl Estradiol;* when used alone, the pregnancy rate is about three times that when used in combination with an estrogen.

In some women with Type V hyperlipoproteinemia, it markedly decreases the concentrations of VLDL and chylomicrons; however, it also lowers HDL and hence is used only when the condition is refractory to other drugs. The drug has weak androgenic properties and may cause deepening of the voice, hirsutism, and acne, and it may cause masculinization of the fetus.

PROGESTERONE

Pregn-4-ene-3,20-dione; Prometrium, Crinone



Progesterone [57-83-0] $C_{21}H_{30}O_2$ (314.47).

Preparation—From animal ovaries, synthesized from stigmasterol, or better from diosgenin (extracted from *Dioscorea mexicana,* a Mexican yam). The latter synthesis involves acetolysis, chromic acid oxidation, cleavage of the ketoester diacetate with boiling acetic acid to 16-dehydropregnenolone acetate, which on catalytic reduction yields pregnenolone acetate. Saponification of the acetate ester to the 3β-alcohol followed by Oppenauer oxidation affords progesterone. Progesterone in pure form was first isolated, from corpus luteum, in 1934 by Butenandt.

Description—White or creamy white, crystalline powder; odorless and stable in air; melts about 128°; a polymorphic modification melts about 121°.

Solubility—Practically insoluble in water; soluble in alcohol, acetone, or dioxane; sparingly soluble in vegetable oils.

Comments—Its plasma half-life is only about 5 min, so it is extremely difficult to achieve effective blood levels with any convenient dosage schedules. It can be given intramuscularly as a suspension or solution in oiland intravaginally. Recently a Micronized progesterone formulation is available for oral administration.

One intrauterine contraceptive device (Progestasert, *Alza*) contains 38 mg of progesterone in silicone oil. The hormone is said to enhance the contraceptive effectiveness of the device by a local effect on the endometrium and by effects on sperm motility, capacitation, and metabolism. Progesterone is released at an average rate of 65 μg daily for 1 year, at which time the device is replaced. The device increases the risk of pelvic inflammation and actinomycotic infections.

HORMONAL CONTRACEPTIVES

MECHANISMS—The various mechanisms whereby hormonal contraceptives can prevent conception are complex. The mechanisms involved vary with the particular agent(s) in a preparation, the dose(s), and whether a cyclic or continuous schedule is used. It is probable that several mechanisms operate simultaneously with some preparations.

SUPPRESSION OF GONADOTROPIC OUTPUT—During the menstrual cycle, there are two periods of elevated FSH secretion, a sharp peak just preceding ovulation and a long wave beginning just before menstruation. In sufficient doses, estrogens can suppress both phases by feedback actions on both the hypothalamus and the anterior hypophysis; FSH and LH output is desynchronized at the early peak, ovulation may be prevented, and the estrogen-progestin priming of the uterus is defective. Estrogens also suppress the hypophyseal output of LH. Progestins also can suppress the LH peak (by an action at the hypothalamus, only), but their action is weak, owing to their antiestrogenic effects, which oppose the suppressant actions of endogenous and exogenous estrogen. Very high doses of progestins are necessary to suppress LH output, unless the progestin is combined with an estrogen. A progestin alone desynchronizes the FSH and LH output, thus sometimes preventing ovulation; long-term use of a combination of progestin and estrogen depresses the output of both gonadotropins and more consistently prevents ovulation.

OVARIAN EFFECTS—Estrogens and progestins decrease the ovarian response to their respective gonadotropins. The result may be a failure to ovulate or, if ovulation does occur, a smaller, hyposecreting corpus luteum, the latter especially when a progestin is in the contraceptive preparation.

TUBAL EFFECTS—In some species progestins and in others estrogens accelerate the ciliary and peristaltic egg transport in the fallopian tubes and increase secretions. Consequently, the ovum arrives in the uterus before the endometrium is prepared for nidation. The tubal effects of these hormones in women may involve a tubal action.

EFFECTS ON THE ENDOMETRIUM—Long-acting injectable progestins in appropriate doses cause endometrial atrophy. Oral preparations vary according to the drug and the dose, some permitting a normal endometrium and others causing regression. In combination with estrogens, progestins effect a decrease in tortuosity and secretion of the endometrial glands with thinning of the endometrium after several cycles of use.

EFFECTS ON THE CERVIX—Estrogens favor a thin and watery secretion, while progestins promote more-viscous cervical secretions that impede the mobility of sperm. In the combination contraceptives, the progestins predominate.

EFFECTS ON CAPACITANCE—Capacitance is the ability of the sperm to penetrate into the ovum. Progestins are thought to decrease capacitance, by an unknown mechanism, probably involving prostaglandins. It is speculated that the low-dose, continuously administered progestin contraceptives are effective by the anticapacitant action.

TYPES OF PREPARATIONS—The first oral contraceptives to be marketed were progestin-estrogen combinations. In some preparations, called *monophasic* combinations, the progestin and estrogen are present in fixed amounts, so that blood levels rise and fall together, in contrast to the levels in the normal menstrual cycle, in which one estrogen peak appears 11 days in advance of the combined estrogen-progesterone peak. With the combined preparations, an artificial menstrual cycle is induced by using the contraceptive for only 20 to 21 days of every 28; if they were to be used continuously instead, no regular menses would occur, but breakthrough bleeding would occur eventually.

The artificial menses caused by the cyclic use of combination contraceptives usually is not normal but oligemic. During the 7 to 8 days in which no hormones are taken, some products provide placebo or iron tablets in lieu of the combination; in these products, the pills are packaged to be taken serially by number. Over the years since combinations appeared on the market, the estrogen content has been decreased considerably in several products because of the possible adverse effects of the estrogen component.

Attempts to develop more nearly physiological regimens have led to the so-called *biphasic* and *triphasic* combinations.

In the former, the progestin dose is increased during the last 11 days of the medication cycle; in the latter, the progestin/estrogen ratio is changed 3 times during the cycle by altering the doses of either progestin or estrogen or both.

Continuous progestin-only oral products do not contain any estrogen and furthermore contain the progestin in amounts smaller (the so-called *mini-pill*) than those used in combination products. The dose is small enough not to prevent ovulation and menstruation in most users, yet to act sufficiently on the uterus, cervix, or capacitance to prevent conception. However, the efficacy is lower than that of combination or sequential products. A progesterone-containing IUD and continuous- progestin injectable products, repository forms of progestins, also are available.

Emergencyl have been used, to prevent pregnancy in girls or women who are caught without contraceptive preparation; these preparations, however, are not for routine use. They are effective if taken within 72 hr after coitus.

EFFICACY AND FAILURES—The efficacy of an oral contraceptive depends on the type and the dose of hormonal ingredients. The combined type, which contains relatively high doses of estrogens, is nearly 100% effective when taken correctly; failures probably can be attributed to the negligence of the user. There appears to be a finite, though small, probability of ovulation and hence of later conception if a single pill is missed, because of the rebound oversecretion of the gonadotropins. If one pill is skipped, the user should take it immediately upon discovery of the skip and take the rest on their schedule; if two or more are missed, she should additionally use other methods of contraception until her next cycle. Lowering the estrogen content in combination preparations decreases the side effects but increases the risk of pregnancy. The long-acting combinations have a relatively high failure rate. The continuous low-dose oral progestin products have a failure rate several times that of combination products.

ADVERSE EFFECTS—The adverse effects vary in incidence and severity according to the type of preparation. Most side effects are from the estrogens in combination contraceptives, but progestins also cause adverse effects. The estrogen-progestin ratio is important to the type and incidence of side effects. A summary of the dose-related side effects of oral contraceptives is shown in Table 77-10.

Oligomenorrhea, or low menstural flow, occurs in 20% to 80% of users of combination and some continuous progestin contraceptives, and amenorrhea occurs in some. The greatest offenders are the 19-nortestosterone derivatives. Spotting and breakthrough bleeding that is unpredictable or irregular in onset may also occur; sometimes such bleeding is more voluminous than in regular menstruation.

Other side effects can occur such as tiredness, weakness, malaise, changes in libido, dizziness, and nonspecific headaches. An increase in the incidence of migraine headaches is especially notable in some patients; the estrogen component appears to be responsible. Weight gain occurs with some but not all preparations; salt and water retention is caused mostly by estrogen components, whereas anabolic effects are caused by higher doses of the 19-nortestosterone-derived progestins (not the 17α-hydroxyprogesterones).

Chloasma occurs in about 4% of users of combination contraceptives during the first year and 37% by the fifth year; it is attributable to the combined action of the two active components. Milk flow in lactating women may be decreased by an average of 50% when combination preparations are used. Estrogen-containing contraceptives also cause an uncommon choreiform movement.

Serious side effects of oral contraceptives are multiple. A reversible hypertension is observed in approximately 15% of users of estrogen-containing contraceptives. The prevalence of hypertension increases with duration of use and is greater in older women. Incidence of thromboembolic disorders, including stroke and myocardial infarction, is higher in women using oral contraceptives; the relative risk may be several times greater in users than in control populations. Further, the risk increases sharply in women over 35 years who are smokers.

Contraceptive use also has been associated with increased evidence of benign liver tumors. The relative risk of liver tumors appears to rise with duration of use of the drugs. In one study, mestranol-containing preparations were implicated almost exclusively, thus indicating that the type of synthetic estrogen might be important. The risk of gallbladder disease is increased twofold in contraceptive users. Fetal abnormalities may result if the mother continues to take the pill after becoming pregnant. Neuroocular lesions have been associated with use of oral contraceptives. Some other possible complications of contraceptive use include breast cancer (pill use actually protects against the development of benign breast lesions) and cancer of the uterus, cervix, and vagina. Any of the other side effects of estrogens or progestins given above also may be caused by these drugs.

Irregular bleeding is initially a problem for some women with depot progestin administration. However, after 1 year most women are completely amenorrheic. Patients taking oral contraceptives must be informed of their effectiveness and risks.

Table 77-10. Summary of Dose-Related Side Effects of Oral Contraceptives

Estrogen excess	*Progestin excess*
Nausea	Increased appetite
Cervicomyxorrhea	Weight gain
Melasma	Tiredness, fatigue
Migraine headache	Hypomenorrhea
Hypertension	Acne, oily skin
Breast tenderness	Hair loss
Edema	Depression
Estrogen deficiency	*Progestin deficiency*
Early or midcycle breakthrough bleeding	Late breakthrough bleeding
Increased spotting	Amenorrhea
Hypomenorrhea	Hypermenorrhea

MALE CONTRACEPTIVES

Since 1980 there has been considerable effort to develop male contraceptives. In China, gossypol, a polyphenol-aldehyde isolated from cottonseed oil, has been under investigation since the mid-1950s. It is an inhibitor of human sperm acrosin and an LDD isoenzyme known as LDH-C. It also interferes with epididymal function and elicits structural alterations. A clinical trial in over 4000 healthy men found gossypol to be 99.9% effective as a contraceptive. However, it causes hypokalemia and other untoward effects and has a narrow margin of safety. Its effects are irreversible in 10 to 20% of users. Investigations of related compounds are in progress.

The inhibitory effect of testosterone and other androgens on hypothalamic release factor signalling and anterior pituitary secretion of gonadotropins results in decreased spermatogenesis, and aspermia may result from prolonged, vigorous use. Because of the adverse effects, however, (see the introduction under *The Testicular Hormones*), this approach has limited promise. Low-dose androgen-progestin combinations, which suppress anterior pituitary release of LH/FSH with less intense androgenic side effects, are being investigated also.

A more encouraging approach is the use of analogs of GnRH, such as goserelin, nafarelin, buserelin, and leuprolide, which cause a down-regulation of pituitary release hormone receptors during continuous administration. Both steroidogen-

esis and spermatogenesis are diminished reversibly. Decreased libido occurs, so to be acceptable to many men, use must be supplemented with androgens. The Sertoli cell peptide, inhibin, and related proteins, which inhibit the anterior pituitary release of FSH, are under active investigation but are not ready for clinical trials. They, too, probably will decrease libido and hence may not be acceptable to a large percentage of potential users.

Perhaps the most promising but nascent developments are vaccines against one or more spermatic proteins. The sperm lactic dehydrogenase, LDH-C4, and possibly various protamines are presently investigational targets for monoclonal and other antibodies. The first vaccines for human use are likely to be against LDH-C4. The effects of vaccines, are not likely to be readily reversible, although some memory immune cells have relatively short lifetimes.

THE TESTICULAR HORMONE (TESTOSTERONE)

The testis has a dual function, to produce the germ cell (the sperm) and supply the male hormone (testosterone). Two clearly defined groups of cells are found in the testes; the one group in the seminiferous tubules produces the sperm, while the other, clustered in between the tubules, consists of interstitial cells (Leydig cells). The spermatogenic tissue produces an exocrine secretion and probably also androgens needed for spermatogenesis.

The interstitial cells are the seat of production of a steroid hormone, testosterone. However, it is mainly the metabolite dihydrotestosterone that stimulates and maintains the secondary sex organs; these are the penis, prostate gland, seminal vesicles, vas deferens, and scrotum. It also exerts sustaining effects on the spermatogenic cells, and it stimulates the development of bone, muscle, nerves, skin and hair growth, and emotional responses to produce the characteristic adult masculine traits. Testosterone, itself, regulates the anterior pituitary release of LH. This group of combined actions of this hormone is termed androgenic actions. Testosterone also antagonizes a number of the effects of estrogens and sometimes is employed clinically for this purpose. This is especially important in the suppression of metastatic carcinoma of the breast. Since it promotes development of the clitoris, which is an anatomical homolog of the penis, androgens may increase the libido of women.

The naturally occurring androgens (androsterone and testosterone) are derivatives of androstane. Testosterone and its esters (testosterone propionate) and derivatives (methyltestosterone) are the most commonly used androgenic steroids. In addition to their androgenic properties, however, these compounds exert widespread anabolic effects and promote the retention of calcium. In attempts to dissociate the virilizing and anabolic properties (for use in women) a number of compounds with high anabolic:androgenic ratios have been prepared. However, it has not been possible yet to abolish completely the androgenic effects. A summary of the comparative actions of androgens and anabolic agents is shown in Table 77-11.

USES—For replacement therapy in men who have climacteric symptoms or in men or youths with hypogonadism (eunuchism, Klinefelter's syndrome). They have been employed to facilitate development of adult masculine characteristics when the adolescent process has been delayed. In cryptorchidism they may be used adjunctively with gonadotropins. They also are very useful in therapy of patients with hypopituitarism and with Addison's disease. They are of value in the treatment of frigidity and occasionally in impotence. The use of androgens for relief of impotence not associated with evidence of testicular underactivity (psychic causes) is known to be futile in most cases.

Table 77-11. Major Features of Androgens and Anabolic Steroids

ANDROGEN/ ANABOLIC ACTIVITY		COMMENTS
Androgens		
Testosterone	1:1	Given IM/transdermally; inactive orally
Methyltestosterone	1:1	Orally active; short half-life (2.5 hr)
Fluoxymesterone	1:2	Orally active; long half-life (10 hr)
Danazol	—	Weak androgen; orally active
Anabolic steroids		
Oxymetholone	1:3	Orally active
Oxandrolone	1:3–1:13	Orally active
Nandrolone phenpropionate	1:3–1:6	Given IM
Stanozolol	1:3–1:6	Orally active

Low doses of androgens have been used in pituitary dwarfism to accelerate growth, but care must be exercised not to arrest growth by epiphyseal closure. They also are used sometimes to promote hematopoiesis. In doses that are 10 to 200 times larger than normal, anabolic steroids increase athletic performance and aggressiveness. Their use has been condemned by the American College of Sports Medicine. Because of their potential for some serious adverse effects and their potential abuse these drugs are highly publicized for their inherent risks. Female performance is improved, but at the expense of virilization and acne vulgaris.

With estrogens, androgen therapy may be efficacious in the treatment of the menopause. The anabolic effects are possibly of some benefit in the postclimacteric person, and they may retard osteoporosis, although many authorities do not believe that any lasting benefit is achieved. They also help relieve vasomotor instability in postmenopausal women in whom estrogens alone do not relieve symptoms. In functional dysmenorrhea androgens may give relief through an antiestrogenic action, although they also are combined often with estrogens to treat this disorder. They may be used to treat endometriosis. They also may be used in the treatment of postpartum breast engorgement and for suppression of lactation.

Testosterone and related compounds find widespread application in the palliative treatment of cancer of the breast in women. Its use in men with prostatic cancer, however, is contraindicated.

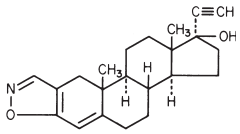
SIDE EFFECTS—Androgens cause hirsutism, deepening or hoarseness of the voice, precocious puberty and epiphyseal closure in immature males, increased libido (in both male and female), priapism, oligospermia and testicular atrophy (from negative feedback on LH and FSH production), enlargement of the clitoris in the female, flushing, decreased ejaculatory volume and sperm population, gynecomastia (from conversion to estrogens), hypersensitivity, acne, weight gain, edema, and hypercalcemia. Prolonged use increases aggressivenessWhile paranoia-like and other psychotic behavior has been reported. Biliary stasis and jaundice occur. There have been a few cases reported of hepatoma following long-term therapy. The 17α-methylated androgens are more prone to disturb liver function (peliosis hepatis, cholestasis, and hepatic failure) than are the nonsubstituted drugs. Blood lipid changes associated with increased risk of atherosclerosis are seen, including decreased HDL and sometimes increased LDL. Hypercalcemia requires discontinuation of therapy, and edema requires diuretic therapy.

Except in the treatment of breast cancer, a reduction in dosage is indicated upon virilization in women. The adminis-

tration of androgens to patients on anticoagulant therapy may increase the effect of anticoagulants and, thus, may require an adjustment of the dose of the latter. Likewise, dosage of insulin or oral hypoglycemic agents may require adjustment when anabolic androgens are administered to diabetic patients.

DANAZOL

(17α)-Pregna-2,4-dien-20-yno[2,3-*d*]isoxazol-17-ol, Chronogyn; Danocrine



[17230-88-5] $C_{22}H_{27}NO_2$ (337.46).

Preparation—Danazol is a derivative of ethisterone (17α-ethynyltestosterone) in which an isoxazole ring is fused to the 2,3-position of the steroid nucleus. Methods for preparing such steroidal heterocycles have been described by Manson et al. *J Med Chem* 1963; 6:1; also in US Pat 3,135,743.

Description—Pale yellow, crystalline powder; melts about 225°.

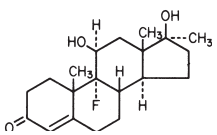
Solubility—Practically insoluble in water; sparingly soluble in alcohol.

Comments—An *impeded* androgen (ie, weak androgenic activity). It binds to androgen, glucocorticoid, and progesterone receptors, but it evokes no glucocorticoid, progestational, or estrogenic effects except that it suppresses the release of LH and FSH, even in women. It suppresses ovarian steroidogenesis, induces the hepatic metabolism of progesterone, and binds to α-macroglobulin, causing partial displacement of other steroids. It is used in the treatment of endometriosis in patients who do not respond to or cannot tolerate other drug therapy and in the management of fibrocystic breast disease and periareolar abscesses. It may prevent attacks of hereditary angioedema. It increases platelet populations in idiopathic and immune thrombocytopenias. However, it also can cause thrombocytopenia. It relieves migraine in some persons.

Androgenic side effects include deepening of the voice in women, acne, edema, mild hirsutism, decrease in breast size, oiliness of the skin and hair, weight gain, and clitoral hypertrophy. Hypoestrogenic manifestations include amenorrhea; vasomotor instability; vaginitis with itching, burning, and vaginal bleeding; and emotional lability. It also may cause muscle cramps, asthenia, rhabdomyolysis, testicular atrophy, and rare hematuria. It has an adverse effect on plasma lipids. In doses over 400 mg a day, it may cause hepatic injury, including carcinoma. It has been reported to lower serum levothyroxine levels.

FLUOXYMESTERONE

(11β,17β)-Androst-4-en-3-one, 9-fluoro-11,7-dihydroxy-17-methyl-, Halotestin



[76-43-7] $C_{20}H_{29}FO_3$ (336.45).

Preparation—From 17-methyltestosterone first by introduction of a hydroxyl group at position 11 through oxidation with a microorganism (such as *Pestalotia* or *Aspergillus*), followed by dehydration, epoxidation, and treatment with HF, as for *Betamethasone.*.

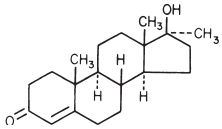
Description—White or practically white, odorless, crystalline powder; melts about 240° with some decomposition.

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

Comments—The same actions, uses, and limitations as the androgens (page 1390).It is approximately five times more potent than testosterone and is orally effective. Nevertheless, it is less effective than testosterone in hypogonadism and is seldom used to initiate treatment but rather for maintenance. In addition to the side effects of testosterone, this drug may cause occasional cholestatic jaundice, gynecomastia, oligospermia after prolonged use, and hypersensitivity. It sometimes is combined with an estrogen for treatment of postmenopausal osteoporosis. The half-life is about 10 hr.

METHYLTESTOSTERONE

(17β)-Androst-4-en-3-one, 17-hydroxy-17-methyl-, Android; Methitest



[58-18-4] $C_{20}H_{30}O_2$ (302.46).

Preparation—From dehydroepiandrosterone (prepared from cholesterol) by subjecting it to a Grignard reaction with CH_3MgI followed by an Oppenauer oxidation. The first reaction creates the tertiary carbinol structure at C_{17}, while the second oxidizes the secondary carbinol group at position 3 to carbonyl and causes a rearrangement of the double bond from the 5,6- to the 4,5-position.

Description—White or creamy white crystals or a crystalline powder; odorless; stable in air, but slightly hygroscopic; affected by light; melts about 165°

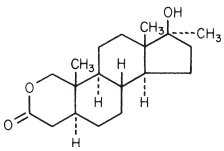
Solubility—Practically insoluble in water; soluble in alcohol, methanol, ether, or other organic solvents; sparingly soluble in vegetable oils.

Comments—The same actions, uses, and limitations as the androgens. It is effective orally. In addition to the side effects caused by testosterone, it may cause oligospermia, hypersensitivity with dermatological manifestations, and a rare type of cholestatic jaundice.

It is metabolized rapidly by the liver and undergoes first-pass metabolism. By the buccal route, potency is twice that by the oral route. The half-life is about 2.5 hr.

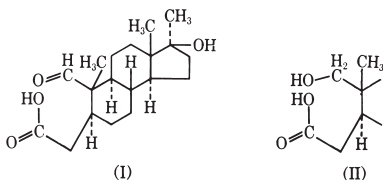
OXANDROLONE

(5α,17β)-2-Oxaandrostan-3-one, 17-hydroxy-17-methyl-, Oxandrin



17β-Hydroxy-17-methyl-2-oxa-5α-androstan-3-one [53-39-4] $C_{19}H_{30}O_3$ (306.44).

Preparation—Methyldihydrotesterone is converted into the corresponding 1,2-dehydro compound by bromination followed by dehydrobromination. Ring A is then ruptured through ozonization and subsequent hydrolysis to yield the aldehyde-acid (I). Reduction of the formyl group in I yields the expected hydroxy acid implied in the partial structure (II) which is lactonized to oxandrolone.



(I) (II)

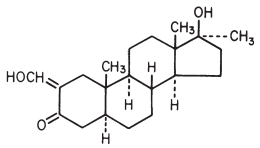
Description—White, odorless, crystalline powder; stable in air but darkens when exposed to light; melts about 225°.

Solubility—1 g in 5200 mL water, 57 mL alcohol, <5 mL chloroform, 860 mL ether, or 69 mL acetone.

Comments—Although strictly speaking not a steroid, its configuration is that of a 17-methyl androgenic steroid. Its anabolic actions are strong relative to its androgenic actions. Consequently, it is used in the treatment of chronic wasting diseases, conditions in which negative nitrogen balance exists. The drug may cause virilization in children or women, especially if the recommended doses are exceeded. The potential toxicity is that of the androgens, but the incidence and severity are less than with testosterone. It may affect liver function tests adversely, and the possibility of cholestatic jaundice must be kept in mind. Leukopenia also has been reported. It is contraindicated in prostatic cancer, breast cancer in some women, pregnancy, nephrosis, and premature and newborn infants. It is also available as an IND for treatment of constitutional delay of growth and puberty.

OXYMETHOLONE

(5α,17β)-Androstan-3-one, 17-hydroxy-2-(hydroxymethylene)-17-methyl-, Anadrol



[434-07-1] $C_{21}H_{32}O_3$ (332.48).

Preparation—17β-Hydroxy-17-methylandrostan-3-one (17-methyldihydrotestosterone) is reacted with ethyl formate and sodium hydroxide by stirring the mixture under nitrogen for several hours, thus forming the 2-(sodoxymethylene) derivative. Treatment of the washed sodium compound with cold dilute hydrochloric acid liberates the oxymetholone, which may be purified by recrystallization from ethyl acetate. *J Am Chem Soc* 1959; 81:427.

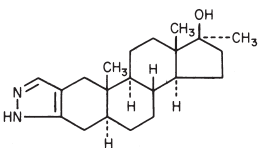
Description—White to creamy white crystals or crystalline powder; odorless and stable in air; tautomeric in nature and can exist as either tautomer or as a mixture of both, the exact composition depending on solvent and rate of crystallization; melts about 175°.

Solubility—1 g in >10,000 mL water, 40 mL alcohol, 5 mL chloroform, 82 mL ether, or 14 mL dioxane.

Comments—An androgenic steroid with relatively greater anabolic activity than androgenic activity. Consequently, it is employed mainly to promote nitrogen anabolism and weight gain in cachexia and debilitating diseases and after serious infections, burns, trauma, or surgery. It may be used for its erythropoietic effects in the treatment of hypoplastic and aplastic anemias. Side effects include nausea, vomiting, anorexia, burning of the tongue, increased or decreased libido, acne, suppression of gonadotropin secretion, virilization (especially in women and children), gynecomastia in males, oligospermia, sodium retention and edema, abnormal liver function tests, cholestatic jaundice, decrease in several clotting factors, and hemorrhagic diathesis in the presence of anticoagulants.

STANOZOLOL

(5α,17β)-2′*H*-Androst-2-enol[3,2-*c*]pyrazol-17-ol, 17-methyl-, Winstrol



[10418-03-8] $C_{21}H_{32}N_2O$ (328.50).

Preparation—17-Methyl-5α-androstan-17β-ol-3-one is converted into its 2-formyl derivative, which is then condensed with hydrazine hydrate. US Pat 3,030,358.

Description—Nearly colorless, odorless, crystalline powder; exists in two forms: *needles,* melting about 155°, and *prisms,* melting about 235°.

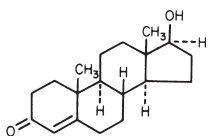
Solubility—1 g in >1000 mL water, 41 mL alcohol, 74 mL chloroform, or 370 mL ether.

Comments—An androgen with relatively strong anabolic and weak androgenic activity. Consequently, it is employed mainly to promote nitrogen anabolism and weight gain in cachexia and debilitating diseases and after serious infections, burns, trauma, or surgery. It may have an erythropoietic effect in hypoplastic and aplastic anemias. It also is used in the prophylaxis of hereditary angioedema, which is now the only approved use.

Side effects include increased or decreased libido, virilization (especially in women and children), sodium retention and edema, hypercalcemia, insomnia, restlessness, chills, hemorrhage in patients on anticoagulants, acne, and hepatic dysfunction. Potentially, any of the side effects of testosterone may occur. However, these rarely occur during the usual 5-day course.

TESTOSTERONE

(17β)-Androst-4-en-3-one, 17-hydroxy-,



17β-Hydroxyandrost-4-en-3-one [58-22-0] $C_{19}H_{28}O_2$ (288.43).

Preparation—First isolated in crystalline form by Laquer in 1935 who obtained it from animal testes. Although small amounts of testosterone may be extracted from testicular material, the synthetic commercial supply is derived from cholesterol. The key intermediate in the synthesis is dehydroepiandrosterone, which can be treated further, by either chemical or microbiological processes, to yield testosterone. US Pat 2,236,574.

Description—White or slightly creamy white crystals or crystalline powder; odorless; stable in air; melts about 155°.

Solubility—Practically insoluble in water; 1 g in about 6 mL of dehydrated alcohol, 1 mL chloroform, or 100 mL ether; soluble in vegetable oils.

Comments—See the introduction to this section, page. It is not effective orally because it is destroyed in the liver on absorption. Its plasma half-life is 10 to 20 min. However, two different transdermal preparations are now available to use as replacement therapy for primary or secondary hypogonadism in men. One is placed on scrotal skin *(Testoderm)* and provides a maximum serum concentration within 2 to 4 hr and returns to baseline within 2 hr after removal. Daily applications of transdermal systems are applied at 10 PM and left in place for 22 to 24 hr. The nonscrotal transdermal preparation *(Androderm)* is applied at two sites (on back, abdomen, upper arms, or thighs) and should never be applied to the scrotum because it is a higher-dose preparation. Side effects from transdermal preparations include local irritation at sites of application. It is also available as a topical gel and implantable pellets.

ANDROGEN HORMONE INHIBITORS AND ANTIANDROGENS

Drugs may be used to suppress the effects of androgens by inhibition of gonadotropin production or by inhibition of enzymes involved in the production of androgen or their precursors. Analogs of the hypothalamic gonadotropin-releasing hormone, GnRH, can be given in a continuous release preparation to inhibit pituitary LH and suppress production of testosterone in the testis. Although testosterone levels fall after a month of therapy with GnRH analogs, an initial increase in testosterone occurs. Inhibitors of the 17-hydroxylation of progesterone or pregnenolone can lead to decreased levels of androgen precursors. More-specific inhibition of androgenic effects can achieved by inhibition of the 5α-reductase enzyme that converts testosterone to dihydrotestosterone, the active androgenic hormone in specific tissues such as prostate, seminal vesicles, epididymis, and skin. Other drugs are classified as antiandrogens if they can specifically block testosterone receptors. The most important drugs currently available as androgen hormone inhibitors and antiandrogens are shown in Table 77-12.

The subcutaneous injection of leuprolide or other GnRH analogs (goserelin, nafarelin, and buserelin) has been used successfully in the treatment of prostatic carcinoma. The combination of a GnRH analog with finasteride, an inhibitor of 5α-reductase, can inhibit the initial stimulation of testosterone

Table 77-12. Features of Androgen Hormone Inhibitors and Antiandrogens

	COMMENTS
Androgen Hormone Inhibitor	
Finasteride	Inhibits 5α-reductase in prostate
Leuprolide acetate	GnRH agonist injected SC; inhibits gonadotropin secretion resulting in decreased gonadal testosterone production
Goserelin	GnRH agonist similar to leuprolide in action
Antiandrogens	
Cyproterone acetate	Antagonist at androgen receptors
Flutamide	Competitive antagonist at androgen receptors

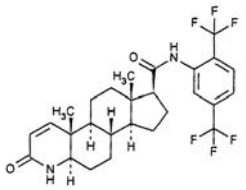
production and provide a more effective inhibition of androgenic activity. Finasteride is used in the treatment of benign prostate hypertrophy and male pattern baldness.

The antiandrogens or testosterone receptor antagonists are used in the treatment of conditions associated with androgen excess such as hirsutism, excessive libido, and prostate cancer. Flutamide is a potent nonsteroidal antiandrogen that competitively blocks nuclear androgen receptors in prostate tissue. It is used in the treatment of prostatic carcinoma.

Other drugs are under development in the area of androgen suppression and antagonism or receptors that should improve the efficacy and reduce the side effects of these agents. Common adverse effects of these agents in men are gynecomastia, decreased libido, and infertility.

DUTASTERIDE

Androst-1-ene-17-carboxamide, (5α,17β)-*N*-[2,5-bis(trifluoromethyl)phenyl]-3-oxo-4-aza-, Avodart



[164656-23-9] $C_{27}H_{30}F_6N_2O_2$ (528.54).

Preparation—By a multi-step synthesis from diosgenin. See *J Med Chem* 1995; 38:3189, WO95 07927 and *Ann Rep Sankyo Res Lab* 2000; 52:1-14.

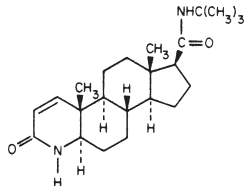
Description—White to pale yellow crystals melting about 245°.

Solubility—(mg/mL) ethanol (44); methanol (64); PEG 400 (3); insoluble in water.

Comments—It is indicated for the treatment of symptomatic benign prostatic hyperplasia in men with an enlarged prostate to reduce symptoms.

FINASTERIDE

4-Azaandrost-1-ene-17-carboxamide, (5α-17β)-*N*-(1,1-dimethyl-ethyl)-3-oxo-, Proscar



[98319-26-7] $C_{23}H_{36}N_2O_2$ (372.55).

Preparation—*J Am Chem Soc* 1988; 110:3319.

Description—White to off-white crystals; melts about 257°.

Solubility—Very slightly soluble in water or dilute acid or base; freely soluble in alcohol or chloroform.

Comments—An androgen hormone inhibitor that acts by competitive inhibition of steroid 5-reductase, which converts testosterone to potent 5-dihydrotestosterone (DHT) in the prostate gland, liver, and skin. DHT induces its effects by binding to androgen receptors in cell nuclei of organs containing this enzyme. It is used to treat symptomatic benign prostatic hyperplasia. A lower-dose preparation is used to treat male pattern baldness. The drug generally is tolerated well, with reports of impotence (3.7%), decreased libido (3.3%), and decreased volume of ejaculation (2.8%).

FLUTAMIDE

For the full monograph, see page 1573.

Comments—An orally active and potent competitive inhibitor of nuclear androgen receptors in target tissues such as the prostate, seminal vesicles, and adrenal cortex. It is used in the treatment of prostatic cancer that is clinically localized and is given in combination with a GnRH analog (eg, goserelin and leuprolide acetate). Its pharmacological activity is substantially due to the principal metabolite, 2-hydroxyflutamide. Approximately half of the drug is eliminated in the urine within 72 hr, and the hydroxylated metabolite has a half-life that varies with the dose from 6 to 22 hr. A high incidence of gynecomastia and some GI discomfort are observed. Some cases of severe hepatotoxicity were reported. Periodic liver function tests should be performed.

CHAPTER 78

General Anesthetics

Michael R Borenstein, PhD

General anesthetics are a remarkably diverse group of chemical agents with the common property of inducing a profound but reversible central nervous system (CNS) depression resulting in loss of consciousness. The mechanism of action of these drugs has not been fully elucidated and may represent a number of non-specific pharmacologic processes as diverse as their structures. No one particular cellular target can explain the myriad of brain functions affected by, nor has any pharmacologic antagonist to general anesthetics been discovered. Thus, it is safe to assume that a number of physicochemical events are involved in the production of general anesthesia. Included among these may be effects at cell membranes and proteins, as well as enzyme and receptor systems.

The ideal anesthetic agent should possess the following characteristics: rapid and pleasant induction and withdrawal from anesthesia, skeletal muscle relaxation, analgesia, high potency, a large therapeutic index, non-flammability, and chemically inertness with regard to anesthetic delivery devices. In practice it is common to employ a variety of drugs since no one agent meets all these criteria.

The route of administration of general anesthetics is via inhalation or intravenous injection. This chapter reviews the volatile compounds in clinical use, as well as a number of parenterally administered agents that produce loss of consciousness and some degree of analgesia or muscle relaxation. There are a number of drugs discussed elsewhere that often play an adjunct role in general anesthesia these include opioids, muscle relaxants, and benzodiazepines.

A general note of caution with regard to general anesthetic administration and the recent increased use of natural products has been issued by the American Society of Anesthesiologists. It is recommend that patients stop taking herbal medications at least 2 to 3 weeks before surgery in order to decrease the risk of adverse effects resulting from an enhancement or prolongation of anesthetic effects. This is particularly important in those patients using St. John's Wort, *Hypericum perforatum*.

INHALATION ANESTHETICS

In 1846 William Morton reported the first use of diethyl ether as a volatile inhaled agent to produce surgical anesthesia. This was followed by the introduction of chloroform, nitrous oxide, and the halogenated hydrocarbons in the 1950s. Although neither diethyl ether or chloroform are in widespread clinical use today, they served as the structural templates for synthetic manipulations that have produced today's potent congeners. The volatile anesthetics in common clinical use are either halogen-substituted ethers or extensively halogenated alkanes. In addition, there are inorganic gases with relatively weak anesthetic activity that must be administered in combination with opiates, muscle relaxants, or other agents in order to produce acceptable surgical anesthesia.

Inhalation anesthetics are produced from volatile liquids or gases. Thus, they require the use of specialized delivery systems employing various combinations of vaporizers, absorbers, and flowmeters to deliver a constant and precisely controlled amount of drug to the respiratory system of the patient. Rapid metabolism and pulmonary excretion aid in the reversal of the anesthetic state. There are several physicochemical parameters that describe the efficacy of volatile anesthetics. The minimal alveolar concentration (MAC) is a measure of anesthetic potency as reflected in the concentration of anesthetic agent in the alveoli required to produce immobility in 50% of adult patients subjected to a noxious stimulus, typically a surgical incision. As the concentration of anesthetic in the lungs increases, a concomitant rise in blood concentration will follow. The blood solubility of anesthetics is reflected in the blood/gas partition coefficient and determines how rapidly surgical anesthesia is attained. MAC and partition coefficient values are inversely related to potency and time to onset of anesthesia, respectively.

Modern inhalation anesthetics are conveniently divided into potent carbon-based drugs and relatively weak anesthetics such as nitrous oxide and the still experimental xenon. The difference lies in the fact that the potent inhalation agents provide the entire anesthetic requirement in the presence of an adequate amount of oxygen. The inorganic anesthetics must be administered in an appropriate combination with opioids, muscle relaxants, or hypnotic adjuvants.

HALOGENATED ALKANES

HALOTHANE

Ethane, 2-bromo-2-chloro-1,1,1-trifluoro-, Fluothane

2-Bromo-2-chloro-1,1,1-trifluoroethane [151-67-7] $C_2HBrClF_3$ (197.38); contains 0.008% to 0.012% thymol, by weight, as a stabilizer.

Preparation—Commercially available 2-chloro-1,1,1-trifluoroethane is subjected to direct bromination, and halothane is isolated from the reaction product by fractional distillation.

Description—Colorless, mobile, nonflammable, heavy liquid; characteristic odor resembling that of chloroform; sweet taste and produces a burning sensation; distills between 49° and 51°; specific gravity between 1.872 and 1.877 at 20°.

Solubility—Slightly soluble in water; miscible with alcohol, chloroform, ether, or fixed oils.

Comments—Introduced into clinical practice in 1956, it is the only volatile anesthetic to contain a bromine atom that may contribute to its potency. It has an intermediate solubility (blood/gas partition coefficient, 2.5) and low MAC (0.7%). Halothane causes dose-dependent vasodilation, myocardial depression, and decreases in sympathetic tone. Like the other potent inhalation anesthetics, halothane provides muscle relaxation and in addition has a low incidence of nausea and vomiting.

Halothane is subject to oxidative degradation to hydrochloric and hydrobromic acid, as well as phosgene. For this reason it is stored in amber-colored bottles with the preservative thymol. It is reactive with most metals except titanium, nickel, or chromium. As a myocardial depressant, halothane decreases cardiac output to 80% of normal at 1 MAC and 70% of normal at 2 MAC. The drug also sensitizes the myocardium to the dysrhythmic actions of epinephrine more than the ether-based anesthetics. This effect is accentuated by hypercarbia. Like all other potent inhalation anesthetics, halothane decreases the normal ventilatory responses to hypoventilation and hypoxemia.

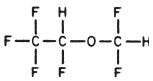
A relatively large amount of the administered dose of halothane is metabolized. This has been associated with its hepatotoxicity and led to the development of the newer ether anesthetics (see below).

HALOGENATED ETHERS

Fluorinated derivatives of diethyl ether were developed in an attempt to improve upon the adverse effect profile of halothane. As a class, they are nonflammable, stable, and nonarrhythmogenic. They differ in their degree of metabolism and effects on respiration, circulation, or the CNS.

DESFLURANE

Ethane, (±)-2-(difluoromethoxy)-1,1,2,2-tetrafluoro-, Suprane



[57041-67-5] $C_3H_2F_6O$ (168.04)

Description—Extremely volatile; nonflammable and not explosive at clinical concentrations.

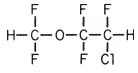
Solubility—Insoluble in water; soluble in organic solvents.

Comments—Approved for clinical use in the US in 1993. It is minimally metabolized (0.02%) and has a low solubility (blood/gas partition coefficient, 0.42), leading to a rapid onset and recovery and extensive use in the outpatient surgical procedure environment. Its low boiling point necessitated the development of a heated vaporizer to ensure consistent drug delivery. Desflurane is less potent (MAC, 6.0%) than the other ethers.

Dose-related decreases in blood pressure and cardiac output are similar to isoflurane. Increases in heart rate and blood pressure have been noted upon introduction of the agent because of stimulation of the sympathetic nervous system following the production of carbon monoxide. These effects may be minimized by the use of new carbon monoxide absorbents. Desflurane is the most pungent of the inhalation anesthetics, causing breath-holding and coughing, and is not recommended for inhalation induction of general anesthesia in children. Desflurane either increases or does not change intracranial pressure (ICP) in patients with space-occupying tumors. It causes cerebral vasodilation and dose-dependent decreases in the cerebral metabolic rate of oxygen consumption ($CMRO_2$) similar to isoflurane and sevoflurane.

ENFLURANE

Ethane, 2-chloro-1-(difluoromethoxy)-1,1,2-trifluoro-, Ethrane



2-Chloro-1,1,2-trifluoroethyl difluoromethyl ether [13838-16-9] $C_3H_2ClF_5O$ (184.49).

Preparation—May be synthesized by a series of reactions starting with trifluorochloroethylene. US Pats 3,469,011 and 3,527,813.

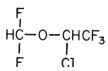
Description—Clear, colorless, volatile liquid; pleasant hydrocarbon like odor; boils at 56.6°; nonflammable.

Solubility—Soluble in water to the extent of 0.275%, and water-soluble in enflurane to the extent of 0.13%; miscible with organic solvents.

Comments—Introduced in 1973, it has intermediate blood solubility (blood/gas partition coefficient, 1.9; MAC, 1.7) and excellent muscle relaxant properties. Approximately 2–10% is hepatically metabolized to produce fluoride but at low enough levels to preclude nephrotoxicity. An increase in metabolism is seen in the obese patient and those taking isoniazid or other hydrazine compounds. Enflurane produces spiking discharges on the electroencephalogram (EEG) at high doses. Its use is avoided in epileptics, patients at risk for nephrotoxicity, and those with a history of malignant hyperthermia.

ISOFLURANE

Ethane, 2-chloro-2-(difluoromethoxy)-1,1,1-trifluor-, Forane, AErrane [Veterinary]



1-Chloro-2,2,2-trifluoroethyl difluoromethyl ether [26675-46-7] $C_3H_2ClF_5O$ (184.49).

Preparation—Trifluoroethanol is methylated with dimethyl sulfate to form the methyl ether, which is then chlorinated to the dichloromethyl ether, $CF_3CHClOCHCl_2$. This latter compound, on treatment with $HF/SbCl_5$ forms the product. See *J Med Chem* 1971; 14:517.

Description—Low-boiling liquid (48.5°) with a slight odor; nonflammable.

Solubility—Miscible with most organic solvents including fats or oils; practically insoluble in water.

Comments—Similar to its isomer enflurane it was approved for use in the US in 1979. Its has a good safety record, acceptable physical properties (blood/gas partition coefficient, 1.5; MAC, 1.15), and a low rate of metabolism (0.2%). Its irritating pungent odor requires the use of intravenous induction agents. It can cause uterine relaxation and is contraindicated in patients with a history of malignant hyperthermia.

SEVOFLURANE

Propane, 1,1,1,3,3,3-hexafluoro-2-(fluoromethoxy)-, Ultane

[28523-86-6] $C_4H_3F_7O$ (200.06)

Description—Nonflammable, highly volatile.

Solubility—Insoluble in water.

Comments—Approved for clinical use in the US in 1995. It has a low solubility (blood/gas partition coefficient, 0.69) that is slightly higher than that of nitrous oxide and desflurane and an intermediate potency (MAC, 2.05%). Three to 5% of the drug is metabolized in the body, with a by-product being inorganic fluoride. Although fluoride toxicity (high-output renal failure) was a concern with this agent, it has not been seen in a clinical context. Sevoflurane is also subject to degradation by the basic environment present in the carbon dioxide absorbent in the gas delivery system. The breakdown products include pentafluoroisopropenyl fluoromethyl ether (PIFE) also know as Compound A, a substance associated with renal injury in rats and non-human primates. Clinical conditions including low fresh gas flows through the vaporizer and pre-existing renal failure in the patient are relative contraindications to using this agent. Thus far, renal injury due solely to sevoflurane has not been reported.

Dose-related decreases in blood pressure and cardiac output are similar to those seen with isoflurane. Sevoflurane is the least pungent of the potent inhaled agents and is used commonly for inhalation induction of anesthesia in children. It is a potent bronchodilator and can be used to treat acute bronchoconstriction. It is similar to isoflurane in its effect on cerebral hemodynamics, decreasing ICP with hyperventilation, decreasing $CMRO_2$, and preserving the response of the cerebral vasculature to carbon dioxide. The physical properties of sevoflurane allow a smooth, rapid inhalation induction and a quick emergence from anesthesia. The addition of nitrous oxide to sevoflurane during induction decreases induction time and decreases excitatory phenomena such as movement.

INORGANIC GASES

Only one agent is currently approved for use in the US; however, clinical trials of the inert gas Xenon indicate promise as an effective anesthetic with a reduced cardiovascular adverse effect profile.

NITROUS OXIDE

Dinitrogen Monoxide; Laughing Gas

Nitrogen oxide (N_2O) [10024-97-2]; contains not less than 99.0%, by volume, of N_2O (44.01). The remainder is chiefly nitrogen.

Preparation—Usually by heating ammonium nitrate to about 170° to produce nitrous oxide and water. Nitrous oxide is furnished in compressed form in metallic cylinders.

Description—Colorless gas, without appreciable odor or taste; specific gravity 1.53; 1 L, at a pressure of 760 torr at 0°, weighs about 1.97 g.

Solubility—1 volume dissolves in about 1.4 volumes of water at 20° under normal pressure; freely soluble in alcohol; soluble in ether or oils.

Comments—The narcosis-producing effects of nitrous oxide (N_2O) were described by Sir Humphry Davy in 1799. It is a powerful analgesic and a weak anesthetic (MAC, 105%) with a rapid onset and recovery (blood/gas partition coefficient, 0.47) available as a compressed gas. It is often used in combination with other anesthetics as part of a *balanced technique* or as an adjunct to potent inhalation agents to decrease the concentration necessary to achieve MAC. Nitrous oxide is considered to be nonflammable but will support combustion. It has been suggested that nitrous oxide causes ordination of the cobalt atom in vitamin B_{12} resulting in an inhibition of methionine synthetase activity, leading to megaloblastic anemia after prolonged (days) administration. The same mechanism is presumably responsible for the nitrous oxide induced increases in total homocysteine plasma levels which are associated with an increase in perioperative myocardial ischemia.

Nitrous oxide has a minimal effect on respiration, although hypoxic drive is blunted. Cardiac output is maintained with increasing dose, presumably through mild sympathetic stimulation. In clinical situations where there are enclosed air-containing spaces, such as inner ear surgery, abdominal surgery, sitting craniotomy, or pneumothorax, nitrous oxide will diffuse into the space 35 times faster than nitrogen diffuses out, resulting in expansion of the air-containing spaces. There is evidence that nitrous oxide may increase postoperative nausea and vomiting. It has wide utility in dental procedures where full anesthesia is not essential. Recent reports have indicated that the use of nitrous oxide during general anesthesia in gas-filled eyes may have disastrous visual results caused by gas expansion and elevated intraocular pressure.

INTRAVENOUS ANESTHETICS

The parenteral route for the administration of general anesthetics offers the advantage of less cumbersome delivery systems when compared to the inhalation route. A major disadvantage is the lack of control regarding the time course for the anesthetic effect. Inhalation anesthetics are dosed in response to the hemodynamic parameters of the patient, and adequate levels can be monitored with end-tidal measurement of the respiratory gas. A similar monitor of the dose-effect ratio is not currently available for intravenous anesthetics, so a rough dose estimate must be made on the basis of the population pharmacodynamics and pharmacokinetics. Wide variations exist between patients and clinical situations, making accurate titration of intravenous agents difficult.

Interestingly, the precise pharmacologic targets for these agents have been more fully defined than those for the inhalation anesthetics, nevertheless actions at single sites do not account for the profound anesthesia produced by these compounds. The inhibitory GABA receptor appears to be a primary mediator for the activity of many of these agents but the opioid, NMDA, serotonin, or muscarinic receptors may also be involved.

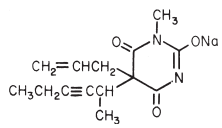
Similar to the inhalation agents, there is no ideal intravenous anesthetic and combinations of both are common. Intravenous drugs have found a particularly useful role in the induction of general anesthesia, which is often maintained by the addition of inhalation anesthetics or other adjuvant agents including opioids and benzodiazepines.

Barbiturates

The ultra short-acting barbiturates produce rapid unconsciousness but lack analgesic or muscle relaxant activity and are therefore typically used as induction agents or for short procedures. There are two classes of barbiturates used in anesthesia, thiobarbiturates such as thiopental, and oxybarbiturates such as methohexital. The drugs differ in potency, metabolism, and clinical use, as reviewed below. Common to all barbiturates is the proscription in patients with latent or clinical porphyria. Induction of cytochrome enzyme systems predisposes such patients to a possibly fatal episode.

METHOHEXITAL SODIUM

2,4,6(1*H*,3*H*,5*H*)-Pyrimidinetrione, (±)-1-methyl-5-(1-methyl-2-pentynyl)-5-(2-propenyl)-, monosodium salt; Brevital Sodium



Sodium 5-allyl-1-methyl-5-(1-methyl-2-pentynyl)barbiturate [309-36-4] $C_{14}H_{17}N_2NaO_3$ (284.29).

Preparation—1-Butynyl magnesium bromide is treated with acetaldehyde, and the resulting alcohol is treated with PCl_5 to produce 2-chloro-3-pentyne. Condensation with ethyl cyanoacetate in the presence of sodium ethylate yields ethyl 1-methyl-2-pentynylcyanoacetate which, on similar further condensation with allyl bromide, yields ethyl (1-methyl-2-pentynyl)allylcyanoacetate. Reaction with *N*-methylurea yields the iminobarbituric acid, which, on acid-catalyzed hydrolysis, forms methohexital. Neutralization with sodium hydroxide produces the sodium salt.

The two diastereoisomers of the barbituric acid have been designated as α- and β-forms in the literature. The α-form is the one used medicinally (the β-form causes undesirable side effects) and is formed almost exclusively by the above process. The malonic ester synthesis described under *Barbital* (RPS-18, p 1067) is not used because it yields mainly the unwanted β-form.

Description—White to off-white hygroscopic powder; essentially odorless; solutions are alkaline to litmus.

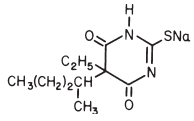
Solubility—Soluble in water.

Comments—Used primarily for short, mildly painful procedures and induction of general anesthesia. An induction dose of 1 mg/kg reliably produces unconsciousness in 30 sec; the pharmacological effect terminates with rapid redistribution from the brain to peripheral sites. Recovery from methohexital is more rapid, and there is less myocardial depression than with thiopental. Intravenous injection may be painful, and tremor, coughing, and hiccups occur occasionally. Methohexital has been used to elicit spiking discharges on the EEG in patients undergoing testing for seizure activity. In the anesthetic realm, it has been used during closed reduction of fractures, electroconvulsive therapy, cardioversion, and testing of automatic defibrillators.

Methohexital is metabolized only in the liver, causing induction of cytochrome enzymes. Intravenous injection may result in anaphylaxis (1/30,000), and seizures are reported after a continuous infusion (1/3).

THIOPENTAL SODIUM

4,6-(1*H*,5*H*)-Pyrimidinedione, 5-ethyldihydro-5-(1-methylbutyl)-2-thioxo-, monosodium salt; Thiopentone Sodium; Pentothal Sodium



Sodium 5-ethyl-5-(1-methylbutyl)-2-thiobarbiturate [71-73-8] $C_{11}H_{17}N_2NaO_2S$ (264.32).

Preparation—In the same manner as *Amobarbital* (RPS-20, p 1415), using 2-bromopentane as the alkyl halide and the ethyl 1-methylbutylmalonate is condensed with thiourea [$CS(NH_2)_2$].

Description—White to off-white, crystalline powder or a yellowish white to pale greenish yellow hygroscopic powder; may have a disagreeable odor; aqueous solution is alkaline to litmus; solutions decompose on standing and, on boiling, precipitation occurs. Carbon dioxide also causes precipitation in the solution.

Solubility—Soluble in water or alcohol; insoluble in absolute ether, benzene, or solvent hexane.

Incompatibilities—Thiopental precipitates in acid solutions.

Comments—Used for induction of general anesthesia, brain protection therapy, and as an anticonvulsant. It is not used for short procedures requiring unconsciousness and amnesia because recovery occurs faster with methohexital or propofol. A single induction dose (3–5 mg/kg) will cause unconsciousness in 30 to 40 sec, and its action is terminated by redistribution of drug away from the brain. Pain at the injection site is less common than with methohexital or propofol. There is a transient decrease in blood pressure (20%) and a compensatory increase in heart rate on injection. Hypovolemic patients are at risk for major hemodynamic sequelae because of the vasodilation caused by thiopental. Intra-arterial injection leads to arterial thrombosis and necrosis of the involved limb.

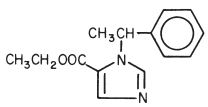
Thiopental is metabolized mainly in the liver, although the kidney and muscle tissue may participate. Intravenous injection has been associated with anaphylaxis and porphyria attacks in susceptible individuals.

Thiopental has been used to treat acute increases in ICP and as a brain protectant during surgical procedures in which there is risk of ischemia due to lack of blood flow. Monitoring of the EEG is helpful in determining the thiopental dose needed to cause burst suppression. Although the mechanism of this effect is not certain, it is thought that decreasing oxygen consumption or free radical scavenging is involved.

Nonbarbiturates

ETOMIDATE

1*H*-Imidazole-5-carboxylic acid, (±)-1-(1-phenylethyl)-, ethyl ester, Amidate



(+)-Ethyl (1-(α-methylbenzyl)imidazole-5-carboxylate [33125-97-2] $C_{14}H_{16}N_2O_2$ (244.99).

Preparation—From a-methylbenzyl amine and ethyl chloroacetate in 8 steps.

Description—White or yellow crystals or amorphous; melts about 67°.

Solubility—Insoluble in water; soluble in common polar organic solvents.

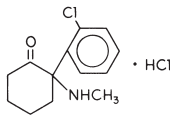
Comments—A hypnotic agent used for induction of general anesthesia. Intravenous injection of this water-soluble agent at 0.3 mg/kg leads to a rapid loss of consciousness within one arm-to-brain circulation time. Etomidate is known for its cardiovascular stability and quick emergence after a single dose because of rapid redistribution. Adverse reactions include pain on injection, respiratory depression (less than the barbiturates), and myoclonus. Myoclonic activity results from a disinhibition of subcortical structures and is not associated with seizure activity on EEG. Adrenocortical suppression has been reported for induction doses and is more common after an intravenous infusion of etomidate. This effect is due to an inhibition of 11-β-hydroxylase activity lasting 4 to 8 hr after an induction dose. The clinical significance of this finding remains unclear but suggests the choice of other agents in the critical care setting where adrenocortical dysfunction may lead to mortality.

Metabolism of etomidate takes place in the liver. Recovery from etomidate anesthesia is associated with a greater incidence of nausea and vomiting, and emergence delirium has been noted after long infusions.

Etomidate is an alternative to barbiturate induction in patients with unstable cardiovascular systems, in hypovolemic patients, and as a supplement to other anesthetic agents in a balanced technique. Although it decreases ICP, $CMRO_2$, and EEG activity as thiopental does, its efficacy as a brain protectant has been questioned recently.

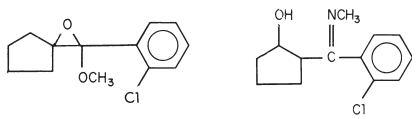
KETAMINE HYDROCHLORIDE

Cyclohexanone, 2-(2-chlorophenyl)-2-(methylamino)-, hydrochloride; Ketaject, Ketalar



(±)-2-(*o*-Chlorophenyl)-2-(methylamino)cyclohexanone hydrochloride [1867-66-9] Base [6740-88-1] $C_{13}H_{16}ClNO.HCl$ (274.19).

Preparation The product resulting from a Grignard reaction involving *o*-chlorobenzonitrile and bromocyclopentane is treated in the presence of strong alkali to form the epoxy compound (I). Reaction of this (I) with methylamine yields the imine (II), which rearranges on heating in the presence of hydrochloric acid. Belgian Pat 634,208.



I II

Description—White, crystalline powder with a characteristic odor; solutions are acid to litmus; melts between 258° and 261° with decomposition; pH (1 in 10 solution) between 3.5 and 4.1.

Solubility—1 g in 5 mL water, 14 mL alcohol, 60 mL chloroform, or 60 mL absolute alcohol.

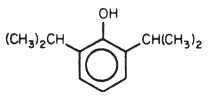
Comments—Unique as an intravenous anesthetic in that it provides anesthetic, sedative, amnesiac, and analgesic action. Induction doses (1–2 mg/kg) produce surgical anesthesia within 30 sec. Patients maintain ventilation and cardiovascular function. Ketamine produces a state of *dissociative anesthesia;* patients may appear awake and be noncommunicative yet experience intense analgesia and amnesia. Some protective reflexes (gag, laryngeal tone, spontaneous ventilation) remain intact.

Intravenous injection is not painful, and the action of the drug is terminated by redistribution. Ketamine is metabolized by the liver (CYP3A4 predominates). Tolerance to the drug may develop after repeated dosing. Cardiovascular effects resemble sympathetic stimulation (increases in heart rate, cardiac output, blood pressure), possibly through direct interaction with the sympathetic nervous system. *In vitro,* ketamine is a myocardial depressant. Thus, patients with depleted catecholamine stores (trauma, critical illness) may experience cardiovascular collapse upon induction with ketamine. Emergence delirium (1% of patients) is characterized by visual and auditory hallucinations that may continue up to 24 hr after administration. This effect is attenuated by coadministration of benzodiazepines or other anesthetic agents. Patients receiving ketamine should not be released from care until recovery is complete and should be accompanied by a responsible adult.

Ketamine is used as an intravenous induction agent in adults and as an intramuscular injection in difficult-to-manage children (4 mg/kg). It is used for short painful procedures (ie, burn wound dressing, emergency induction for c-section). It may also be given by mouth. Ketamine is a bronchodilator and so is useful for asthmatic patients but should be avoided in clinical situations with cardiovascular and neurosurgical concerns.

PROPOFOL

Phenol, 2,6-diisopropyl-, Diprivan



[2078-54-8] $C_{12}H_{18}O$ (178.27)

Preparation—See *J Org Chem* 21:712, 1956.

Description—Oily liquid; melts about 19°, pK_a 11.

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

Comments—Propofol has a rapid onset (within one arm-brain circulation time), and its pharmacological action is terminated by redistribution. Pain on injection is common unless the drug is injected into a large vein or preceded by injection of a local anesthetic or potent opioid. Rapid recovery is facilitated by a short initial distribution half-life (2–8

min), with clearance by glucuronide and sulfate conjugation and possibly extrahepatic site metabolism with less than 0.3% excreted unchanged.

An induction dose (1.5–2.5 mg/kg) leads to a greater decrease in blood pressure than with thiopental, through vasodilation and a direct myocardial depressant effect. There is little or no change in heart rate or cardiac output. Dose-dependent respiratory depression occurs in 25 to 35% of patients after an initial dose; it is also a bronchodilator and decreases the normal response to hypoxia and hypercarbia. Propofol decreases $CMRO_2$ and ICP and is reported to have brain-protectant qualities. Substantial decreases in blood pressure leading to clinically significant decreases in cerebral perfusion pressure limits it application in neuroanesthesia. Side effects include precipitation of excitatory motor activity (myoclonus and opisthotonus) and antiemetic properties. It is not a trigger for malignant hyperthermia (MH) and is the agent of choice in patients susceptible to MH. Propofol is contraindicated in critically ill pediatric patients where it has been shown to produce a "propofol syndrome" consisting of metabolic acidosis and cardiac failure.

Propofol is used as an induction agent for general anesthesia and as a maintenance hypnotic under constant intravenous infusions. It has found utility in the outpatient surgical environment. Patients tend to awake quickly from a propofol-based anesthetic with, at times, a feeling of euphoria. There is a significant amnestic effect at high doses.

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CHAPTER 79

Local Anesthetics

Local anesthetics reversibly block impulse conduction in any part of the nervous system and in all nerves, including sensory, motor, and autonomic types. They often are used to produce a transient loss of sensation in a circumscribed area of the body without causing a general loss of consciousness. This action can be used to block pain sensation—or sympathetic vasoconstrictor impulses—to specific areas of the body. Hence, local anesthetics are used to prevent pain in surgical procedures, dental manipulations, injury, and disease. The synthetic local anesthetic agents may be divided into two groups: the slightly soluble compounds and the soluble compounds. The slightly soluble local anesthetics are used only for surface (topical) application, since their slow absorption renders them safe for use on ulcers, wounds, and mucous surfaces. The anesthesia that they induce is not as complete as that induced by soluble compounds, but the duration is longer. Many soluble anesthetics also may be used for topical anesthesia. On the other hand, only soluble local anesthetics of relatively low toxicity should be injected.

Local anesthesia induced by injectable agents is designated according to the technique or anatomical site of the injection. Infiltration anesthesia refers to injection directly into the area that is painful or is to be subjected to surgical trauma. Field block is accomplished by administering the local anesthetic to a region of the nerve proximal to the site to be anesthetized. Peripheral nerve block, commonly called regional anesthesia, places the anesthetic agent in direct contact with the nerve or nerve plexus. Paravertebral nerve block places the anesthetic agent in direct contact with the nerve as it exits the intervertebral foramina. Epidural and caudal blocks are similar; caudal block is an epidural block in the caudal region. Subarachnoid block, commonly called spinal anesthesia, but more correctly spinal analgesia, requires that the anesthetic be placed within the subarachnoid space so that the anesthetic agent mixes with spinal fluid.

The use of a hyperbaric (heavy) solution or hypobaric (light) solution and proper positioning of the patient on the operating table permits manipulation of anesthesia for various body areas.

Local anesthetics prevent both the generation and the conduction of the nerve impulse. The excitable membrane of nerve axons maintains a transmembrane potential of −90 to −60 mV. During excitation, the sodium channels open, and a fast inward sodium current quickly depolarizes the membrane toward the sodium equilibrium potential (+40 mV). As a result of depolarization, the sodium channels close (inactivate), and potassium channels open. The outward flow of potassium repolarizes the membrane toward the potassium equilibrium potential (−95 mV); repolarization returns the sodium channels to the rested state. The transmembrane ionic gradients are maintained by the sodium pump.

When increasing concentrations of a local anesthetic are applied to a nerve fiber, the threshold for excitation increases, the impulse conduction slows, the rate of rise of the action potential declines, the action potential amplitude decreases, and, finally, the ability to generate an action potential is abolished. All these effects result from the binding of the local anesthetic to sodium channels, which in turn blocks the transient permeability to sodium. If the sodium current is blocked over a critical portion of nerve, propagation of an impulse over the blocked area is no longer possible.

When infiltration, conduction, or regional techniques are employed, both nerve fibers and nerve endings are anesthetized. The ease with which a nerve fiber may be anesthetized is related to its type and size. Although there are exceptions, large myelinated nerves usually require a higher concentration of anesthetic solution and more time to be blocked than small nonmyelinated fibers. Accordingly, small nerve fibers concerned with vasoconstriction, temperature, and surface pain are anesthetized most easily, whereas large fibers associated with the sensation of touch, pressure, deep pain, and the sensations from joints and tendons are anesthetized with more difficulty. In spinal anesthesia, it is probable that both sensory and motor nerve fibers are anesthetized. In surface (topical) anesthesia, the sensory nerve endings are the chief nerve structures affected.

The nerve-blocking action of the local anesthetics is pH sensitive. Because these drugs generally are marketed as water-soluble salts, the injected solutions are mildly acidic. To block nerve activity, the local anesthetic must become deprotonated and diffuse through cellular membranes to reach its intracellular site of action. However, because the cationic species is the form of the local anesthetic that interacts preferentially with the sodium channels, molecules that have crossed the membranes must be protonated again to be effective. Changes in extracellular pH can disrupt the balance between protonated and deprotonated forms and interfere with local anesthetic activity. This can occur in areas of tissue damage or inflammation or following multiple administrations of the acidic local anesthetic solutions.

The duration of action of a local anesthetic is proportional to the time during which it is in actual contact with nervous tissues. Consequently, procedures that help localize the drug at the nerve prolong anesthesia. Cocaine itself constricts blood vessels, prevents its own absorption, and has a duration of action longer than most local anesthetics. A vasoconstrictor drug, such as epinephrine, norepinephrine, or levonordefrin, is included frequently in local anesthetic solutions. The presence of one of these drugs in the local anesthetic solution retards absorption of the local anesthetic solution, thereby reducing its systemic toxicity, increasing its duration of action, and increasing its efficiency by decreasing the volume of solution required. The pressor potency relative to epinephrine (shown in parentheses), maximal total dose, and usual concentration are as follows: epinephrine (1), 0.2 mg, 1:50,000 to 1:200,000; norepinephrine (0.6), 0.34 mg,

1:30,000; and levonordefrin (0.5), 1 mg, 1:20,000. While vasoconstriction helps prolong the effects of the local anesthetics, it can be problematic in areas with restricted blood supply. Consequently, it is inadvisable to inject local anesthetics with vasoconstrictors around the base of fingers, toes, or the penis. Some of the vasoconstrictor may be absorbed systemically, causing adverse effects associated with their sympathomimetic actions. Such side effects can be particularly dangerous in the presence of cardiovascular disease or concurrent use of other drugs that enhance sympathetic nervous activity such as monoamine oxidase (MAO) inhibitors or tricyclic antidepressants. In addition, injection of these vasoconstrictor additives into damaged tissue may result in delayed healing.

A number of precautions should be observed when injection anesthesia is contemplated.

Resuscitation equipment and appropriate drugs should be immediately available.

The safe use of these agents in pregnancy, with respect to adverse effects on fetal development, has not been established.

Local anesthetic procedures should be used with caution when there is inflammation and/or sepsis in the region of the proposed injection.

Local anesthetics containing epinephrine should be used with extreme caution in patients on MAO inhibitors, tricyclic antidepressants, phenothiazines, etc, as either severe hypertension or hypotension may occur.

Vasopressor agents used in caudal or other epidural blocks should be used with extreme caution in patients on oxytocic drugs, since the resulting interaction may produce severe persistent hypertension and/or rupture of cerebral blood vessels.

Serious, dose-related cardiac arrhythmias may occur if local anesthetics containing a vasoconstrictor such as epinephrine are employed in patients during or following the administration of chloroform, halothane, cyclopropane, trichloroethylene, or other inhalation anesthetics.

Factors that must be given careful consideration prior to concurrent use of general and local anesthetics include the effect of both agents on the myocardium, the concentration and volume of the vasoconstrictor, and the elapsed time since injection.

Adverse reactions to local anesthetics may be divided into two groups: systemic and local adverse reactions. In general, these reactions are qualitatively similar for all local anesthetic agents.

Systemic adverse reactions usually are associated with high blood levels of the drug and result from overdosage, rapid systemic absorption, or inadvertent intravenous injection. Because local anesthetics can affect all excitable membranes, the reactions usually involve the central nervous and cardiovascular systems.

The initial CNS reactions are excitatory and/or depressant and may be characterized by nervousness, agitation, dizziness, blurred vision, and tremors, followed by drowsiness, convulsions, unconsciousness, and possibly respiratory arrest. Other systemic effects may include nausea, vomiting, chills, pupil contraction, or tinnitus. The excitatory reactions may be very brief or absent, in which case the first manifestation of toxicity may be drowsiness, merging into unconsciousness and respiratory arrest.

Cardiovascular reactions usually require high systemic concentrations, are depressant, and may be characterized by hypotension, cardiovascular collapse, bradycardia, and possibly cardiac arrest. Treatment of a patient with toxic manifestations includes reassurance, maintaining a patent airway, and supporting ventilation using oxygen and assisted or controlled respiration. Should circulatory depression occur, vasopressors, such as ephedrine or metaraminol, and IV fluids may be used. Should a convulsion persist despite oxygen therapy, diazepam given IV is usually the treatment of choice.

Allergic reactions are characterized by cutaneous lesions, urticaria, edema, or anaphylactoid reactions. Untoward reactions from overdosage with epinephrine and other vasoconstrictor agents added to local anesthetics are relatively common. Anxiety, palpitation, dizziness, headaches, restlessness, tremors, tachycardia, anginal pain, and hypertension are observed frequently. These reactions may be differentiated from those caused by local anesthetics in that epinephrine does not produce convulsions and causes tachycardia rather than bradycardia. Reactions of this kind respond to sedatives and oxygen.

Local adverse reactions to these anesthetic drugs, although infrequent, are either cytotoxic or allergic and are manifested by skin discoloration, pain, edema, slough, neuritis, or neurolysis. Eczematoid dermatitis, characterized by erythema and pruritus that proceeds to inflammation, swelling, vesiculation, and oozing, is the predominant local reaction. The aminobenzoic acid derivatives are by far the most likely to cause allergic sensitivity reactions; cross-sensitivity between members of this group often is reported. If a patient is allergic or does not tolerate a particular local anesthetic, it is advisable to use a drug from a different chemical family. Unfortunately, tests for sensitivity such as skin, conjunctival, and patch tests are not reliable for predicting the possibility of allergic reactions.

All local anesthetics are toxic, and the tolerance of patients varies. Safe dosage, therefore, is limited for each drug and must be individualized. The choice of drug, concentration, rate and site of injection, and age and emotional and physical status of the patient are a few factors that must be considered. In general, the smallest amount of the least toxic drug that will serve the purpose should be used, if reactions are to be avoided. In some patients, premedication with diazepam may be advisable to minimize the incidence of toxic reactions. Many local anesthetics occasionally give rise to dermatitis. When this is severe, the use of the anesthetic should be discontinued.

The interested reader is referred to the following reviews on the subject: Courtney KR. Structural elements that determine local anesthetics activity. In *Handbook of Experimental Pharmacology*, vol 81, Strichartz GR, ed. Berlin: Springer-Verlag, 1987, p 53, and McLeskey CH. Rational use of local anesthetics. *NC Med J* 1982; 43:496.

INJECTION ANESTHETICS

Injectable local anesthetic drugs can be divided conveniently into two groups: esters and nonesters. The esters are primarily of the *para*-aminobenzoic acid type and include chlorpromazine, procaine, propoxycaine, and tetracaine. The nonesters are anilides (amides or nonesters) that include lidocaine, mepivacaine, bupivacaine, etidocaine, and prilocaine. This classification is particularly important from the point of view of possible allergic reactions as well as biotransformation. Thus, local anesthetics with an ester linkage (aromatic acid + amino alcohol) such as procaine and those with an amide linkage (aromatic amine + amino acid) such as lidocaine differ significantly in hypersensitivity, metabolism, and duration of action. Hypersensitivity seems to occur most prominently in response to local anesthetics of the ester-type and frequently extends to chemically related compounds. Allergic reactions to the amide type are extremely rare, and substitution of such amide-type, compounds to avoid allergic responses is usually possible.

The metabolic fate of local anesthetics is of great practical importance because their toxicity depends largely on the balance between their rate of absorption and their rate of destruction. The ester-type local anesthetic appears to be hydrolyzed by both liver esterase and plasma esterase. Metabolic degradation by plasma esterase is particularly important in man; human plasma esterase can hydrolyze local anesthetics 4 to 20 times faster than can animal plasma esterases. Consequently, very little of the ester-type agent is available for hydrolysis by liver esterase. Spinal fluid contains little or no esterase; hence, anesthesia produced by intrathecal injection of an ester-type local anesthetic will persist until the local anesthetic agent is absorbed into the blood.

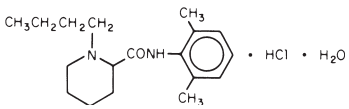
On the other hand, amide-type local anesthetics are degraded by hepatic microsomes; the initial reactions involve *N*-dealkylation and subsequent hydrolysis. Consequently, the amide-type local anesthetics usually have a longer duration of action than the ester type.

Considerable pharmacokinetic data have been accumulated on the amide-type local anesthetics, particularly lidocaine, mepivacaine, bupivacaine, and etidocaine (the data are presented in the respective monographs). Comparatively little such information is available on the older ester-type agents; for the most part their rapid metabolism has hindered most attempts to measure their blood concentrations after less than heroic doses in man. Consequently, most studies with the latter agents deal with potency, toxicity, time for onset, and duration of action. The descriptive phrase *short-acting* suggests a duration of 45 to 75 min, medium-acting, 90 to 150 min, and long-acting, 180 min or longer.

With the exception of solutions for use in spinal anesthesia, local anesthetic solutions should be isotonic to avoid edema, local irritation, and inflammation at the site of injection. Solutions for spinal anesthesia may be isobaric, hypobaric, or hyperbaric, depending on the desired level of anesthesia. The total maximal dosages employed with injection anesthetics vary markedly, depending on the technique used and the patient's age, weight, and physical condition. In general, the physician should administer the smallest volume of the most dilute solution that is effective. For adverse effects and special warnings in the use of these agents, refer to the introductory statement.

BUPIVACAINE HYDROCHLORIDE

2-Piperidinecarboxamide, 1-butyl-*N*-(2,6-dimethylphenyl)-, hydrochloride; Marcaine Hydrochloride; Sensorcaine



1-Butyl-2′,6′-pipecoloxylidide monohydrochloride [14252-80-3] $C_{18}H_{28}N_2O \cdot HCl \cdot H_2O$ (342.91).

Preparation—Similar to that of *Mepivacaine Hydrochloride,* except that butyl bromide instead of dimethyl sulfate is used for alkylation. *J Med Chem* 1971; 14:891.

Description—White, crystalline powder; odorless; melts with decomposition about 250°. pK_a 8.05.

Solubility—1 g in 25 mL water or 8 mL alcohol; slightly soluble in chloroform.

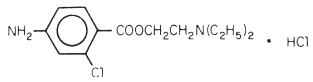
Comments—For local infiltration (0.25% soln), lumbar epidural (0.25%, 0.5%, and 0.75% soln), caudal block (0.25% and 0.5%), peripheral nerve block (0.25% and 0.5% soln), retrobulbar block (0.75% soln), sympathetic block (0.25% soln), and dental block (0.5% soln). It is not used for obstetrical paracervical block or topical anesthesia. The onset of action after local injection is rapid (5 min); however, onset may be delayed as long as 20 min when used for brachial plexus or peridural anesthesia. The duration of peripheral nerve blocks produced may be up to 7 hr, whereas the duration of peridural anesthesia is about 4 hr. Epidural block with 0.75% solution induces complete motor block; hence, abdominal operations requiring complete muscle relaxation may be done. It also has been noted that a period of analgesia persists after the return of sensation; during this time the need for analgesics is reduced. It has a $t_{1/2}$ of 2.7 hr, V_d of 1.04, and a partition coefficient of 130; 84% to 95% of the drug is bound to plasma protein. Consequently, it has a low degree of placental transmission of parenteral local anesthetic and may cause the least fetal depression.

After injection for caudal, epidural, or peripheral nerve block in humans, peak blood levels of approximately 1.2 μg/mL are reached in 30 to 45 min, followed by a decline to insignificant levels within 3 to 6 hr. Like other local anesthetics with an amide structure, it is not detoxified by plasma esterases but is detoxified in the liver, via conjugation with glucuronic acid.

Contraindications, general warnings, precautions, and adverse reactions are similar to those of other amide-type local anesthetics (see *Lidocaine*, page 1484. It is not recommended for children under 12 yr, and the solution for spinal anesthesia should not be used in children under 18 yr. The safe use in pregnancy, with respect to adverse effects on fetal development, has not been established.

CHLOROPROCAINE HYDROCHLORIDE

Benzoic acid, 4-amino-2-chloro-, 2-(diethylamino)ethyl ester, monohydrochloride; Nesacaine, Nesacaine-MPF



2-(Diethylamino)ethyl 4-amino-2-chlorobenzoate monohydrochloride [3858-89-7] $C_{13}H_{19}ClN_2O_2 \cdot HCl$ (307.22).

Preparation—2-Chloro-4-nitrobenzoic acid is reacted with thionyl chloride, and the resulting acid chloride is condensed with 2-(diethylamino)ethanol. Reduction of the nitro ester with iron and acidulated water yields chloroprocaine base, which may be converted into the hydrochloride by dissolving in a suitable solvent and introducing hydrogen chloride.

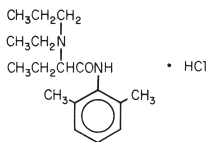
Description—White, crystalline powder; odorless and stable in air; solutions acid to litmus; exhibits local anesthetic properties when placed on the tongue; melts about 175°.

Solubility—1 g in about 20 mL water or about 100 mL alcohol; very slightly soluble in chloroform; practically insoluble in ether. Aqueous solutions are acid to litmus and if discolored, should not be used.

Comments—Infiltration and nerve block (mandibular, infraorbital, or brachial plexus anesthesia, 2% soln; digital, 1%; pudendal, 2%; and paracervical block, 1% soln). Caudal and epidural block, 2 or 3% solution. It is not effective topically. Its onset of action is about 6 to 12 min, and anesthesia lasts from 30 to 60 min; with the addition of epinephrine 1:200,000, duration is increased to 60 to 90 min. For adverse reactions see the introductory statement.

ETIDOCAINE HYDROCHLORIDE

Butanamide, (±)-*N*-(2,6-dimethylphenyl)-2-(ethylpropylamino)-, monohydrochloride; Duranest



(±)-2-(Ethylpropylamino)-2′-6′-butyroxylidide monohydrochloride [3667- 18-0 (free base)] $C_{17}H_{28}N_2O \cdot HCl$ (312.88).

Preparation—Etidocaine is synthesized by the interaction of 2,6-xylidine, 2-bromobutyric acid, and ethyl *n*-propylamine. German Pat 2,162,744 (*CA 77:* 101244c, 1972).

Description—White, crystalline powder; pK_a 7.74 (etidocaine).

Solubility—Soluble in water; freely soluble in alcohol.

Comments—It has a rapid onset (3–5 min) and a prolonged duration of action (5–10 hr). The duration of sensory analgesia is 1.5 to 2 times longer than that of lidocaine; duration in excess of 9 hr is not infrequent in peripheral nerve blocks. It also produces a significant degree of motor blockade and abdominal muscle relaxation when used for peridural analgesia. Because of its tendency to block voluntary expulsive muscles, etidocaine should not be used in vaginal deliveries. This drug also should not be used for spinal anesthesia.

Contraindications, warnings for use, precautions, and adverse reactions are similar to those for lidocaine. Its safe use in pregnancy, with respect to adverse effects of fetal development, has not been established. The use of this agent in children under 14 years has not been investigated.

LIDOCAINE—page 1484.

LIDOCAINE HYDROCHLORIDE

Acetamide, 2-(diethylamino)-*N*-(2,6-dimethylphenyl)-, monohydrochloride, monohydrate; Lignocaine

2-(Diethylamino)-2′,6′-acetoxylidide monohydrochloride [6108-05-0] $C_{14}H_{22}N_2O \cdot HCl \cdot H_2O$ (288.82); *anhydrous* [73-78-9] $C_{14}H_{22}N_2O \cdot HCl$ (270.80).

For the structure of the base, see *Lidocaine,* page 1484.

Description—White, odorless, crystalline powder; slightly bitter taste; melts about 76°. pK_a 7.86 (base).

Solubility—1 g in 0.7 mL water or 1.5 mL alcohol; pH (0.5% solu), 5.0 to 7.0; solutions may be sterilized by autoclaving.

Comments—A widely employed amide-type local anesthetic and antiarrhythmic drug. As a local anesthetic, it is employed for infiltration and field block anesthesia in a concentration of 0.5%; for periph-

eral nerve block in concentrations of 0.5% and 1%; for paravertebral nerve block in a concentration of 0.5% to 1.5%; for epidural or caudal anesthesia in a concentration of 1.5% with 7.5% dextrose; and in subarachnoid block (spinal analgesia) in a concentration of 5% made hyperbaric with 7.5% dextrose. It also is used topically on mucous membranes as a 1% to 4% aqueous solution, 2% jelly, 2.5% and 5% ointment, and 2.0% viscous. It is also used in the form of suppositories for temporary relief of pain associated with inoperative, irritated, or inflamed anorectal conditions.

Some of its injections contain epinephrine to delay absorption, prolong its action, and reduce its toxic effects. Because it is also effective without a vasoconstrictor, it appears to be the anesthetic of choice for use in those individuals who are sensitive to epinephrine and its congeners. In addition, it is so dissimilar in chemical structure to procaine and related anesthetics that it is the agent of choice in individuals sensitive to procaine.

Its local anesthetic action is more rapid in onset, more intense, and of longer duration than that of procaine. It also is more potent than procaine. Because of its local vasodilating action, epinephrine often is combined with lidocaine. When used alone, anesthesia after perineural injection lasts 60 to 75 min; with epinephrine, anesthesia lasts 2 hr or more. This drug and procaine are approximately equally toxic when administered extravascularly in 0.5% solutions; when higher concentrations are used, this is 1 1/2 times as toxic as procaine. By the intravenous route, it is twice as toxic as procaine.

As an antiarrhythmic agent it is administered intravenously for the management of ventricular arrhythmias occurring during cardiac manipulation, such as cardiac surgery, and life-threatening arrhythmias that are ventricular in origin, such as occur during acute myocardial infarction. For this purpose it usually is given in a dose of 50 to 100 mg intravenously at a rate of 25 to 50 mg/min. If the initial injection does not produce the desired clinical response, a second dose (1/3–1/2 the initial dose) may be given after 5 min.

No more than 200 to 300 mg of lidocaine should be administered during a 1-hr period. Smaller doses should be used in cardiac failure, a reduced cardiac output from any cause, and in patients over 60 years. It exhibits a biphasic half-life. The distribution phase ($t_{1/2}$: 7 to 8 min) accounts for the short duration of action after intravenous administration (10–20 min). The terminal elimination half-life is 1 to 2 hr.

Therapeutic antiarrhythmic plasma levels range from 1.5 to 5.5 μg/mL; subjective toxic effect levels range from 3 to 5 μg/mL; and objective adverse manifestations such as muscular irritability, convulsions, and coma appear at plasma levels of 6 to 10 μg/mL. Thus, there is considerable overlap between therapeutic levels and subjective toxic effect levels. Moreover, toxicity may be significantly altered by the coadministration of other drugs. For example, coadministration with propranolol impairs the clearance of lidocaine and enhances toxicity; concomitant intravenous administration of phenytoin and lidocaine may induce excessive cardiac depression; and additive neurological effects may be produced during concurrent administration of procainamide and lidocaine.

It should be emphasized that after administration as a local anesthetic agent, systemic absorption may result in blood concentrations in the usual therapeutic antiarrhythmic, or even toxic, ranges. Plasma levels vary according to the site at which the local anesthetic is injected: subcutaneous, 1.2 μg/mL/100 mg; epidural, 1.1 μg/mL/100 mg; and subcutaneous (abdominal), 0.5 μg/mL/100 mg. Thus, the epidural injection of 25 mL of a 1.5% solution (375 mg) has the potential for producing a plasma level of 4.13 μg/mL, a value well within the range that induces subjective toxic effects (3 to 5 μg/mL) and approaching that which results in objective adverse manifestations (6–10 μg/mL).

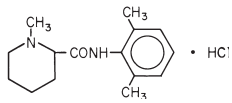
After absorption, it partitions extensively into body tissues. Studies in monkeys indicate that it has a high affinity for spleen (tissue to plasma coefficient 3.5), lung (3.1), kidney (2.8), adipose tissue (2.0), brain (1.2), heart (0.96), and musculoskeletal tissues (0.6). Because of the avidity with which tissues take up the drug, only about 6% of a given dose is found in the blood at steady state. It then redistributes to muscle and adipose tissue, and these tissues become the major storage reservoirs. For more detailed pharmacokinetic data, the interested reader is referred to the excellent review by Benowitz and Meister (*Clin Pharmacokinet* 1978; 3:177).

This drug is a weak base with a pKa of 7.86, $t_{1/2}$ of 1.6 hr, and V_d of 1.3 L/kg; 60% to 80% is bound to plasma protein. Maximal excretion in an acid urine is only 10%. The major portion of this agent is metabolized by the liver microsomal system. Two major metabolites have been identified: monoethylglycinexylidide and glycinexylidide. Animal experiments indicate that both metabolites have antiarrhythmic and convulsant activities; the former has potency similar to this drug itself, while the latter is only 10% to 26% as potent. Both metabolites, after further biotransformation in the liver, are excreted in the urine.

Some adverse CNS effects frequently are observed during therapy. These commonly include drowsiness, dizziness, paresthesia, and euphoria. Typical symptoms with higher doses include confusion, agitation, dysarthria, vertigo, visual disturbances, tinnitus, and nausea. Sweating, muscle tremor, or fasciculations also may occur. Manifestations of severe toxicity include psychosis, seizures, respiratory depression, and coma. Seizures that persist after the administration of oxygen may be controlled by intravenous administration of 2.5-mg increments of diazepam. Caution must be exercised, since overdosage may occur if sufficient time is not allowed for the anticonvulsant action of the individual doses to become apparent. Diazepam has been recommended for prophylaxis of convulsions during local anesthetic therapy.

MEPIVACAINE HYDROCHLORIDE

2-Piperidinecarboxamide, *N*-(2,6-dimethylphenyl)-1-methyl-, monohydrochloride; Carbocaine; Polocaine



1-Methyl-2′,6′-pipecoloxylidide monohydrochloride [1722-62-9] $C_{15}H_{22}N_2O \cdot HCl$ (282.81).

Preparation—Picolinic acid (2-pyridinecarboxylic acid) is condensed with 2,6-xylidine to 2‘,6‘-picolinoxylidide, which is reacted with dimethyl sulfate in xylene solution. Reduction of the pyridine ring followed by treatment with HCl yields the product. *Acta Chem Scand* 1957; 11:1183.

Description—White, odorless, crystalline solid; melts with decomposition about 258°; pH (1 in 50 solution) about 4.5; pK_a 7.73 ± 0.08.

Solubility—Freely soluble in water or methanol; very slightly soluble in chloroform; practically insoluble in ether.

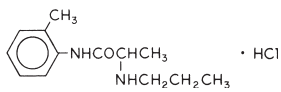
Comments—An amide anesthetic employed for nerve block (1 or 2% soln), paracervical block in obstetrics (1% soln), caudal and epidural block (1, 1.5, or 2% soln), infiltration (1% soln), therapeutic block (1 or 2% soln), and dental procedures (1, 2, or 3% soln). It is not effective topically, except in large doses; therefore it should not be used for this purpose. It has a $t_{1/2}$ of 1.9 hr, a V_d of 1.2 L/kg, and a partition coefficient of 12.1. Approximately 60% to 80% of that in blood is bound to serum proteins.

When used in obstetrics, maternal plasma concentrations vary from 2.9 to 6.9 μg/mL, whereas the umbilical vein concentration varies from 1.9 to 4.9 μg/mL; thus, the fetus is exposed to only 60% to 70% of that in maternal plasma. It has an action similar to that of lidocaine hydrochloride; however, its onset is faster, and its duration of action is somewhat longer.

Anesthesia develops in 3 to 5 min and lasts 2 to 2 1/2 hr. It may be used for many purposes without epinephrine. Thus, it particularly is indicated in circumstances in which epinephrine is contraindicated. The systemic effects are similar to those produced by other local anesthetics. For additional information, see the introductory statement.

PRILOCAINE HYDROCHLORIDE

Propanamide, *N*-(2-methylphenyl)-2-(propylamino)-, monohydrochloride; Citanest



2-(Propylamino)-*o*-propionotoluidide monohydrochloride [1786-81-8] $C_{13}H_{20}N_2O \cdot HCl$ (256.77).

Preparation—*o*-Toluidine is condensed with 2-bromopropionyl bromide, and the resulting 2-bromo-*o*-propionotoluidide is condensed with propylamine to yield prilocaine (base). An acetone solution of the base treated with hydrogen chloride yields the official salt. Brit Pat 839,943.

Description—White, odorless, crystalline powder; initially an acid and then bitter taste, stable in light and air; melts about 167°; pK_a 7.89.

Solubility—1 g in 3.5 mL water, 4.2 mL alcohol or 175 mL chloroform; practically insoluble in ether.

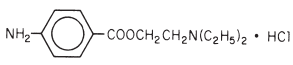
Comments—An amide-type local anesthetic chemically related to lidocaine and mepivacaine. For the most part, it is used for dental procedures and administered either by infiltration or nerve block. An initial dose of 40 to 80 mg (1–2 mL of a 4% solution) is usually sufficient, with a maximum dose of 600 mg (8 mg/kg). Onset of action after infil-

tration averages 1 or 2 min; duration of action is 60 min or longer. For major nerve blocks (epidural), the onset of analgesia is approximately 2 min longer than that for lidocaine; whereas the duration of action is 30 to 60 min longer. Approximately 55% is bound to plasma protein. After 600 mg of the drug, peak plasma levels are reached in 20 min, at which time plasma levels average 4 μg/mL; the same dose with epinephrine also peaks at 20 min, but the plasma level is only 2 μg/mL. Consequently, this drug generally is used without epinephrine. Hence, this local anesthetic is particularly useful for patients who cannot tolerate vasopressor agents, eg, patients with hypertension, diabetes, thyrotoxicosis, or other cardiovascular disorders.

Like other amide-type local anesthetics, prilocaine is not metabolized by plasma esterases; it is metabolized by both the liver and the kidney and excreted by the kidney. One of its metabolites is *o*-toluidine, a substance known to induce methemoglobinemia. Methemoglobin levels up to 15% and cyanosis have been reported following doses of 600 mg or more. Other clinical symptoms of methemoglobinemia, such as tachycardia, fatigue, headache, lightheadedness, and dizziness, may occur at higher doses. Except for methemoglobinemia, its side effects are similar to those observed with other local anesthetics. When methemoglobinemia occurs, it can be reversed by intravenous injection of methylene blue, 1 to 2 mg/kg of a 1% solution administered over a 5-min period. As with other local anesthetics, prilocaine is contraindicated in the presence of shock, severe cardiovascular disease, or heart block. For other adverse effects, see the introductory statement.

PROCAINE HYDROCHLORIDE

Benzoic acid, 4-amino-, 2-(dimethylamino)ethyl ester, monohydrochloride; Novocain



2-(Diethylamino)ethyl *p*-aminobenzoate monohydrochloride [51-05-8] $C_{13}H_{20}N_2O_2 \cdot HCl$ (272.77).

Preparation—2-(Diethylamino)ethanol is made by reacting ethylene chlorohydrin or bromohydrin with diethylamine. The diethylaminoethanol is then heated with *p*-nitrobenzoyl chloride, forming diethylaminoethyl *p*-nitrobenzoate. The NO_2 group is reduced with iron or tin and HCl. US Pat 812,554.

Description—Small, white, odorless crystals or a white crystalline powder; melts about 157°; pK_a 8.7 (base).

Solubility—1 g in 1 mL of water or 15 mL of alcohol; slightly soluble in chloroform; practically insoluble in ether.

Comments—An ester-type local anesthetic. It is used for infiltration (0.25–0.5% soln), peripheral nerve block (0.5–2% soln), and spinal anesthesia (10% soln). It is ineffective when applied topically. The drug has a slower onset of action than lidocaine or prilocaine; its duration of action is short, about 1 hr.

It produces vasodilation, and thus vasoconstrictor drugs such as norepinephrine or levonordefrin may be required to retard absorption, prolong duration of action, and maintain homeostasis. Following absorption, it is hydrolyzed rapidly by esterases in both the plasma and liver (see the introductory statement). Since spinal fluid contains little or no esterase, when given by this route of administration it remains active until it is absorbed into the general circulation.

The products of metabolic degradation include *para*-aminobenzoic acid and diethylaminoethanol; the former inhibits the action of sulfonamides. Therefore, it and other ester-type local anesthetics should not be used in any condition in which therapy with sulfonamide is being employed. This drug and its congeners also interfere with the laboratory determination of sulfonamide concentration in biological fluids. Local anesthetics other than derivatives of *para*-aminobenzoic acid should be used in all circumstances when sulfonamide therapy has been instituted. The IV use of procaine is contraindicated in patients receiving digitalis, anticholinesterase drugs, or succinyl choline. For adverse effects, see the introductory statement.

TETRACAINE—page 1485.

TETRACAINE HYDROCHLORIDE

Benzoic acid, 4-(butylamino)-, 2-(dimethylamino)ethyl ester, monohydrochloride; Amethocaine Hydrochloride; Pontocaine Hydrochloride

2-(Dimethylamino)ethyl *p*-(butylamino)benzoate monohydrochloride [136-47-0] $C_{15}H_{24}N_2O_2 \cdot HCl$ (300.83).

For the structure of the base see page 1485.

Preparation—By dissolving tetracaine (base) in a solvent such as benzene and passing hydrogen chloride into the solution, whereupon the salt precipitates. For the preparation of the base, see *Tetracaine.*

Description—Fine, white, crystalline, odorless powder; slightly bitter taste followed by a sense of numbness; solutions neutral to litmus; melts about 148°; two polymorphic modifications melt about 134° and 139°, respectively; mixtures of these may melt between 134° and 147°; pK_a 8.39. Protect solutions from light.

Solubility—Very soluble in water; soluble in alcohol; insoluble in ether or benzene.

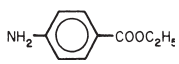
Comments—An ester-type local anesthetic used topically on the eye and in the nose or throat and by infiltration for subarachnoid block (spinal analgesia). When used in the eye, it does not dilate the pupil, paralyze accommodation, or increase intraocular pressure. It is particularly suitable for spinal anesthesia, especially for surgical procedures requiring 2 to 3 hr. Although it is an ester-type local anesthetic, it is only slowly hydrolyzed by plasma and liver esterases. It has a delayed onset of action, often as long as 15 min, but a long duration of action; spinal anesthesia may last as long as 3 hr. Since its *para*-aminobenzoic acid metabolite may antagonize the activity of aminosalicylic acid and sulfonamides, it should not be used in patients receiving these drugs. For information on cautions, contraindications, and adverse effects, see the introductory statement.

TOPICAL ANESTHETICS

The salts and base forms of the esters and amides included in this section are used to produce topical (surface) anesthesia. The salts do not penetrate intact skin, but both forms penetrate abraded or raw, granulated skin surfaces. The base forms relieve pruritus, burning, and surface pain on intact skin but penetrate only to a limited degree. Wounds, ulcers, and burns preferably are treated with preparations that are relatively insoluble in tissue fluids. Mucous membranes of the nose, mouth, pharynx, larynx, trachea, bronchi, and urethra are anesthetized readily by both salt and base forms. Consequently, these agents are used prior to inserting intratracheal catheters, pharyngeal and nasal airways, nasogastric and endoscopic tubes, urinary catheters, laryngoscopes, proctoscopes, sigmoidoscopes, and vaginal specula. Many of these agents also are used in the eye for such procedures as tonometry and gonioscopy, for removal of foreign bodies from the cornea, or for short operative procedures on the cornea or conjunctiva. For precautions, warnings, and adverse effects, see the introductory statement.

BENZOCAINE

Benzoic acid, 4-amino-, ethyl ester; Benzocaine; Anesthesin



Ethyl *p*-aminobenzoate [94-09-7] $C_9H_{11}NO_2$ (165.19).

Preparation—*p*-Nitrobenzoic acid, obtained by nitration of toluene and oxidation of the resulting *p*-nitrotoluene, is converted into the ethyl ester by heating with alcohol and sulfuric acid. The resulting ethyl *p*-nitrobenzoate is reduced with tin and hydrochloric acid.

Description—Small, white, odorless crystals or a white crystalline powder; melts within a 2° range between 88° and 92°; pK_a 2.5.

Solubility—1 g in about 2500 mL water, 5 mL alcohol, 2 mL chloroform, 4 mL ether, or 30 to 50 mL expressed almond oil or olive oil; soluble in dilute mineral acids.

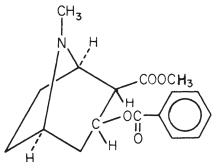
Comments—An insoluble local anesthetic. It usually is employed as an ointment to relieve pain associated with ulcers, wounds, and mucous surfaces. It also is used as a lubricant and anesthetic on intratracheal catheters, pharyngeal and nasal airways, nasogastric and endoscopic tubes, etc. It is included in proprietary creams, lozenges, ointments, powders, sprays, and suppositories to relieve pain of damaged skin surfaces and inflamed mucous membranes, particularly those in the anorectal area. It also is used as an otic preparation for the temporary relief of ear pain. Benzocaine commonly is combined with antitussives, such as dextromethorphan, in cold medications. It acts only as long as it is in contact with the skin or mucosal surface. Peak effect occurs within 1 min after application and lasts for 36 to 60

min. For adverse reactions, see the introductory statement in this chapter.

CHLOROBUTANOL—page 1059.

COCAINE

8-Azabicyclo[3.2.1]octane-2-carboxylic acid, [1*R*-(*exo,exo*)]-3-(benzoyloxy)-8-methyl-, methyl ester



Methyl 3β-hydroxy-1αH,5αH-tropane-2β-carboxylate benzoate (ester) [50-36-2] $C_{17}H_{21}NO_4$ (303.36); an alkaloid obtained from the leaves of *Erythroxylon coca* Lamarck and other species of *Erythroxylon* Linné (Fam *Erythroxylaceae*) or by synthesis from ecgonine or its derivatives.

History—Isolated by Gaedken in 1844 from Brazilian coca leaves, which for many years was the only source of cocaine. At present the alkaloid is obtained principally from Java coca leaves. Brazilian coca leaves contain from 0.5 to 1% methylbenzoylecgonine or cocaine, whereas the Java leaves contain very little cocaine as such. However, there are present in the latter such derivatives as benzoylecgonine, cinnamoylecgonine, methylecgonine, etc, to the extent of 1.5 to 2%, all of which are converted to cocaine in the manufacturing process.

Preparation—By moistening ground coca leaves with sodium carbonate solution, percolating with benzene or other solvents such as petroleum benzin, shaking the liquid with diluted sulfuric acid, and adding to the separated acid solution an excess of sodium carbonate. The precipitated alkaloids are removed with ether, and after drying with sodium carbonate, the solution is filtered and ether distilled off. The residue is dissolved in methyl alcohol and the solution heated with sulfuric acid or with alcoholic hydrogen chloride. This treatment splits off any acids from ecgonine and esterifies the carboxyl group. After dilution with water the organic acids that have been liberated are removed with chloroform. The aqueous solution is concentrated, neutralized and cooled with ice, whereupon methylecgonine sulfate crystallizes. This is benzoylated by heating with benzoyl chloride or benzoic anhydride to about 150°. On adding water and sodium hydroxide methylbenzoylecgonine or cocaine is precipitated. The cocaine is extracted with ether and the solution concentrated to crystallization. For the purification of cocaine recrystallization from a mixture of acetone and benzene generally is preferred.

Total synthesis of cocaine was achieved by Willstäter *et al, Ann* 1923; 434:111.

Description—Colorless to white crystals, or a white, crystalline powder; odorless; melts at about 97°; solution (in diluted HCl) levorotatory; saturated solution alkaline to litmus.

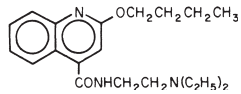
Solubility—1 g in about 600 mL water, 7 mL alcohol, 1 mL chloroform, 3.5 mL ether, about 12 mL olive oil, or 80 to 100 mL liquid petrolatum; very soluble in warm alcohol.

Comments—The first local anesthetic to be discovered. While it is considered too toxic for any anesthetic procedure requiring injection, it is still employed topically in a 1 or 2% solution for anesthesia of the ear, nose, throat, rectum, and vagina because of its intense vasoconstrictive action. When in solution as the hydrochloride salt it is used for local anesthesia of mucous membranes. For topical application (ear, nose, throat, or bronchoscopy) concentrations of 4 to 10% are employed. Besides its local anesthetic properties, cocaine enhances catecholamine systems by interfering with uptake of their transmitters into neuronal terminals. Peak effect is reached within 2 to 5 min and lasts from 1/2 to 2 hr. Toxic symptoms occur frequently because it is absorbed readily and dosage often is not monitored carefully. CNS effects include euphoria and cortical stimulation manifested by excitement and restlessness.

Stimulation of the lower motor centers causes hypertension, tachycardia, and tachypnea. Repeated use results in psychic dependence and tolerance, the euphoric effects of which are almost indistinguishable from those induced by amphetamines. Indeed, knowledgeable human subjects cannot distinguish between the subjective effects induced by the intravenous injection of 8 to 10 mg of the drug and those induced by 10 mg of dextroamphetamine. The drug is abused by intranasal, parenteral, or inhalation administration because of its CNS-stimulating effects. It is listed under Schedule II of the Controlled Substances Act. Severe toxic effects have been reported with doses as low as 20 mg, while the fatal dose is approximately 1.2 g. For adverse reactions, see the introductory statement.

DIBUCAINE

4-Quinolinecarboxamide, 2-butoxy-*N*-[2-(diethylamino)ethyl]-, Nupercainal



2-Butoxy-*N*-[2-(diethylamino)ethyl]cinchoninamide [85-79-0] $C_{20}H_{29}N_3O_2$ (343.47).

Preparation—May be synthesized by the following sequence of reactions: (1) Acetylation of isatin (obtained by oxidation of indigo) to *N*-acetylisatin, (2) rearrangement of 2-hydroxycinchoninic acid by treatment with alkali, (3) formation of 2-chlorocinchoninoyl chloride by reaction with phosphorous pentachloride; (4) conversion to 2-chloro-*N*-[2-(diethylamino)ethyl]cinchoninamide with *asym*-diethylethylenediamine, and (5) heating with sodium butoxide. US Pat 1,825,623.

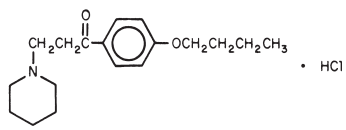
Description—White to off-white powder; slightly characteristic odor; somewhat hygroscopic; darkens on exposure to light; melts about 63°.

Solubility—1 g is soluble in 4600 mL water, in less than 1 mL of alcohol or chloroform, or in 1.4 mL ether.

Comments—Topically, for the temporary relief of pain and itching associated with burns, sunburn, insect bites, or minor skin irritation. Ointment or suppositories are used topically for the relief of the pain and itching of hemorrhoids. Its toxicity caused it to be removed from the US market as an injectable local anesthetic.

DYCLONINE HYDROCHLORIDE

1-Propanone, 1-(4-butoxyphenyl)-3-(1-piperidinyl)-, Dyclone



4′-Butoxy-3-piperidinopropiophenone hydrochloride [536-43-6] $C_{18}H_{27}NO_2 \cdot HCl$ (325.88).

Preparation—*p*-Hydroxyacetophenone is reacted with butyl bromide in a basic environment to produce the butoxy compound, which is reacted with piperidine hydrochloride and formaldehyde in an organic solvent under acidic conditions. US Pat 2,771,391 and 2,868,689.

Description—White crystals or white, crystalline powder; may have a slight odor; melts about 175°; pH (1 in 100 solution) 4 to 7.

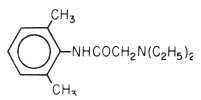
Solubility—1 g in 60 mL water, 24 mL alcohol, or 2.3 mL chloroform. Insoluble in ether or hexane.

Comments—To anesthetize accessible mucous membranes (eg, the mouth, pharynx, larynx, trachea, esophagus, and urethra) prior to various endoscopic procedures. The 0.5% solution also may be used to block the gag reflex and to relieve pain associated with oral or anogenital lesions. Dyclonine-containing lozenges are used to relieve minor sore throat or mouth discomfort. It is contraindicated in cystoscopic procedures following intravenous pyelography; the drug precipitates iodine and interferes with visualization. When instilled into the conjunctival sac, it induces anesthesia without miosis or mydriasis. It also has antimicrobial properties. The clinical significance of this property has not been determined. Because of irritating properties, dyclonine should not be injected. For adverse effects, see the introductory statement.

ETHYL CHLORIDE—see RPS-19, page 1141.

LIDOCAINE

Acetamide, 2-(diethylamino)-*N*-(2,6-dimethylphenyl)-, Xylocaine



2-(Diethylamino)-2′,6′-acetoxylidide [137-58-6] $C_{14}H_{22}N_2O$ (234.34).

Preparation—By chloroacetylation of 2,6-xylidine and condensation of the resulting chloroacetoxylidide and diethylamine.

Description—White or slightly yellow, crystalline powder; characteristic odor; stable in air; melts about 67°; pK_a 7.86.

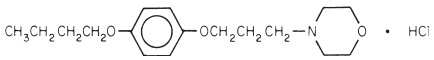
Solubility—Very soluble in alcohol or chloroform; freely soluble in benzene or ether; practically insoluble in water; dissolves in oils.

Comments—A local anesthetic used as an ointment topically on mucous membranes on minor burns, abrasions, and anorectal lesions; also used as an anesthetic lubricant for endotracheal intubation. See *Lidocaine Hydrochloride*.

LIDOCAINE HYDROCHLORIDE—pages 1481 and 1482.

PRAMOXINE HYDROCHLORIDE

Morpholine, 4-[3-(4-butoxyphenoxy(propyl]-, hydrochloride; Tronothane; Proctofoam; Prax



4-[3-(*p*-Butoxyphenoxy)propyl]morpholine hydrochloride [637-58-1] $C_{17}H_{27}NO_3 \cdot HCl$ (329.87).

Preparation—An acqueous mixture of 4-(3-chloropropyl)morpholine and *p*-butoxyphenol is refluxed until condensation is complete. The reaction mixture is cooled, and the base is extracted with benzene. After evaporation of the benzene, the purified base is converted to the hydrochloride with HCl. *J Am Chem Soc* 1951; 73:2281.

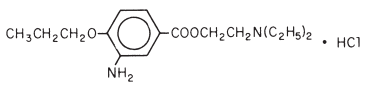
Description—White to nearly white, crystalline powder; numbing taste; may have a light aromatic odor; pH (1 in 100 solution) about 4.5; melts about 182°.

Solubility—1 g in about 35 mL chloroform; freely soluble in alcohol and water; very slightly soluble in ether.

Comments—A surface anesthetic that has low indices of sensitization and toxicity and is unrelated structurally to either ester- or amide-type agents. Consequently, it may be useful in patients sensitive to these classes of drugs. Local anesthesia develops in 3 to 5 min; its potency is comparable to that of benzocaine and is not sufficient to abolish the gag reflex. It is applied locally in a 1% concentration for relief from discomfort and pain in hemorrhoids and rectal surgery, episiotomies, anogenital pruritus, itching dermatoses, and minor burns. It is too irritating to be used in the eye. For adverse effects, see the introductory statement.

PROPARACAINE HYDROCHLORIDE

Benzoic acid, 3-amino-4-propoxy-, 2-(diethylamino)ethyl ester, monohydrochloride; Alcaine; Ak-Taine; Ophthaine; Ophthetic



2-(Diethylamino)ethyl 3-amino-4-propoxybenzoate monohydrochloride [5875-06-9] $C_{16}H_{26}N_2O_3 \cdot HCl$ (330.85).

Preparation—*p*-Hydroxybenzoic acid is reacted with *n*-propyl chloride in alkaline solution and the resulting *p*-propoxybenzoic acid is nitrated to the 3-nitro compound. Treatment with thionyl chloride yields the acid chloride, which is coupled with 2-(diethylamino)ethanol. The resulting nitro ester is reduced to the base, which reacts with an equimolar quantity of HCl to form the hydrochloride. *J Am Chem Soc* 1952; 74:592.

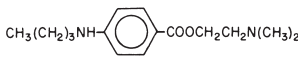
Description—White to off-white, or faintly buff-colored, crystalline powder; odorless; on heating or exposure to air the compound tends to discolor; solutions exposed to air slowly discolor and finally become dark, with some loss of potency; crystals melt within 2° range between 178 and 185°; pK_a 3.2.

Solubility—1 g in about 30 mL water or 30 mL warm alcohol or methanol; insoluble in ether or benzene. Solutions are neutral to litmus.

Comments—An effective ester-type surface anesthetic with a potency about equal to that of tetracaine. It is a useful anesthetic in ophthalmology and induces little or no initial irritation. Its onset of action is rapid; surface anesthesia of sufficient intensity to permit tonometry can generally be obtained within about 20 sec after the instillation of 1 or 2 drops of a 0.5% solution. The duration of such anesthesia is about 15 min. It is useful for most ocular procedures that require topical anesthesia such as cataract extraction, tonometry, removal of foreign bodies and sutures, gonioscopy, conjunctival scraping for diagnosis, and short operative procedures involving the cornea and conjunctiva. Although it is too toxic for use as an injection anesthetic, its ophthalmic use has been relatively free from side effects or untoward reactions. For adverse effects, see the introductory statement.

TETRACAINE

Benzoic acid, 4-(butylamino)-, 2-(dimethylamino)ethyl ester; Pontocaine



2-(Dimethylamino)ethyl *p*-(butylamino)benzoate [194-24-6] $C_{15}H_{24}N_2O_2$ (264.37).

Preparation—Ethyl *p*-aminobenzoate is butylated by refluxing with *n*-butyl bromide and ethanol in the presence of sodium carbonate. The resulting ethyl *p*-butylaminobenzoate is transesterified by heating with 2-(dimethylamino)ethanol in the presence of sodium ethoxide such that the liberated ethanol is distilled continously from the reaction mixture. US Pat 1,889,645.

Description—White, or light yellow, waxy solid; melts about 43°.

Solubility—1 g in 1000 mL water, 5 mL alcohol, 2 mL chloroform, or 2 mL ether.

Comments—See *Tetracaine Hydrochloride,* page 1483.

ACKNOWLEDGMENTS—H Steve White, PhD is acknowledged for his efforts in previous editions of this work.

CHAPTER 80

Antianxiety Agents and Hypnotic Drugs

Laura A Mandos, BS, PharmD

Antianxiety agents that were defined in the past as primarily sedatives are the most commonly used psychotropic medications.[1] The term *sedative* refers to a quieting effect accompanied by relaxation and rest but not necessarily sleep.[2] The term *hypnotic* refers to the production of sleep.[2] Hypnotic drugs are used to produce drowsiness and help the onset and maintenance of sleep. Since most of the current drugs have both sedative and hypnotic actions, the distinction is artificial. A small dose of a drug may act as a sedative, whereas a large dose of the same drug may act as a hypnotic. In this respect, the benzodiazepines have several clear advantages to the older classes of sedative-hypnotic drugs such as the barbiturates: a greater dose margin between anxiolysis and sedation, less abuse potential, a wider therapeutic index, and less tendency to produce tolerance and dependence.[3] Other antianxiety agents can also have an anxiolytic effect without the sedative actions associated with the benzodiazepines. Examples of the nonsedating antianxiety agents include the azapirone buspirone, the selective serotonin reuptake inhibitor antidepressant paroxetine, and the selective serotonin/norepinephrine reuptake inhibitor antidepressant venlafaxine.[4–6] Tricyclic antidepressants that have both serotonergic and noradrenergic effects have also been studied in the treatment of generalized anxiety disorder.[7] Imipramine has been found to be at least as effective as benzodiazepines in the treatment of generalized anxiety disorder.[7] The adverse effect profile of imipramine makes the drug less tolerable than the newer antidepressants. A more in-depth discussion of imipramine, paroxetine, and venlafaxine will be covered in a different chapter. Agents used as sedatives and hypnotics include a large number of compounds of diverse chemical structure and pharmacological properties, which, with the exception of the benzodiazepines (eg, diazepam), buspirone, and the aforementioned antidepressants, have in common the ability to induce a nonselective, reversible depression of the central nervous system (CNS). Thus, inorganic salts (bromide), chloral derivatives (chloral hydrate), acetylenic alcohols (ethchlorvynol), cyclic ethers (paraldehyde), carbamic acid esters of glycols (meprobamate), diureides (barbiturates), piperidinedione derivatives (glutethimide), and some miscellaneous aromatic tertiary alkylamines such as antihistaminics (diphenhydramine) and parasympatholytics (scopolamine) all exhibit pronounced sedative and hypnotic effects. The antihistamines (diphenhydramine) and parasympatholytics (scopolamine) that exhibit sedative and hypnotic effects will be discussed elsewhere.

For convenience, the antianxiety agents will be divided into two categories: benzodiazepines and nonbenzodiazepine anxiolytics. The hypnotic agents will also be divided into two categories: the barbiturates and nonbarbiturate hypnotics. The hypnotic benzodiazepines will be included in this section.

In addition to their use as anxiolytics and hypnotics, the medications discussed in this chapter are also administered as muscle relaxants, preanesthetic medications, anticonvulsants, and therapeutic aids in psychiatry.

As *antianxiety agents,* they are used in the management of anxiety disorders such a generalized anxiety disorder and panic attacks. Anxiety may manifest as a transient situational response to stress, a secondary reaction to a medical condition, or as a primary anxiety disorder. Generalized anxiety disorder (GAD) is a prevalent condition that frequently presents in primary care settings as fluctuating levels of worry associated with insomnia and symptoms of being easily fatigued, feeling irritable or on edge, poor concentration, and skeletal muscle tension. In the general population, GAD is reported to have a lifetime prevalence of 4% to 6%.[8] To meet the DSMIV-TR GAD criteria, patients suffering from generalized anxiety must have been ill on more days than not for a minimum of 6 months. Those who suffer from briefer episodes of generalized anxiety are placed in the residual diagnostic category of anxiety disorder NOS (not otherwise specified).[9] A panic attack is a discrete period of intense fear or discomfort in the absence of real danger that is accompanied by at least four of 13 somatic or cognitive symptoms. Symptoms include palpitations, sweating, trembling or shaking, the sensation of smothering or shortness of breath, feeling of choking, chest pain or discomfort, nausea or abdominal distress, dizziness or lightheadedness, derealization or depersonalization, fear of losing control or "going crazy", fear of dying, paresthesias, and chills or hot flushes.[9] The attack has a sudden onset and builds to a peak rapidly often with a feeling of impending doom. Panic attacks can be unexpected or situationally cued. Regardless of presentation, generalized anxiety disorder and panic attacks can be extremely debilitating and disabling.

Insomnia is a ubiquitous disorder of insufficient sleep or unsatisfying sleep. Insomnia may present as difficulty falling asleep, difficulty staying asleep, or feeling nonrefreshed from sleep. Insomnia can be a primary disorder, a comorbid disorder with a psychiatric, medical or other sleep condition, or an adverse effect of a medication.[10] Insomnia may also be classified by duration: transient meaning two to three nights, short-term meaning less than 3 weeks, or long-term meaning greater than 3 weeks of difficulty sleeping.[11] It should be remembered that not all patients with insomnia require hypnotic drug therapy. Assessment of insomnia should begin with a history obtained from the patient and bed partner and continue with a physical examination. Questioning should be directed at determining predisposing factors, precipitating events, lifestyle, and use of caffeine, alcohol, and drugs (prescription, nonprescription, and illicit). Many patients will respond to nonpharmacologic therapy. Common recommendations include: regular daytime exercise; avoiding large meals at night, avoiding caffeine, tobacco,

and alcohol; reducing evening fluid intake; limiting the use of the bedroom to sleep and sex; maintaining a consistent wake-up time; avoiding or limiting daytime napping; and avoiding bright lights, noise, and temperature extremes.[11] Nonspecific hypnotic therapy should be employed only when specific causes of the insomnia *cannot* be identified and eliminated.

To induce sleep, hypnotic agents are selected on the basis of the characteristics of the insomnia. Some patients have difficulty only in falling asleep and, once asleep, need no drug assistance; a rapidly acting hypnotic drug with a short duration of action will suffice for these patients. Other patients fall asleep readily, but experience one or more periods of wakefulness during the night; a hypnotic drug with a longer duration of action usually is indicated in such cases. Still other patients have trouble falling and staying asleep; a rapidly acting hypnotic drug that exerts an effect throughout part or most of the night is required for such patients. In all cases, however, consideration should be given to what the patient does on the day following a night of drug-induced sleep. Persons who must be alert the following day usually will object to drugs that leave residual sedation, whereas hospitalized patients or individuals with no place to go and nothing to do actually may benefit from the sedative aftereffects the next day.

A number of the sedative-hypnotic drugs have *anticonvulsant* properties. Several benzodiazepines have excellent anticonvulsant actions, and some are used to treat epilepsy. Clonazepam is used alone or as an adjunct in the management of absence (petit mal), petit mal variant, and especially akinetic and myoclonic seizures. Diazepam is used as adjunctive therapy in status epilepticus and severe recurrent seizures as well as treatment of acute seizures resulting from drug overdoses or exposure to toxins.

All barbiturates exhibit anticonvulsant activity, but only phenobarbital, mephobarbital, and metharbital are sufficiently selective to be clinically useful *antiepileptics*. Phenobarbital is useful in the management of generalized tonic-clonic seizures and as adjunctive therapy in complex partial (temporal lobe) seizures.

Sedative and hypnotic agents frequently are used as *preanesthetic medication* and as *adjunctive therapy* in psychiatry. Benzodiazepines and barbiturates are used commonly to allay anxiety and apprehension prior to surgery or other medical and dental procedures. In psychiatry, barbiturates with a short half-life have been used in *narcoanalysis* and *narcotherapy*. Sedative and hypnotic drugs also are employed in the treatment of dependence on CNS depressants. Chlordiazepoxide, diazepam, lorazepam, and oxazepam have all been used to manage symptoms associated with acute alcohol withdrawal.[12]

A number of the sedative-hypnotic drugs cross the placental barrier. Consequently, their chronic use during pregnancy may cause withdrawal effects in the newborn infant. Moreover, many of these substances are excreted in breast milk. Their chronic use during breastfeeding may cause sedation in the nursing infant.

Drowsiness is a side effect common to sedative-hypnotic agents. Patients taking such substances should be cautioned about operating hazardous machinery or operating a motor vehicle while taking such medication. Concurrent use of sedative-hypnotic drugs with alcohol, other CNS depressants, monoamine oxidase (MAO) inhibitors, or tricyclic antidepressants should be avoided. More-detailed information with respect to adverse effects and drug interactions is provided in the introductory statement to each section and in the individual monographs.

Prolonged overdosage with most of these drugs can result in habituation and dependence liability. However, the *dependence risk* varies markedly among the various agents. For example, the dependence risk with benzodiazepines is very low and has been estimated to be as few as one case per 5 million patient-months *at risk* for all recorded cases and one case per 50 million months in therapeutic use. Even though it is likely that in the past problems with benzodiazepines have been underestimated, there is no question that these agents are considerably safer than most other sedative and hypnotic drugs, such as barbiturates. Accordingly, alprazolam, lorazepam, clonazepam, and other benzodiazepines are listed in *Schedule IV* under the *Controlled Substances Act*.

On the other hand, the dependence risk with amobarbital, pentobarbital, and related substances is very high, with severe abuse potential. Consequently, these agents are listed in *Schedule II* under the *Controlled Substances Act*.

Finally, the marketing of buspirone and the antidepressants paroxetine and venlafaxine as anxiolytic agents provide another therapeutic option for treatment of anxiety in patients with a high risk of dependence. Buspirone, paroxetine, and venlafaxine lack significant abuse potential.

BENZODIAZEPINES

Despite the fact that modern guidelines for treating anxiety disorders has evolved from recommending the benzodiazepines to recommending serotonergic agents as first-line therapy, diazepam, lorazepam, alprazolam, and clonazepam remain in the top 200 most frequently prescribed medications in the US.[13,14] In 2002, alprazolam was the only benzodiazepine in the top 20 most frequently prescribed generic drugs.[14] These findings demonstrate the great popularity enjoyed by the benzodiazepines despite public perception that benzodiazepine use has diminished over the last decade.

The benzodiazepines are not general depressants of the CNS like the barbiturates, ethanol, and various other sedative-hypnotic agents and general anesthetics. There are marked differences among the various agents in selectivity, pharmacological profile, clinical usefulness, and pharmacokinetic properties (Table 80-1). Moreover, they do not induce a true "anesthetic effect," since awareness is still present and total muscular relaxation is not obtained even after large doses. Anterograde amnesia may take place, and this creates the illusion that anesthesia has occurred. True surgical anesthesia can be obtained only when benzodiazepines are combined with other drugs that depress the CNS.

Acting through its gamma-aminobutyric acid A ($GABA_A$) receptor, the amino acid neurotransmitter GABA is the major inhibitory neurotransmitter in the brain. $GABA_A$ receptors are ligand-gated channels, meaning the neurotransmitter-binding site and an effector ion channel is part of the same macromolecular complex. Benzodiazepines produce their effects by binding to a specific site on the $GABA_A$ receptor. The pharmacologic effects of benzodiazepines can be explained by an increase of GABA inhibitory impulses mediated via the benzodiazepine receptor. They do so by allosterically regulating the receptor (changing its conformation) so that it has a greater affinity for GABA.[15] The pharmacology of the $GABA_A$ receptor is complex; $GABA_A$ receptors are the primary site of action not only of the benzodiazepines but also of the barbiturates and some of the intoxicating effects of ethanol. Benzodiazepines and barbiturates act at separate binding sites on the receptor to potentiate the effects of GABA. In addition, each drug increases the affinity of the receptor for each other.[16] The cellular mechanisms, pharmacokinetics, basic pharmacology, and clinical pharmacology of the benzodiazepines have been reviewed by MacDonald and Olsen.[17]

The benzodiazepines are used in the symptomatic relief of anxiety and tension states resulting from a stressful environment or emotional factors. They also are useful in psychoneurotic states characterized by tension, anxiety, apprehension, fatigue, depression symptoms, or agitation, and the benzodiazepine alprazolam has been approved for treatment of panic attacks. Chlordiazepoxide, lorazepam, oxazepam, and diazepam also are useful in acute alcohol withdrawal to provide symptomatic relief from acute agitation, tremors, and impending delirium tremens and hallucinosis.

Table 80-1. Benzodiazepine Anxiolytics

AVAILABLE PREPARATIONS	ORAL DOSAGE EQUIVALENCY (MG)	TIME TO PEAK PLASMA LEVEL (H)	PROTEIN BINDING (%)	ELIMINATION HALF-LIFE (H) PARENT COMPARED	ACTIVE METABOLITE	METABOLIC PATHWAY
Alprazolam (Xanax and generics)	0.5	1–2	80	12–15	One	Oxidation
Chlordiazepoxide (Librium and generics)	10	1–4	96	5–30	Four	N-dealkylation Oxidation
Clonazepam (Klonopin and generics)	0.25	1–4	85	30–40	None	Nitroreduction
Clorazepate (Tranxene and generics)	7.5	1–2	97	Prodrug	Two	Oxidation
Diazepam (Valium and generics)	5	0.5–2	98	20–80	Two	Oxidation
Lorazepam (Ativan and generics)	1	2–4	85	10–20	None	Conjugation
Oxazepam (Serax and generics)	15	2–4	97	5–20	None	Conjugation

Data from Kirkwood CE, Melton ST. Anxiety Disorders. In: DiPiro JT, Talbert RL, Yee GC, et al., eds. *Pharmacotherapy: A Pathophysiologic Approach, Fifth Edition.* New York: McGraw Hill, 2002. and Arana GW and Rosenbaum JF. *Handbook of Psychiatric Drug Therapy,* 4th ed. Philadelphia: Lippincott Williams and Wilkins, 2000.

Clonazepam is useful alone or as an adjunct in the management of several types of epileptic seizures. Diazepam is used as an adjunct therapy to endoscopic procedures, in the management of acute skeletal muscle spasm, and, by parenteral injection, in status epilepticus, to control convulsions resulting from overdosage with local anesthetics and other severe recurrent convulsive seizures. The benzodiazepines also are useful adjunct therapy in the management of apprehension and anxiety that precedes or accompanies surgical procedures and disease states.

Benzodiazepines are similar in mechanism of action as well as side effect profile. They differ in terms of potency and pharmacokinetic parameters (see Table 80-1).[18,19] After oral administration, the time to peak plasma level varies from 1 to 4 hours, depending on the formulation given. Protein binding varies from 80% with alprazolam to 98% with diazepam. The extent to which benzodiazepines interact with other protein-bound drugs is not known; the absence of reports of such adverse interactions suggests that such competition is not of clinical significance.

The benzodiazepines are metabolized by hepatic microsomal enzymes to form demethylated, hydroxylated, and oxidized products that pharmacologically active. The active metabolites are then conjugated with glucuronic acid and the resulting glucuronides are inactive. The glucuronides are more water-soluble than the parent compound and are readily excreted in the urine. Clorazepate, chlordiazepoxide, diazepam, and flurazepam are transformed to active metabolites, primarily to *N*-demethylated products with a longer half-life than the parent drug. This metabolite may be particularly significant in the elderly, newborns, or those with severe liver disease. Lorazepam, oxazepam, and temazepam are conjugated with glucuronic acid to form inactive metabolites and are a safer choice of medication in the elderly or patient with impaired hepatic function.[19] Benzodiazepines cross the placental barrier and are excreted in human milk.

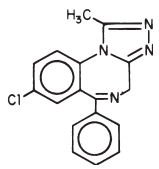
Patients on these drugs should be warned about potential effects induced by the concomitant use of alcohol or other CNS depressants such as other antianxiety and hypnotic drugs, tricyclic antidepressants, opiate analgesics, antipsychotics, and antihistamines, including nonprescription sleep aids and cold remedies. They also should be warned not to operate a motor vehicle or hazardous machinery while on these drugs.

Side effects most commonly reported after the use of benzodiazepines include drowsiness, fatigue, confusion, dizziness, weakness, ataxia, syncope, venous thrombosis, and phlebitis at the site of the injection. Other, less frequent side effects include anterograde amnesia, blurred vision, diplopia, and nystagmus; urticaria and rash; hiccups; changes in salivation; constipation; changes in appetite; bizarre behavior; antisocial acts; neutropenia; and jaundice. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, and sleep disturbances also have been reported; should these occur the drug should be discontinued. Since significant amounts of benzodiazepines are found in maternal and cord blood, these agents are not recommended for obstetrical use. The safe use of benzodiazepines in children under 12 years has not been established.

Physical and *psychological dependence* may occur, especially following prolonged use, although dependence also can occur with short-term, high-dose treatment. Symptoms of benzodiazepine dependence can resemble those associated with barbiturate or alcohol dependence and include slurred speech, ataxia, and drowsiness. Abrupt discontinuation of long-term benzodiazepine treatment can result in severe withdrawal symptoms as with other CNS depressants. To prevent such consequences, these drugs should be withdrawn gradually. Individuals known to be addictive-prone or those whose history suggests they modify drug dosage on their own initiative should not be given the drug. Withdrawal symptoms resemble those resulting from barbiturate withdrawal. The benzodiazepines are listed in *Schedule IV* under the *Controlled Substances Act*.

ALPRAZOLAM

4*H*-[1,2,4]Triazolo[4,3-*a*][1,4]benzodiazepine, 8-chloro-1-methyl-6-phenyl-, Xanax



[28981-97-7] $C_{17}H_{13}ClN_4$ (308.77).

Preparation—See *J Med Chem* 1977; 20:1694.

Description—White crystals; melts about 228°.

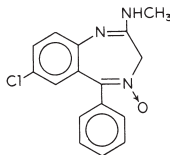
Solubility—Practically insoluble in water; soluble in methanol or ethanol.

Comments—For the management of anxiety disorders or the short-term relief of the symptoms of anxiety. It also is indicated for the adjunctive treatment of anxiety associated with mental depression. Alprazolam also has been found to be effective in the short-term (4- to 10-week) treatment of panic disorder with or without agoraphobia. Although not evaluated in well-controlled studies, the drug has been used effectively for 8 months or longer. In many patients, discontinuation of alprazolam results in a relapse of panic attacks and anxiety. After oral

administration peak plasma levels are reached in 1 to 2 hr, and half-life is 12 to 15 hr. Thus, it has a short to medium half-life compared with other benzodiazepines. Accumulation is minimal during multiple dosage, and steady-state plasma concentration usually is attained within 2 to 3 days. Elimination is rapid following discontinuation of therapy. Therefore, chronic therapy should not be terminated abruptly. Medical problems and adverse effects are similar to those for other benzodiazepines. See the introductory statement.

CHLORDIAZEPOXIDE

3*H*-1,4-Benzodiazepin-2-amine, 7-chloro-*N*-methyl-5-phenyl-, 4-oxide; Libritabs; Menrium



7-Chloro-2-(methylamino)-5-phenyl-3*H*-1,4-benzodiazepine 4-oxide [58-25-3] $C_{16}H_{14}ClN_3O$ (299.76).

Preparation—For the preparation of chlordiazepoxide, see *Chlordiazepoxide Hydrochloride,* below.

Description—Yellow, practically odorless, crystalline powder; sensitive to sunlight; melts about 242°; pK_a 4.6.

Solubility—1 g in >10,000 mL water, 50 mL alcohol, 6250 mL chloroform, or 130 mL ether.

Comments—See *Chlordiazepoxide Hydrochloride*.

CHLORDIAZEPOXIDE HYDROCHLORIDE

3*H*-1,4-Benzodiazepin-2-amine, 7-chloro-*N*-methyl-5-phenyl-, 4-oxide, monohydrochloride; Librium

[438-41-5] $C_{16}H_{14}ClN_3O.HCl$ (336.22).

For the structure of the base, see above.

Preparation—By condensation cyclization of 2-amino-5-chlorobenzophenone oxime with chloroacetyl chloride to form 6-chloro-2-chloro methyl-4-phenylquinazoline 3-oxide, which subsequently is reacted with methylamine in methanol solution. US Pat 2,893,992.

Description—White or nearly white, crystalline powder; odorless; sensitive to sunlight; melts about 215° with decomposition.

Solubility—1 g in 10 mL water or 40 mL alcohol.

Comments—Indicated for the relief of anxiety and tension, withdrawal symptoms of acute alcoholism, preoperative apprehension and anxiety, and adjunct therapy in various disease states in which anxiety and tension are prominent features. Its efficacy for long-term use (ie, for longer than 4 months) has not been established; therefore, the need for continued therapy with the drug should be reevaluated periodically. It has a pK_a of 4.6 and a half-life of 8 to 20 hr. During chronic administration, accumulation occurs, not only of the parent substance but also of three active metabolites (desmethylchlordiazepoxide, demoxepam, and desoxydemoxepam). Demoxepam has a half-life of 37 (range, 28–63) hr and desoxydemoxepam of 44 (range, 39–61) hr. These metabolites probably contribute to the overall activity of this drug, since they are pharmacologically active in animals. Steady-state plasma levels of chlordiazepoxide, desmethylchlordiazepoxide, and demoxepam average 0.75, 0.54, and 0.36 μg/mL, respectively. It is excreted in the urine; 1–2% is excreted unchanged, and 3–6% as a conjugate.

As with other benzodiazepines, this drug requires the same warnings and precautions regarding its use in patients with known hypersensitivity, elderly and excessively depressed individuals, pregnant and lactating mothers, patients with known renal and hepatic impairment, patients on other CNS-depressant drugs, and patients with a history of either drug addiction or indiscriminate alteration of drug dosage.

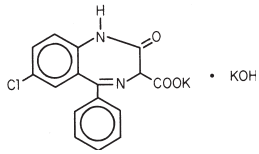
Chlordiazepoxide is also available commercially in anxiolytic products, combined with anticholinergic (clidinium) and anti depressant (amitriptyline) agents. The therapeutic value of these fixed combinations has not been established.

Adverse reactions include drowsiness, ataxia, confusion, skin eruptions, edema, menstrual irregularities, nausea and constipation, extrapyramidal symptoms, and decreased libido in some patients; blood dyscrasias (agranulocytosis), jaundice, and hepatic dysfunction have occasionally been reported. Paradoxical reactions of rage, excitement, stimulation, hostility, and depersonalization have sometimes followed administration to severely disturbed patients. Rashes, nausea, headache, and decreased tolerance to alcohol also have been reported. The chronic administration of large doses of chlordiazepoxide hydrochloride may result in the development of tolerance and physical dependence.

CLONAZEPAM—page 1503.

CLORAZEPATE DIPOTASSIUM

1*H*-1,4-Benzodiazepine-3-carboxylic acid, 7-chloro-2,3-dihydro-2-oxo-5-phenyl-, potassium salt, compound with potassium hydroxide (1:1); Tranxene



[57109-90-7] $C_{16}H_{11}ClK_2N_2O_4$ (408.92).

Preparation—2-Amino-5-chlorobenzonitrile is treated with phenylmagnesium bromide, and the resulting ketimine is condensed via deamination with diethyl aminomalonate. The diester is then saponified with KOH in aqueous methanol, and the resulting dipotassium dicarboxylate cyclizes via isomerization. US Pat 3,516,988.

Description—Fine, light-yellow, practically odorless, crystalline powder; slightly burning taste; sensitive to light, moisture, and excessive heat; aqueous solutions are unstable (clear, light-yellow, and alkaline to litmus).

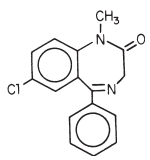
Solubility—Very soluble in water; very slightly soluble in alcohol; insoluble in chloroform, ether, benzene, or acetone.

Comments—For the symptomatic relief of anxiety associated with neurosis, psychoneuroses with symptoms of anxiety, acute alcohol withdrawal, and other conditions in which anxiety is a prominent feature and as adjunctive therapy in the management of partial seizures. This substance is hydrolyzed in the stomach to desmethyldiazepam, a metabolic precursor of oxazepam and also a metabolite of both chlordiazepoxide and diazepam. The metabolite is absorbed rapidly (1–2 hr); the volume of distribution is 0.93 to 1.47 L/kg, and the half-life ranges from 50 to 100 hr. Desmethyldiazepam accumulates for about 7 days and then reaches a steady state. Consequently, clorazepate can be given once a day as well as in divided doses.

It requires the same warnings and precautions regarding use with other drugs, in hypersensitive individuals, during pregnancy and in young children, in elderly and excessively depressed patients, in patients with impaired renal or hepatic function, and in patients with a history of drug addiction as other benzodiazepines. Drowsiness is the most common adverse effect. Less-common untoward reactions include dizziness, various gastrointestinal (GI) complaints, nervousness, blurred vision, dry mouth, headache, and mental confusion. Other adverse reactions include insomnia, transient rashes, fatigue, ataxia, genitourinary complaints, irritability, diplopia, depression, and slurred speech. Hypotension, decreased hematocrit, and abnormal liver and kidney function also have been reported.

DIAZEPAM

2H-1,4-Benzodiazepin-2-one, 7-chloro-1,3-dihydro-1-methyl-5-phenyl, Valium; Zetran; Diazepam Solution



[439-14-5] $C_{16}H_{13}ClN_2O$ (284.74).

Preparation—2-(Methylamino)-5-chlorobenzophenone in ethereal solution is reacted with bromoacetyl bromide to form 2-(2-bromo-*N*-methylacetamido)-5-chlorobenzophenone. The latter is then reacted with ammonia in methanol solution, whereby the bromine is replaced by amino followed by cyclization through a dehydration involving the hydrogens of the amino group and the oxygen of the starting phenone. The crude diazepam may be purified by recrystallization from ether. US Pat 3,136,815.

Description—Off-white to yellow, practically odorless, crystalline powder; stable in the air; melts about 133°; pK_a 3.7, 3.2.

Solubility—1 g in 333 mL water, 16 mL alcohol, 2 mL chloroform, or 39 mL ether.

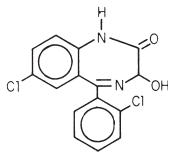
Comments—A benzodiazepine indicated for the symptomatic relief of tension and anxiety, acute alcohol withdrawal, and adjunctive therapy in skeletal muscle spasms and preferred by many clinicians for the

management of status epilepticus. It is used preoperatively because of its ability to relieve anxiety, sedate, and cause light anesthesia and anterograde amnesia. It is absorbed well after single oral doses (pK_a 3.3), leading to rapid onset of clinical effects. Initially these effects may be transient due to extensive distribution to body tissues.

After distribution is complete, elimination is slow, with a half-life of 20 to 50 hr. Effective plasma levels vary from 0.2 to 0.5 μg/mL. With chronic administration, the drug and its major active metabolite, desmethyldiazepam, accumulate and reach a steady state in about 7 days. Consequently, it may take this long to achieve maximal sedative and antianxiety effects, at which time the patient can usually be maintained by giving the drug once or twice a day. Patients on the drug should be cautioned not to drive an automobile or to operate dangerous machinery until a few days after the drug has been discontinued.

LORAZEPAM

2*H*-1,4-Benzodiazepin-2-one, 7-chloro-5-(2-chlorophenyl)-1,3-dihydro-3-hydroxy-; Ativan



[846-49-1] $C_{15}H_{10}Cl_2N_2O_2$ (321.16).

Preparation—Syntheses of a number of substituted 1,4-benzodiazepin-2-ones, including lorazepam, have been described by Bell et al (*J Med Chem* 1968; 11:457; see also *J Org Chem* 1962; 27:1691). It differs from oxazepam in having a 5-*o*-chlorophenyl substituent in place of the 5-phenyl.

Description—White to off-white powder; no characteristic odor; melts about 173° with decomposition; pK_a 1.3, 11.5.

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

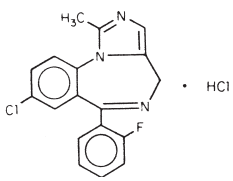
Comments—A benzodiazepine used orally for anxiety and transient situational stress. Its effectiveness for long-term use (more than 4 months) has not been assessed. It is used parenterally for *preanesthetic* medication, producing sedation and decreased ability to recall events related to the surgery. It is absorbed rapidly after oral administration; peak plasma levels after a 2-mg dose are about 20 ng/mL, and maximal clinical effects occur within 2 hr after administration. Its mean plasma half-life is about 12 hr, whereas that of its conjugated metabolite, lorazepam glucuronide, is about 18 hr. Approximately 85% is bound to plasma proteins. There is no evidence of its accumulation on administration for up to 6 months.

Adverse reactions, if they occur, usually appear at the beginning of therapy and disappear on continued medication or on decreasing the dose. Sedation is the most frequent adverse reaction (15.9%) and may persist up to 6 to 8 hours following an injection. Other common side effects include dizziness (6.9%), weakness (4.2%), and unsteadiness (3.4%). Less-frequent adverse effects are disorientation, depression, nausea, headache, sleep disturbance, agitation, dermatological symptoms, eye function disturbance, GI symptoms, and autonomic manifestations. The incidence of sedation and unsteadiness usually increases with age.

It requires the same warnings and precautions regarding use with other drugs, in hypersensitive individuals, during pregnancy and in young children, in elderly and excessively depressed patients, in patients with impaired renal or hepatic function, and in patients with a history of drug addiction that other benzodiazepines require.

MIDAZOLAM HYDROCHLORIDE

4*H*-Imidazo[1,5-*a*][1,4]benzodiazepine, 8-chloro-6-(2-fluorophenyl)-1-methyl-, monohydrochloride; Versed



[59467-96-8]$C_{18}H_{13}ClF_3N.HCl$ (362.23); [59467-70-8] (335.76) (base).

Preparation—One method starts with 2-amino-4-chloro-2′-fluorobenzophenone in eight steps. See *J Org Chem* 1978; 43:936 and 4480.

Description—Colorless crystals melting about 159°; pK_a 6.2.

Solubility—Soluble in water.

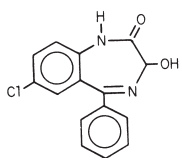
Comments—An imidazobenzodiazepine, short-acting CNS depressant. The sedative potency of midazolam is likely two to four times that of diazepam. It is administered intramuscularly for preoperative sedation and perioperative amnesia. The oral syrup carries the same indications. Because of its relatively rapid onset and short duration, it is considered by some clinicians to be the best benzodiazepine for preoperative use with short surgical procedures. Midazolam also is administered by the intravenous route, often combined with a narcotic, for conscious sedation associated with minor surgical or dental procedures or for short diagnostic or endoscopic procedures. It has been used IV as part of balanced anesthesia (eg, nitrous oxide and oxygen). It also has been administered orally for preoperative sedation and short-term management of insomnia. Midazolam is absorbed rapidly from IM injection sites, and pharmacological effects are apparent within 5 to 15 min and maximal in 20 to 60 min. The duration of action of this drug is 1 to 6 hr. Following IV injection, onset of sedation and amnesic effect is usually within 1 to 5 min. After oral dosing, midazolam is absorbed rapidly from the GI tract and achieves maximum plasma concentration within 1 hr; however, up to 60% is altered with first-pass hepatic metabolism to 1-hydroxymethylmidazolam or 4-hydroxymidazolam. Approximately 95% of midazolam is bound to plasma proteins, and it is excreted principally as a conjugated metabolite in the urine.

Midazolam can cause serious respiratory depression or arrest, especially with high doses, when given IV for conscious sedation. Consequently, it should only be given IV in hospital or ambulatory-care facilities that are equipped to provide respiratory and cardiac monitoring and render resuscitative care if necessary. Patients with chronic obstructive pulmonary disease (COPD) are particularly sensitive to midazolam-induced respiratory depression. There also have been rare reports of hypotensive responses to this drug that required treatment, although changes in blood pressure and heart rate frequently occur after parenteral administration of midazolam. Adverse responses to this drug, which are similar to the side effects of other benzodiazepines, include excessive sedation, drowsiness, prolonged emergence from anesthesia, euphoria, dysphoria, confusion, agitation, sleep disturbance, weakness, lethargy, slurred speech, nausea and vomiting, blurred vision, and visual disturbances. Some local tenderness following parenteral administration of midazolam has been reported but appears to be less than with other benzodiazepines.

Similar cautions should be used for midazolam as used for other benzodiazepines. Midazolam is a potent drug, and dosing should be individualized for the patient. It should not be administered during pregnancy. Midazolam will potentiate the action of other CNS depressants.

OXAZEPAM

2*H*-1,4-Benzodiazepin-2-one, 7-chloro-1,3-dihydro-3-hydroxy-5-phenyl-, Serax



[604-75-1] $C_{15}H_{11}ClN_2O_2$ (286.72).

Preparation—2-Amino-5-chlorobenzophenone is acylated with chloroacetyl chloride, and the product is refluxed with sodium iodide to form the iodoacetamido compound (I). Reaction of I with hydroxylamine effects dehydration and dehydrohalogenation to form the benzodiazepine derivative (II). Treatment of II with acetic anhydride causes rearrangement to oxazepam, which is simultaneously esterified to acetate. Saponification liberates oxazepam.

Description—Creamy white to pale-yellow powder; practically odorless; bitter taste; stable in light and non-hygroscopic; melting point indefinite; pH (1 in 50 suspension) 4.8 to 7.0.

Solubility—1 g in >10,000 mL water, 220 mL alcohol, 270 mL chloroform, or 2200 mL ether.

Comments—A congener of chlordiazepoxide and diazepam; it is a mild sedative useful in the management and control of anxiety, tension, agitation, irritability, and related symptoms, particularly in elderly patients. Also, it is useful for the control of acute tremulousness, inebriation, or anxiety associated with alcohol withdrawal. Unlike diazepam,

this drug is absorbed slowly after oral administration (1–4 hr) and has a simple, one-step elimination pathway without active intermediate metabolites. Its half-life is short (5–15 hr), there is little accumulation, and full therapeutic effect can be expected with the first few doses. However, several daily doses may be necessary to reach a clinical steady state. Excessive and prolonged use may result in the development of physical dependence on the drug. Withdrawal symptoms following abrupt discontinuance of oxazepam are similar to those seen with barbiturates.

As with other sedative agents, patients on this drug should be cautioned against driving automobiles or operating dangerous machinery. Other warnings, contraindications, and precautions are similar to those for other benzodiazepines. Untoward effects include transient mild drowsiness, dizziness, vertigo, headache, and, rarely, syncope. Mild paradoxical reactions such as excitement and excessive stimulation also have been recorded.

Other side effects that have been observed include rashes, nausea, lethargy, edema, slurred speech, tremor, and altered libido. More severe reactions include leukopenia and jaundice. Fortunately, the latter reactions only occasionally are observed. Patients on the drug should be observed carefully for the appearance of other untoward effects characteristic of benzodiazepine drugs.

Benzodiazepine Combinations

Some examples of benzodiazepine combinations (with milligrams/unit provided) are as follows:

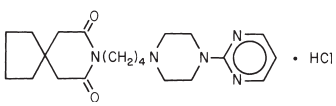
Chlordiazepoxide with Amitryptyline Hydrochloride [Limbritol, Limbritol DS *(Roche)*]—5 or 10 mg with 12.5 or 25 mg, respectively.
Chlordiazepoxide Hydrochloride with Clidinium Bromide [CDP Plus *(Gold Line);* Clindex *(Rugby);* Clindibrax *(Pharmaceutical Basics);* Clinoxide *(Geneva Generics, Halsey);* Librax *(Roche);* Lidox *(Major);* Lidoxide *(Interstate)*—5 mg with 2.5 mg, respectively.

NONBENZODIAZEPINE ANXIOLYTIC AGENTS

An anxiolytic drug that is structurally and pharmacologically distinct from the benzodiazepines and barbiturates is the arylpiperazine derivative, buspirone. This drug is distinguished from the other sedatives because it relieves anxiety without causing drowsiness or impairing psychomotor function and appears to lack abuse potential. Hydroxyzine is a piperazine derivative chemically unrelated to the benzodiazepines, barbiturates, or meprobamate. Hydroxyzine has demonstrated clinical efficacy in the management of neuroses and in emotional disturbances manifested by anxiety, tension, agitation, or apprehension.

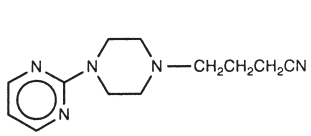
BUSPIRONE HYDROCHLORIDE

Azaspiro[4,5]decane-7,9-dione, 8-[4-[4-(2-pyrimidinyl)-1-piperazinylbutyl-, monohydrochloride; BuSpar

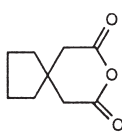


[33386-08-2] $C_{21}H_{31}N_5O_2.HCl$ (421.97).

Preparation—Piperazine and 2-chloropyrimidine are reacted to form 2-(1-piperazinyl)pyrimidine (I). Treatment of I with γ-chlorobutyronitrile *N*-alkylates the free piperazinyl nitrogen atom to yield II. With spirocyclopentane-1, 3′-glutaric anhydride, the free base of buspirone is produced, which is then converted to the hydrochloride; *J Med Chem* 1969; 12:876, and *ibid,* 1972; 15:477.



(II)



(III)

Description—White, crystalline solid melting about 200°; pK_a 1.22 and 7.32.

Solubility—1 g in 1 mL water, 50 mL alcohol.

Comments—An antianxiety agent that is unrelated either chemically or pharmacologically to the benzodiazepines, barbiturates, or other sedative/anxiolytic drugs. It is used in the management of anxiety disorders, the short-term relief of the symptoms of anxiety, or phobic neurosis. Although its long-term effectiveness as an anxiolytic has not been proven, there are reports of use in patients for 6 to 12 months without apparent loss of clinical benefit. The antianxiety effects of buspirone in general have been found to be comparable to that of the benzodiazepines, with some exceptions, while causing fewer adverse CNS side effects, such as sedation, psychomotor impairment, or dependence. Buspirone has been used successfully as an anxiolytic in patients who experience disinhibition or aggressive behavior when taking benzodiazepines. The mechanism of its anxiolytic effect is not known, but appears to be different from that of the benzodiazepines and barbiturates and likely involves multiple transmitter systems, particularly those of a serotonergic nature. It is absorbed rapidly and undergoes extensive first-pass metabolism. However, buspirone tends to have a slow onset of antianxiety action, which can cause patients to be discouraged during initial therapy. Peak plasma levels of 1 to 6 mg/mL usually occur within 40 to 90 min; approximately 95% is bound to plasma protein; 29–63% is excreted in the urine, and 18–38% in the feces. Elimination half-life of the unchanged drug is about 2 to 3 hr.

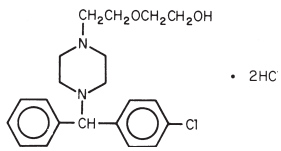
Even though it appears that this drug has no abuse potential and does not induce either tolerance or psychological dependence, patients on the drug should be monitored closely. Although animal studies suggest that the drug does not cause fetal damage, use during pregnancy should be limited to those clearly in need of the medication. Since it is excreted in breast milk, administration to nursing women is not recommended. Safety and efficacy in children under 18 years has not been established.

Common adverse effects include dizziness, nausea, headache, nervousness, drowsiness, lightheadedness, excitement, and mood changes. Chest pain, tachycardia, syncopy, hypo- and hypertension, sore throat, blurred vision, rashes, leukopenia, and shortness of breath also have been observed. Patients should notify their physician if any abnormal chronic muscle movements occur. Although buspirone generally does not impair psychomotor function at usual therapeutic doses, there is enough individual variation that patients should be warned that their ability to perform mental or motor tasks may be impaired.

DOXEPIN HYDROCHLORIDE—page 1520. See *Psychopharmacologic Agents* chapter.

HYDROXYZINE HYDROCHLORIDE

Ethanol, 2-[2-[4-[(4-chlorophenyl)methyl]-1-piperazinyl]ethoxy]-, dihydrochloride; Atarax



[2192-20-3] $C_{21}H_{27}ClN_2O_2.2HCl$ (447.83).

Preparation—By condensing *p*-chlorobenzhydryl chloride (I) with *N*-[2-(2-hydroxyethoxy)ethyl]piperazine (II). Conversion to the hydrochloride may be effected by dissolving the base in a double molar quantity of hydrochloric acid and evaporating the solution to dryness.

It may be synthesized by treating benzaldehyde with *p*-chlorophenylmagnesium bromide and reacting the resulting *p*-chlorobenzhydrol with a suitable halogenating agent. II may be synthesized by interaction of piperazine and ethylene oxide.

Description—White, odorless powder; melts with decomposition about 200°.

Solubility—1 g in 1 mL of water, 4.5 mL of alcohol, 13 mL of chloroform or >1000 mL of ether.

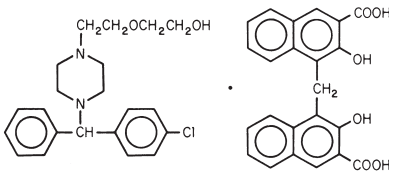
Comments—A piperazine derivative used for the management of neuroses and emotional disturbances characterized by anxiety, tension, agitation, apprehension, or confusion. This includes its use in anxiety and apprehension associated with organic diseases, alcoholism, allergic conditions, pre- and postoperative conditions, and cardiac conditions. Hydroxyzine also is used to control motion sickness, and nausea and vomiting of various causes. It is contraindicated in early pregnancy and in patients who have shown a previous hypersensitivity to it. Like most other sedatives it should be used with caution, with proper dose adjustment in patients on other CNS-depressant drugs. Therefore, when used as preanesthetic medication with other agents, such as meperidine and a barbiturate, the dosage should be adjusted on an individual basis. Be-

cause of its anticholinergic action, the effects of hydroxyzine may be additive with those of atropine and other belladonna alkaloids. Since the drug may cause drowsiness, the patient should be warned not to drive a car or operate hazardous machinery while on the drug.

Adverse reactions are relatively mild and include drowsiness and dryness of the mouth. Less frequent side effects are dizziness, ataxia, agitation, and anxiety. Involuntary motor activities, including rare instances of tremor and convulsions, have been reported. Because of marked local irritation and possible tissue necrosis, hydroxyzine should not be administered by subcutaneous, intra-arterial, or IV injection. Clinical studies substantiate the absence of toxic effects on the liver or blood. *The potentiating effect of this drug must be taken into consideration when it is used in conjunction with CNS-depressants such as narcotics and barbiturates.*

HYDROXYZINE PAMOATE

Ethanol, 2-[2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]-, compd with 4,4′-methylenebis[3-hydroxy-2-naphthalenecarboxylic acid] (1:1); Vistaril



[10246-75-0] $C_{21}H_{27}ClN_2O_2.C_{23}H_{16}O_6$ (763.29).

Preparation—Hydroxyzine, prepared as described under *Hydroxyzine Hydrochloride,* is reacted with an equimolar portion of 4,4′-methylenebis[3-hydroxy-2-naphthoic acid].

Description—Light-yellow, practically odorless, powder.

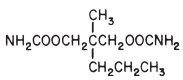
Solubility—1 g in >1000 mL water, 700 mL alcohol, >1000 mL chloroform, >1000 mL ether, or 10 mL dimethylformamide.

Comments—See *Hydroxyzine Hydrochloride.*

IMIPRAMINE HYDROCHLORIDE—see *Psychopharmacologic Agents* chapter.

MEPROBAMATE

1,3-Propanediol, 2-methyl-2-propyl-, dicarbamate



[57-53-4] $C_9H_{18}N_2O_4$ (218.25).

Preparation—2-Methyl-2-*n*-propyl-1,3-propanediol, in toluene solution, is condensed at about 0° with phosgene in the presence of dimethylaniline to yield the chloroformate diester, which is then subjected to ammonolysis to form the dicarbamate ester.

Description—White powder; characteristic odor and a bitter taste; melts within a range of 2° between 103° and 107°.

Solubility—Slightly soluble in water; freely soluble in alcohol or acetone; sparingly soluble in ether.

Comments—A propanediol derivative chemically related to mephenesin, indicated for the management of *anxiety disorders* or for the short-term relief of the *symptoms of anxiety*. Anxiety or tension associated with the stress of everyday life usually does not require treatment with an anxiolytic. It is contraindicated in patients with acute, intermittent porphyria and in patients allergic to meprobamate or related agents, such as carisoprodol, mebutamate, or carbromal. Much like the barbiturates, physical and psychological dependence is known to occur after chronic use of high doses. Sudden withdrawal of the drug after prolonged, excessive use should be avoided to minimize withdrawal effects. Withdrawal symptoms usually appear 12 to 48 hr after discontinuation of meprobamate and usually cease within the next 12 to 48 hr. The drug should not be prescribed for patients with a history of drug abuse or those known to increase the dosage of drugs on their own initiative. Patients should be warned not to attempt potentially hazardous tasks or take other CNS-depressant drugs while on this drug. The drug should be used with caution in elderly or debilitated patients, epileptic patients, patients with compromised hepatic or renal function, and patients with suicidal tendencies. It is capable of producing a variety of side effects and untoward reactions. Briefly, these include *CNS:* drowsiness, ataxia, dizziness, slurred speech, headache, vertigo, weakness, paresthesias, impaired visual accommodation, euphoria, overstimulation, and paradoxical excitement; *GI:* nausea, vomiting, and diarrhea; *cardiovascular:* palpitation, arrhythmias, syncope, and hypotensive crises; *allergic or idiosyncratic:* a variety of reactions including various skin, blood, and hypersensitivity reactions (also, Stevens- Johnson syndrome and bullous dermatitis) have been observed: *hematological:* agranulocytosis, aplastic anemia, and rare cases of thrombocytopenic purpura have been reported. Exacerbation of porphyric symptoms also has been observed.

Plasma half-life ranges from 6 to 17 hr (average 10 hr). Therapeutic blood levels range from 0.5 to 2.0 mg%; levels of 3 to 10 mg% usually correlate with mild-to-moderate symptoms of overdosage, ie, stupor or slight coma; and levels of 10 to 20 mg%, with deeper coma requiring intensive therapy, with some fatalities occurring. At levels above 20 mg% more fatalities than survivors can be expected. It is evident, therefore, that the drug should be employed with the same discretion as other CNS-depressant agents and with due cognizance of the possibility of untoward effects.

PAROXETINE HYDROCHLORIDE—see *Psychopharmacologic Agents* chapter.

VENLAFAXINE HYDROCHLORIDE—see *Psychopharmacologic Agents* chapter.

BARBITURATES

The introduction of barbital in 1903 and phenobarbital in 1912 initiated the barbiturate era. For over half a century they reigned as the preeminent sedative-hypnotic agents. Although several so-called nonbarbiturates attempted to displace the barbiturates from time to time, it was not until chlordiazepoxide was marketed in 1961 that their position was challenged seriously. The benzodiazepine hypnotics and several of the nonbenzodiazepine hypnotics (zolpidem, zaleplon) have replaced the use of barbiturates as hypnotics. Barbiturates are rapidly tolerated, have a high risk of abuse and dependence, and a narrow margin of safety, and significant drug interactions.[20] Because of the safety considerations, the barbiturates have few indications as hypnotics.

The development of clinical pharmacokinetic data on hypnotic drugs revealed that the traditional classification of barbiturates into long-, intermediate-, and short-acting compounds bears little relation to the rate of elimination of these agents in man. Moreover, these data indicate that onset (rate of absorption) and duration of action (rate of elimination) are essential factors to be considered in their use. In general, barbiturate salts are absorbed rapidly, in contrast to the free acids. Liver disease tends to decrease the elimination rate of these substances, whereas renal insufficiency may give rise to accumulation of polar metabolites. For these reasons and for ready reference, the elimination half-lives, apparent volumes of distribution, and clearance values of barbiturates are summarized in each monograph.

Although traditionally used as nonspecific CNS depressants for daytime sedation and short-term treatment of insomnia, the barbiturates generally have been replaced by the benzodiazepines for these purposes. However, they are still given for preoperative medication to allay anxiety and facilitate induction of anesthesia. The anticonvulsant barbiturates, such as phenobarbital, mephobarbital, and metharbital, are still useful alternatives for the long-term management of generalized tonic-clonic and cortical focal seizures and are given intravenously for the management of acute convulsive episodes, such as status epilepticus, eclampsia, meningitis, tetanus, and toxic reactions to strychnine or local anesthetics. The barbiturates also are administered rectally to infants and children when oral or parenteral therapy may be undesirable.

Elixirs of certain barbiturates are still available for use as somnifacients and sedatives for children, despite the availability of more effective agents. They also are used in the relief of colic, excitation, and restlessness due to illness. Sedative doses may be administered as frequently as 3 to 4 times a day in cases of pylorospasm, whooping cough, nausea, and vomiting of functional origin, etc.

Barbiturates are contraindicated in patients with a history of porphyria. They should be used with caution in patients with

impaired hepatic or renal function and in debilitated patients with depressed respiration. They also are contraindicated in persons with known previous addiction to the sedative/hypnotic drugs. Moreover, they should not be used in women of childbearing age, since their safe use in pregnancy has not been established. Patients on barbiturates should avoid alcoholic beverages as well as other CNS depressants and refrain from driving an automobile or operating hazardous machinery while receiving such drugs.

Drug interactions are relatively common in patients taking barbiturates in combination with other drugs. For this reason patients on these drugs should be monitored closely. The most common problems relate to the ability of barbiturates (especially phenobarbital) to induce the hepatic microsomal enzyme system and increase the rate of metabolism of coumarin anticoagulants, tricyclic antidepressants, oral contraceptives, corticosteroids, digitoxin, phenytoin, phenothiazines, doxycycline, and other agents. Accordingly, the effectiveness of these agents may be decreased when given to a patient already on a barbiturate, and contrariwise, patients on both a barbiturate and one of these agents may experience adverse effects if the barbiturate is discontinued during chronic therapy, ie, a patient on coumarin may hemorrhage if the barbiturate is stopped and the anticoagulant dosage is not readjusted.

Barbiturates (especially phenobarbital) may competitively inhibit the metabolism of some drugs, such as phenytoin. Barbiturates have been shown to decrease the GI absorption of dicumarol and griseofulvin. Some barbiturates potentiate the adverse effects of tricyclic antidepressants by competing for the same hydroxylating enzymes. MAO inhibitors, valproic acid, chloramphenicol, and acute alcoholic intoxication inhibit the metabolism of barbiturates. Chronic alcoholic intoxication, on the other hand, increases the metabolism of barbiturates. Concomitant use of ether or curare-like drugs may produce additive respiratory depression. It also has been suggested that sulfisoxazole competes with thiopental for plasma-protein binding sites and decreases the amount of the latter necessary for anesthesia. Finally, additive depressant effects may occur with concomitant use of barbiturates and other CNS-depressant drugs.

Adverse reactions to barbiturates include:

CNS: somnolence, agitation, confusion, hyperkinesia, ataxia, nightmares, lethargy, paradoxical excitement, nervousness, hallucinations, insomnia, anxiety, and dizziness.
Respiratory: apnea, hypoventilation, respiratory depression, bronchospasm, and circulatory collapse.
Cardiovascular: bradycardia, hypotension, and syncope.
Hypersensitivity: rashes, angioneurotic edema, fever, serum sickness, morbiliform rash, urticaria, exfoliative dermatitis, and Stevens-Johnson syndrome.
Other: physical and psychological dependence, headache, blood dyscrasias, myalgia, neuralgia, and arthritic pain.

For these and other reasons mentioned in this section, their indiscriminate use should be avoided.

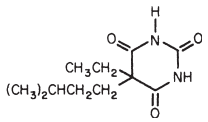
Accidental and suicidal deaths from acute barbiturate poisoning are encountered, but the incidence has decreased with their diminished use. Treatment varies with the degree of intoxication. In general, emergency measures in acute poisoning are directed toward maintenance of respiration and cardiac function, followed by gastric decontamination. The latter is accomplished by gastric lavage, administration of activated charcoal (20–25 g in a child, 50 g in an adult) by gastric lavage tube, and a saline cathartic to clear the gut. In severe intoxication, measures to enhance elimination of absorbed barbiturate may be necessary, such as diuresis, urine alkalinization, dialysis, and hemoperfusion. The prognosis in barbiturate poisoning, with adequate medical care, is very good; mortality is less than 1%.

Continual use of barbiturates can result in tolerance, which encourages an increase in dosages. Tolerance to the effects of barbiturates on mood, sedation, and hypnosis is greater than tolerance to respiratory depression; consequently, with tolerance comes a decrease in the therapeutic index.

Serious withdrawal symptoms, including convulsions and psychoses, may occur when a barbiturate is withheld from dependent patients. In some chronically intoxicated individuals, even though they have no previous history of epilepsy, major convulsive seizures follow the sudden withdrawal of barbiturate. It is advisable to reduce the dose of barbiturate gradually in both epileptic and nonepileptic patients when cessation of chronic barbiturate medication is contemplated. It also should be emphasized that barbiturate therapy is contraindicated in patients with a history of drug addiction.

AMOBARBITAL

2,4,6(1*H*,3*H*,5*H*)-Pyrimidinetrione, 5-ethyl-5-(3-methylbutyl)-, Amylobarbitone; Amytal



5-Ethyl-5-isopentylbarbituric acid [57-43-2] $C_{11}H_{18}N_2O_3$ (226.27).

Preparation—A typical method starts with monochloroacetic acid, which is treated with sodium cyanide to form cyanoacetic acid; the latter is reacted with hydrochloric acid in the presence of alcohol, yielding the diethyl ester of malonic acid. This ester, in absolute alcohol solution, is treated with the theoretical quantity of metallic sodium to replace one hydrogen of the CH_2 group, then a slight excess of the theoretical amount of an ethylating agent, such as ethyl bromide, is added. The second hydrogen is replaced similarly, using isopentyl bromide as the alkylating agent. The diethyl ester of ethyl isopentyl malonic acid thus obtained is heated in an alcoholic solution, in the presence of sodium, with urea. Sodium amobarbital is formed, from which amobarbital is liberated with HCl. The alkylation of the CH_2 group of the malonic ester, whether the alkyls are both the same as in barbital or different, as in amobarbital, may be done in two stages, introducing one alkyl group at a time.

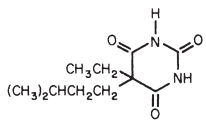
Description—White, crystalline, odorless, bitter powder; pH (saturated solution) about 5.6; melts within a 3° range between 156° and 161°.

Solubility—1 g in about 1300 mL of water, 5 mL of alcohol, about 17 mL of chloroform, or 6 mL of ether; soluble in solutions of fixed alkali hydroxides and carbonates.

Comments—A *sedative* and *hypnotic*. It may be used in any condition that requires sedation, ranging from relief of anxiety and tension to hypnotic doses for preanesthetic medication. Because of tolerance, its use as a hypnotic is limited to 2 weeks. See the introductory statement on *Barbiturates*. It is a *Schedule II* drug under the *Controlled Substances Act*.

AMOBARBITAL SODIUM

2,4,6(1*H*,3*H*,5*H*)-Pyrimidinetrione, 5-ethyl-5-(3-methylbutyl)-, monosodium salt; Amylobarbitone Sodium; Amytal Sodium



Sodium 5-ethyl-5-isopentylbarbiturate [64-43-7] $C_{11}H_{17}N_2NaO_3$ (248.26).

Preparation—By reacting amobarbital with a solution containing a chemically equivalent quantity of sodium hydroxide or sodium carbonate, evaporating to dryness, and crystallizing the residue from a solution in a suitable solvent such as alcohol.

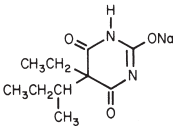
Description—White, friable, hygroscopic, odorless, granular powder with a bitter taste; pH (1 in 20 solution) 9.6 to 10.4.

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

Comments—A *hypnotic* and *sedative*. It is indicated for sedation and relief of anxiety, preanesthetic medication, and the control of acute convulsive disorders. The onset of action varies from 45 to 60 min, half-life is approximately 25 hr, and duration of action is 6 to 8 hr. See the introductory statement on *Barbiturates*. It is a *Schedule II* drug under the *Controlled Substances Act*.

BUTABARBITAL SODIUM

2,4,6(1*H*,3*H*,5*H*)-Pyrimidinetrione, 5-ethyl-5-(1-methylpropyl)-, monosodium salt; Butisol Sodium



Sodium 5-*sec*-butyl-5-ethylbarbiturate [143-81-7] $C_{10}H_{15}N_2NaO_3$ (234.23).

Preparation—By preparing butarbital using a method similar to that for *Amobarbital,* using ethyl bromide and *sec*-butyl bromide as the alkylating agents. Then treating an alcoholic solution of butabarbital with an equimolar quantity of NaOH and removing the solvent by evaporation.

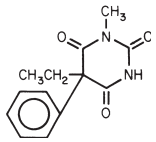
Description—White, bitter powder; pH (1 in 10 solution) 9.5 to 10.2.

Solubility—1 g in 2 mL of water, 7 mL of alcohol, 7000 mL of chloroform, or >10,000 mL of ether.

Comments—A *sedative* and *hypnotic*. Used for short-term treatment of insomnia. Because of tolerance, barbiturates lose efficacy after 2 weeks of use. See the introductory statement on *Barbiturates*. It is a *Schedule III* drug under the *Controlled Substances Act*.

MEPHOBARBITAL

2,4,6(1*H*,3*H*,5*H*)-Pyrimidinetrione, 5-ethyl-1-methyl-5-phenyl-, Prominal; Phemitone; Mebaral



5-Ethyl-1-methyl-5-phenylbarbituric acid [115-38-8] $C_{13}H_{14}N_2O_3$ (246.27).

Preparation—The diethyl ester of ethylphenylmalonic acid is prepared by the general method described under *Amobarbital* and is then condensed with *N*-methylurea in the presence of sodium ethylate. The resulting sodium mephobarbital is treated with HCl, whereupon mephobarbital crystallizes.

The *N*-methylurea is prepared as follows. Methylamine is passed into a mixture of sulfuric acid and absolute alcohol until the mixture is alkaline. Potassium cyanate then is added, and the mixture is refluxed overnight, whereupon the monomethyl ammonium cyanate produced initially by metathesis rearranges (Wöhler) to *N*-methylurea.

Description—White, crystalline powder; odorless; bitter taste; saturated solution acid to litmus; melts about 178°; pK_a 8.8.

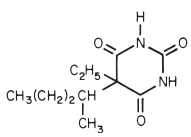
Solubility—1 g in >1000 mL water, >1000 mL alcohol, 50 mL chloroform, or >1000 mL ether; soluble in solutions of fixed alkali hydroxides or carbonates.

Comments—A barbiturate with strong *sedative* and *anticonvulsant* actions but a relatively mild *hypnotic* action. Hence, it is used for relief of anxiety, tension, and apprehension and as an antiepileptic in the management of generalized tonic-clonic (grand mal) and absence (petit mal) seizures. See also the introductory statement on *Barbiturates*.

METHOHEXITAL SODIUM—page 1476.

PENTOBARBITAL

2,4,6(1*H*,3*H*,5*H*)-Pyrimidinetrione, 5-ethyl-5-(1-methylbutyl)-, Nembutal



5-Ethyl-5-(1-methylbutyl)barbituric acid [76-74-4] $C_{11}H_{18}N_2O_3$ (226.27).

Preparation—By the general method described under *Amobarbital*, using ethyl bromide and 1-methylbutyl bromide as alkylating agents.

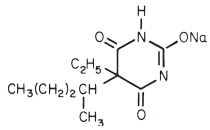
Description—White to practically white, fine powder; practically odorless; melts about 130°.

Solubility—1 g in >2000 mL water, 4.5 mL alcohol, 4 mL chloroform, or 10 mL ether.

Comments—see *Pentobarbital Sodium*. It is a *Schedule II* drug under the *Controlled Substances Act*.

PENTOBARBITAL SODIUM

2,4,6(1*H*,3*H*,5*H*)-Pyrimidinetrione, 5-ethyl-5-(1-methylbutyl)-, monosodium salt; Pentobarbitone Sodium; Soluble Pentobarbital; Nembutal Sodium



Sodium 5-ethyl-5-(1-methylbutyl)barbiturate [57-33-0] $C_{11}H_{17}N_2\ NaO_3$ (248.26).

Preparation—By the process given for *Amobarbital*, using 2-bromopentane instead of ethyl bromide to react with one of the hydrogens in the CH_2 of the malonyl group. It then is converted into the soluble sodium salt by the addition of the required amount of NaOH.

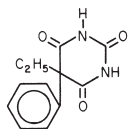
Description—White, odorless, crystalline granules or a white powder with a slightly bitter taste; pH (1 in 10 solution) 10.0 to 10.5 when used in parenterals; otherwise, 9.7 to 10.2; solutions decompose on standing, heat accelerating the decomposition; $pK_{a}1$ 8.17; $pK_{a}2$ 12.67.

Solubility—Very soluble in water; freely soluble in alcohol; practically insoluble in ether.

Comments—Used as a *sedative* or *hypnotic* for the short-term (up to 2 weeks) management of insomnia and as preanesthetic medication. It also is indicated, in anesthetic doses administered intravenously, for control of certain convulsive syndromes. This barbiturate is thought to reduce cerebral blood flow and thereby decrease edema and/or intracranial pressure. See also the introductory statement on *Barbiturates*. It is a *Schedule II* drug under the *Controlled Substances Act*.

PHENOBARBITAL

2,4,6(1*H*,3*H*,5*H*)-Pyrimidinetrione, 5-ethyl-5-phenyl-, Phenylethylmalonylurea; Phenobarbitone; Luminal



5-Ethyl-5-phenylbarbituric acid [50-06-6] $C_{12}H_{12}N_2O_3$ (232.24).

Preparation—Benzyl chloride is converted into phenylacetic ester (ethyl phenylacetate) by treating with sodium cyanide and then hydrolyzing with acid in the presence of alcohol. The ester is condensed in the presence of alcohol and metallic sodium with ethyl oxalate, forming diethyl sodium phenyloxaloacetate. HCl is added to liberate diethyl phenyloxaloacetate, which on being distilled at 180° splits off carbon monoxide and forms phenylmalonic ester [$C_6H_5CH(COOC_2H_5)_2$]. The hydrogen of the CH in the phenylmalonic ester is then ethylated, and the resulting ethylphenylmalonic ester condensed with urea as described under *Amobarbital*.

Description—White, odorless, glistening, small crystals or a white crystalline powder, which may exhibit polymorphism; stable in air; pH (saturated solution) about 5; melts about 176°; pK_a 7.6.

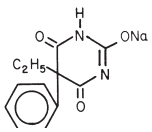
Solubility—1 g in about 1000 mL water, 10 mL alcohol, about 40 mL chloroform, or 15 mL ether.

Comments—This classical barbiturate is a *sedative, hypnotic,* and *antiepileptic* drug. In appropriate doses it is used in neuroses and related tension states when mild, prolonged sedation is indicated, as in hypertension, coronary artery disease, functional GI disorders and preoperative apprehension. In addition, it has specific usefulness in the symptomatic therapy of *epilepsy*. It is especially useful in patients with generalized tonic-clonic seizures (grand mal) and complex partial (psychomotor) seizures. Effective doses usually produce a degree of drowsiness or sluggishness. Phenobarbital also has been found to be effective in the treatment and prevention of hyperbilirubinemia in neonates. Approximately 80% of an oral dose is absorbed, and peak plasma levels are reached in 16 to 18 hr. Because of its slow onset of action, phenobarbital generally is not used orally to treat insomnia, but is used to help withdraw people who are physically dependent on

other CNS depressants. The apparent volume of distribution is 0.7 to 1 L/kg. Therapeutic plasma levels range from 10 to 30 μg/mL. About 45 to 50% of the drug is bound to plasma protein. Apparent plasma half-life varies from 50 to 120 hr in adults and 40 to 70 hr in children. Approximately 65% of the drug is metabolized (largely to the inactive *p*-hydroxyphenyl derivative), and 35% is excreted by the kidney unchanged. Plasma clearance is slow and approximates 0.004 L/kg/hr. With the exception of metharbital and mephobarbital, this is the only barbiturate effective in epilepsy. See the introductory statement on *Barbiturates*.

PHENOBARBITAL SODIUM

2,4,6(1*H*,3*H*,5*H*)-Pyrimidinetrione, 5-ethyl-5-phenyl-, monosodium salt; Sodium Phenobarbital; Soluble Phenobarbital; Phenobarbitone Sodium; Luminal Sodium



Sodium 5-ethyl-5-phenylbarbiturate [57-30-7] $C_{12}H_{11}N_2NaO_3$ (254.22).

Preparation—By dissolving phenobarbital in an alcohol solution of an equivalent quantity of NaOH and evaporating at low temperature.

Description—Flaky crystals or white, crystalline granules, or white powder; odorless; bitter taste; hygroscopic; solutions alkaline to phenolphthalein and decompose on standing; pH (1 in 10 solution) 9.2 to 10.2.

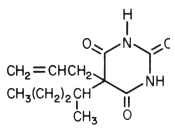
Solubility—Very soluble in water; soluble in alcohol; practically insoluble in ether or chloroform.

Comments—Because it is soluble in water, it may be administered parenterally. It is given by slow intravenous injection for control of acute convulsive syndromes. For additional information see *Phenobarbital* and the introductory statement on *Barbiturates*.

Note: Doses should be reduced significantly in elderly or debilitated patients. No barbiturate should be given parenterally without full knowledge of its particular characteristics, dosage, and recommended rate of administration. Because of potentially severe respiratory depression, phenobarbital sodium should not be administered at a rate that exceeds 60 mg/min.

SECOBARBITAL

2,4,6(1*H*,3*H*,5*H*)-Pyrimidinetrione, 5-(1-methylbutyl)-5-(2-propenyl)-, Seconal



5-Allyl-5-(1-methylbutyl)barbituric acid [76-73-3] $C_{12}H_{18}N_2O_3$ (238.29).

Preparation—By the general method described under *Amobarbital*, using allyl bromide and 1-methylbutyl bromide as alkylating agents at the 5-position.

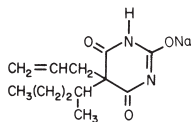
Description—White, amorphous or crystalline, odorless powder; slightly bitter taste; pH (saturated solution) about 5.6; melts about 98°.

Solubility—Very slightly soluble in water; freely soluble in alcohol, ether, or solutions of alkali hydroxides; soluble in chloroform.

Comments—A *sedative* and *hypnotic*. See also *Secobarbital Sodium* and the introductory statement on *Barbiturates*. It is a *Schedule II* drug under the *Controlled Substances Act*.

SECOBARBITAL SODIUM

2,4,6(1*H*,3*H*,5*H*)-Pyrimidinetrione, 5-(1-methylbutyl)-5-(2-propenyl)-, monosodium salt; Quinalbarbitone Sodium; Seconal Sodium



Sodium 5-allyl-5-(1-methylbutyl)barbiturate [309-43-3] $C_{12}H_{17}N_2NaO_3$ (260.27).

Preparation—By treatment of secobarbital with a chemically equivalent portion of NaOH as described under *Phenobarbital Sodium*.

Description—White, odorless, hygroscopic powder; bitter taste; pH (1 in 20 solution) 9.7 to 10.5; solutions decompose on standing, heat accelerating the decomposition.

Solubility—Very soluble in water; soluble in alcohol; practically insoluble in ether.

Comments—A short-acting barbiturate widely used *sedative* and *hypnotic*. The drug also is used, in anesthetic doses intravenously, for the control of certain acute convulsive conditions, such as those associated with tetanus, status epilepticus, and toxic reactions to strychnine and local anesthetics. Within 2 hr after oral administration, 90% is absorbed from the GI tract. The effect after a hypnotic dose occurs in 15 to 30 min with oral or rectal administration and persists for 1 to 4 hr. The elimination half-life is about 30 hr. Secobarbital has been used rectally in children to induce anesthesia. See the introductory statement on *Barbiturates*. It is a *Schedule II* drug under the *Controlled Substances Act*.

THIOPENTAL SODIUM—page 1476.

Barbiturate Combinations

Some examples of barbiturate combinations (with milligrams/unit provided) are as follows:

Butalbital, Acetaminophen and Caffeine [Fioricet *(Sandoz)*]—50, 325, and 40 mg, respectively.

Butalbarbital, Aspirin and Caffeine [Fiorinal *(Sandoz)*]—50, 325, and 40 mg, respectively.

NONBARBITURATE HYPNOTICS

Benzodiazepine Hypnotics

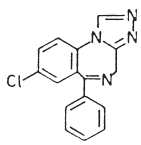
Benzodiazepines markedly influence CNS activity of humans in both the awake and sleep state. In the waking human electroencephalogram (EEG), alpha activity is decreased, fast activity (primarily beta) is increased, and the energy content of the EEG is decreased.

With respect to sleep, the benzodiazepines decrease sleep latency and decrease the number of awakenings and the time spent in Stage 0 (wakefulness). They also increase the awakening threshold. The time spent in Stage 1 (descending drowsiness) is decreased by flurazepam, and lorazepam, but increased by chlordiazepoxide, diazepam, and oxazepam. The time spent in Stage 2 (major fraction of non–rapid eye movement (REM) sleep) is increased by all benzodiazepines. The time spent in Stages 3 and 4 (slow wave sleep) usually is decreased; however, a few agents may increase these stages. Because of suppression of Stage 4 sleep, diazepam has been used to prevent night terrors in adults. Please refer to Table 80-2 for a discussion of the pharmacokinetic parameters of the benzodiazepine hypnotics.[21, 22]

The benzodiazepines increase the latency to REM sleep, decrease REM sleep time, and increase the number of REM cycles. Total sleep time is increased by the benzodiazepines. The greatest increase is observed in subjects with the shortest baseline sleep time. In such individuals, total sleep time may increase threefold.

ESTAZOLAM

4*H*-[1,2,4]Triazolo [4,3-*a*][1,4]benzodiazepine, 8-chloro-6-phenyl-, ProSom



[29975-16-4] $C_{16}H_{11}ClN_4$ (294.74).

Table 80-2. Benzodiazepine Hypnotics

AVAILABLE PREPARATIONS	ORAL DOSAGE EQUIVALENCY (MG)	TIME TO PEAK PLASMA LEVEL (H)	PROTEIN BINDING (%)	ELIMINATION HALF-LIFE (H) PARENT COMPARED	ACTIVE METABOLITE	METABOLIC PATHWAY
Estazolam (ProSom and generics)	2	2	93	12–15	One	Oxidation
Flurazepam (Dalmane and generics)	30	1	97	8	Three	Oxidation N-dealkylation
Quazepam (Doral)	15	2	>95	39	Two	Oxidation N-dealkylation
Temazepam (Restoril and generics)	30	1.5	98	10–15	None	Glucuronidation
Triazolam (Halcion and generics)	0.25	1	90	2	One	Oxidation

Data from Curtis JL, Germaine DM. Sleep Disorders. In: DiPiro JT, Talbert RL, Yee GC, et al, eds. *Pharmacotherapy: A Pathophysiologic Approach,* 5th ed. New York: McGraw Hill, 2002., Arana GW and Rosenbaum JF. *Handbook of Psychiatric Drug Therapy, Fourth Edition.* Philadelphia: Lippincott Williams and Wilkins, 2000, and http://www.efactsweb.com. Accessed June 25, 2003.

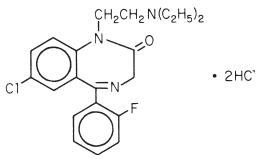
Preparation—From 7-chloro-1,3-dihydro-5-phenyl-2*H*-benzo-[1,4]-diazepin-2-thione and formylhydrazine in boiling *n*-butyl alcohol; see *J Org Chem* 1964; 29:231, and *J Med Chem* 1971;14:1078.

Description—White crystals; melts at about 230°.

Comments—A triazolobenzodiazepine derivative that structurally resembles alprazolam and triazolam. Estazolam has an intermediate half-life: the peak plasma concentration is reached 1.5 to 2 hr after oral administration. It undergoes hepatic microsomal oxidation and has an elimination half-life of 2 to 15 hr. Some clinicians believe that triazolobenzodiazepines, such as estazolam, cause more serious toxicity and withdrawal reactions than other benzodiazepines. The adverse effects of estazolam are like those of other benzodiazepines and include sedation, drowsiness, dizziness, incoordination, and possible recall impairment. Sudden discontinuation can cause significant transient rebound insomnia. Because use of benzodiazepines during pregnancy can result in fetal damage, estazolam should not be administered to pregnant women. Since the elimination of this drug may be slowed in geriatric patients, the doses of estazolam should be individualized carefully for this age group.

FLURAZEPAM HYDROCHLORIDE

2*H*-1,4-Benzodiazepin-2-one, 7-chloro-1-[2-(diethylamino)ethyl]-5-(2-fluorophenyl)-1,3-dihydro-, dihydrochloride; Dalmane



[1172-18-5] $C_{21}H_{23}ClFN_3O.2HCl$ (460.81).

Preparation—Aqueous CrO_3 is added dropwise to an acetic acid solution of 2-aminomethyl-5-chloro-1-2-(diethylamino)ethyl-3- (*o*-fluorophenyl)indole dihydrochloride, and the mixture is stirred overnight. US Pat 3,567,710.

Description—Off-white to yellow, crystalline powder; slight odor to odorless; melts with decomposition about 212°; moderately hygroscopic; pK_a 1.9, 8.2.

Solubility—1 g in 2 mL water; 4 mL alcohol; slightly soluble in chloroform.

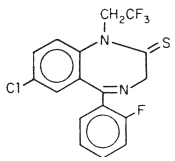
Comments—A benzodiazepine widely used in short-term treatment (up to 4 weeks) of all types of insomnia such as difficulty in falling asleep, frequent nocturnal awakenings, and/or early morning awakening. It also is used in acute and chronic medical situations in which restful sleep is desirable. It is absorbed rapidly from the GI tract and rapidly metabolized by the liver. Following a single oral dose, peak plasma concentrations ranging from 0.5 to 4.0 ng/mL are reached in 60 min. After 7 to 10 days of treatment the major metabolite, N^1-desalkylflurazepam, reaches steady-state levels 5- to 6-fold higher than the 24-hr levels observed on day 1. The parent compound disappears rapidly from the blood; *N*-desalkylflurazepam remains active and has a half-life that ranges from 47 to 100 hr. The major urinary metabolite is conjugated N^1-hydroxyethylflurazepam and accounts for 22–55% of the dose.

This drug is excreted primarily in the urine. Less than 1% is excreted in the urine as N^1-desalkylflurazepam. The onset of sleep ranges from 15 to 45 min. Maximum effectiveness may not be achieved for 3 or 4 nights. Thus, the metabolite is responsible for the clinical effect as well as the residual effects that persist after the drug is discontinued. It requires the same warnings and precautions regarding use with other drug therapy, in hypersensitive individuals, during pregnancy, in children under 12 years, in elderly and excessively depressed patients, in patients with impaired renal or hepatic function, and in patients with a history of drug addiction that other benzodiazepines require.

Adverse reactions include dizziness, drowsiness, lightheadedness, ataxia and falling (especially in elderly or debilitated persons), and severe sedation. The last usually is due to drug intolerance or overdosage. Other reported side effects include headache, heartburn, upset stomach, nausea, vomiting, diarrhea, constipation, GI pain, nervousness, talkativeness, apprehension, irritability, weakness, palpitation, chest pains, body and joint pain, and genitourinary complaints. Less frequently, sweating, flushes, blurred vision, difficulty in focusing, burning eyes, faintness, hypotension, shortness of breath, pruritus, rash, dry mouth, bitter taste, excessive salivation, anorexia, euphoria, depression, slurred speech, confusion, restlessness, hallucinations, and paradoxical reactions (excitement, stimulation, and hyperactivity) have been observed.

QUAZEPAM

2*H*-1,4-Benzodiazepine-2-thione, 7-chloro-5-(2-fluorophenyl)-1,3-dihydro-1-(2,2,2-trifluorethyl)-, Doral



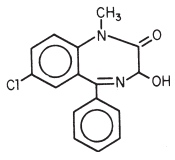
[36735-22-5] $C_{17}H_{11}ClF_4N_2S$ (386.79).

Preparation—It is synthesized in a manner similar to that for midazolam; *J Med Chem* 1974; 16:1354.

Comments—A benzodiazepine with a relatively long elimination half-life (39.3 hr). It is used for the short-term (up to 4 weeks) management of insomnia. Its two principal metabolites (2-oxoquazepam and *N*-desalkylflurazepam) are pharmacologically active with long elimination ($t_{1/2s}$, 40.2 and 69.5 hr). These long half-lives likely account for the drowsiness and hangover effects that persist for 2 to 3 days following discontinuation of therapy. However, because of its slow elimination, this drug is unlikely to cause significant withdrawal such as hyperexcitability or rebound insomnia. Adverse effects, drug interactions, and precautions appear to be similar to those of other benzodiazepines.

TEMAZEPAM

2*H*-1,4-Benzodiazepin-2-one, 7-chloro-1,3-dihydro-3-hydroxy-1-methyl-5-phenyl-, Restoril



[846-50-4] $C_{16}H_{13}ClN_2O_2$ (300.74).

Preparation—The synthesis is similar to that of oxazepam, using 2-(methylamino)-5-chlorobenzhydrol as the starting material. See *J Org Chem* 1962; 27:1691.

Description—White crystals melting about 120°.

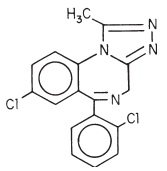
Solubility—Very slightly soluble in water; sparingly soluble in alcohol; pK_a 1.6.

Comments—A hypnotic drug indicated for the short-term (up to 5 weeks) relief of *insomnia* associated with difficulty falling asleep, frequent nocturnal awakenings, and/or early morning awakenings. Oral bioavailability is relatively slow (mean times to peak concentration, 2 to 3 hr); 96% is bound to plasma proteins. Volume distribution ranges from 1.4 to 1.5 L/kg, and clearance from 1.10 to 1.36 mL/kg/min. The elimination half-life varies from 3 to 38 hr (mean, 14.7 hr). It is conjugated with glucuronic acid and excreted in the urine. Since metabolic enzyme induction does not appear to occur after 5 to 7 days of administration, tolerance to repeated use is not troublesome.

Adverse effects are usually mild and diminish with continued administration. Those observed most frequently include morning drowsiness, dizziness, lethargy, confusion, and GI disturbances (anorexia, diarrhea). Other, less-frequent adverse effects include vertigo, dryness of the mouth, paresthesias, tachycardia, panic reactions, nystagmus, paradoxical excitement, and hallucinations. Precautions and possible drug interactions are the same as those for other benzodiazepines. Dysmorphogenic changes in rib formation have been observed in two animal species given 50 to 100 times the human therapeutic dose. Use during pregnancy should be avoided if possible.

TRIAZOLAM

4*H*-1,2,4-Triazolo[4,3-*a*][1,4]benzodiazepine, 8-chloro-6-(2-chlorophenyl)-1-methyl-, Halcion



[28911-01-5] $C_{17}H_{12}Cl_2N_4$ (343.21).

Preparation—Ethyl α-aminoacetate and 2-amino-2′,4-dichlorobenzophenone are reacted in pyridine, which upon elimination of the elements of water and ethanol yields 7-chloro-5-(2-chlorophenyl)benzodiazepin-2-one. The latter, with P_2S_5 forms the 2-thiono derivative, which when treated with acetyl hydrazide gives the 2-acetamidoimino compound (I). Upon heating I over 200°, water is eliminated to form the triazole ring of triazolam. See Ger Pat 2,533,924.

Description—Tan crystals from isopropyl alcohol; melts about 235°.

Solubility—Very slightly soluble in water; slightly soluble in alcohol.

Comments—In the short-term management (up to 6 weeks) of insomnia characterized by difficulty in falling asleep, frequent nocturnal awakenings, and/or early morning awakenings. It is absorbed rapidly after oral administration; approximately 90% is bound to plasma proteins. Time to peak concentration is 1 hr. Volume distribution ranges from 0.8 to 1.3 L/kg. The elimination half-life is 2.0 (1.7–5.2) hr. The metabolites have little if any hypnotic activity. Common adverse effects include drowsiness, dizziness, and headache. Hallucinations and marked confusion also have been reported. Some reports suggest that anterograde amnesia and other side effects, such as confusion, bizarre behavior, agitation, and hallucinations may occur more often with triazolam than with most of the other benzodiazepines. Thus, patients using this drug should be monitored and treatment discontinued if such symptoms appear. Prescribers should be alert to the usual drug interactions common to benzodiazepines. The safe use of this drug during pregnancy or lactation has not been established.

MISCELLANEOUS HYPNOTICS

In addition to the benzodiazepines and barbiturates discussed in the previous two sections, there are a number of other agents that possess hypnotic properties. These are derived from several heterogeneous structures, including alcohols (ethchlorvynol), chloral hydrate, cyclic ether (paraldehyde), piperidinediones (glutethimide, methyprylon), imidazopyridines (zolpidem) and pyrazolopyrimidines (zaleplon). In addition to their hypnotic properties, several of these substances possess anticonvulsant, antispasmodic, local anesthetic, and weak antihistaminic properties. Zolpidem is an imidazopyridine agent that is an agonist at the benzodiazepine omega$_1$ receptor component of the $GABA_A$ receptor.[23] Zolpidem has shown weaker anxiolytic, anticonvulsant, and myorelaxant effects than benzodiazepines.[24] Today, zolpidem is the most commonly prescribed hypnotic, and it ranked 38th out of the top 200 most commonly prescribed medications in 2002.[14] Zaleplon, like zolpidem, acts as a selective agonist at the benzodiazepine omega$_1$ receptor subunit of the $GABA_A$ receptor complex in the brain.[25]

The older hypnotics, including ethchlorvynol, chloral hydrate, methprylon, glutethimide, and paraldehyde, do not differ qualitatively from the barbiturates in their desirable and undesirable effects. Hence, patients should be cautioned about concomitant use of alcohol or other CNS depressants and warned about operating a motor vehicle or hazardous machinery while on such drugs. It should be remembered that safe and effective use of many of these agents during pregnancy and in pediatric patients has not been established. Also, many of these agents will produce physical dependence and habituation when taken chronically in excessive doses. For this reason, glutethimide is listed in *Schedule II* under the *Controlled Substances Act*. Other substances in this section have lower abuse potential and are listed in *Schedule IV*. Nevertheless, they all should be used with caution in patients with a previous history of drug dependence. Again, due to safety considerations, use of these agents has largely been replaced by the hypnotic benzodiazepines and the nonbenzodiazepines zolpidem and zaleplon.

CHLORAL HYDRATE

1,1-Ethanediol, 2,2,2-trichloro-, Chloral

$CCl_3CH(OH)_2$ Chloral hydrate [302-17-0] $C_2H_3Cl_3O_2$ (165.40).

Preparation—By hydration of trichloroacetaldehyde (chloral) obtained by action of chlorine on alcohol.

Description—Colorless, transparent, or white crystals; aromatic, penetrating, and slightly acrid odor; slightly bitter, caustic taste. Melts about 55°; slowly volatilizes in air.

Solubility—1 g in 0.25 mL water, 1.3 mL alcohol, 2 mL chloroform, or 1.5 mL ether; very soluble in olive oil.

Comments—Principally for the short-term (2-week) treatment of insomnia. It is used preoperatively to allay anxiety and to induce sedation and/or sleep. It is used postoperatively as an adjunct to opiates and other analgesics to control pain. It also has been used to produce sleep prior to EEG evaluations. It is also effective in reducing anxiety associated with the withdrawal of alcohol and other drugs such as opiates and barbiturates.

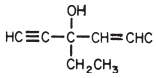
Following oral administration, chloral hydrate is converted rapidly to trichloroethanol (TCE), which is largely responsible for its hypnotic action. Other metabolites are trichloroacetic acid (TCA) and trichloroethanolglucuronide (TCEG). Peak plasma levels of TCE and TCEG are reached in 20 to 60 min; plasma half-lives are 8.0 (7.0–9.5) hr and 6.7 (6.0–8.0) hr for TCE and TCEG, respectively. The half-life for TCA is 4 days. These data suggest that this drug has desirable properties, since the half-life of its active metabolite is short. The formation of TCA is a matter of concern, since its effect on the patient is unknown. It must be used with caution in patients receiving oral anticoagulants because TCA displaces warfarin from plasma protein binding sites; it is likely that dicumarol is affected similarly. Also, concomitant administration of alcohol and chloral hydrate should be avoided; significant potentiation may occur.

Gastric irritation occurs in some patients. Paradoxical excitement is observed rarely. The continued use of large doses causes peripheral vasodilation, hypotension, ventilatory depression, arrhythmias, and myocardial depression. Overdosage produces symptoms similar to those caused by barbiturate overdosages and may result in coma. Patients with serious heart, kidney, or liver disease should not be given this drug. If gastritis is present, the drug may be administered by rectum in olive oil as a retention enema. The acute toxic oral dose for adults is approximately 10 g; death has been reported after as little as 4 g, and individuals have survived after ingesting 30 g.

For oral use, it is sometimes given in a flavored syrup. As alkali causes decomposition of chloral hydrate, it is important that the vehicle not be alkaline.

ETHCHLORVYNOL

1-Penten-4-yn-3-ol, 1-chloro-3-ethyl-, Placidyl



[113-18-8] C_7H_9ClO (144.60).

Preparation—By reacting ethyl chlorovinyl ketone (I) with lithium acetylide under Grignard reaction conditions. The alkoxide addition complex reacts readily with dilute acid to form crude ethchlorvynol, which is extracted with a suitable water-immiscible organic solvent such as ether and is subsequently purified by distillation. Compound I may be prepared in good yield by addition of propionyl chloride to acetylene at a temperature of about 40° in the presence of zinc chloride. US Pat 2,746,900.

Description—Colorless to yellow liquid with a characteristic pungent odor; darkens on exposure to light and air; specific gravity 1.068 to 1.071; refractive index 1.476 to 1.480; boils about 170°.

Solubility—Immiscible with water; miscible with most organic solvents.

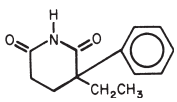
Comments—A mild hypnotic that induces sleep within 15 min to 1 hr and has a duration of action of approximately 5 hr. Elimination half-life varies from 10 to 25 hr. Its effect is less profound and not as predictable as that obtained with benzodiazepines. It is indicated as short-term (up to 1 week) hypnotic therapy in insomnia. This drug is thought to have little effect on REM sleep; hence, REM rebound is not a major problem. It has been reported to increase the metabolism of coumarin anticoagulants by enzyme induction; patients on oral anticoagulants should be monitored closely when this drug is started or stopped. It is contraindicated in patients with porphyria and those with known hypersensitivity to the drug.

Patients should be cautioned about concomitant use of alcohol, barbiturates, other CNS depressants, or MAO inhibitors, since such combinations may produce exaggerated depressant effects. Also, they should be warned against operating a motor vehicle or hazardous machinery while on the drug. The excessive chronic use of large doses has been reported to cause psychic and physical dependence, tolerance, and withdrawal symptoms much like that caused by chronic use of barbiturates or alcohol and including severe convulsions when the drug is discontinued. It should not be used in patients with a history of drug abuse, mental depression, or suicidal tendencies, and the drug should be withdrawn gradually from patients taking excessive quantities. The drug is metabolized primarily by the liver, although the kidneys appear to contribute also.

Side effects, such as nausea, mental confusion, headache, and dermatitis, have been observed in some patients. In addition, hypotension, blurring of vision, dizziness, facial numbness, and allergic reactions have been reported. There have been rare reports of cholestatic jaundice and a few instances of thrombocytopenia. The safe and effective use of this agent during pregnancy and in pediatric patients has not been established.

GLUTETHIMIDE

2,6-Piperidinedione, 3-ethyl-3-phenyl-, Doriden



2-Ethyl-2-phenylglutarimide [77-21-4] $C_{13}H_{15}NO_2$ (217.27).

Preparation—Benzyl cyanide in toluene solution is treated with ethyl chloride in the presence of sodamide to yield α-ethylbenzyl cyanide. This is then caused to undergo addition (Michael condensation) to methyl acrylate under the catalytic influence of piperidine, thus forming methyl 4-cyano-4-phenylhexanoate (I). After purifying by low- pressure distillation, I is cyclized in acid medium. The cyclization may be represented as involving hydration of the cyanide group to amide and saponification of the ester, followed by dehydration between the amide and carboxyl groups.

Description—White, crystalline powder; saturated solution slightly acid; melts about 88°.

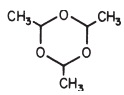
Solubility—Freely soluble in ethyl acetate, acetone, ether, or chloroform; soluble in alcohol or methanol; practically insoluble in water.

Comments—A hypnotic used to induce sleep in all types of insomnia. Overdosage is less likely to depress respiration but more likely to cause hypotension than most barbiturates. The onset of action begins about 30 min after the administration of a hypnotic dose and generally lasts from 4 to 8 hr. Oral absorption is variable, with peak plasma level times between 1 and 6 hr. Elimination half-life varies from 5 to 22 hr, with an average value of 11.6 hr. It is contraindicated in hypersensitive patients, and patients should be warned about the concomitant use of alcohol and other CNS-depressant drugs. Patients also should be cautioned about engaging in activities that require alertness until 4 or 5 hr have elapsed following ingestion of the drug. It induces liver microsomal enzymes; therefore, therapy in patients on coumarin anticoagulants may require adjustment of the coumarin dose during and upon cessation of such therapy.

Adverse reactions include a generalized rash (in this case the drug should be withdrawn); occasionally, a purpuric or urticarial rash; exfoliative dermatitis has been observed rarely; nausea, hangover, paradoxical excitation, and blurred vision have occurred. Some of these side effects may be due to the anticholinergic activity of this drug. Porphyria or blood dyscrasias (thrombocytopenic purpura, aplastic anemia, or leukopenia) also have been reported. Habituation and physical dependence, like that which occurs with the barbiturates, may result from the prolonged administration of excessive doses. It is currently a *Schedule II* drug under the *Controlled Substances Act*. The drug should be used with caution in patients with a history of drug abuse.

PARALDEHYDE

1,3,5-Trioxane, 2,4,6-trimethyl-, Paracetaldehyde; Paral



2,4,6-Trimethyl-*s*-trioxane [123-63-7] $C_6H_{12}O_3$ (132.16); a trimer of acetaldehyde.

Caution—*It is subject to oxidation to form acetic acid. It may contain a suitable stabilizer.*

Preparation—By treating acetaldehyde with small quantities of sulfur dioxide, hydrochloric acid, carbonyl chloride, or zinc chloride; almost complete conversion occurs, and by freezing the liquid and then distilling the crystallized material, if necessary, the pure compound is produced.

Description—Colorless, transparent liquid; a disagreeable taste and a strong, characteristic, but not unpleasant or pungent odor; specific gravity about 0.99; does not congeal below 11° and distills at 120° to 126°; in contact with air it slowly oxidizes to acetic acid.

Solubility—1 mL in about 10 mL water or about 17 mL boiling water; miscible with alcohol, chloroform, ether, or volatile oils.

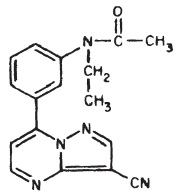
Incompatibilities—*Acids* convert it into acetaldehyde, which is prone to oxidation.

Comments—One of the oldest *sedatives* and *hypnotics*. It is absorbed rapidly after oral administration and produces sleep within 10 to 15 min after a 4- to 8-mL dose. It is detoxified by the liver (70–80%) and 11%–28% is excreted by the lungs. A negligible amount is excreted in the urine. Its chief disadvantage is that, being in part excreted through the lungs, it imparts an odor to the exhaled air, causes irritation, and thus should not be used in patients with asthma or other pulmonary diseases. Also, it has an unpleasant taste and may irritate the throat and gastric mucosa unless dispensed in suitable vehicles and should not be used in patients with gastroenteritis. It is poorly soluble in water; hence, it usually is prescribed in combination with alcoholic liquors, elixirs, etc. The drug also can be taken in milk, fruit juices, or iced tea or with cracked ice. Finally, it can be administered as a rectal retention enema in olive oil. It is effective in status epilepticus but should be reserved for patients who do not respond to phenobarbital. It occasionally is employed as an *obstetrical analgetic,* in which case large doses are administered, usually by rectum.

PROMETHAZINE HYDROCHLORIDE—page 1545.
PYRILAMINE MALEATE—see RPS-19, page 1227.
SCOPOLAMINE HYDROBROMIDE—page 1408.

ZALEPLON

Acetamide, *N*-[3-(3-cyanopyrazolo[1,5-*a*]pyrimidin-7-yl)phenyl]-*N*-ethyl-; Sonata



3′-(3-Cyanopyrazolo[1,5-*a*]pyrimidin-7-yl)-*N*-ethylacetamide [151319-34-5] $C_{17}H_{15}N_5O$. (305.34).

Preparation—The condensation of *m*-acetylacetanilide with N-(dimethoxy-methyl)dimethylamine forms 3-[3-(dimethylaminoacrylyl) derivative (I). Alkylation of I with ethyl iodide and sodium hydride ethylates the amido nitrogen and the pyrazolopyrimidine ring is closed with 3-aminopyrazine-4-carbonitrile in hot acetic acid. US Pat 4,626,538.

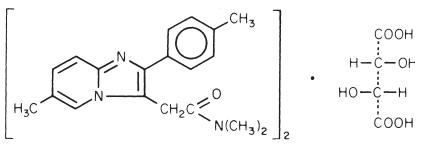
Description—Off-white powder; melts about 186°. Over the range of pH 1 to 7, log P (octanol-water partition coefficient) is 1.23.

Solubility—Practically insoluble in water; sparingly soluble in ethanol or propylene glycol.

Comments—A nonbenzodiazepine hypnotic from the pyrazolopyrimidine class. While zaleplon has a chemical structure that is unrelated to benzodiazepines or barbiturates, it acts as a selective agonist at the benzodiazepine omega$_1$ receptor subtype on the GABA$_A$ receptor complex in the brain.[25] Subunit modulation of the GABA-BZ receptor is hypothesized to be responsible for its hypnotic properties. It is rapidly and almost completely absorbed following oral administration. Zaleplon has an absolute bioavailability of 30% because of extensive first-pass metabolism.[26] Peak plasma concentrations are attained within 1 hour of administration with a mean elimination half-life of one hour. Because of its rapid onset of action, zaleplon should only be ingested immediately prior to going to bed or after the patient has gone to bed. Metabolism of zaleplon is primarily by oxidation via the enzyme aldehyde oxidase to 5-oxo-zaleplon, an inactive metabolite. Zaleplon is also metabolized to desethylzaleplon via the cytochrome P4504A4 system, which is a minor metabolic pathway.[25] Total protein binding is about 60%, independent of concentrations between 10 to 1000 ng/mL. A high fat/heavy meal will delay the t_{max} of zaleplon by approximately 2 hours and decrease the C_{max} by approximately 35% with no change in the AUC or elimination half-life.[26] For faster sleep onset it should not be administered with, or immediately following, a meal. Like other hypnotics, zaleplon may produce additive CNS depressant effects when coadministered with other psychotropic medications, antihistamines, ethanol, and other drugs that produce CNS depression.[26] The most common side effects are headache, drowsiness, dizziness, and lightheadedness.[25] There are no studies of zaleplon in pregnant women so its use is not recommended in this population.

ZOLPIDEM TARTRATE

Imadazolo[1,2-*a*]pyridine-3-acetamide, *N,N,*6-trimethyl-2-(4-methylphenyl)-, [*R*-(*R,*R**)]-2,3-dihydroxybutanedioate; Ambien**



[99294-93-6] $(C_{19}H_{21}N_3O)_2.C_4H_4O_6$ (764.88).

Preparation—The condensation of *p*-(bromomethyl)benzophenone and 5-methyl-2-pyridineamine yields 2-(*p*-tolyl)-6-methylimidazolo[1,2-*a*]pyridine. This latter compound, with dimethylamine and formaldehyde, in a classic Mannich reaction, adds the dimethylamino group on position-3, which is quaternized with methyl iodide, and the quaternary group is replaced with a nitrile, followed by conversion of the CN to the *N,N*-dimethylamide; the title compound. US Pat 4,382,938 (1983). *Drugs of the Future* 1987; 12:777.

Description—White to off-white crystals melting about 196°; pK_a 6.2 (for the base).

Solubility—(Salt) Soluble 23 mg/mL in water.

Comments—Zolpidem is an imidazopyridine agent that is an agonist at the benzodiazepine omega$_1$ receptor component of the GABA$_A$ receptor.[23] Three subtypes of the omega receptor have been identified, and zolpidem in vitro binds to the omega$_1$ receptor preferentially. This selective binding may explain the relative absence of myorelaxant and anticonvulsant effects as well as the preservation of deep sleep (stages 3 and 4) in human.[27] It is absorbed rapidly in the GI tract; with a mean elimination half-life of 2.6 (range 1.4–3.8) hr. Total protein binding is about 93%, independent of concentration between 40 and 790 ng/mL. When taken with food the mean AUC and C_{max} were decreased by 15 and 25%, respectively, and mean T_{max} was prolonged by 60% (from 1.4 to 2.2 hr) with no change in $t_{1/2}$. For faster sleep onset it should not be administered with, or immediately following, a meal. The most common side effects are drowsiness, dizziness, and diarrhea.[24] Zolpidem may produce additive CNS depressant effects when combined with other psychotropic agents, antihistamines, or alcohol. These combinations should be avoided.

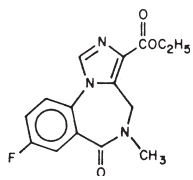
There have been no well controlled studies examining the effects of zolpidem in pregnant women. Use during pregnancy only if clearly needed.[27] The use of zolpidem in nursing mothers is not indicated.

BENZODIAZEPINE ANTAGONIST

Because of the widespread use and the growing abuse of the benzodiazepines, attempts have been made to develop selective benzodiazepine antagonists to treat suspected benzodiazepine overdoses. These efforts have met with some success, and the Food and Drug Administration (FDA) has approved the use of flumazenil (Mazicon) as an adjunct to conventional therapy for overdosing with the benzodiazepines.

FLUMAZENIL

4*H*-Imidazo[1,5-*a*][1,4]benzodiazepine-3-carboxylic acid, 8-fluoro-5,6-dihydro-5-methyl-6-oxo-, ethyl ester; Romazicon



[78755-81-4] $C_{15}H_{14}FN_3O_3$ (303.29).

Preparation—Sarcosine and 6-fluorisatoic anhydride are condensed to 7-fluoro-5-methylbenzo[1,4]diazepin-2,5-dione. The dione, with ethyl α-isonitriloacetate forms a Schiff base through nucleophilic reaction with the amido hydrogen atom. A Claisen condensation closes the imidazole ring between positions 1 and 2 on the diazepine ring to yield the product. US Pat 4,316,839.

Description—White crystals melting about 202°.

Solubility—Insoluble in water; slightly soluble in aqueous acid.

Comments—An imidazobenzodiazepine that binds directly to the benzodiazepine (BDZ) recognition site on the GABA/BDZ receptor complex. It acts as a selective competitive antagonist to block the CNS actions of the benzodiazepines. Flumazenil only blocks the psychomotor, cognitive, and memory impairment caused by the benzodiazepines and has no effect on the actions of other CNS depressants (eg, ethanol, barbiturates, or general anesthetics). The effects are dose-dependent, with approximately 0.1 to 0.2 mg of flumazenil causing partial antagonism, and 0.4 to 1.0 mg producing complete blockade of benzodiazepine effects. After IV administration, the reversal of BDZ effects occurs within 1 to 2 min, with peak inhibition at 6 to 10 min. However, because of extensive first-pass elimination, oral administration results in low plasma drug concentration and is not recommended. Extensive and rapid ($t_{1/2}$ = 0.7–1.3 hr) hepatic metabolism results in no active metabolites. Despite a rapid clearance (31–78 L/hr), flumazenil can block benzodiazepine effects up to 6 hr. This drug was found to improve psychomotor performance, coordination, short-term memory loss, and subjective feelings of pain and drowsiness within 30 min of administration to patients pretreated with midazolam.

Flumazenil is to be used as an adjunct to, not a substitute for, proper airway and circulatory management in the case of BDZ overdosing. Although large IV doses produce no serious side effects in healthy volunteers, in BDZ-dependent patients this BDZ antagonist can provoke severe withdrawal effects such as anxiety, panic attacks, hot flashes, tremors, and seizures. Consequently, flumazenil generally is not to be used in patients with BDZ-dependence. Deaths have resulted from using this drug in patients with serious underlying diseases or in patients who overdosed on BZs in combination with large amounts of nonbenzo-

diazepine drugs (eg, tricyclic antidepressants). In such cases, the flumazenil blocks the protective action of the BZs and unmasks the toxic effects of the other drugs. In the absence of BZs, it causes no serious adverse effects.

Besides the treatment of BZD overdoses, flumazenil has been used to reverse the sedative effects of BDZ used for general anesthesia. It has been suggested that this drug is able to reverse hepatic encephalopathy in some patients with acute and chronic liver failure. However, its effects are short-lasting.

Flumazenil should be titrated to the desired pharmacological effect by administering a series of small infusions (not a single large bolus) through a freely flowing IV tube in a large vein.

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