CHAPTER 61

Adverse Drug Reactions and Clinical Toxicology

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Drug availability and use have risen steadily for the last several decades. In 1961, only 656 drugs were marketed in the United States. By 1989, this number had increased to 8,000, and by 2003 more than 11,700 drugs are marketed in the United States.[1, 2] A total of 60% of the world's drugs are first introduced in the US,[3] and an average of 30 new molecular entities (ie, a new chemical entity marketed for the first time in the US) have been approved each year from 1993 to 2002,[4] a 42% increase over the period from 1975 to 1985.[1] Two thirds of patient visits to a physician result in a prescription,[3] resulting in 3.3 billion outpatient prescriptions filled in 2001.[5] In that same year, prescription pharmaceutical sales totaled $208 billion.[5] Prescription drug spending is projected to approach $4 billion by 2011.[6] Additionally, consumers are using an increasing number of over-the-counter medicines, dietary supplements, and "natural" or alternative products.

Medications unquestionably have provided tremendous benefits to society. Whether preventing childhood illness through vaccination, treating or preventing infections with antimicrobials, or forcing cancer into remission with antineoplastic agents, the benefits of modern drug therapy are immense. However, such therapy is not without risk. Encephalitis has been associated with vaccines; allergic reactions to antimicrobials are well documented; and antineoplastic agents can severely impair a patient's immune system, exposing them to life-threatening infections. The negative and undesirable effects of drug therapy are adverse drug reactions or ADRs.

All medical products, whether drugs, biologicals, diagnostic agents (eg, radiocontrast dye), natural products, or nutritional agents can cause adverse reactions. These reactions may be caused by the drug itself or one of its metabolites; from an interaction between two or more drugs or between a drug and food; or may be caused by an excipient in the product, such as a dye or preservative. Some reactions occur with most or all drugs in the class, so called "class effects," for example cough from angiotensin converting enzyme inhibitors. Other reactions are unique to the drug. Among antibiotics, chloramphenicol causes aplastic anemia, a reaction rarely seen with other antimicrobials. Some drugs can affect multiple organ systems; for example, amiodarone may cause pulmonary fibrosis, dermatological reactions, hyper- or hypothyroidism, ophthalmologic changes, and arrhythmias. Adverse effects from other drugs can be highly specific, for example, toxicity from aminoglycoside antibiotics is limited primarily to the kidney and vestibular/cochlear systems. And while drugs and biologicals marketed in the US are required to be proven safe and effective, safe does not mean risk-free. Thus, the decision to use any medicinal product is always the result of examining its risk to benefit ratio.

What is an ADR?

Although there are many definitions of an adverse drug reaction,[7,8,9] an internationally accepted description is that of the World Health Organization (WHO):

> "A response to a drug that is noxious and unintended, and that occurs at doses normally used in humans for the prophylaxis, diagnosis, or therapy of disease or for the modification of physiological function."[10]

Notably, this definition tacitly excludes the failure of a drug to have its intended effect (ie, a therapeutic failure), and situations of drug abuse, drug overdose, or poisonings.

It is important to distinguish an *adverse drug reaction* from an *adverse drug event (ADE)*. While the two terms have been used interchangeably, the differences are important. An adverse drug reaction is the result of the intrinsic properties of the drug and cannot be prevented. An adverse drug event is an injury resulting from medical intervention related to a drug[11] and includes ADRs, but also includes preventable reactions, including those caused by human error. The WHO definition of an ADR does not necessarily include drugs administered or taken in error or given by an erroneous method.

Tremendous attention has been paid to adverse medical events and medical errors, which includes adverse drug events, largely as a result of the Institute of Medicine publication *To Err is Human: Building a Safer Health System.*[12] This report reviewed and summarized the literature on medical errors in the US health care system and concluded that between 44,000 and 98,000 deaths occur annually as a result of preventable medical mistakes. Drug-related errors account for an estimated 7,000 of these deaths.

As progress is made toward better assessment and management of drug risk, the line between adverse drug reactions and adverse drug events blurs. While much of the research in recent years has been on identifying risk factors for adverse drug events and ADE prevention, much of what is learned can apply to ADRs as well. Indeed, comprehensive management of drug risk requires that adverse drug reactions and adverse drug events be considered equally. To this end, FDA has identified four sources of risk from medical products: known side effects (both avoidable and unavoidable), medication errors, product defects, and "remaining uncertainties," which include side effects not yet known or reported, long-term effects, and unstudied uses and unstudied populations.[13] *All* sources of risk must be considered and evaluated to truly improve drug safety. While the focus of this chapter will be on adverse drug reactions, references to adverse drug events are made throughout.

How Common Are ADRs?

An exact incidence rate for adverse drug reactions is difficult to determine for several reasons. Different trials and national re-

porting programs have used differing definitions of an ADR, resulting in varying reporting rates. Differing means of gathering ADR data (eg, computerized vs manual surveillance), differing areas of research (eg, all hospitalized patients vs a specific unit within a hospital vs an ambulatory setting), differences in reporting statistics (eg, adverse reactions may be reported as a percentage, a rate per unit of time, or a rate per number of doses dispensed), underreporting of reactions, and difficulty in determining numerators and denominators for drug exposure and drug use, all lead to heterogeneous results and difficulty in defining a precise figure or comparing figures.

To address some of these issues, a meta-analysis of published studies of adverse drug reactions in hospitalized patients was conducted.[14] Thirty-nine studies meeting predetermined criteria were reviewed, and an overall incidence of serious and fatal ADRs was determined. The authors included only prospective trials and excluded "possible" ADRs in an effort to improve the quality of the data (ie, only definite ADRs were studied). Notably, only trials that used the WHO definition of an ADR were included and trials that reported adverse events from medication errors were excluded. The overall incidence of serious ADRs (defined as an ADR that required hospitalization, prolonged hospitalization, was permanently disabling, or resulted in death) was found to be 6.7%. The incidence of fatal ADRs was 0.32%. Based upon 1994 hospitalization figures, the authors estimated that over 2 million hospitalized patients experienced a serious ADR during that year; in over 1.5 million of these cases the ADR was the cause of hospitalization. Additionally 76,000–106,000 deaths due to ADRs were projected, making ADRs between the 4th and 6th leading cause of death in the US for that time period. The range of ADRs occurring during hospitalization reported from other trials varies tremendously between 1.5 and 43.5%,[1] as does the number of deaths from ADRs (200–200,000 annually[15]). Interestingly, the aforementioned Institute of Medicine report[12] estimated between 44,000 and 98,000 deaths annually from *all* medical errors, making fatality from adverse drug reactions possibly more common than fatality from all medical errors combined.

The frequency of ADRs in non-hospital settings is less well reported but is becoming increasingly available, often as part of medical error research. For example, a study of nursing home residents examined the incidence and preventability of adverse drug events.[16] Of the adverse drug events documented, 50% were considered nonpreventable and therefore adverse drug reactions resulting in an ADR rate of 0.94 per 100 resident months. Based upon these figures, 175,000 ADRs may occur in US nursing homes annually. A review of drug misadventuring[1] noted between 2% and 50% of ambulatory patients experienced an ADR; a more recent trial reported a much lower rate, 0.19%, of all hospital outpatient visits were due to an adverse drug reaction.[17]

The occurrence of ADRs in the non-adult population is also less well studied than in the adult age group. However, studies in vulnerable populations such as pediatrics and the elderly are increasing. One trial of adverse drug events in hospitalized pediatric patients found 5.3 nonpreventable adverse drug reactions per 1000 patient-days,[18] while 15.1 ADRs per 1000 children was reported through a network of pediatricians seeing patients in an ambulatory setting.[19] A trial in ambulatory Medicare enrollees found the overall adverse drug event rate to be 50.1 per 1000 person-years; of these events, 72% were nonpreventable ADRs (36.3 ADRs per 1000 patient-days).[20]

A largely unexplored and poorly quantified area is adverse reactions to alternative or "natural" products, the use of which may rival that of traditional medicines. Numerous reports document the toxicities of such products. For example, several deaths and complications have been reported with ephedra,[21] and hepatotoxicity has been described with chaparral.[22] Because herbal products are considered dietary supplements and not drugs, manufacturers are not required to seek premarket approval from the Food and Drug Administration (FDA), perform a risk-benefit analysis, or perform safety surveillance after the product is launched. In fact, it is FDA and not the product sponsor that is tasked with proving the safety, or lack thereof, of alternative products, which is the reverse of the requirements for drugs and biologicals. To assist with this assessment, the Institute of Medicine has proposed a framework for FDA to evaluate the safety of dietary supplements.[23]

How Costly Are ADRs?

The cost associated with ADRs is considerable and takes many forms. Studies have consistently shown that patients experiencing an ADR have longer hospitalizations, sometimes doubling the length of stay, relative to the non-affected population.[24–28] Not surprisingly, the cost of hospitalization for such patients is greater as more resources are used to manage and treat drug-induced illnesses.[27,28] One matched case-control study at a tertiary care hospital found the cost of hospitalization for patients experiencing an adverse drug reaction to be $2200 greater relative to control patents who did not experience an ADR.[28] Similar results have been found in other trials.[29] FDA has estimated that if the incidence of hospitalizations related to adverse drug reactions can be reduced by just 2%, the annual cost savings to the nation would be $368 million.[30] In addition to the direct increase in the cost of hospitalization, there is the cost to patients themselves in terms of lost time at work, decreased productivity, and possibly permanent disability. Patients or their families may utilize legal means to seek financial remuneration if a serious ADR is experienced. Litigation costs can be significant and place a burden on the court system, individual practitioners, and health care institutions. For example, there were greater than 4,200 lawsuits filed against the maker of troglitazone (Rezulin), after it was linked to hepatotoxicity and several deaths.[31] Although uncommon, some manufacturers have filed for bankruptcy as a result of ADR-related litigation.[32] Additionally, litigation influences liability and malpractice insurance costs for health care providers and institutions, contributing to the malpractice insurance crisis experienced in several states.[33] A final consideration is the cost of lost confidence and distrust of health care providers and the health care system. A patient's fear of drug-related harm may cause delays in seeking medical assistance at some future point when it is truly needed, possibly causing prolonged illness and severe outcome. The total annual cost to the nation of ADRs is difficult, if not impossible, to quantify but is certainly quite large and is likely in the billions of dollars.[28,34,35]

Classification of Adverse Drug Reactions

Adverse drug reactions have historically been placed into two broad classes: A and B.[8,36] Type A reactions are common and predictable with most identified prior to marketing. Type A reactions are dose related and result directly from the pharmacological action of the drug, but can be due to drug-drug interactions, drug-food interactions, or concomitant illness as well. About 80% of all ADRs fall into this category. Although type A reactions are common and have high morbidity, they usually have low mortality. Examples of type A reactions include hypoglycemia from oral sulfonylureas, tachycardia from albuterol, or diarrhea from an antibiotic. By contrast, type B reactions are uncommon, cannot be predicted, are not dose-related, and have no relation to the pharmacological action of the drug. In most cases, the mechanisms involved in type B reactions are unknown. Although rare in occurrence, mortality from type B reactions can be high. These reactions predominantly affect the liver, skin, and hematopoietic systems. Type B reactions include hypersensitivity reactions such as anaphylaxis from penicillin, idiosyncratic reactions such as malignant hyperthermia from an antipsychotic, and pseudoallergic reactions such as flushing and hypotension from vancomycin. Type B reactions may be influenced by genetic and environmental factors and are frequently not discovered until after a drug is marketed.

Additional classifications, types C, D, E, and F have been suggested.[8,36] Type C reactions are uncommon, dose- and time-related, and associated with the cumulative dose of the drug. Prolonged corticosteroid administration causing adrenal suppression and benzodiazepine dependence are examples of type C reactions. Type D reactions are rare, delayed in onset and are usually dose-related. Examples include carcinogenesis, teratogenesis, and tardive dyskinesia from antipyschotic agents. Type E reactions are withdrawal symptoms. These generally occur shortly after stopping the drug and are uncommon; opiate withdrawal is an example of this reaction type. Last, a type F reaction is an unexpected failure of therapy. These reactions are common, dose-related, and may result from drug-drug interactions. Note that type F reactions may not be considered an ADR under the WHO definition.

ADRs can also be classified according to their onset or severity. The timing of the reaction can be acute (occurring within 1 hour of exposure), subacute (occurring within 24 hours of exposure), or latent (appearing 2 or more days after drug exposure). Reaction severity may be mild (bothersome but not requiring treatment or a change in therapy), moderate (requiring a change in therapy, treatment, or continued hospitalization), or severe or significant. FDA defines significant reactions as those that are fatal, life-threatening, permanently or significantly disabling, require or substantially prolong hospitalization, results in a congenital abnormality, or require an intervention to prevent permanent impairment or damage.

Risk Factors for ADRs

Many factors appear to increase the likelihood of an adverse drug reaction, including age, multiple medications, duration of drug exposure, gender, concurrent illness, narrow therapeutic index drugs, and genetics. Recognition of these risk factors is important in ultimately leading to their prevention.

AGE—The very young and the very old are particularly vulnerable to ADRs. Young children, especially neonates, lack fully developed organs for drug metabolism and elimination. As children grow, drug dosing can be affected by changes in body weight, drug distribution, and drug elimination. Many reports have shown the incidence of ADRs increases with increasing age, being the highest in the very elderly.[37,38] Age-related changes in body composition and organ function, such as decreased liver and kidney function, and increased sensitivity to medications predispose the elderly patient to drug toxicity. Additionally, this population tends to use more drugs and have more illnesses than younger age groups.[39] Last, neither pediatrics nor geriatrics is generally included in the clinical trials conducted to gain drug approval. Thus, experience is limited in these populations.

CONCURRENT MEDICINES—Taking multiple prescription medicines, over-the-counter drugs, and/or alternative or natural products increases the risk of experiencing an adverse drug reaction. The number and severity of adverse reactions increase disproportionately with the number of drugs taken, and some trials have found that the best predictor of ADRs is the number of concurrent medicines. One study over an 18-month period found that patients who experienced an ADR had almost three times the drug exposures as those who did not.[40] Clearly the potential for drug-drug interactions increases as the number of medical products used rises.

DURATION OF THERAPY—The greater the degree of drug exposure, the greater the likelihood an ADR will occur. This is particularly true for already predisposed persons (the very young and very old), and or those with existing organ dysfunction such as renal or hepatic failure.

GENDER—Females have a 1.5- to 1.7-fold greater risk of developing an ADR compared to males.[41] A review of drug safety over a 10-year period found that almost three-quarters of the reactions reported were in women.[42] Numerous explanations for these disparities have been suggested, including overdosing, gender-based differences in pharmacokinetics and pharmacodynamics, differences in immunological and hormonal makeup, women are more likely to report adverse events than men, or women take more medications than men.[41] Women are another group that as historically been poorly represented in clinical trials.

COMORBID CONDITIONS—Patients with concurrent medical problems are more likely to experience an adverse drug reaction than comparatively healthy persons. Illnesses such as congestive heart failure, malnutrition, obesity, hepatitis, cirrhosis, or diabetes can alter the pharmacokinetics and pharmacodynamics of drugs, leading to drug accumulation and toxicity. Additionally, such patients are typically using multiple medicines, further increasing their risk.

NARROW THERAPEUTIC INDEX DRUGS—Again noting that the majority of ADRs are dose-related, those drugs with little separation between therapeutic and toxic concentrations are highly associated with adverse reactions. Examples include aminoglycosides, anticonvulsants, digoxin, heparin, theophylline, and warfarin.

ETHNICITY AND GENETICS—It is well known that there are inherited or genetic differences to drug response. Responses may vary from minimal effect to the desired therapeutic response to an untoward result, manifested as an ADR. Some, but not all, of this variability can be attributed to differences in the genes encoding for drug-metabolizing enzymes, drug transporters, or drug targets. In fact, adverse drug reactions are often the clinical events that ultimately lead to discovery of such genetic variations. The study of these differences is called pharmacogenetics.[43] Pharmacogenetics can influence drug therapy in one of three ways.[43] First are genetic polymorphisms that are associated with altered drug metabolism. Increased or decreased drug metabolism can alter the concentration of a drug and/or its metabolites, whether active, inactive, or toxic. For example, 5–10% of the population carries two decreased activity alleles for the drug-metabolizing enzyme CYP2D6. These "poor metabolizers" can have a higher frequency of toxicity from antidepressants metabolized via this enzyme because of decreased elimination and drug accumulation. A recent study found that 59% of the drugs cited in ADR studies are metabolized by at least one enzyme with a variation known to cause poor drug metabolism.[44] Second, genetic variations can produce unexpected or idiosyncratic reactions, such as hemolytic anemia in persons with a deficiency in glucose-6-phosphate dehydrogenase. Last, genetic variation in a drug target or transporter can alter the clinical response and frequency of toxicity. For example, 1–2% of the population may have mutations in the genes encoding for cardiac ion channels, predisposing them to sudden cardiac death due to long-QT syndrome after exposure to antiarrhythmics or certain drugs such as terfenadine.

Reporting Requirements and Hospital-Based Adverse Drug Reaction Monitoring

Institutional settings play an important role in monitoring and reporting adverse drug reactions and having a program for this function is a requirement for gaining accreditation by the Joint Committee on Accreditation of Healthcare organizations (JCAHO). Development and coordination of the program commonly falls to the pharmacy department, although the most effective programs involve all disciplines.[45] An ADR program must have the following basic components: (a) a definition of an ADR that clearly describes what is a reportable adverse drug reaction; (b) a method of monitoring and reporting adverse drug reactions; (c) a system for evaluating reactions for severity, causality, and preventability; and (d) a system for using the results of the ADR program. The guidelines published by the American Society of Health-System Pharmacists (ASHP) provide a detailed explanation of each of these components.[9]

Hospital-based programs use several methods for detecting adverse reactions, including retrospective chart review, concurrent surveillance, and prospective monitoring. JCAHO requires hospitals to have a concurrent monitoring system in place, while ASHP recommends both concurrent and prospective monitoring programs. In particular, prospectively identifying high-risk drugs and high-risk patients and utilizing knowledge of the risk factors for ADRs can help with the monitoring and ultimately the prevention of adverse reactions. Concurrent monitoring, particularly when coupled with ongoing advances in information technology, is clearly superior to retrospective monitoring of adverse drug reactions.[28]

Once reported, an adverse reaction is evaluated for its severity, causality, and preventability. Determining the causality of a drug reaction (ie, the likelihood that the drug in question is the reason for the reaction) is somewhat arbitrary but usually assigns the probability to one of a few categories such as definite, likely, possible, and unlikely. Several algorithms are available, some complex, to assist with this assessment, but often clinicians must rely upon clinical judgment, literature review, and communication with the manufacturer or other health professionals to make a determination. Regardless of the method used, assessing the causal relationship involves several elements: the timing between drug administration and the appearance of the reaction (also called the temporal or chronological relationship); (b) whether the drug was withdrawn or a specific antidote administered with improvement in the symptoms (positive dechallenge); (c) whether the drug was reintroduced or the dose increased with recurrence or worsening of the symptoms (positive rechallenge); (d) whether the reaction has been previously described or reported; (e) whether objective data (eg, drug levels, other laboratory findings) support that the reaction is an ADR; and (f) whether the reaction has an alternative etiology, ie, can it be explained by an existing condition or another agent? Many algorithms use a weighted scoring system, allocating points for responses to questions about each of these areas.[46] Perhaps the most widely used algorithm is that by Naranjo et al.[47] The reaction must also be categorized by its severity as previously described.

It is becoming increasingly important to also assess the *preventability* of an ADR and criteria for making such a determination have been published.[48] As noted, drug errors resulting in adverse reactions account for significant morbidity and mortality. Determining which ADRs are preventable and at what point in the medication process an error occurred will help to identify ways to improve the medication system.

Information gained from ADR programs should be shared with all health care providers and should be integrated into hospital quality assurance and performance improvement programs. In some institutions a dedicated Drug Safety Committee or Medication Safety Committee may oversee this function, in others it falls to the Pharmacy and Therapeutics Committee.

Drug Development and Its Relation to Adverse Drug Reactions

As noted above, all drugs and biologicals marketed in the US must be shown to be safe and effective. FDA, based upon information submitted by the pharmaceutical sponsor or developer, evaluates the data supporting these outcomes. The drug is approved if its benefits, as it's intended to be used in the proposed population, outweigh its foreseeable risks. The tolerance for toxicity is higher for drugs that treat serious or life-threatening illnesses, such as antineoplastic drugs.

Safety and efficacy data are generated in the preclinical animal and toxicology studies and the premarketing human testing that all drugs and biologicals are required to undergo, known as phase I, II, and III testing.[49] Phase I trials are generally focused on drug safety. Studies are usually conducted in healthy volunteers and assess the most common acute side effects and evaluate the size of doses subjects can safely take without a high frequency of adverse reactions. Phase II trials involve small numbers of patients with the disease to be treated. Although the primary focus of these trials is efficacy, safety data on short-term use are also gathered. Phase III trials involve several hundred to several thousand patients with the primary goals of confirming drug efficacy and safety at the doses to be used once the drug is marketed.

It's important to note that the overall safety goal of prelicensure research is not to identify every ADR that may occur, but instead to establish the common dose-related effects that might be expected from its approved use, whether predictable or not. Most drugs approved by FDA are done so with a few thousand patient exposures, which may be sufficient to detect a reaction occurring in 1 of every 500–1000 patients.[50] However, for idiosyncratic reactions, rare side-effects (for example occurring in 1 in 10,000 patients), or reactions that may require a long induction period, premarketing clinical trials generally do not enroll enough subjects to detect such reactions and are too short in duration. But there are other limitations that prevent establishing a drug's entire toxicity profile before it's approved for use.[51,52] Since the aim of premarketing trials is to show drug efficacy, such trials frequently exclude patients with complicated medical histories, significant comorbid conditions, or those who are receiving other drugs, since this may hinder establishing the drug's effectiveness. Therefore, the type and frequency of ADRs that will occur once the drug is used in a broader population using differing medications is unknown. Drug companies also generally seek drug approval for a single indication. Once marketed, the drug may be used to treat entirely different illnesses or diseases from what was studied. Premarketing trials have also historically excluded pediatric patients, pregnant or breast-feeding women, and elderly patients; how these populations will react to new drugs is frequently unknown. Significant headway has been made in addressing this last shortcoming, however, with rules adopted in 1997 and 1998 requiring pediatric safety data on new drugs, a specific "Geriatric use" section in the labeling of all drugs and biologicals, and the requirement that guidance documents be developed on the inclusion of women and minorities in clinical trials.[53,54]

Recognizing the limitations of prelicensure studies, the FDA frequently requires that a drug manufacturer conduct one or more *postmarketing* phase IV trials as a condition of drug approval. Such trials are designed to further evaluate drug safety and efficacy, often in specific populations (eg, children), confirm safety in the target population and look for chronic effects from prolonged use.[52] However, one report suggests that phase IV trials are rarely completed as required, calling into question the ability of the FDA to monitor and enforce compliance with this requirement.[55]

Drug-Development: Toxicokinetics and Toxicodynamics

Early in drug development, the toxicity of a candidate compound must be assessed to determine if further development and progression to human trials is warranted. This typically involves administration of doses that are several-fold higher than the human pharmacological dose eventually used. Such research obviously cannot be performed in humans, so *preclinical* (sometimes called *nonclinical*) toxicity studies in animals are undertaken. However, the majority of animal toxicity data generated during preclinical studies cannot be extrapolated to humans without an understanding of the pharmacokinetics and pharmacodynamics involved. The kinetics of a compound when given at toxic doses is termed *toxicokinetics.* More specifically, toxicokinetics is the study of the absorption, distribution, metabolism, and excretion (ADME) of a xenobiotic (a foreign, natural, or synthetic chemical) at higher than therapeutic doses resulting in toxicity or excessive exposure.[56] The study of the relationship between the toxic levels of xenobiotics and the

ultimately observed clinical illness is *toxicodynamics*.[56,57] Toxicokinetics and toxicodynamics are areas of increasing importance in drug development and risk assessment that are relevant to the prediction of ADRs and their management. Although the WHO definition of an ADR excludes drug overdose and poisoning (ie, situations typically resulting in toxic drug exposure), toxicokinetic data gained during preclinical and toxicology testing in animals is relevant to treatment in humans. Furthermore, toxicokinetic and toxicodynamic studies are a prerequisite for all drugs submitted to FDA for approval, a requirement that extends globally as well as a result of the International Conference on Harmonization (see International Drug Monitoring).[58]

Although toxicokinetics follows many of the same principles and mathematical models as pharmacokinetics,[56] it is important to note the differences between these two disciplines. The essential difference is that the kinetics of a compound is frequently altered when that compound is administered at toxic doses compared to pharmacological doses. For example, high doses can alter drug solubility in the intestinal tract, leading to precipitation and differing patterns of absorption. High drug doses can overwhelm or saturate many processes, eg, enzymatic metabolism, protein binding, and active tubular secretion, leading to non-linear kinetics. The altered kinetics of a drug taken or administered at toxic levels may ultimately lead to cellular toxicity, manifested as the clinical symptoms of poisoning or overdose.[59]

The ultimate goal of toxicokinetic (TK) and toxicodynamic (TD) studies is to relate the adverse reactions from drug toxicity observed in animals (both short term and long term) to safety and toxicity in humans, as well as to formulate strategies to manage human toxicity.[60,61] TK/TD data are used in a variety of ways to meet this goal.[62] For example, researchers may use initial TK/TD data to validate the choice of animal species and to provide information that will help in the design of subsequent experiments to provide animal safety data. Selecting the animal species that most closely models human toxicokinetics and pharmacokinetics is key to determining the safe starting dose of a candidate drug for human trials. TK data may be used to modify dose administration (ie, the dose administered, the route of administration, the time of administration, frequency of administration, dosage form, etc.). Clinicians use TK/TD data to assist in establishing the margin of safety between preclinical safety trials and human trials and to determine the mechanism of toxicity. Pharmacokineticists use TK/TD data to help design pharmacokinetic studies to validate human safety and efficacy. Pathologists may use TK data to relate the pathology found on necropsy (eg, lesions) to drug exposure and to determine the target organs for toxicity that will eventually be part of the adverse drug reaction monitoring in future trials. Reproduction and developmental toxicologists use TK data to aid in dose selection for reproduction and teratology studies, which will assist in monitoring for Type D (long-term) reactions in humans. Although much of the TK/TD data are discovered in preclinical animal trials, such data are in fact generated and refined throughout the entire drug development process, including postmarketing drug safety surveillance, which will be discussed later. Interested readers are referred to more in-depth discussions on the increasing role of toxicokinetics and toxicodynamics in drug development[63,64] and to references that describe fundamental toxicokinetic and toxicodynamic principles and models.[56,61,65]

Drug Development: Pharmacogenomics

As noted earlier, genetics plays an important role in drug response. Pharmacogenomics harnesses the information gained from genome-wide research, notably the Human Genome Project, to understand the inherited differences in drug response between individuals as well as to optimize drug therapy based upon a person's specific genetic information.[43,66] Applying advances in pharmacogenomics to drug development means there is the potential to stop many adverse reactions that are currently considered nonpreventable. The implication is that determining *a priori* an individual's genetic makeup, coupled with the knowledge of a drug's pharmacology may allow drug selection that optimizes the desired clinical response while reducing the risk of an adverse drug reaction. Additionally, coupling genetic advances with toxicokinetics is leading to the emerging field of *toxicogenomics,*[67] providing a genetic understanding for the response to toxic drug exposure. Undoubtedly as information on pharmacogenomics, pharmacogenetics, and toxicogenomics grows, drug developers will conduct trials in populations with specific genotypes and phenotypes to develop a clearer understanding of the ADRs that may be anticipated and how best to avoid them. Readers are referred to Chapter 62 for a more in depth discussion of pharmacogenetics and pharmacogenomics.

POSTMARKETING SAFETY SURVEILLANCE— The previously mentioned problems in detecting ADRs during premarket drug testing are well recognized by FDA. Additionally, drug approval times have become increasingly shorter[50] and critically important drugs can reach the market quickly by shortening the length of time required for premarket testing or eliminating some phases of testing altogether.[68] Thus, drugs can be marketed with less and less knowledge of their full toxicity profile. Accordingly, significant effort has been made to observe drugs after their approval to monitor their continued safety. This effort, termed *postmarketing safety surveillance*, also falls under the authority of FDA. The goals of the postmarketing surveillance system are to detect potential adverse drug reactions that were not seen in prelicensure trials as well as problems that may arise when a drug is used in ways or in populations that were not studied or anticipated. Postmarketing surveillance also provides an opportunity to ascertain toxicokinetic and toxicodynamic parameters in situations of human poisoning and drug overdose that were not possible during drug development. Such data assist clinical toxicologists in developing treatment strategies and can lead to revised drug labeling, requests by FDA for further safety assessment, or to phase IV postmarketing trials. Readers are referred to Chapter 103 on poison control and to detailed toxicokinetic references for more information.[56,57,65]

FDA utilizes a passive system for postmarketing safety surveillance that relies upon voluntary reporting of ADRs from health professionals and consumers, mandatory reporting by drug manufacturers, and reports from ongoing clinical trials. Manufacturers must file within 15 days of their detection or notification reports of any serious reaction not listed in the current product labeling, and any reports of drug overdose, cancer, or congenital defects. In addition to these "15-day" reports, manufacturers must submit periodic reports at least annually and as often as quarterly that describe serious labeled reactions and all nonserious reactions, as well as any reports of an increased frequency of serious, labeled reactions and deaths, beyond what might be anticipated from increased drug use alone.[69]

Supplementing the manufacturer reports are voluntary reports from health professionals and consumers via the MedWatch program, which was started in 1993 under the Centers for Drug Evaluation and Research (CDER) at FDA. Although postmarketing surveillance by health professionals was established prior to this, MedWatch was designed to emphasize the responsibility of health care providers to identify and report adverse reactions related to the use of not only drugs and biologics, but to medical devices and certain nutritional products as well. Importantly, causality is not a prerequisite for MedWatch reporting; *suspicion* that a medical product may be related to a serious event is sufficient reason to submit a MedWatch report.

While health professionals are encouraged to report any ADR considered significant, not every ADR need be reported. To do so would overwhelm FDA resources and reduce its ability to identify significant reactions. FDA is most interested in reports of serious reactions, defined as any event that is fatal, life-threatening, is permanently or significantly disabling, requires or prolongs hospitalization, results in a congenital abnormality, or requires an intervention to prevent permanent impairment

or damage. MedWatch reports may be filed by completing a MedWatch form and mailing or faxing it to the FDA (forms are available in numerous medical and pharmacy journals, as well as reference texts such as the Physician's Desk Reference or AHFS Drug Information or it may be downloaded from the FDA web site); by filing the report electronically via the FDA web page (http://www.fda.gov/medwatch/report/hcp.htm); or by telephone (1-800-FDA-1088).[70] A separate program, the Vaccine Adverse Event Reporting System (VAERS) managed jointly by the Centers for Biologics Evaluation and Research (CBER) at FDA and Centers for Disease Control and Prevention (CDC), performs a similar function to the MedWatch program but focuses solely on postmarketing safety surveillance of vaccines.[71] Also, the Center for Food Safety and Applied Nutrition (CFSAN) is scheduled to have an adverse event reporting system (CAERS) operational by mid-2003 that will track and perform trend analysis on adverse reactions to dietary supplements, foods, and cosmetics.[72]

Both MedWatch and manufacturer reports are entered into a computerized database, the Adverse Event Reporting System (AERS). AERS contains more than 2 million reports that are continually analyzed, looking for trends in reactions or "safety signals". A safety signal is a seeming excess of adverse reactions associated with a drug's use, although it may also be a single well-documented case report. Safety signals may alert FDA to new unlabeled ADRs, an observed increase in the severity or specificity of an already known ADR, an increase in the frequency of a known ADR, new drug interactions (drug-drug, drug-food, or drug-supplement), or to confusion with a product's name, labeling, packaging or use. Such signals may form the basis for further epidemiological research.

Pharmacoepidemiology and Pharmacovigilance

Pharmacoepidemiology is the study of the use and effects of drugs in human populations.[73] A branch of pharmacoepidemiology is pharmacovigilance, which is defined as the postapproval scientific and data gathering activities related to the detection, assessment, understanding, and prevention of adverse events or other product-related problems.[74] The safety signals detected during postmarketing surveillance can prompt epidemiologic studies to support or refute the signals observed and determine the need for further regulatory action.[3,70,75] Among other purposes, epidemiologic studies are also necessary to establish a causal relationship between the drug and the reaction and to quantify the degree of risk, both relative and absolute, that an ADR may pose to patients. Knowledge of these risks is important for practitioners to assist in their decision making process when prescribing drugs.[75] The overriding question that attempts to be answered is: Do the benefits of the drug continue to outweigh its risks for the population described in its labeling? To the extent possible, how the toxicity compares with other available therapies for the same disease is also considered. Examples of the types of studies that may be performed include case report reviews, case series, case-control studies, cohort studies, and possibly randomized clinical trials. More serious ADRs have been identified first in case reports than by any other method of detection.[70] Case reports are best at detecting rare or unusual reactions that occur during initial or prolonged drug use and are the major source for generating hypotheses about adverse drug effects. Case reports do, however, have several important limitations. They are subject to reporter bias and erroneous reporting; they are poor at detecting increases in common reactions or ADRs that occur remotely in time from the actual drug use; and there is no link between prescribing patterns and reporting rates.[70] Thus the need for the other types of studies mentioned, each with its own particular strengths and weaknesses. An in-depth discussion of pharmacoepidemiology and pharmacovigilance is beyond the scope of this chapter. Interested readers are referred to dedicated texts for more information on this field.[73]

Response to Significant ADR Detection

Once a significant toxicity has been detected and validated, FDA has several options.[76] Usually the first step is to modify the drug's labeling and communicate the new information (eg, new contraindications, warnings, adverse reactions, and precautions) to health professionals. Such communication may be from the pharmaceutical manufacturer or FDA (known within the FDA as "Dear Doctor" letters). Sometimes changes to the prescribing information are surrounded by a black box (so called "black box" warnings) to bring them greater attention. In some instances Medication Guides are used and may be developed before a drug is marketed if significant risk is identified early. These are written information specifically for patients that highlight significant risks and advise patients on how to detect and avoid them. The Medication Guide must be distributed when the prescription is dispensed. Medication Guides are not used indiscriminately; on average only 5-10 products a year may warrant this action. In other cases, a drug is designated as a "second line" therapy, to be used only in patients in whom other treatments have failed. FDA may also restrict distribution of a drug, making it available only under certain circumstances, to certain prescribers, or via certain institutions.

As a last step, FDA may also request that a drug be removed from the market. While this is usually done voluntarily by the pharmaceutical company after discussion with FDA, FDA may also withdraw marketing approval and forcibly remove the drug. This has only been done once when FDA removed the antidiabetic drug phenformin, citing it as an imminent hazard to the public health because of several cases of drug-related lactic acidosis. Removal of a drug from the market is not always permanent. If additional safety processes can be developed, a drug may reintroduced. Such was the case with the antidepressant bupropion, removed because it caused seizures in bulimic patients,[77] and alosetron, a drug for irritable bowel syndrome in women that was removed after cases of fatal ischemic colitis were discovered.[76] Both agents were reintroduced after additional safeguards were put in place. It is important to recognize that despite often receiving the most attention, withdrawing a drug from the market is seldom the first action taken by FDA when new safety information is discovered. Instead, this action usually follows several efforts to improve patient safety by one or more of the previously mentioned means. As stated earlier, FDA also examines the risk to benefit ratio a drug provides relative to other therapies, if they exist. For example, postmarketing surveillance revealed that terfenadine, a nonsedating antihistamine, was found to produce serious cardiac arrhythmias in patients with liver failure or when used in combination with certain drugs. Terfenadine remained on the market, despite these toxicities, with revised labeling and warnings to health care providers because there were no safer therapeutic alternatives. Once a similar but safer agent became available (fexofenadine), terfenadine was withdrawn.[76]

How Effective is Postmarketing Surveillance?

Each year, approximately 25,000 MedWatch reports and 270,000 manufacturer reports are submitted to the AERS, and 12,000–14,000 reports are submitted to the VAERS.[3] Of the MedWatch reports, pharmacists have been the leading reporters among health professionals, although direct consumer reporting has been steadily increasing.[78,79] These reports have lead to the detection of significant adverse drug effects leading to numerous labeling changes, tighter restrictions on use, and several drug removals. In 2002 alone, FDA averaged 30 safety changes to product labeling each month. Also, an average of 43 safety alerts were issued every month from 1997 to 2002. Safety-based market withdrawal has been remarkably consistent over the past two decades. From 1981 to 2002, 584 new molecular entities were approved and marketed in the US. During this time, 20 drugs

(3.4%) were withdrawn from the market for safety reasons. Following a clustering of 5 drug withdrawals from 1997 to 1998, concern was raised that the shortened review time at FDA had undermined its ability to properly and objectively assess drug safety.[80] Shorter review times are largely the result of the 1992 Prescription Drug User Fee Act (PDUFA), which provided additional resources to FDA to expedite drug review and improve efficiency. Fees paid by the pharmaceutical industry fund the additional resources. The contention that serious, unanticipated adverse effects were occurring more commonly after PDUFA has not been substantiated, however. A review of the frequency of drug removal before and after implementation of PDUFA demonstrated about the same percentage of withdrawals for both periods of time.[50] Another study compared the rate of labeling changes of new molecular entities in the 11-year period prior to PDUFA to the 3-year period after its implementation.[13] Significant labeling changes due to adverse effects detected after drug approval were made to 51.5% of drugs in the pre-PDUFA period compared to 30.3% following PDUFA. Therefore, while efficiency at FDA improved following PDUFA allowing for more rapid review time and drug approval, it was not at the expense of drug safety.

An analysis of how frequently postmarketing surveillance identifies important ADRs found that 10.2% of all new molecular entities (NMEs) approved in the US between 1975 and 1999 acquired a black box warning or were withdrawn from the market.[81] The estimated probability of one of these events occurring over a 25-year period was 20%. Eighty-one major changes to drug labeling occurred over the study period, including addition of one or more black box warnings per drug, or drug withdrawal. Half of these changes occurred within 7 years of drug launch and half of the withdrawals within 2 years. Labeling changes were most commonly made for hepatotoxicity, hematologic toxicity, cardiovascular toxicity, and pregnancy risk. Another study looked at postmarketing drug dosage changes in new molecular entities approved between 1980 and 1999. Twenty-one percent of the NMEs underwent a dose change, 79% of these changes were a dose reduction. Almost 25% of all dose-related changes were attributed to renal-hepatic impairment and enzyme-mediated drug interactions.[82]

Further Enhancing Drug Safety

Notwithstanding the success of premarket testing and postmarket safety monitoring noted above, significant drug toxicity and patient harm continues to occur. The reasons are several. First, premarket clinical trials (ie, phase I, II, and III studies) continue to be conducted with the limitations already noted. In order for new drugs to become available rapidly and with reasonable cost, this is unlikely to change. However, improved premarketing assessment of the risks new medicines may pose and better integration and planning of pre- and postmarketing safety research can advance drug safety. FDA has drafted a concept paper to address these specific areas with the ultimate goal of publishing a guidance document on premarketing risk assessment for the pharmaceutical industry by late 2004.[83] Second, despite the large number of ADR reports received by FDA and the fact that national reporting has improved since the introduction of MedWatch, it is estimated that only 1–10% of ADRs are reported,[84] a trend not unique to the US.[85] In hospitals with ADR monitoring programs, it is estimated that only 1 in 20 ADRs are reported.[86] The reasons for underreporting of ADRs are numerous and well documented[87,88] and include lack of knowledge of a reporting program, lack of knowledge on how and what to report, fear of litigation, the time required to make a report, the inability to determine causality, the belief that most reactions are already reported and not unique, and the belief that the responsibility for reporting a reaction belongs to someone else. Underreporting is a significant drawback to passive postmarket safety monitoring because it delays the detection of significant ADRs. The system has also been criticized for the lack of timeliness and detail in the reports received. Communication is also a key area that needs improvement. For example, research shows that "Dear Doctor" letters and labeling changes that are used to convey important safety information are relatively ineffective tools to manage drug risk[89]; more aggressive approaches using explicit language and utilizing available information technology are more effective but are not consistently employed.[90,91] Noting these problems, a task force was convened by the Commissioner of the FDA to examine how the agency manages the risks associated with medical products, looking at both the quality of FDA's premarketing risk assessment as well as the strengths and weaknesses of its postmarketing surveillance program.[13] The task force concluded that although the current system functioned as intended, the time was right for a new framework of drug risk assessment and management. In the years following its proposals, several of the task force recommendations have been implemented.

Improvements in premarketing and postmarketing safety continue building upon the recommendations of the task force. Notably, FDA is developing three guidance documents for the pharmaceutical industry to improve drug risk assessment and management that will be finalized in 2004. One is the guidance for premarketing risk assessment already mentioned.[83] Additionally, FDA is proposing that drug sponsors develop a risk management program to address safety. Such a program will include information beyond the drug's approved labeling and may consist of specialized education materials for health professionals and/or patients, or methods to modify prescribing, dispensing, and use of drugs to minimize risk.[92] A third guidance document addresses postmarketing surveillance and what constitutes good pharmacovigilance practices.[74] A concept paper on each topic was introduced in early 2003 for public comment.

FDA is committed to better utilization of information technology to develop a "health information infrastructure" that will lead to earlier recognition of adverse drug effects and more rapid and meaningful communication of new information to health professionals.[3] One way FDA is meeting this goal is by utilizing active surveillance systems to augment the existing passive system is to improve the timeliness of ADR monitoring. This has already begun with vaccines,[13,93] and automated real-time drug safety data collection has started.[94] Additionally, improved data mining techniques for rapidly detecting safety signals within the AERS have been developed.[95]

FDA has joined with a number of public and private organizations to improve patient safety. For example FDA recently partnered with a managed care organization and with the Center for Medicare and Medicaid Services. This collaboration will allow FDA to access high-quality data that can be used to analyze safety concerns in large patient populations. FDA plans on forming similar partnerships that will provide additional, timely information from modern electronic sources to FDA on the safety of medical products.[94]

Other possibilities for augmenting the current system of drug safety surveillance include establishing registries of significant reactions (eg, hepatotoxicity, bone marrow toxicity), creating a network sentinel sites (emergency departments, hospitals, or clinics) that would provide surveillance for specific drugs in specific settings or populations (for example AIDS clinics could be identified and supported for monitoring of new antiretroviral medicines), and establishing an independent drug safety board, similar to the National Transportation Safety Board, which would have the responsibility of investigating significant adverse reactions.[13, 96]

Recognizing the importance of rapidly and effectively communicating safety information, FDA has undertaken a number of initiatives to improve this area. Working with the National Library of Medicine, FDA will electronically distribute up-to-date, comprehensive medication information for use in information systems that support patient care. FDA has also developed new Web-based communication methods to better inform consumers and health care professionals about the risks associated with medical product use.[94]

In the first quarter of 2003, FDA proposed many additional far-reaching changes to drug safety, safety monitoring, and safety reporting.[94,97,98] Among these were:

- Mandating bar code labeling on all prescription and OTC drugs, biologicals, and vaccines.
- Adopting a new internationally accepted definition for *suspected* adverse drug reaction (SADR). Adoption of this definition will require reporting of a reaction unless the drug company is *certain* that the product is not the cause, thus increasing the number of reports made to FDA and improving safety signal generation.
- Requiring that greater emphasis be devoted to serious SADRs that have the potential for significant impact on the public health, with less importance and resources placed on non-serious SADRs. Additionally, more detailed information will be required for reports of serious SADRs increasing the value of such reports.
- Requiring reports of all unexpected reactions for which a determination of serious or nonserious cannot be made.
- Mandating reporting of medically significant reactions, whether expected or unexpected, and whether or not considered serious such as those that may jeopardize the patient and/or require medical or surgical intervention to treat the patient.
- Mandating reporting of safety findings from animal or human studies, or other information, that is sufficient to consider changes in product administration.
- Establishing postmarketing periodic safety update reports that conform to international standards and use internationally accepted terminology to describe and classify SADRs.
- Requiring submission from industry of spontaneously reported individual cases of serious, expected SADRs that occur *outside* the US (current rules only require reporting of such cases if they occur domestically).
- Requiring that a health care professional at the company speak *directly* to the initial reporter of an SADR when additional information is needed.
- Requiring that a licensed physician at the pharmaceutical company be responsible for the content and medical interpretation of postmarketing safety reports submitted to FDA.
- Requiring companies to submit to FDA, within 15 calendar days, all reports they receive of actual or potential *medication errors* occurring in the US whether they resulted in a serious SADR, nonserious SADR, or no SADR at all. This also includes potential medication errors that do not involve a patient but instead describe information or a complaint about packaging, labeling, or similar product names.

These changes will be adopted internationally. Once implemented, the net effect will be to improve the prevention of medication errors and enable FDA to more quickly identify adverse reactions associated with the use of drugs and biologicals and to take more timely action to reduce patient harm.

International ADR Monitoring

FDA is a member of the World Health Organization (WHO) Programme for International Drug Monitoring. The program houses the Global Database on Adverse Drug Reactions and, similar to FDA's AERS, the data collected are used to generate early warning signals of potential adverse reactions. Currently over 70 countries participate in the program that was established in 1968 with the goal of increasing early recognition of new and unexpected adverse reactions. Additionally, the program offers guidance and training courses on pharmacovigilance and establishes internationally accepted definitions for terms used in ADR reporting.[99] FDA and the US pharmaceutical industry also have had substantial input into the development of the standards proposed by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and in the World Health Organization's Council for International Organization of Medical Sciences (CIOMS) drug safety working groups. In addition to efforts to harmonize the drug and biological product application process worldwide, these proposals establish international standards for safety reporting (including terminology used in reports, format of reports, and timing of reports) developed jointly by the US, the European Union, Canada, Switzerland, and Japan to improve the quality, consistency, and usefulness of these reports. Many of the proposed enhancements to the US pre- and postmarketing safety programs noted above are a direct result of participation in ICH. As the pharmaceutical industry becomes an increasingly global enterprise, participation in international drug safety endeavors will become increasingly important.

Summary

Drug use continues to increase in the US and will likely do so for many years to come. While drug therapy offers tremendous benefits, it does so with the potential for patient harm. Adverse drug reactions are a significant cause of morbidity and mortality and have a significant financial, emotional, and societal impact. ADRs are part of a spectrum of drug safety that includes adverse drug events that may be due to medical error. There are numerous risk factors for developing ADRs; the role genetics plays in drug response is being increasingly recognized and will likely have an impact on future drug development and testing. Progress is being made toward comprehensive risk management that addresses both ADRs and ADEs. Postmarketing safety monitoring of drugs is essential, as not all reactions a drug may cause are known at the time of its approval. Institutional settings can play a significant role in monitoring for ADRs. Although postmarketing surveillance has functioned as intended, significant improvements are needed to make drug therapy safer. Several initiatives are underway that will meet this goal.

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CHAPTER 62

Pharmacogenomics

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Administering an identical dose of the same medication to apparently similar patients can often lead to quite different clinical responses. While variable response to drugs will be influenced by many environmental and demographic factors such as age, concomitant medications, kidney or liver function, and diet, there remains a significant degree of variation that cannot be explained by external causes. This suggests that a major component of inter-individual differences in drug response is inheritable. In fact, it has been proposed that genetics may account for 20–95% of variability in drug disposition and effects.[1] There are now several examples where inter-individual differences in drug response have been traced to heritable genetic variations (genetic polymorphisms) in genes encoding drug metabolizing enzymes, drug transporters, or drug targets.[2–4] While it is clearly important to identify environmental factors that influence the effect of medications, inherited determinants of drug response remain stable for an individual's lifetime, can effect agents across number of different drug classes, and the effects can be profound.

Clinical observations of inherited differences in the effects of drugs were first documented in the 1950s,[5–7] and led to the early development of the field of *pharmacogenetics*. More recently, as a result of the successful sequencing of the entire human genome and the development of genome wide analysis techniques, pharmacogenetics has been redefined by a broad spectrum of academia and industry, giving rise to *pharmacogenomics*. The goal of pharmacogenomics is to elucidate the inherited basis for inter-individual differences in drug response, using genome-wide approaches to identify the genetic polymorphisms that determine an individual's response to specific medications. In addition to conventional targeted genetic studies to identify functional variants, the field includes such diverse areas as RNA-based microarray analysis and genome-wide DNA analysis to identify the major genetic sites (loci) associated with altered drug effects.

Because a key principle in the practice of pharmacotherapy is the optimization of drug treatment through the identification of those patient-specific variables that affect the likelihood of a clinical response or toxicity, this chapter will focus on the examination of the genetic basis of differences in drug response. The discussion will center on well-described examples of variations in specific human genes that are involved in drug disposition and effect. However, in order to provide an adequate context for the specific examples, one must start with a brief background on the history and principles of modern genomics. Finally, technological considerations, along with current and future applications of pharmacogenomics will be examined.

THE HUMAN GENOME

The Human Genome Project

In 1990, the Human Genome Project was officially initiated in the United States under the direction of the National Institutes of Health and the U.S. Department of Energy with a 15-year, $3 billion plan for completing the genome sequence of humans. This enormous multi-national effort was undertaken by a number of public and private laboratories, known collectively as the International Human Genome Sequencing Consortium (IHGSC). The IHGSC first announced a draft sequence of the human genome in 2000, and by April of 2003, the entire 3.1 gigabases that makes up the human genome was essentially complete.[8,9] In other words, greater than 99% of what can be done with current technology was done, and virtually all of the bases were identified in their proper order. Political leaders from the United States, Britain, China, France, Germany, and Japan issued a joint proclamation honoring their scientists who worked on the project, hailing their work as one of the most significant scientific breakthroughs of modern times.

While much is now known about the structure the human genome, many mysteries remain. It is known, for instance, that less than 2% of the human genome are sequences that actually code for proteins, while over 50% represents repetitive sequences of several types, whose function is less well understood.[8] Moreover, it is still not known precisely how many genes the human genome contains. Current data indicate that the human genome includes approximately 30,000 to 35,000 genes—a number that is substantially smaller than was previously thought.[8] Only about half these genes have recognizable DNA-sequence patterns, or motifs, that suggest their possible function. Furthermore, while it was once dogma that one gene encodes one protein, it now appears that, through the mechanism of alternative splicing, more than 100,000 different proteins can be derived from these 30,000 to 35,000 genes.[9] In addition to alternative splicing, a number of "epigenetic" phenomena, such as methylation, phosphorylation, and histone modification, can alter the effect of a gene.[10–12] Furthermore, a complex array of molecular signals allows specific genes to be "turned on" (expressed) or "turned off" in specific tissues and at specific times. It is widely accepted that every human gene contains inherited genetic variants or mutations.[13] Mutations known to cause disease have been identified in approximately 1000 genes. However, it is likely that nearly all human genes are capable of causing disease or altering response to drug treatment if their function is altered significantly.

Variation in the Human Genome

One characteristic of the human genome with medical and social relevance is that, on average, two unrelated persons share over 99.9% of their DNA sequences.[13] However, given that more than 3 billion base pairs constitute the human genome, this means that the DNA sequences of two unrelated individuals differ at millions of bases. Since a person's genotype represents the blending of parental genotypes, we are each thus heterozygous at about 3 million genetic loci. Many efforts are currently under way, in both the academic and commercial sectors, to catalogue these variants, commonly referred to as "single-nucleotide polymorphisms" (SNPs), and to correlate these specific genotypic variations with specific phenotypic variations relevant to health.

The Single Nucleotide Polymorphism (SNP) Consortium was established in 1999 as a collaboration of several companies and institutions within the larger IHGSC to produce a public resource of genetic variation in the human genome. SNPs, as the name implies, are single nucleotide changes in the DNA sequence that are present in the genome, and therefore, represent inheritable genetic variations. More than 1.4 million SNPs were identified in the initial sequencing of the human genome,[13] with over 60,000 of these in the regions encoding for the proteins, and it is anticipated that >10 million common SNPs will ultimately be identified. Some of these SNPs have already been associated with significant changes in the metabolism or effects of medications and are beginning to make their way into clinical medicine as important molecular diagnostic tools.[2–4] Because most drug effects are determined by the complex interplay of gene products that influence both the pharmacokinetics and pharmacodynamics of medications, pharmacogenomics is increasingly focused on polygenic determinants of drug effects, including inherited difference in drug targets (eg, receptors) and drug disposition (eg, metabolizing enzymes, transporters). The human genes involved in many pharmacogenetic traits have now been identified, their molecular mechanisms detailed and their clinical importance more clearly defined. In some cases, SNP–phenotype correlations occur as a direct result of the influence of the SNP on health. However, more commonly, the SNP is merely a marker of biologic diversity that happens to correlate with health because of its proximity to the genetic factor that is the actual cause of the clinical phenotype.[14] In this sense, the term "proximity" is only a rough measure of physical closeness. More specifically, proximity means that, as genetic material has passed through 5000 generations from our common ancestral pool, recombination between the SNP and the actual genetic factor has occurred only rarely. In genetic terminology, the SNP and the actual genetic factor are said to be in linkage disequilibrium.[15,16]

As an extension of the current efforts to catalogue individual SNPs and correlate them to phenotype, efforts are being made to map and use haplotypes.[14–16] Whereas a SNP represents a single-base variant, a haplotype represents a considerably longer sequence of nucleotides (averaging about 25,000 bases), that tend to be inherited together.[15,17] SNPs and haplotypes will be the key to the association studies (ie, studies of affected persons and control subjects) necessary to identify the genetic factors in complex, common diseases, just as family studies have been important to the identification of the genes involved in monogenic conditions. Also, until whole-genome sequencing of individual patients becomes feasible clinically, the identification of SNPs and haplotypes will prove instrumental in efforts to use genomic medicine to individualize health care.

Types of Genetic Variations

There are a number of ways to categorize genetic changes or mutations. One is according to the causative mechanism, whereas another is according to their functional effect. When classified according to the mechanism, point mutations—that is, a change in a single DNA base in the sequence—are the most common. There are many types of point mutations. One type is a missense mutation, or a substitution that encodes for an alternative amino acid, because of the way in which it changes the three-base sequence, or codon, for the amino acid. Nonsense mutations are typically a more dramatic type of point mutation that changes the codon to a "stop" codon, a codon that causes the termination of the protein instead of producing an amino acid. Another type of genetic change is the frame-shift mutation, which changes the way the cell's transcription machinery reads the sequence of the gene downstream from the site of the mutation, often leading to a premature stop codon.

In terms of functional effect, rather than mechanism, most variants in the human-genome sequence have no apparent phenotypic effect. Among these are silent mutations, which replace one base with another, so that the resultant codon still encodes for the same amino acid. Also, mutations may not change the behavior of the resulting protein if the altered codon substitutes one amino acid for another that produces very little change in the function of the protein. These are referred to as "conservative mutations." In contrast, nonconservative mutations replace an amino acid with a very different one and are more likely to affect the phenotype.

Although genetic mutations can result in altered protein function by a variety of means, the most common is loss of function. Loss-of-function mutations alter the phenotype of the affected individual by decreasing the quantity or the functional activity of a protein. Typically, loss of function mutations are the most easily identified due to their "all-or-none" phenotypic outcome. Therefore, examples of heritable genetic changes involving loss of function are plentiful. For instance, mutations in the glucose-6-phosphate dehydrogenase *(G6PD)* gene on the X chromosome decreases the functional activity of the enzyme, leading to acute hemolytic anemia if a male (who would have only one copy of the X chromosome) with the mutation is exposed to certain drugs, including sulfonamides, primaquine, and nitrofurantoins.[18] Furthermore, since genes involved in metabolism do not exist merely to handle pharmacologic agents, variants that cause severe *G6PD* deficiency also lead to hemolytic anemia when affected males ingest fava beans (favism), since the enzyme is also important in the degradation of a toxic component of the beans.[19,20] Additional well described examples of loss of function mutations in drug metabolizing enzymes include cytochrome P450 2D6 (CYP2D6),[21,22] thiopurine methyltransferase (TPMT),[23,24] and dihydropyrimidine dehydrogenase (DPD).[25,26] Alternatively, some mutations can result in a gain of function, whereby the protein can take on some new function or is simply more highly expressed. While fewer gain of function mutations have been identified, likely due to the subtlety of their phenotypic effects, some examples include mutations in the genes that cause such neurologic disorders as Huntington's disease and spinocerebellar ataxia which appear to lead to neuropathologic abnormalities by producing proteins with abnormally improved function.[27,28] Gain-of-function mutations are often dominantly inherited, since a single copy of the mutant gene is sufficient to alter function.

Although it was previously assumed that mutations in the approximately 98.5% of the genome that does not code for proteins do not affect the phenotype, several recent examples of non-coding mutations with important phenotypic implications have changed this perception. Indeed, while the vast majority of these "non-coding" mutations do not affect protein function, other so called "regulatory mutations" may ultimately prove as important in the variability of drug metabolism and etiology of common diseases as the coding region variants. Such regulatory mutations act by altering the expression of a gene, and therefore, the level of its protein product. For instance, a regulatory mutation could lead to the loss of expression of a gene, to unexpected expression in a tissue in which it is usually silent, or to a change in the time at which it is expressed. Examples of regulatory mutations associated with disease include those in

the flanking region of the *FMR1* gene (causing fragile X syndrome),[29] a regulatory site of the type I collagen gene (increasing the risk of osteoporosis),[30] and an intronic regulatory site of the calpain-10 gene (increasing the risk of type 2 diabetes mellitus).[31] More recently, a regulatory mutation with important implications for drug metabolism has been identified in the gene that encodes cytochrome P450 3A5 (Schuetz Nat. Med. 2001).[32]

GENETIC POLYMORPHISMS INFLUENCING DRUG DISPOSITION

Metabolism typically converts a drug to metabolites that are more water soluble and thus more easily excreted.[33] Metabolism can also convert prodrugs into therapeutically active compounds, and it may even result in the formation of toxic metabolites. Pathways of drug metabolism are classified as either phase I reactions (ie, oxidation, reduction, and hydrolysis) or phase II conjugation reactions (eg, acetylation, glucuronidation, sulfation, and methylation).[33] The names used to refer to these pathways for drug metabolism are purely historical, so phase II reactions can precede phase I reactions. However, both types of reactions typically convert relatively lipid-soluble drugs into relatively inactive and more water-soluble metabolites, allowing for more efficient systemic elimination.

Approximately 40 years ago, the finding that impairment in the hydrolysis of the muscle relaxant succinylcholine by butyrylcholinesterase was an inherited trait served as a seminal event in the development of the field of pharmacogenetics. Approximately 1 in 3500 white subjects is homozygous for the gene encoding an atypical form of the enzyme butyrylcholinesterase.[5] Individuals who have this inherited trait are relatively unable to hydrolyze succinylcholine, thus prolonging the drug-induced muscle paralysis and resulting apnea. At almost the same time as the discovery of inherited variability in butyrylcholinesterase activity, it was determined that genetic variability in the phase II metabolic inactivation by N-acetylation could result in striking differences in half-life and plasma concentrations of drugs metabolized by *N*-acetyltransferase. Such drugs include the antituberculosis agent isoniazid,[34] the antihypertensive agent hydralazine,[35,36] and the antiarrhythmic drug procainamide,[37] and this genetic variation had clinical consequences in each of these cases.[38] These early examples of the influence of inheritance on the clinical effects of a drug set the stage for subsequent studies of genetic variation in other pathways of drug biotransformation.

The subsequent elucidation of functional polymorphisms in *CYP2D6* represents an excellent example of both the potential clinical implications of pharmacogenetics and the process by which pharmacogenetic research led from the phenotype to an understanding of molecular mechanisms at the level of the genotype. Similar approaches were subsequently applied to other phase I drug metabolizing enzymes, including CYP2C19, CYP2C9, DPD, and CYP3A5. While it is now known that polymorphisms exist in every human gene involved in drug metabolism, the functional and clinical implications of most of these genetic variants are still under investigation. Table 62-1 lists selected examples of clinically relevant genetic variations involving drug-metabolizing enzymes and transporters. While for most of the genes listed in this table, the molecular basis of inherited variation in the drug-metabolizing enzymes has been determined, in some cases, the polymorphism has been found to be associated with a clinically important phenotype without an understanding of the underlying molecular mechanism. There are more than 30 families of drug metabolizing enzymes in humans,[2,39] and essentially all have genetic variants, many of which translate into changes in the proteins they encode. In the discussion that followings, several of the most well described phenotype/genotype associations within the area of drug metabolism and transport are presented, along with some examples of how the ever increasing knowledge of the pharmacogenomics of drug disposition might be applied in the future.

Pharmacogenetics of Phase I Drug Metabolism

CYTOCHROME P4502D6—The cytochrome P450 enzyme CYP2D6 is probably the most extensively studied polymorphic drug metabolizing enzyme in humans and was the first to be characterized at the molecular level.[40] As was common in the pre-genomics era, the discovery of inherited differences in CYP2D6 activity was in part serendipitous, initially stemming from an investigator's own personal experience with marked hypotension following a dose of the antihypertensive agent debrisoquine. Subsequent studies determined that a significant proportion of the general population had an impaired ability to hydroxylate, and therefore, inactivate debrisoquin. Approximately 5–10% of white subjects were found to have a relative deficiency in their ability to oxidize debrisoquin.[41] These individuals also had an impaired ability to metabolize the antiarrhythmic and oxytocic drug sparteine.[42] Subjects who were considered "poor metabolizers" of these two drugs had lower urinary concentrations of metabolites and higher plasma concentrations of the parent drug than did subjects who were "extensive metabolizers." Furthermore, the drugs had exaggerated effects in the poor metabolizers, and family studies demonstrated that poor oxidation of debrisoquin and sparteine was inherited as an autosomal recessive trait.[41,42] In other words, subjects with poor debrisoquin metabolism had inherited two copies of a gene or genes that encoded an enzyme with either decreased CYP2D6 activity or one with no activity at all. Over 30 medications have now been identified as substrates for CYP2D6, and it has been shown that this genetic polymorphism translates into either exaggerated or diminished drug effects, depending on whether the enzyme inactivates (eg, nortriptyline, fluoxetine) or activates (eg, codeine) the medication.[43–45]

A plot of the ratio of urinary debrisoquin to 4-hydroxydebrisoquin—a so-called metabolic ratio—is shown in Figure 62-1. The higher the metabolic ratio, the less the metabolite is excreted. Therefore, subjects with poor metabolism are shown at the far right of the graph, with a few subjects at the far left of the frequency distribution who are now classified as having ultrarapid metabolism.[46,47] Therefore, individuals with genetic variants of *CYP2D6* can have either a slow or rapid acetylator phenotype. Debrisoquin and sparteine represent "probe drugs"—compounds that could be used to classify subjects as having either poor metabolism or extensive metabolism. That strategy, the administration of a probe compound metabolized by a genetically polymorphic enzyme, has become a standard technique used in many pharmacogenetic studies. Unfortunately, even though it is useful for research purposes, the approach is not easily adapted for the routine clinical laboratory. Furthermore, phenotypic studies involving probe drugs are often unreliable due to the many sources of error that accompany pharmacokinetic research, as well as the concern over a lack of substrate specificity. Therefore, the application of molecular genetic techniques to pharmacogenetics not only has made it possible to determine underlying molecular mechanisms responsible for genetic polymorphisms, but also has created the possibility of high-throughput clinical tests that can be performed with DNA isolated from a single blood sample. This approach can then easily be adapted for routine diagnostic use in clinical laboratories.

The application of molecular genetic techniques resulted in the cloning of a complementary DNA (cDNA) and the gene encoding CYP2D6.[48,49] Those advances, in turn, made it possible to characterize a series of genetic variants that led to either low levels of CYP2D6 activity or no activity. The genetic changes ranged from single-nucleotide polymorphisms that altered the

Table 62-1. Genetic Polymorphisms in Genes that Can Influence Drug Metabolism and Transport

ENZYME	SUBSTRATE	CLINICAL CONSEQUENCE OF POLYMORPHISM
Phase I enzymes		
CYP1A1	Benzo(a)pyrine, phenacetin	Possible increased or decreased cancer risk
CYP1A2	Acetaminophen, amonafide, caffeine, paraxanthine, ethoxyresorufin, propanalol, fluvoxamine	Decreased theophylline metabolism
CYP1B1	Estrogen metabolites	Possible increased cancer risk
CYP2A6	Coumarin, nicotine, halothane	Decreased nicotine metabolism and cigarette addiction
CYP2B6	Cyclophosphamide, aflatoxin, mephenytoin	Significance unknown
CYP2C8	Retinoic acid, paclitaxel	Significance unknown
CYP2C9	Tolbutamide, warfarin, phenytoin, NSAIDS	Anitcoagulant effect of warfarin
CYP2C19	Mephenytoin, omeprazole, hexobarbital, mephobarbital, propranolol, proquanil, phenytoin	Peptic ulcer response to omeprazole
CYP2D6	Beta blockers, antidepressants, antipsychotics, codeine, debrisoquin, dextromethorphan, encainide, flecainide, fluoxetine, guanoxan, methoxy-amphetamine, phenacetin, propafenone, sparteine	Tardive dyskinesia from antipsychotics; narcotic side effects, efficacy and dependence; imipramine dose requirement; beta blocker effects
CYP2E1	Acetaminophen, ethanol	Possible effect on alcohol consumption; possible increased cancer risk
CYP3A4/3A5/3A7	Macrolides, cyclosporine, tacrolimus, calcium channel blockers, midazolam, terfenadine, lidocaine, dapsone, quinidine, triazolam, etoposide, teniposide, lovastatin, alfentanil, tamoxifen, steroids, benzo(a)pyrene	Tacrolimus dose requirement in pediatric cardiac transplant patients
Aldehyde dehydrogenase	Cyclophosphamide, vinyl chloride	SCE frequency in lymphocytes
Alcohol dehydrogenase	Ethanol	Increased alcohol consumption and dependence
Dihydropyrimidine dehydrogenase (DPD)	5-fluorouracil	Increased 5-fluorouracil toxicity
NQO1 (DT-diaphorase)	Ubiquinones, menadione, mitomycin C	Menadione-associated urolithiasis; decreased tumor sensitivity to mitomycin C; possible increased cancer risk
Phase II Enzymes		
N-acetyltransferase (NAT1)	Aminosalicylic acid, aminobenzoic acid, sulfamethoxazole	Possible increased cancer risk
N-acetyltransferase (NAT2)	Isoniazid, hydralazine, sulfonamides, amonifide, procainamide, dapsone, caffeine	Hypersensitivity to sulfonamides; amonafide toxicity; hydralazine-induced lupus; isoniazid neurotoxicity and hepatitis
Glutathione transferase (GSTM1, M3, T1)	Busulfan, aminochrome, dopachrome, adrenochrome, noradrenochrome	Possible increased cancer risk; cisplatin induced ototoxicity
Glutathione transferase (GSTP1)	13-cis retinoic acid, busulfan, ethacrynic acid, epirubicin	Possible increased cancer risk
Sulfotransferases	Steroids, acetaminophen, tamoxifen estrogens, dopamine	Possible increased or decreased cancer risk; clinical outcome in women receiving tamoxifen for breast cancer
Catechol-O-methyltransferase	Estrogens, levodopa, ascorbic acid	Decreased response to amphetamine; substance abuse; levodopa response
Thiopurine methyltransferase	Mercaptopurine, thioguanine, azathioprine	Thiopurine toxicity and efficacy; risk of second cancers
UDP-glucuronosyl-transferase (UGT1A1)	Irinotecan, troglitazone, bilirubin	Irinotecan glucuronidation and toxicity
UDP-glucuronosyl-transferase (UGT2B)	Opiods, morphine, naproxen, ibuprofen, epirubicin	Significance unknown
Transport Proteins		
Bile salt export pump (BSEP)	Bile acid conjugates	Increased risk of intrahepatic cholestasis of pregnancy
Multidrug resistance gene 1 (MDR1)	Several anticancer agents, most CYP3A4 substrates, digoxin	Decreased p-glycoprotein expression and increased digoxin bioavailability
Organic anion transporter (OATP)	Pravastatin, benzylpenicillin	Decreased total and renal clearance of pravastatin
Organic cation transporter 1 (OCT1)	Serotonin, dopamine, creatinine, procainamide, desipramine, amantidine	Significance unknown
MDR-related proteins (MRP's)	Glutathione, glucuronide and sulfate conjugates, nucleoside antiviral agents	Significance unknown

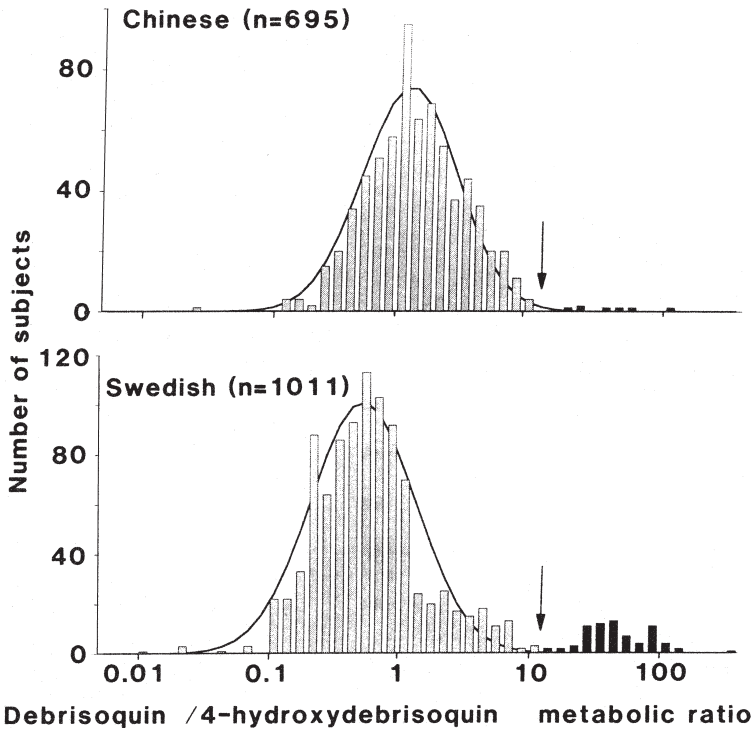

Figure 62-1. Frequency distribution of debrisoquin urinary metabolic ratios. Urinary metabolic ratios of debrisoquin to its metabolite, 4-hydroxydebrisoquin, are shown for 695 Chinese subjects and 1011 Swedish subjects. The arrows indicate the cutoff point between subjects with poor metabolism as a result of decreased or absent CYP2D6 activity and subjects with extensive metabolism. (From Bertilsson L, Lou YQ, Du YL, et al. *Clin Pharmacol Ther* 1992; 51:388.)

amino acid sequence of the encoded protein to single-nucleotide polymorphisms that altered RNA splicing or even deletions of the *CYP2D6* gene.[50] In addition, some subjects with very rapid CYP2D6-mediated metabolism have been shown to have multiple copies of the *CYP2D6* gene.[46] Such subjects may theoretically have an inadequate therapeutic response to standard doses of the drugs metabolized by CYP2D6. Although the occurrence of multiple copies of the *CYP2D6* gene is relatively infrequent among northern Europeans, in East African populations, the frequency can be as high as 29 percent.[51] In total, more than 75 *CYP2D6* alleles have now been described.

CYTOCHROME P4502C SUBFAMILY—In humans, the CYP2C subfamily of cytochrome P450's account for approximately 18% of the CYP content in the liver and catalyzes roughly 20% of the CYP-mediated metabolism of drugs.[52] Historically, the first polymorphism discovered in the CYP2C subfamily was a well-described deficiency in the ability to metabolize the anticonvulsant drug mephenytoin.[53] As in the case of CYP2D6, the inherited nature of the variability in metabolism was first identified phenotypically using a model substrate. Population studies performed in the 1980s using mephenytoin as the probe drug determined that individuals could be segregated into two phenotypic groups, extensive metabolizers (EMs) or poor metabolizers (PMs).[54] The PM trait is autosomal recessive, and is present in 3–5% of Caucasians and 12–23% of Asian populations.[55] Subsequent investigations determined that the inherited variability in the metabolism of mephenytoin was due to genetic variations in the gene coding for CYP2C19. In addition to mephenytoin, CYP2C19 catalyzes the metabolism of several proton pump inhibitors such as omeprazole,[56,57] diazepam,[58] thalidomide,[59] and some barbiturates.[60,61] Furthermore, CYP2C19 is partially responsible for the inactivation of propranolol,[62] as well as the metabolic activation of the antimalarial drug proquanil.[63] At least seven different inactivating mutations in *CYP2C19* have been described, including null mutations that prevent the expression of the protein, as well as single amino acid changes that effect the catalytic activity of the protein.[55]

CYP2C19 catalyzes the 5-hydroxylation of omeprazole, and the metabolism of omeprazole has been found to correlate closely with the metabolism of mephenytoin.[56] Following a single dose of omeprazole, the plasma area under the concentration time curve (AUC) is significantly higher in *CYP2C*19 PMs than EMs. The significant increase AUC is because PM individuals have a 10-fold lower oral clearance of omeprazole. Furthermore, it has also been shown that *CYP2C19* genotype predicts the likelihood of cure of *H pylori* infection in peptic ulcer patients receiving omeprazole and amoxicillin. In one study, the cure rate was 100% in patients homozygous for the PM genotype, 60% in heterozygous PM/EM patients, and 29% in homozygous EM patients.[64] Patients with the homozygous PM genotype had markedly highly plasma omeprazole concentrations and higher gastric pH, leading to higher antibacterial activity of amoxicillin. Several other proton pump inhibitors are also metabolized by CYP2C19, and therefore, their activity may also be dependent on *CYP2C19* genotype.[65–67]

The anti-anxiolytic agent diazepam is demethylated by CYP2C19. Plasma diazepam half-lives are dramatically longer in individuals who are homozygous for the defective *CYP2C19*2* allele compared to those who are homozygous for the wildtype allele. Furthermore, the half-life of the desmethyldiazepam metabolite is also longer in the *CYP2C19* PMs.[68] Asian populations have been reported to have slower diazepam metabolism than Caucasians, which has been attributed to the high frequency of the *CYP2C19*2* allele in Asians.[58] As a result, diazepam induced toxicity may occur as a result of slower metabolism, and it has, therefore, been recommended that care be used when dosing diazepam in Asian individuals.

CYP2C9 is the major CYP2C subfamily member in the liver and is primarily responsible for the oxidative metabolism of many clinically important compounds, including warfarin,[69] phenytoin,[70] tolbutamide,[71] glipizide,[72] and losartan.[73] As with *CYP2C19*, multiple genetic variants of *CYP2C9* have been described. Six distinct polymorphisms, designated *CYP2C9*1*, **2*, **3*, **4*, **5*, and **6*, have been identified in the sequence for the CYP2C9 protein, with *CYP2C9*1* considered the wild type allele and the others as variants.[74] Because they were identified first, the *CYP2C9*2* and **3* alleles have undergone the most thorough *in vitro* and *in vivo* investigation of the known variants. In contrast, considerably less is known about the more

recently identified **4*, **5* and **6* alleles. The variant **2* and **3* alleles are found quite commonly in Caucasians (roughly 35%), however, they are significantly less prevalent in African-American and Asian populations.[74] *In vitro* data have consistently demonstrated that the *CYP2C9*2* and **3* alleles are associated with reduced enzymatic oxidation of a variety of 2C9 substrates compared with *CYP2C9*1*.[75,76,77,78] In addition, multiple *in vivo* investigations and clinical case reports have associated genotypes expressing the *CYP2C9*2* and **3* alleles with significant reductions in the metabolism and clearance of selected CYP2C9 substrates.[55]

Genetic polymorphisms in *CYP2C9* have been linked to both toxicity and dosage requirements for optimal anticoagulation with warfarin.[79] Patients with *CYP2C9* genetic variants *2 and *3 have a higher risk of acute bleeding complications than patients with a wild-type genotype,[80] and require 15–30% lower maintenance doses of warfarin to achieve the target INR.[79–81] Because warfarin dosing can be titrated to a clear effect endpoint (ie, INR), genotyping *CYP2C9* is not widely used in clinical practice. However, the recent demonstration that patients with a variant *CYP2C9* genotype take a median of 95 days longer to achieve stable dosing compared with the wild-type group, providing an important example of how genotype studies can reduce the time a patient is receiving inadequate warfarin therapy.[79] In addition, the inclusion of these *CYP2C9* SNPs among a panel of several thousand genotypes determined in a single genetic test, as discussed below, may allow the utilization of *CYP2C9* genotype to select the optimal starting dose of warfarin.

DIHYDROPYRIMIDINE DEHYDROGENASE—Another important example of the pharmacogenetics of phase I drug metabolism involves metabolism of the antineoplastic agent fluorouracil. In the mid-1980s, fatal central nervous system toxicity developed in several patients after treatment with standard doses of fluorouracil.[82,83] The patients were shown to have an inherited deficiency of dihydropyrimidine dehydrogenase (DPD), an enzyme that metabolizes fluorouracil and endogenous pyrimidines. While the exact frequency of DPD deficient patients is unknown, severe fluorouracil toxicity occurs in individuals with reduced DPD activity (below 100 pmol/min/mg protein). Several variant alleles for the gene encoding DPD have now been described that place patients at risk for toxic effects when they are exposed to standard doses of fluorouracil.[84] Approximately 3% of the general population are thought to carry heterozygous mutations that inactivate DPD, and 0.1% are homozygous for the inactivating mutations. Total DPD deficiency (ie, homozygous mutants) is associated with severe neurological disorders due to impaired endogenous pyrimidine metabolism.[85] However, individuals who are heterozygous for the inactivating mutation exhibit no phenotype until challenged with fluorouracil. Therefore, pharmacogenetics of DPD and its effect on the metabolism of fluorouracil serve as an excellent illustration of the importance of genetic variation in the context of drug therapy. Indeed, inherited variability in the response to drugs is most critical in the case of an agent with a narrow therapeutic index. Fluoruracil-induced toxicity can be life threatening in patients with severe DPD deficiency, and prospective determination of DPD genotype may be useful for identifying those individuals at high risk for unacceptable toxicity.

CYTOCHROME P4503A SUBFAMILY—The human CYP3A subfamily plays a critical role in the metabolism of more drugs than any other phase I enzyme.[86] CYP3A enzymes are expressed in the liver and small intestine and thus contributes to oral absorption, first-pass, and systemic metabolism.[87] Although CYP3A expression has been shown to vary by as much as 40-fold in the liver and small intestine,[88] CYP3A-dependent *in vivo* drug clearance appears to be normally distributed, suggesting that the wide inter-individual variability is the result of complex interaction between genes and environment. The expression of the CYP3A enzymes are highly inducible,[89] and therefore, the wide range in enzyme activity levels may be due to factors such as variable homeostatic control mechanisms, up- or down-regulation by environmental factors (eg, alcohol, concomitant drugs, or diet), and genetic polymorphisms.

Unlike other human P450s (eg, CYP2D6) there is no evidence of a deleted or 'null' allele for CYP3A4. However, more than 30 SNPs have been identified in the CYP3A4 gene.[88] Generally, variants in the coding regions of CYP3A4 occur at allele frequencies of <5% and appear as heterozygous with the wild-type allele. These coding variants may contribute to, but are not likely to be the major cause, of inter-individual differences in CYP3A-dependent clearance. The most common variant in CYP3A4, CYP3A4*1B, is an A392G transition in the promoter region referred to as the nifedipine response element.[90] Although the results of one clinical study indicated that the CYP3A4*1B polymorphism may be associated with a slower oral clearance of cyclosporine,[91] the functional impact of the CYP3A4*1 polymorphism on CYP3A4-mediated drug metabolism remains controversial.[92] In contrast, there are several reports about its association with various disease states including prostate cancer,[93] secondary leukemias,[94] and early puberty.[95] Linkage disequilibrium between CYP3A4*1B and another CYP3A allele (CYP3A5*1) may be the true cause of the clinical phenotype.[96]

In contrast to CYP3A4, clinically relevant genetic variation in CYP3A5 has been demonstrated. CYP3A5 is polymorphically expressed in adults with detectable expression in about 10–20% in Caucasians, 33% in Japanese, and 55% in African Americans.[32] The primary cause for its variable expression is a mutation (CYP3A5*3) that confers low CYP3A5 expression as a result of improper mRNA splicing and reduced translation of a functional protein.[32] The CYP3A5*3 allele frequency varies from approximately 50% in African Americans to 90% in Caucasians. Functionally, microsomes from a homozygous CYP3A5*3/*3 liver contains very low CYP3A5 protein and displays reduced catalytic activity towards the model substrate midazolam.[97] Additional intronic or exonic mutations (CYP3A5*5, *6, and *7) also alter splicing and result in premature stop codons or exon deletions.[88] While several CYP3A5 coding variants have been described, they occur at relatively low allelic frequencies and their functional significance has not yet been established. Because CYP3A5 is the primary extrahepatic CYP3A isoform, its polymorphic expression has be implicated in disease risk and the metabolism of endogenous steroids or drug in tissues other than liver (eg, lung, kidney, prostate, breast, leukocytes). Furthermore, the presence of CYP3A5 genotype has been linked to tacrolimus dose requirements to maintain adequate immunosuppression in solid organ transplant patients.[98,99]

CYP3A7 is the form of CYP3A enzyme expressed in fetal liver during development. Although hepatic expression appears to be significantly down-regulated after birth, CYP3A7 protein and mRNA have been detected in some adults.[100] Recently, increased CYP3A7 mRNA expression has been associated with the replacement of a 60 nucleotide fragment of the CYP3A7 promoter with the corresponding region from the CYP3A4 promoter (CYP3A7*1C allele).[101] This promoter "swap" results in increased gene expression due to enhanced transcriptional activation through the transfer of the pregnane X receptor (PXR) response element. PXR signaling serves as a central regulator of inducible CYP3A expression, as well as several other genes involved in drug detoxification.[89] Polymorphisms have recently been identified in PXR,[102,103] suggesting that the observed variability in CYP3A enzymatic activity may, in part, be due to inherited differences in the upstream signaling proteins that control induction of gene expression.

The genetic basis for polymorphic expression of CYP3A5 and CYP3A7 has now been established. Substrate specificity and tissue distribution of these enzymes can differ from that of CYP3A4, such that the impact of variability in CYP3A5 and CYP3A7 expression on drug disposition will be both drug and tissue dependent. In addition to genetic variation, other factors

that may affect CYP3A expression include tissue-specific splicing, variable control of gene transcription by endogenous molecules (circulating hormones) and exogenous molecules (diet or environment), and genetic variations in proteins that may regulate constitutive and inducible CYP3A expression (nuclear receptors). Thus, the complex regulatory pathways may confound evaluation of the effect of individual CYP3A genetic variations on drug disposition, efficacy and safety. However, because of the major contribution of the CYP3A subfamily to the metabolism of drugs, it is critically important that the genetic and epigenetic factors involved in the variability in this pathway be better understood.

Pharmacogenetics of Phase II Drug Metabolism

***N*-ACETYLTRANSFERASE—**The *N*-acetylation of isoniazid represents one of the earliest examples of inherited variation in phase II drug metabolism. Wide inter-individual variability exists in the rates at which isoniazid acetylated.[34] The original population studies demonstrated that the rate of isoniazid acetylation is an inherited trait, with individuals being classified as either slow or rapid acetylators (Fig 62-2). The distribution of the acetylator phenotype shows a striking ethnic variation.[104] For example, the proportion of slow acetylators in the Japanese population is about 10%, in the Chinese population about 20%, and among Caucasians about 60%. Molecular cloning studies demonstrated that there are two N-acetyltransferase (*NAT*) genes in humans, *NAT1* and *NAT2*.[105] The NAT2 protein is the specific protein isoform that acetylates isoniazid. Seven missense (G191A, T341C, A434C, G590A, A803G, A845C, and G857A) and four silent (T111C, C282T, C481T, and C759T) substitutions have been identified thus far in the *NAT2* coding sequence.[106] To date, 27 unique *NAT2* alleles have been identified in humans, with *NAT2*4* considered the wildtype allele since it does not contain any of the known substitutions. However, *NAT2*4* is not the most common allele in many ethnic groups, including Caucasians and Africans. *NAT2* alleles containing the G191A, T341C, A434C, G590A, and/or G857A missense substitutions are associated with slow acetylator phenotype, while the other known nucleotide changes do not appear to affect enzyme activity.[107] Laboratory investigations on the recombinant proteins demonstrate that multiple mechanisms exist for the reduction in enzyme activity, including altered catalytic activity, decreased protein expression, and protein instability.[108,109] Striking ethnic differences exist in the frequencies of these missense substitutions in various ethnic populations, and these differences correspond to ethnic differences in frequency of the slow acetylator phenotype.

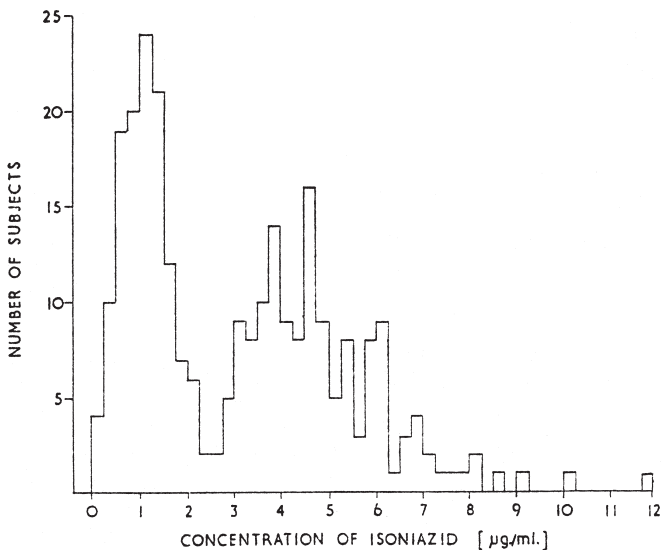

Figure 62-2. Frequency distribution of isoniazid acetylation. Plasma isoniazid concentrations were measured in 267 subjects 6 hours after an oral dose. The bimodal distribution in the rate of acetylation is due to genetic polymorphism within the*N*-acetyltransferase 2 gene. (From Price Evans DA, Manley KA, McKusick VA *BMJ* 1960; 2:485.)

Isoniazid is metabolized to acetylisoniazid via NAT2.[107] Acetylisoniazid undergoes further chemical hydrolysis to acetylhydrazine, which is then metabolized by CYP2E1 to a hepatotoxic intermediate. Importantly, the hydrolysis product acetylhydrazine is also acetylated by NAT2 to form a non-toxic metabolite. Acute or chronic hepatitis is a commonly encountered toxicity in patients receiving isoniazid-containing regimens for tuberculosis, with a reported incidence as high as 36%.[38] Several studies have investigated the relationship between acetylator status and the risk of hepatitis.[110–112] While the earliest of these studies suggested that rapid acetylators might have an increased risk of drug-induced hepatitis, several more recent studies concluded that slow acetylators have a greater susceptibility to developing hepatotoxicity. Most of the studies conducted to date have used phenotyping to determine acetylator status, however, at least one recent study using genotyping confirmed the association between slow acetylator status and increased risk of hepatitis.[113] Because of this important genotype/phenotype relationship, it has been recommended that patients determined to be slow acetylators be monitored more regularly during therapy for signs of overt hepatotoxicity.

The anticancer agent amonafide represents an example of how one might use pharmacogenetic information to guide the drug development process.[114] Amonafide is a DNA intercalating agent and topoisomerase II inhibitor that is extensively metabolized to active and inactive metabolites. Acetylation of amonafide by NAT2 results in a metabolite of similar potency compared to the parent drug.[115] During the initial clinical trials, it was determined that the pharmacokinetics of amonafide was highly variable. Because of the importance of NAT2 to the disposition of amonafide, these early investigations also included phenotyping for acetylator status. It was demonstrated that the production of the acetylated metabolite was a major determinant of myelosuppression, since fast acetylators had significantly greater toxicity than slow acetylators.[116] Interestingly, the area under the plasma concentration-time curve of amonafide was significantly greater in the fast acetylators, who would have been expected to have a higher clearance and a lower area under the plasma concentration-time curve. This appeared to be an unusual finding compared with other drugs metabolized by *N*-acetylation. For most drugs, slow acetylators are at greater risk of adverse reactions. This unexpected finding was shown to be due to inhibition of parent amonafide oxidation by *N*-acetylamonafide.[116] Once the relationship between acetylator status and myelosuppression was identified, subsequent studies prospectively dosed amonafide based on each individual's acetylator status.[117] Although the clinical development of amonafide was later abandoned due to a lack of anti-tumor activity and unacceptable toxicity, it still serves as an example of how clinical decisions regarding drug therapy may ultimately be guided by genetic considerations.

In addition to their role in the metabolism of clinically administered drugs, phase I and II metabolizing enzymes are thought to play an important role in host defense against environmental toxins. Several well known environmental carcinogens, such as aromatic amines and heterocyclic amines, are present in cigarette smoke and cooked meats.[118] Aromatic and heterocyclic amines have been shown to induce tumors in multiple experimental models. Following *N*-oxidation, *N*-hydroxy-aromatic and *N*-hydroxy-heterocyclic amines are further activated by the *N*-acetyltransferases to unstable acetoxy intermediates, which react spontaneously with DNA to form carcinogenic DNA adducts.[119] Thus, it has been hypothesized that *NAT1* and *NAT2* genotype may be related to an individual's

risk of environmentally induced cancers. While several epidemiological studies suggest that *NAT1* and *NAT2* genotype may contribute to ones predisposition to cancers,[120–123] there is a great deal of inconsistency in the published results. These inconsistencies are likely due to the difficulty one has in controlling for all of the possible contributory aspects of an epidemiologic study. Factors such as population differences in carcinogen exposures, genotyping and/or phenotyping methods, insufficient sample sizes, and the confounding effects of other susceptibility genes and factors all lead to noise in the final conclusions. Associations between slow *NAT2* acetylator genotypes and bladder cancer and between rapid *NAT2* acetylator genotypes and colorectal cancer are the most consistently reported associations.[(119)] Although individual risks associated with *NAT1* and/or *NAT2* genotypes are generally small, they increase when combined with measures of aromatic and heterocyclic amine carcinogen exposures. Ethnic differences in *NAT1* and *NAT2* genotype frequencies may be a factor in observed differences in cancer incidence. Large-scale molecular epidemiological studies that investigate the role of *NAT1* and *NAT2* genotypes together with other genetic susceptibility gene polymorphisms and biomarkers of carcinogen exposure are critical to improve our understanding of the role of the *NAT1* and *NAT2* acetylation polymorphisms in cancer risk.

THIOPURINE METHYLTRANSFERASE—One of the most mature examples of applied clinical pharmacogenomics involves the genetic polymorphism of thiopurine methyltransferase (TPMT). TPMT catalyzes the S-methylation of the thiopurine agents azathioprine, mercaptopurine, and thioguanine.[124] These agents are used for a wide range of indications, including childhood leukemia, rheumatoid arthritis, inflammatory bowel disease, dermatologic disorders, and solid organ transplantation. The cytotoxic mechanism of these agents is mediated via the incorporation of thioguanine nucleotides (TGN) into DNA. Thiopurines are themselves inactive prodrugs that require activation to TGN to exert cytotoxicity.[125] Metabolic activation is a complex process catalyzed by multiple enzymes, the first of which is hypoxanthine phosphoribosyl transferase. Alternatively, these agents can be inactivated via oxidation by xanthine oxidase or methylation by TPMT. In bone marrow, TPMT is the only inactivation pathway for the thiopurines. Furthermore, TPMT activity is highly variable and polymorphic, such that approximately 90% of individuals have high enzyme activity, 10% have intermediate activity, and 0.3% have low or no detectable activity.[126,127] Family studies have shown that TPMT activity is inherited as an autosomal codominant trait. As a result, patients who inherit TPMT deficiency accumulate excessive cellular concentrations of TGN, predisposing them to potentially fatal hematological toxicity.[128]

The molecular basis for polymorphic TPMT activity has been determined for the majority of individuals with this observed deficiency.[129] At least 8 TPMT variant alleles have been identified, with 3 of the alleles (*TPMT*2*, *TPMT*3A*, *TPMT*3C*) accounting for about 95% of patients with intermediate or low enzyme activity. The mutant allele *TPMT*2* is defined by a single nucleotide transversion (G238C) in the coding sequence, leading to an amino acid substitution at codon 18 (Ala>Pro).[130] *TPMT*3A* contains two nucleotide transition mutations (G460A and A719G), leading to amino acid substitutions at codon 154 (Ala>Thr) and codon 240 (Tyr>Cys),[131] whereas *TPMT*3C* contains only the A719G transition mutation.[131,132] All three alleles are associated with lower enzyme activity, owing to decreased protein stability and enhanced rates of protein degradation.[23]

Phenotypic deficiency in TPMT activity is a fairly rare event. Furthermore, studies in Caucasian, African, and Asian populations have revealed that the frequency of these mutant *TPMT* alleles differs among various ethnic populations. In Caucasians, *TPMT*3A* is the most common mutant *TPMT* allele (3.2–5.7% of *TPMT* alleles), whereas *TPMT*3C* has an allele frequency of 0.2–0.8% and *TPMT*2* represents 0.2–0.5% of *TPMT* alleles.[24,125] East and West African populations have a frequency of mutant alleles similar to that of Caucasians, but all mutant alleles in the African populations are *TPMT*3C*.[133] Among African Americans, *TPMT*3C* is the most prevalent allele, but *TPMT*2* and *TPMT*3A* are also found, reflecting the integration of Caucasian and African-American genes in the US population.[134] In Asian populations, *TPMT*3C* is the predominant mutant allele.

The presence of *TPMT*2, TPMT*3A, or TPMT*3C* is predictive of phenotype. In other words, patients who are heterozygous for these alleles have intermediate activity, and subjects homozygous for these alleles are TPMT deficient.[24,134] In addition, compound heterozygotes (*TPMT*2/3A, TPMT*3A/3C*) are also TPMT deficient, as would be expected.[24] Whereas most studies have used erythrocytes as a surrogate tissue for measuring TPMT activity, studies have also shown that TPMT genotype determines TPMT activity in leukemia cells,[127,135] as would be expected for germline mutations. Therefore, the enthusiasm for TPMT pharmacogenetics has been stimulated by the finding that TPMT genotype identifies patients who are at risk of toxicity from mercaptopurine or azathioprine. Numerous studies have shown that TPMT-deficient patients are at very high risk of developing severe hematopoietic toxicity when treated with conventional doses of thiopurines,[136,137] while others have shown that patients who are heterozygous at the TPMT gene locus are at intermediate risk of dose-limiting toxicity.[138–140] In a study of 67 patients treated with azathioprine for rheumatic disease, six patients (9%) were heterozygous for mutant TPMT alleles,[138] and therapy was discontinued in five of the six patients because of low white blood cell counts within one month of starting treatment. In contrast, patients with wild-type TPMT received therapy for a median of 39 weeks without complications compared with a median of 2 weeks in patients heterozygous for mutant TPMT alleles.[138] A second study in Japanese patients with rheumatic disease receiving azathioprine recently confirmed the importance of a heterozygous TPMT genotype for predicting toxicity.[140] Furthermore, TPMT-deficient patients with acute lymphoblastic leukemia were able to tolerate full doses of mercaptopurine for only 7% of scheduled weeks of therapy, whereas heterozygous and homozygous wild-type leukemia patients tolerated full doses for 65% and 84% of scheduled weeks of therapy, respectively.[139] Collectively, these studies demonstrate that the influence of TPMT genotype on hematopoietic toxicity is most dramatic for homozygous mutant patients, but is also of clinical relevance for heterozygous individuals, who represent about 10% of patients treated with these medications. TPMT deficiency has also been linked to a higher risk of second malignancies among patients with acute lymphoblastic leukemia, including topoisomerase-inhibitor-induced acute myeloid leukemia[(141,142)] and radiation-induced brain tumors.[143] Therefore, knowledge of a patient's genotypic TPMT status permits patient-specific dosages that reduce the risk of acute toxicity from thiopurine medications and may identify those at higher risk of second malignancies.

URIDINE DIPHOSPHATE-GLUCURONOSYLTRANSFERASES—Uridine diphosphate-glucuronosyltransferases (UGTs) are microsomal phase II enzymes that catalyze the glucuronidation of numerous endogenous and exogenous substrates.[144] Human UGTs are further classified into UGT1 and UGT2 families.[145] The UGT1 gene consists of at least 13 unique forms with a variable exon 1 and common exons 2 to 5. As a result, the UGT1 subfamily is further classified into multiple isoforms, ie, UGT1A1, UGT1A3, UGT1A4, up to UGT1A12. The UGT1A1 isoform is responsible for the conjugation of bilirubin,[146] along with the glucuronidation of irinotecan and troglitazone.[147] Clinically relevant polymorphisms in UGT1A1 are associated with familial hyperbilirubinemic syndromes such as Crigler-Najjar syndromes type I (CN-I) and type II (CN-II), and Gilbert's syndrome. CN-I syndrome is a rare disorder associated with severe unconjugated hyperbilirubinemia.[148] Patients with CN-I syndrome have absent or reduced UGT1A1 activity with correspondingly high serum levels of unconjugated biliru-

bin.[149,150] Gilbert's syndrome is a more mild form of chronic unconjugated hyperbilirubinemia, with serum bilirubin levels usually <3 mg/dl, although higher levels are sometimes seen.[150] A wide ethnic variation in the incidence of Gilbert's syndrome has been reported, ranging from 0.5 to 19% in various groups.[151,152,153] Gilbert's syndrome is typically associated with a polymorphism in the regulatory region of the UGT1A1 promoter. A variant $(TA)_7TAA$ sequence in the UGT1A1 promoter, instead of wildtype $(TA)_6TAA$, results in reduced UGT1A1 expression levels and lower enzymatic activity.[154,152] In addition the $(TA)_7$ alleles, three other alleles with five, six, or eight TA repeats [$(TA)_5$, $(TA)_6$, and $(TA)_8$] have been identified.[155] The $(TA)_5$ and $(TA)_8$ alleles are primarily present in African populations, and occur at much lower frequencies than the $(TA)_6$ and $(TA)_7$ alleles.

UGT1A1 plays several roles in the metabolic inactivation of the anticancer drug irinotecan. Irinotecan (CPT-11) is a camptothecin derivative used in the treatment of metastatic colorectal cancer. Irinotecan is a prodrug, since it requires activation by carboxylesterases to SN-38 (7-ethyl-10-hydroxycamptothecin) in order to exert its antitumor activity mediated by the inhibition of topoisomerase I. SN-38 is in turn glucuronidated to form the inactive SN-38 glucuronide (SN-38G).[156] SN-38 is associated with severe episodes of diarrhea occurring shortly after irinotecan therapy.[157] Because of its extensive biliary excretion,[158] SN-38 is secreted directly into the lumen of gastrointestinal tract, resulting in high local tissue exposures to this very toxic compound. Glucuronidation of SN-38 to the inactive SN-38G via UGT1A1 protects against irinotecan-induced intestinal toxicities due to increased conversion to the inactive SN-38G and increased renal elimination of the more polar conjugated form.[159] Patients with the $(TA)_7$ polymorphism have significantly lower rates of SN-38 glucuronidation rates than those with the wildtype allele. In addition, more severe diarrhea is seen in patients who are either heterozygous or homozygous for the $(TA)_7$ sequence.[160] The association between UGT1A1 genotype and risk of irinotecan-induced diarrhea might be exploited in the future in order to prospectively identify those individuals with a greater susceptibility to chemotherapy induced gastrointestinal toxicity.

Pharmacogenetics of Drug Transporters

Although passive diffusion accounts for some drug and metabolite distribution, increased emphasis is being placed on understanding the role of membrane transporters in absorption of oral medications across the gastrointestinal tract, excretion into the bile and urine, distribution of drug into "therapeutic sanctuaries," such as the brain and testes, and transport into sites of action, such as cardiovascular tissue, tumor cells, and infectious microorganisms. The most widely studied class of membrane transporters belong to the adenosine triphosphate (ATP)-binding-cassette (ABC) family of membrane transporters, which share many physicochemical characteristics. ABC family members include P-glycoprotein, MRP1-6 (multidrug resistance proteins), OCT (organic cation transporter), OAT (organic anion transporter), and SPGP (sister of Pgp). While it has been established that Pgp is not an essential protein for life, since genetically engineered mice lacking the protein appear normal until they are challenged with toxic compound, Pgp function is critical to the cellular and systemic clearance of many commonly used pharmacologic agents. Moreover, other members of the ABC family play critical physiologic roles in transport of endogenous substances, such as bilirubin and glutathione conjugates, as well as some medications. Although polymorphisms in ABC family members have been have been reported,[161] and such genetic variation may have functional significance for drug absorption and elimination, the full clinical relevance of polymorphisms in drug transporters has yet to be fully elucidated.

ABCB1 (MDR1)—Transport proteins play an important role in regulating the absorption, distribution and excretion of many medications. The many members of the ABC family of transporters are among the most extensively studied proteins involved in drug disposition and effect.[162] Among these, Pgp is the 170 kd transmembrane protein encoded by the human *ABCB1* gene (also named *MDR1*). The principal function of Pgp is the energy-dependent cellular efflux of a wide variety of substrates, including bilirubin, several anti-cancer drugs, cardiac glycosides, immunosuppressive agents, glucocorticoids, HIV-1 protease inhibitors, and many other medications.[161–163] As a result of the striking overlap in substrate specificity between Pgp and CYP3A4, it is believed that this transporter plays a role in the bioavailability and/or biliary excretion of more drugs than any other. The relatively high expression of Pgp in normal tissues involved in drug uptake and elimination suggests that it plays a vital role in excreting xenobiotics and metabolites into urine, bile, and the intestinal lumen.[164] Furthermore, Pgp in the blood-brain barrier has been shown to limit CNS accumulation of many drugs, including digoxin, ivermectin, vinblastine, dexamethasone, cyclosporine A, domperidone, and loperamide.[165,166]

Pgp expression is highly variable among individuals, the molecular basis of which is still being explored. Among the many possible explanations for this observed variability in Pgp expression and function may be inherited differences in the *ABCB1* gene. Figure 62-3 graphically depicts the functional consequences of polymorphisms in *ABCB1*. A synonymous SNP (ie, a SNP that does not change the amino acid encoded) in exon 26 (3435C>T) has been identified, and despite the fact that the 3435C>T polymorphism does not result in an amino acid substitution, the variant has been associated with decreased duodenal Pgp expression. Patients who are homozygous for the variant allele had more than two-fold lower duodenal Pgp levels compared to patients with the homozygous wildtype genotype.[167] Furthermore, laboratory studies have demonstrated that the rate of in vitro efflux of the Pgp substrate rhodamine in CD56+ natural killer cells is significantly higher in subjects homozygous for wildtype 3435C compared to those homozygous for the 3435T variant.[168] A clinical pharmacokinetic study of digoxin, a known Pgp substrate, also demonstrated significantly higher oral bioavailability in subjects with the 3435TT genotype (Fig 62-3A), consistent with the hypothesis that lower duodenal Pgp expression results in increased oral drug absorption.[169] However, results of other pharmacokinetic studies have shown that the 3435TT genotype is associated with lower plasma concentrations of fexofenadine[170] (Fig 62-3B) and nelfinavir[171] (Fig 62-3C), contradicting the hypothesis that this polymorphism results in increased oral bioavailability.

To further confuse the issue of the functional importance of the 3435C>T polymorphism, it has also been shown that the recovery of CD4 count in HIV infected patients receiving protease inhibitors was significantly greater and more rapid in patients with the wildtype TT genotype than in patients with either CT or CC genotypes[171] (Fig 62-3D), despite lower plasma levels of the protease inhibitors. It is not mechanistically clear how greater efficacy (CD4 recovery) could be linked to a polymorphism associated with lower plasma drug concentrations.

Recently, a second, non-synonymous polymorphism (ie, a SNP causing an amino acid change) was identified in exon 21 (2677G>T) of ABCB1. The 2677T variant allele, resulting in a alanine to serine amino acid substitution, has been associated with increased Pgp function *in vitro* and lower plasma fexofenadine plasma concentrations[170] (Fig 62-3E). Interestingly, the 3435T allele has been shown to be in incomplete linkage disequilibrium with the 2677T allele. In other words, individual who inherit the 3435T allele have a reasonable probability of also inheriting the 2677T allele, with their potentially opposite effects on drug transport. Recently, results from renal transplant patients receiving the immunosuppressive agent tacrolimus, demonstrated that the dose required to achieve

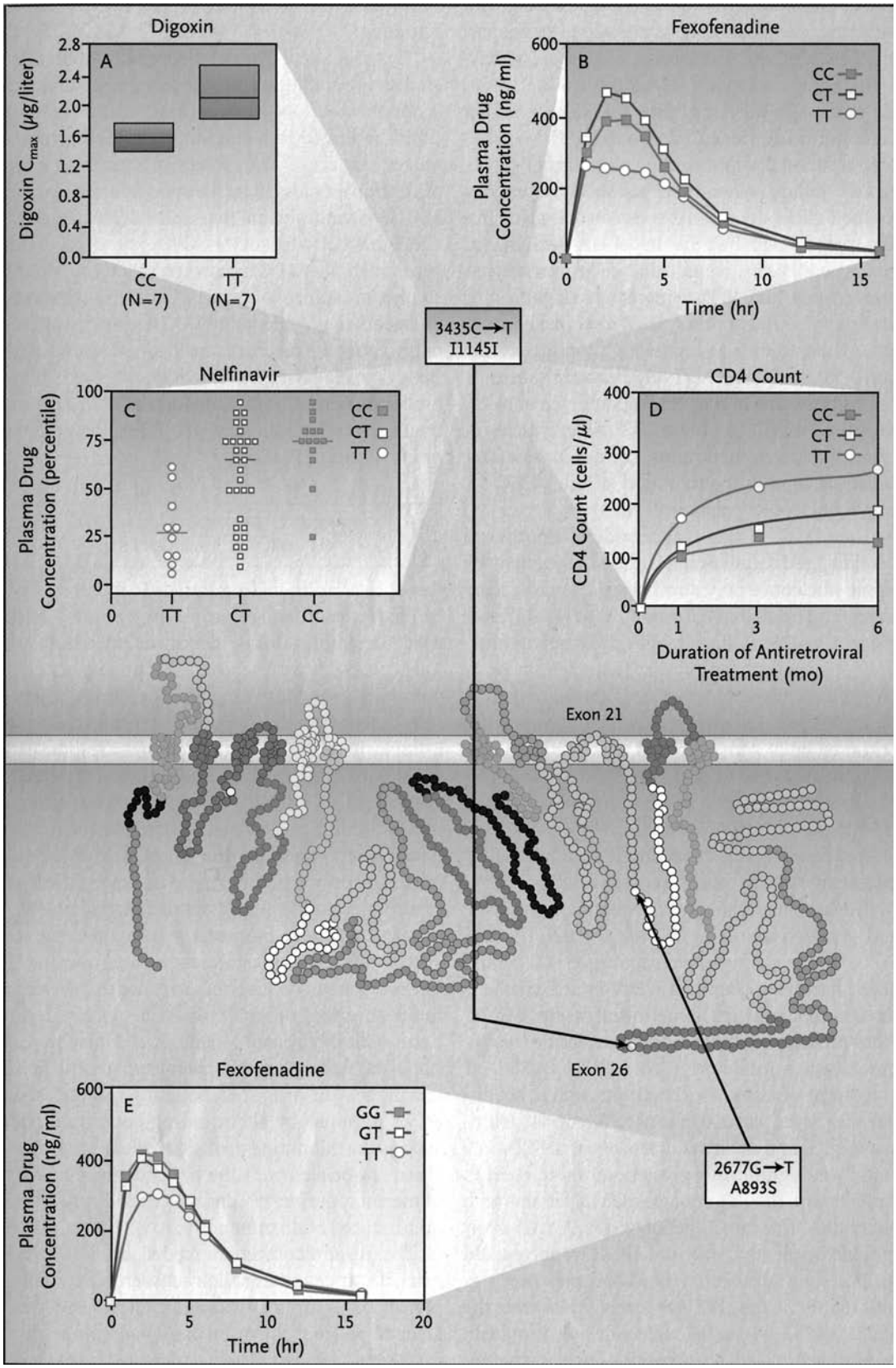

Figure 62-3. Functional consequences of genetic polymorphisms in the human p-glycoprotein transporter gene (*MDR1* or *ABCB1*). The schematic of the human P-glycoprotein was adapted from Kim RB, Leake BF, Choo EF, et al. *Clin Pharmacol Ther* 2001; 70:189, with each circle representing an amino acid and each color a different exon encoding the corresponding amino acids. Two SNPs in the human *ABCB1* gene have been associated with altered drug disposition (Panels A,B,C,E) or altered drug effects (Panel D) in humans. The synonymous SNP in exon 26 (nucleotide 3435 C>T SNP), has been associated with higher digoxin oral bioavailability in patients homozygous for the T nucleotide[167] (Panel A), but lower plasma concentrations after oral does of fexofenadine[170] (Panel B) and nelfinavir[171] (Panel C). This SNP has also been linked to better CD4 cell recovery in HIV infected patients treated with nelfinavir and other antiretroviral agents (Panel D).[171] The SNP at nucleotide 2766 (G>T) has been associated with lower fexofenadine plasma concentrations in patients homozygous for the T nucleotide at position 2766(Panel E).[170] Panels A-E have been adapted from the original reports of Kim RB, Leake BF, Choo EF, et al. *Clin Pharmacol Ther* 2001; 70: 189; Hoffmeyer S, Burk O, von Richter O, et al. *Proc Natl Acad Sci U S A* 2000; 97: 3473. and Fellay J, Marzolini C, Meaden ER, et al. *Lancet* 2002; 359: 30. (From Evans WE, McLeod HL. *N Engl J Med* 2003; 348:538.) See Color Plate 23.

optimal immunosuppression was correlated with *ABCB1* genotype.[99] In patients one month after tacrolimus introduction, dose requirements were 40% higher in 2677T homozygotes than wild-type patients, consistent with the finding that the 2677T variant results in increased Pgp activity. Similar results have been seen in pediatric cardiac transplant patients.[98] The results of haplotype analyses suggest that both the 2677T and 3435T polymorphisms might be associated with tacrolimus dose requirements. The potential co-segregation of polymorphisms with opposite effects on protein function may explain the conflicting results reported when the investigators look only at the contribution of one genetic variant and not both. The pharmacogenomics of *ABCB1*, therefore, serves a good example of the importance of considering multiple polymorphisms within the same gene (or haplotype) when evaluating the relationship between genotype and phenotype.

ORGANIC ION TRANSPORTERS—Organic anion transporter polypeptides (OATPs) and organic cation transporters (OCTs) are two major classes of secretory transporters expressed differentially in the kidney, liver, blood-brain barrier, lung, heart, intestine, placenta, and testis.[172] OATPs are mainly important for the hepatic uptake of large organic anions, organic cations and uncharged substrates,[173] whereas OCTs mediate uptake of predominantly small organic cations and anions in liver and kidney.[174] The many different members of the OATP family have partially overlapping and partially distinct substrate preferences for organic solutes such as bile salts, steroid conjugates, thyroid hormones, anionic oligopeptides, drugs, and toxins.[172] Although significant progress has been made in the characterization of these important classes of transporters at the molecular level, there is still much to learn about the functional and clinical importance of genetic variations in these secretory pathways. However, several non-synonymous variants in the OATP-C gene have recently been identified, and individuals with certain commonly occurring polymorphisms have a reduced clearance of the cholesterol-lowering agent pravastatin.[175–177] While the example of pravastatin represents the first report of a genotype/phenotype association within the organic anion transporter family, this highlights the potential for other important associations between genetic variants of transporters and clinical outcome. In addition, the paucity of published data regarding the pharmacogenomics of drug transporters underscores how little is currently known about many of the most important pathways of drug elimination and distribution.

GENETIC POLYMORPHISMS IN DRUG TARGETS

Genetic Polymorphisms Associated with Effects on Drug Response and Toxicity

There has recently been growing interest in determining genetic variations in drug targets, with the overall goal of defining their impact on drug efficacy and/or toxicity. A drug target, in this context, is defined as either the direct protein target of a drug (eg, a receptor or enzyme), proteins involved in a pharmacologic response (eg, signal transduction proteins or downstream proteins), or proteins associated with disease risk or pathogenesis that is somehow altered by the drug. The major objective of drug target pharmacogenomics research is to identify the inherited basis for interindividual variability in drug response and toxicity, particularly when the variability is not explained by differences in pharmacokinetics. Although studies of the pharmacogenetics of drug metabolism date back to the 1950s, the literature on drug target pharmacogenetics essentially began in the mid to late 1990s. In addition, the field of pharmacogenetics is moving from a monogenic (single gene or pharmacogenetic) to a polygenic (multiple genes or pharmacogenomic) approach, largely because of the acknowledgement that most drug effects are due to the complex interaction between several genes involved in both pharmacokinetics and cellular drug response. Furthermore, this shift towards a polygenic focus has been greatly facilitated by the recent development of new molecular tools for high throughput genotyping.

Most of the early pharmacogenetic studies of therapeutic drug targets focused on a single polymorphism within a single gene, with the gene of interest being the direct target of the drug. Although single polymorphism drug target studies have identified numerous associations between polymorphisms and the anticipated alteration in drug response, such studies have also been somewhat disappointing with respect to the lack of consistency of the findings. For example, the insertion/deletion polymorphism of the angiotensin converting enzyme (ACE) gene is one of the most extensively studied of all the drug target polymorphisms.[3] The homozygous deletion (DD) genotype has been associated with increased ACE activity and heterozygous ACE genotypes have been associated with various clinical effects of ACE inhibitors, including renoprotective effects,[178] blood pressure reduction,[179] left ventricular hypertrophy reduction,[180,181] and improvements in endothelial function.[182] However, the results of studies are not always in agreement since some investigators have found no association between response and ACE genotype,[180] some have shown that the homozygous insertion (II) genotype is associated with better drug response,[183,184] and others have shown that the DD genotype is associated with the best response.[181–185]

Drug target genes for which clinically relevant polymorphisms have been identified are listed in Table 62-2. The table includes examples of polymorphisms that have associated with both altered therapeutic drug response and risk of drug-induced toxicity. In addition to examples of polymorphisms in genes that encode for proteins that are direct targets of a drug (eg, β_2-adrenergic receptor), there are several examples where the genetic variant has an indirect effect on drug response (eg, apolipoprotein E). In other words, the polymorphism occurs in a gene that encodes a protein that is not a direct drug target for the therapeutic response nor involved in drug clearance or disposition. However, the genetic variation still results in altered response to drug treatment. Unlike many of the gene-therapeutic drug response associations, gene-drug toxicity relationships tend to be more robust across studies. In this case, when a drug known to cause a certain adverse event is given to an individual with a particular genetic polymorphism that has been associated with the adverse event, the result is a marked increase in the degree or risk of toxicity. For example, the use of oral contraceptive in patients with Factor V or prothrombin mutations leads to a significantly higher risk of a thrombotic event than in patients with the mutation alone or with oral contraceptive use alone.[186] Similarly, gene mutations in cardiac potassium and sodium channels that are associated with long QT syndrome are also associated with increased risk of clarithromycin-induced Torsade de Pointes.[187] The relative predictability of the relationship between a given polymorphism and drug-induced toxicity represents a useful therapeutic paradigm. Indeed, the clinical utility of pharmacogenomics of drug targets may emerge most rapidly as a valuable molecular diagnostic tool to identify those individuals who are most at risk for an adverse drug effect. The potential importance of direct target polymorphisms is illustrated below by the β_2-adrenergic receptor, while the apolipoprotein E gene represents an example of how polymorphisms can result in indirect effects on drug response. Finally, the relatively recent discovery of a genetic variation in thymidylate synthase is discussed as an example of how pharmacogenomics may ultimately be used to optimize drug therapy.

B_2-ADRENERGIC RECEPTOR—The β_2-adrenergic receptor is a G protein–coupled receptor that interacts with endogenous catecholamines and various medications. These receptors are widely distributed and play an important role in regulating cardiac, vascular, pulmonary, and metabolic functions.[188] Studies of the many physiologic functions of the β_2-adrenergic receptor in humans have revealed substantial interpatient variation in receptor function and responsiveness to stimulation. In the heart, activation of β_2-adrenergic receptor

Table 62-2. Genetic Polymorphisms in Genes that Can Influence Drug Response and Toxicity

GENE/PROTEIN	DRUG	CONSEQUENCE OF POLYMORPHISM
ACE	ACE inhibitors (eg, enalapril)	Renoprotective effects; blood pressure reduction; left ventricular mass reduction; endothelial function improvement; ACE inhibitor induced cough
Bradykinin B2 receptor	ACE inhibitors	ACE inhibitor induced cough
β_2-adrenergic receptor	β_2-agonists (eg, albuterol)	Bronchodilation; susceptibility to agonist-induced desensitization; cardiovascular effects (eg, increased heart rate, peripheral vasodilation)
Gs protein α	β-blockers (eg, propranolol)	Antihypertensive effect
ACE	Fluvastatin	Lipid changes (decreased LDL and apoliprotein B); progression/regression of atherosclerotic lesions
Platelet FC receptor (FCRII)	Heparin	Heparin induced thrombocytopenia
Glycoprotein IIIa subunit of glycoprotein IIb/IIIa receptor	Aspirin/glycoprotein IIb/IIIa inhibitors (eg, abciximab)	Antiplatelet effect
ALOX5	Leukotriene biosynthesis inhibitors (eg, ABT-761- zileuton-derivative)	Improvement in FEV_1
Estrogen receptor	Conjugated estrogens	Bone mineral density increases
Sufonylurea receptor	Sulfonylureas (eg, tolbutamide)	Sulfonylurea-induced insulin release
Inositol-p1p	Lithium	Response of manic depression
Dopamine receptors (D2, D3, D4)	Antipsychotics (eg, haloperidol, clozapine, thioridazine)	Antipsychotic response (D2, D3, D4); antipsychotic-induced tardive dyskinesia and acute akathisia (D3); (D3); hyperprolactinemia (D2)
Dopamine receptor	Levodopa and dopamine	Drug induced hallucinations
5HT2A, 5HT6	Antipsychotics (eg, clozapine)	Clozapine response; typical antipsychotic response and long term outcomes
G protein β3	Antidepressants (various)	Response to antidepressant therapy
Seratonin transporter (5-HTT)	Antidepressants (eg, clomipramine, fluoxetine, paroxetine, fluvoxamine)	5-HT neurotransmission antidepressant response
Ryanodine receptor	Anesthetics (eg, halothane)	Malignant hyperthermia
Thymidylate synthase	5-fluorouracil	Response to 5-fluorouracil based therapy
Ion channels (HERG, KvLQT1, Mink, MiRP1)	Erythromycin, terfenadine, cisapride, clarithromycin, quinidine	Increased risk of drug-induced Torsade de pointes
Methylguanine methyltransferase	Carmustine	Response of glioma to carmustine methyltransferase
Cholesterol ester transfer protein (CETP)	Statins	Slowing of progression of atherosclerosis by pravastatin
HLA-B*5701	Abacavir	Hypersensitivity reaction

results in an increased rate and force of cardiac muscle, whereas β_2-adrenergic receptor stimulation in the lungs acts to relax airway smooth muscle. Influences on lipolysis in subcutaneous fat have also been described, possibly through regulation of lipid mobilization, energy expenditure, and glycogen breakdown. Several polymorphisms in the β_2-adrenergic receptor have been identified, and their effects on β_2-agonist mediated response have been the focus of multiple investigations.

Understanding the molecular basis for variability in the β_2-adrenergic receptor has been facilitated by the identification of five distinct single nucleotide polymorphisms, each associated with either altered expression, down regulation, or coupling of the receptor.[188] Alteration at amino acid 16 (Arg>Gly) appears to have relevance in pulmonary disease, with patients homozygous for Arg exhibiting a greater response to β_2-agonist medications.[189,190] For example, the FEV_1 response to oral albuterol is 6.5-fold higher in patients with an Arg/Arg genotype at amino acid 16 compared with Gly/Gly patients, even though similar plasma drug concentrations are achieved.[189] In contrast, the alteration at codon 27 (Gln>Glu) does not appear to influence lung function, but there is an association between the Gln/Gln genotype and an increased incidence of obesity.[191,192] This relationship appears to be more prominent in men and can be overcome with exercise.[191]

While the β_2-adrenergic receptor alleles for amino acid 16 (frequency 0.61) and 27 (frequency 0.43) are relatively common and have been investigated thoroughly for their clinical relevance, a third much less common allele has been studied for in vivo function. A variation at amino acid 164 (Thr>Ile) with an allele frequency of 0.05 has been associated with probability of survival in patients with congestive heart failure.[193] Patients with congestive heart failure and the Thr/Ile genotype have a significantly poorer one-year survival rate compared to those with Thr/Thr (42 vs. 76%). Moreover, patients with the Thr/Ile genotype show blunted cardiac beta(2)-AR responsiveness, which may help explain the decreased survival of patients with this genotype in the setting of congestive heart failure.[194] The potential clinical importance of the Thr>Ile variant has led to the suggestion that patients with the Ile164 polymorphism and heart failure should be considered as candidates for early aggressive intervention or cardiac transplantation.

Although the three genetic variants discussed represent the most widely studied β_2-adrenergic receptor polymorphisms, at least 13 distinct variant alleles have been identified.[195] As a result of the many possible receptor genotypes, the importance of haplotype structure versus individual SNPs in determining receptor function and pharmacological response has been investigated. Interestingly, out of a possible 8,192 unique β_2-adrenergic receptor haplotypes, only 12 distinct haplotypes have been observed among subjects from several different ethnic groups.[195] Subsequent assessment of the relationship between response to β-agonist therapy in asthma patients and genetic variation revealed a better association of haplotype and bronchodilator response, than could be found with any single polymorphism.[195] This is not surprising, as haplotype structure in the case of a gene with many polymorphisms in varying degrees of linkage disequilibrium should be a better predictor of phenotypic consequences than any ony variant. Examples such as the β_2-adrenergic receptor has provided the impetus to develop simple but robust molecular methods to determine haplotype structure for many important genes in patients.[196]

APOLIPOPROTEIN E—Human apolipoprotein E (apoE) plays an important role in lipid metabolism and neurobiology through its interactions with the low density lipoprotein (LDL)

receptor and cell surface heparin sulfate proteoglycans.[197–200] ApoE exists as three major genetic variants, apoE2, apoE3, and apoE4, each differing by a cysteine or arginine at amino acids 112 and 158. ApoE3, the most common variant, contains cysteine at 112 and arginine at 158, whereas apoE2 contains two cysteines and apoE4 contains two arginines.[201] These differences have profound effects on both the physical stability and biological function of apoE.[202] For example, while both apoE3 and apoE4 bind to the LDL receptor with high affinity, apoE2 exhibits defective LDL receptor binding.[6] In addition, the presence of the apoE4 allele is associated with elevated plasma cholesterol levels and an increased risk for both coronary artery and Alzheimer's disease.[203–205]

In addition to the increased risk of disease, genetic variability in apoE also appears to have a predictive role in the response to drug treatment in patients with Alzheimer's disease and those receiving lipid lowering therapy.[206–209] In a study of the acetylcholinesterase inhibitor tacrine for patients with Alzheimer's disease, 83% of individuals without the apoE4 genotype showed improvement in total response and cognitive response after 30 weeks of drug treatment compared to only 40% of patients with the apoE4 genotype.[210] However, the greatest individual improvement in this particular study was seen in a patient with the unfavorable apoE4 genotype, underscoring that a single gene will not always be predictive of response to a given treatment.[210] Indeed, additional studies have indicated that the interaction between tacrine therapy and apoE genotype was strongest for women, suggesting that the complexity of efficacy prediction goes beyond analysis of one gene.[211] Although the molecular basis for an association between apolipoprotein genotype and tacrine efficacy has not been elucidated, it has been postulated that apoE4 plays a role in cholinergic dysfunction in Alzheimer's disease in a way that cannot be consistently overcome by therapy with acetylcholinesterase inhibitors such as tacrine. A randomized, placebo controlled study of the noradrenergic/vasopressinergic agonist S12024 in patients with Alzheimer's disease found the greatest protection of cognition in patients with the apoE4 genotype.[212] Should these results be confirmed, it may offer a rational approach for prospective selection of initial therapy for Alzheimer's disease, with S12024 or similar medications being recommended for patients with the apoE4 genotype.

In addition to the association between apoE genotype and response drug therapy for Alzheimer's disease, phenotypic and genotypic analyses have shown an association between apoE status and response to lipid lowering medications.[209,213,214] Most studies have demonstrated that patients with the apoE2 genotype have the greatest decrease of LDL cholesterol after drug therapy (E2 > E3 > E4). The association has been observed after treatment with a wide range of lipid lowering agents, including probocol, gemfibrozil, and many different HMG CoA-reductase inhibitors (ie, "statins").[209] However, a significant influence of apoE genotype on response to lipid lowering agents has not been observed in all studies.[209] In addition, although apoE4 genotype was associated with less reduction in total cholesterol and LDL and a smaller increase in HDL after fluvastatin therapy, there was no apparent influence of genotype on coronary artery disease progression or clinical events.[215] Thus, prospective clinical evaluations with robust clinical endpoints and sufficient sample size are needed to better quantitate the benefit of apoE genotype in the treatment of hyperlipidemia. The potential utility of apoE genotype must be balanced by concerns that it could be used by insurance companies, health systems, and federal programs to identify those at 'high risk' for development of Alzheimer's disease, coronary artery disease, and possibly other illnesses.[208]

THYMIDYLATE SYNTHASE—Thymidylate synthase (TS) is a key enzyme in the synthesis of pyrimidine nucleotides, by catalyzing the methylation dUMP to dTMP. The TS reaction is the sole source of *de novo* thymidylate in the cell and is essential for DNA replication.[216] The critical role of TS in nucleotide metabolism has made it an important target for a variety of anticancer drugs including 5-fluorouracil and the 5-fluorouracil <prodrug>, capecitabine, and to a lesser extent methotrexate.[216,217] Inhibition of TS by these agents causes tumor cell death depleting the intracellular pool of dTTP. Despite their clinical utility, resistance to TS inhibitors is an all too common problem. Fluoropyrimidine resistance arises through a variety of mechanisms, including elevated TS protein expression resulting from increases in *TS* transcription and translation.[218–221] A polymorphism within the 5'-untranslated region of the *TS* gene, consisting of tandem repeats of a 28 base pair fragment, has been implicated in modulating TS mRNA expression and TS mRNA translational efficiency.[222] Although there have been reports of four, five, and nine repeats within certain African and Asian populations, the vast majority of individual human *TS* alleles harbor either a double repeat (*2R*) or a triple repeat (*3R*) for this polymorphism, creating genotypes of *2R/2R*, *2R/3R*, and *3R/3R*.[223,224] Individuals that are homozygous for the *3R* have been shown to have elevated levels of TS mRNA and protein in their tumors compared with *2R* homozygotes.[225]

In recent pharmacogenomic studies evaluating the impact of TS polymorphisms on the clinical outcome in patients with locally-advanced or metastatic colorectal cancer treated with 5-fluorouracil based chemotherapy regimens, patients with the 3R/3R polymorphism showed no significant response or survival benefit from chemotherapy, whereas those with the 2R/2R or 2R/3R genotype showed significant better responses and gains in survival time from treatment.[226,227] In addition, it has been shown that patients with metastatic colon cancer treated with the 5-fluorouracil prodrug capecitabine who are homozygous for the 3R allele have a dramatically poorer probability of a response to treatment.[228] Additional data in children with acute lymphoblastic leukemia (ALL) indicates that TS polymorphisms are associated with response to treatment, as well as risk of disease, for other cancers.[229,230] Children with the 3R/3R genotype have been shown to have a poorer clinical outcome following treatment for ALL. Methotrexate, one of the key drugs in treatment regimens for ALL, is metabolized intracellularly to long-chain methotrexate polyglutamates, which then act as inhibitors of TS. Therefore, association between *TS* genotype and outcome in ALL makes sense mechanistically. The growing number of independent clinical investigations that point to a strong relationship between *TS* polymorphisms and outcome in patients with cancer has led some clinicians to recommend routine screening of *TS* genotypes to help guide therapeutic decisions. In the case of colon cancer, where there are now several active drugs to choose from when designing a treatment regimen, the ability to use genetic information to help decide which drug therapy might be best for each individual represents a clinically useful application of pharmacogenomics.

APPLIED PHARMACOGENOMICS

Technological Considerations

Although the examples provided in this chapter serve to illustrate the clinical importance of single nucleotide polymorphisms, for many of the genes that play a role in the regulation of drug activity, the true functional impact of genetic variations is not known. Furthermore, even for genes for which the genetic variants have been fully characterized with respect to function, results of genotype-phenotype investigations can be contradictory. For example, in the case of the drug transport gene MDR1, the 3435C>T has been associated with lower duodenal expression of the transport protein and either higher (eg, digoxin)[167] or lower (eg, fexofenadine)[170] drug concentrations in patients following oral dosing. Such contradictory results may be due to the presence complex multi-gene interactions so that the analysis of a single gene locus is not sufficient to explain the clinical outcome. Indeed, it is clear that in most cases, drug disposition and effect are

complex processes involving multiple genetic pathways. Therefore, considerable time and effort has now been invested in the production of large libraries of single nucleotide polymorphisms[231] that can be investigated for a possible association with drug response. These efforts include nonprofit ventures (eg, The SNP Consortium) that release all information to the public free of charge, as well as private SNP libraries from a number of biotech companies (eg, Genset, Celera Genomics, Incyte). SNPs may serve as both physical landmarks and as genetic markers whose transmission can be followed from generation to generation. According to theoretical models, if the genotype of a group of individuals with a certain phenotype (eg, poor drug clearance) and a group with a different phenotype (eg, rapid drug clearance) are studied, certain genotypes may be consistently associated with those individuals who have the disease. Owing to linkage disequilibrium, alleles of genetic markers in close proximity to the actual phenotype modifying mutation are often found to be associated with the phenotype in question, even though they themselves are not involved in the phenotype itself. This molecular/population genetic approach also provides a strategy to identify genes associated with other phenotypes, such as drug toxicity or therapeutic benefit. This approach can be used for genome-wide mapping in which no genes or genomic regions are assumed to be associated with the drug effect under investigation.

The number of subjects and the numbers of markers needed for such a study depend on the level of contribution of the specific locus to the complex trait. In other words, a single causative mutation is easier to find than an alteration that is one of several contributors to the phenotype. It has been estimated that 60,000 markers, at 50-kb spacing, are needed to cover the genome in an association study of 1,000 individuals (eg, 500 patients with toxicity and 500 patients tolerating therapy).[129] If 1,000 individuals were to be genotyped for 60,000 markers, 60,000,000 genotyping assays would have to be completed. This approach would require a dramatic advance in high throughput genotyping techniques in order to be used in a timely and cost-efficient manner. An alternative, more practical approach uses an educated guess as to which of the genes in the human genome are likely to be important contributors to a given clinical phenotype.[232] This "candidate gene approach" narrows the search to the most likely informative polymorphisms in these genes. Such an approach is especially useful for classes of agents with clearly defined biochemistry, allowing for rational candidate gene selection. The candidate gene approach substantially reduces the number of loci under evaluation, but may miss important genes with no anticipated role in the particular phenotype in question. It is through efforts such as these that the next wave of pharmacogenetic predictive tools will emerge, requiring extensive in vitro and in vivo functional analyses to determine the role of each specific SNP in selecting optimal drug therapy.

Although the principles of pharmacogenomics have been around for decades, the more recent rapid development of the field has been the direct result of new technological advances in high throughput DNA and mRNA analysis and in the processing of these large data sets in an efficient manner. The most dramatic change has been the introduction of gene arrays for the simultaneous assessment of multiple genes. Initial studies used robotics-based systems to "imprint" a series of genes onto a silicone-coated glass slide. By labeling the mRNA of interest with a fluorescent probe, a correlation could be found between the fluorescence intensity emitted by each gene and the level of gene expression. The gene array approach has been modified to use large gene clones from the Human Genome Project, smaller fragments for specific genes, and cDNA derived from differential expression projects. The arrays are currently constructed on nylon filters or glass slides, with slides allowing greater density of genes per experiment and nylon generally being more reproducible. Improvements in robotics and fluid physics has allowed for the ability to evaluate up to 64,000 genes on a single 1-inch by 1 inch slide. The gene expression arrays have enabled a degree of genomic analysis not feasible in the recent past. It is estimated that the quantity of data available from a single array containing 64,000 genes (generated in approximately 48 hours) would have taken a researcher over 20 years to complete by Northern blot analysis.

As in the case of gene expression analysis, the ability to obtain information on patient genotype in a rapid manner has also greatly improved in the past few years. Strategies such as fluorescence energy transfer detection, fluorescence polarization, real-time PCR, time-of-flight mass spectrometry, oligonucleotide ligation/flow cytometry, HPLC fragment analysis, and mini-sequencing have all been used to increase the throughput of genotype information from genomic DNA. Currently, analysis of 1,000 to 5,000 genotypes per day is routine in many pharmacogenomics laboratories, with automated multiplex assays extending this to 100,000 genotypes per day. While the ideal approach for rapid genotyping is not yet clear, a large amount of effort is currently being expended to test various approaches in the clinical setting. However, as the speed and efficiency with which genotyping can be performed increases, the need for improved methods of data analysis becomes critical.

Computational biology, or bioinformatics, has been instrumental in the development of pharmacogenomics. The gene expression arrays and high throughput genotyping techniques generate a large amount of data in a single experiment, much more than can be evaluated using commonly available spreadsheets or manual approaches. Therefore, software has been developed that not only captures the experimental data, but includes the comparison of results with existing genome databases, generation of dendrograms for sequence homology, and pattern recognition to pull together genotypes with similar patterns of expression, as part of the initial algorithm. This provides the investigator with a powerful and comprehensive output on which rapid interpretation and implementation of data can be made.

The development of glass and nylon membrane microarrays has revolutionized the way gene expression is evaluated in all areas of medicine, including pharmacology. Initial studies focused on gene expression along biologic pathways and provided an increased understanding of the regulation of cellular proliferation and the cell's response to nutrient stimulation.[233] Gene expression arrays have also been used in the molecular classification of disease and have highlighted the great genetic heterogeneity among cells with histologically similar appearance.[234,235] For example, gene expression profiling has been used to identify subclasses of patients with diffuse large B-cell lymphoma (DLBCL). The clinical heterogeneity of DLBCL is such that 40% of patients respond well to current therapy, whereas the remainder eventually die of their disease. By using a "lymphochip" containing 17,856 genes that are preferentially expressed in lymphoid cells, investigators have demonstrated the presence of two molecularly distinct forms of the disease: germinal center B-like DLBCL and activated B-like DLBCL. More importantly, patients with germinal center B-like DLBCL have a superior overall survival following chemotherapy than those with activated B-like DLBCL.[234] Based on each individual's gene expression profile, a patient with activated B-like DLBCL will not benefit from standard therapy, and experimental treatment approaches should be considered. Alternatively, a patient with germinal center B-like DLBCL may be currently "over treated" because of their "good risk" status, and treatment strategies with more manageable side-effect profiles may need to be considered. As the basic understanding of the underlying molecular biology of diseases such as DLBCL increases, gene profiling will become more sophisticated, allowing for the discrimination of many more subclasses with associated differences in outcome and best clinical management.

Molecular Diagnostics for Optimizing Drug Therapy

Just as gene expression array analysis may someday allow investigators to define a genetic "therapeutic signature" for specific agents and diseases, "SNP" arrays have been developed to facilitate the rapid and efficient genotyping of individuals across a wide range of genetic pathways. While both *de novo* (static) and post-treatment (dynamic) analysis of gene expression in normal and disease tissues are used for gene expression analysis, array-based genotyping is required only once, since a persons genotype is stable throughout their lifetime. In this regard, automated systems are currently being developed to allow the rapid determination of an individual's genotype for genes that are known to be involved in the pathogenesis of their disease, in the metabolism and disposition of medications, and in the critical targets of drug therapy. This strategy is illustrated by Fig 62-4, which depicts various genes that one might choose to include on a SNP assay to help guide drug selection and drug dosing for patients with acute lymphoblastic leukemia (ALL).[236] It has previously been shown that polymorphisms in drug-metabolizing enzymes can have a significant effect on toxicity and efficacy of medications used to treat patients with ALL,[237] and that individualization of drug dosages can improve clinical outcome. Moreover, it has been established that the genotype of leukemic blasts is an important prognostic variable that can be used to guide the intensity of treatment.[238] Furthermore, genetic polymorphisms are known to exist for various cytokines and other determinants of host susceptibility to infection, as well as polymorphisms in cardiovascular, endocrine, and other receptors that may be important determinants of an individual's susceptibility to drug toxicity. Therefore, by putting all of these polymorphic genes on a single ALL "SNP chip," one would potentially have a valuable molecular diagnostic tool that would allow the rapidly and objective selection of optimal drug therapy for each individual.

The potential is enormous for pharmacogenomics to yield a powerful set of molecular diagnostics that will become routine tools by which clinicians select medications and drug doses for individual patients. Furthermore, unlike essentially all biochemical tests (serum creatinine, bilirubin, etc), a patient's genotype would only need to be determined once for a given gene, because it will not change. Using the amount of DNA that can be isolated from a few milliliters of blood, it is possible to determine thousands of genotypes. Currently available techniques such as primer extension followed by minisequencing (eg, Pyrosequencing), allele-specific signal (eg, Taqman, fluorescence polarization, molecular beacons) or mass spectrometry (eg, Sequenome) have brought high throughput genotyping within the reach of most clinical scientists. Ultimately, the process will be to collect a single blood sample from each patient (DNA can be stored for decades), submit a small aliquot for analysis of a panel of genotypes (eg, 20,000 SNPs in 5,000 genes), and test for those that are important determinants of drug disposition and effects. Patient-specific genotyping results will need to be stored in a secure electronic repository that can be queried as new treatment decisions are made. These genotyping results will not be easily interpreted if reported as a list of SNPs, rather will need to be formatted and interpreted according to the patient's diagnosis and treatment options. These new tools will not replace the more conventional biochemical tests that are now routinely used to assess organ function and disease progression, rather they will complement these tests, and provide additional tools for selecting medications that are optimal for each patient. It is likely that clinical pharmacists will have an increasingly important role in the safeguarding and interpretation of pharmacogenetic data.

The translation of pharmacogenetics into clinical practice is already underway, but will continue to evolve for decades to come. There are currently several examples where genotypes are already being used prospectively for the selection of medications and drug doses.[2,239,240] At present, these clinical applications are limited to medications with narrow therapeutic indices, such as anticancer agents, and for genes with discrete, well described functional polymorphisms (eg, TPMT, DPD, and UGT1A1), but as additional pharmacogenomic relationships are identified, the use of genetically-targeted therapy will expand to include a broad range of medications. The field of

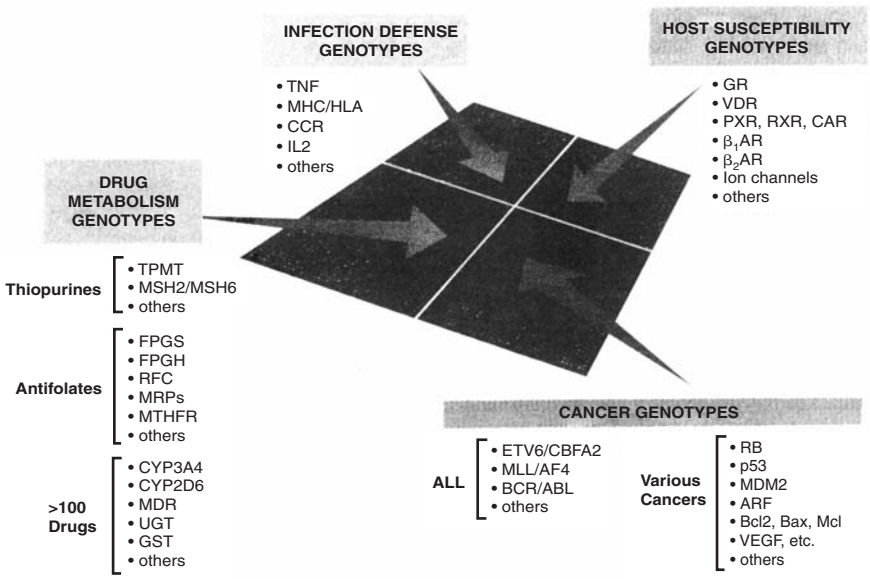

Figure 62-4. Molecular diagnostics of pharmacogenomic traits. DNA arrays are being made for automated, high-throughput detection of functionally important mutations in genes that are important determinants of drug effects, such as drug-metabolizing enzymes, drug targets (receptors), disease pathogenesis, and other polymorphic genes that influence an individual's susceptibility to drug toxicities or environmental exposures (such as pathogens, carcinogens, and others). This figure exemplifies components of a potential diagnostic DNA array for genes that could influence a patient's response to chemotherapy for acute lymphoblastic leukemia, including genes that determine drug metabolism, disease sensitivity, and the risk of adverse effects of treatment (cardiovascular or endocrine toxicities, infections, and so forth). (Reprinted with permission from Evans WE, Relling MV. *Science* 1999; 286:487. Copyright 1999 AAAS.)

pharmacogenomics is growing rapidly, fueled by dozens of genomic companies, academic centers and large pharmaceutical companies that are incorporating pharmacogenomic studies into clinical trials during the earliest stages of drug development.[241,242] Furthermore, several biotechnology companies are working to develop more efficient and less expensive high throughput methods for determining genotypes and haplotypes. In the future, the greatest challenge will not be the ability to determine an individual's genotype (or haplotype), rather it will be the strategy for precisely determining the associations between the genetic determinants and drug response.

Pharmacogenomics and Drug Development

The rapid acceleration of growth in the field of pharmacogenomics has been heavily influenced by the pharmaceutical industry and its desire for a more rational drug development process.[242] Potential industrial applications of pharmacogenomics extend from identification of novel targets against which new therapies can be designed to speeding up the clinical development and approval process. As a result, many companies have invested enormous human and financial resources in the area of pharmacogenomics with the goal determining the role genetic variability in human disease. The pharmaceutical industry is currently utilizing both human and mouse SNP arrays in an attempt to find specific genes or genomic loci that are associated with disease. Once identified, the genetic determinant of a particular disease becomes the target for new drug development. Similar approaches are also being conducted using gene expression arrays, where disease tissue is used to produce mRNA for comparison with normal reference tissue. The goal of these approaches is sometimes referred to as "gene hunting," and arrays covering the broadest range of known and unknown genes are the most useful. Important genetic variants may either be putative modulators of the disease phenotype or represent novel mechanisms of disease pathogenesis. Furthermore, pharmacogenomics has the potential to streamline the drug development process, by decreasing the number of patients required to show efficacy in early clinical trials.[243] If, for example, a certain genotype is shown to be associated with a higher probability of response to a given investigational drug, one would require fewer subjects with that particular genotype to show a benefit compared to a trial that included individuals with all the possible genotypes.

Gene expression arrays are also being applied to define the mechanism of action for new compounds or to screen for direct influence of an agent on a specific pathway. Targeted agents developed in the most mechanistically guided program can often lead to surprises during *in vivo* evaluation. For example, inhibitors of HMG-CoA reductase, initially developed as cholesterol lowering agents, were subsequently found to inhibit farnesyl transferase activity in the cell-signaling pathway of the ras oncogene.[244] Using gene expression arrays, one can generate a profile of the changes in gene expression in response to a drug, thereby yielding a greater understanding of mechanisms of action. Gene expression arrays can also be used during screening of candidate compounds. By constructing arrays for genes involved in a pathway of interest, *in vivo* gene expression dynamics can be used as a quantifiable measure of drug activity. This results a more rational approach to optimization of drug therapy and design of new agents based on actual *in vivo* observations in patients, rather than by animal models or theory alone.

Pharmacogenomics as a Public Health Tool

Although the promise of pharmacogenomics is enormous, it is likely to have the greatest initial benefit for patients in developed countries, owing to expense, availability of technology and the focus of initial research. However, pharmacogenomics will ultimately be a useful tool throughout the world. It has long been appreciated that there are ethnic variations in disease risk, disease incidence, and response to treatment.[245] In addition, as discussed in this chapter, the frequency distribution of polymorphisms in most of the human genes studied differ among various racial groups. Therefore, one approach to applying pharmacogenomics to public health is through SNP allele frequency analysis in defined populations. For example, analysis of TPMT genotype in world populations suggests that TPMT-mediated toxicity from azathioprine or mercaptopurine would likely be lower in Japanese or Chinese populations than Caucasians.[125] In contrast, a higher frequency of the TPMT mutant allele is found in the Ghanaian and Kenyan populations,[125] suggesting that these racial groups would be at a greater risk for thiopurine-induced toxicity. Moreover, even greater ethnic diversity has been demonstrated for other polymorphic drug-metabolizing enzymes (eg, NAT2, CYP2D6, CYP2C19), and such will likely be the case for other traits like direct or indirect drug targets. Therefore, by combining the understanding of associations between genetic variability and drug response or toxicity with the knowledge about the ethnic distribution of various polymorphisms, public health officials will be able to make broad recommendations about the safe and appropriate use of medications in each of the world's populations. This general approach will have broad applications to the development of clinical practice guidelines and national formularies in developing countries.

While in theory using the knowledge of ethnic differences will be important to most of the world's populations, such an approach is significantly limited in geographic regions with extensive genetic mixing. For example, it is known that the African American population has a great degree of geographic and social mixing that provide a basis for wide genetic heterogeneity. This is illustrated in by a comparison of TPMT mutations between African American and West African populations. Although the *TPMT*3C* allele is the most frequently observed variant in both populations, it represents 100% of the mutant alleles in West Africans and 52% in African Americans.[133,134] Interestingly, the remaining African American mutant alleles are the *TPMT*2* and *TPMT*3A*[134] alleles that are common in Caucasians. Therefore, great care must be taken when applying pharmacogenomics to public health issues, and testing at the genetic level in each patient will remain the most definitive approach.

A number of issues influencing the development of pharmacogenomics include several that are of a practical or nonscientific nature. One important limitation to the broad application of pharmacogenomics is the availability of inexpensive gene expression arrays, cost-effective high throughput genotyping, and disseminated bioinformatics resources. Currently, there is considerable growth in the number of companies offering both genomics analysis on a fee-for-service basis and the equipment for user-maintained instruments. As technology and competition bring down the high initial capital costs of array and genotype systems, the potential for general application of these approaches will be further enhanced. Currently, the technology for gene expression and genotype assessment is only affordable in the pharmaceutical research and development setting or in the context of funded academic research. A thorough pharmacoeconomic analysis will ultimately be required to justify and direct the future scope of pharmacogenomics for clinical medical practice. However, once an individual's genotype has been correctly determined, it does not need to be repeated and can be stored for a multitude of potential applications. One can certainly envision a time in the future when each individual will have their genetic information recorded in a secure database, accessible only to authorized health care providers, to be used for disease risk assessment or as a guide in therapeutic decision-making. For example, this potentially web-based compilation of an individuals' genotype could be used by the clinical pharmacist when making recommendations regarding the choice of medications, appropriate dosing, or risk of potential side effects.

Absolutely critical to the future application of pharmacogenomics to clinical medicine, is the protection of the patients' right to privacy. While patient confidentiality is at the very heart of good medical care, genetic information adds a new layer of ethical complexity. In addition to pharmacogenomic data, an individuals' genotype contains features that will ultimately be associated with many other measures of outcome such as the risk of some future illness. While this information may be useful with respect to screening or chemopreventative strategies, a patient may want to keep such genetic data confidential. As a result, the ethics of genetic testing is currently an active area for discussion and debate. A system of trust and internal control has historically been utilized to prevent the inappropriate use of genetic information. Although this approach has been generally successful, with breach of trust being a rare event, the field of bioethics is now focused on prevention of potential or theoretical abuses of genetic information against individuals. Most of the discussion and debate centers around what information is needed, who should have access, and how should the information be used. Ethical issues such as these are obviously challenging, since the insurance carrier paying for the genetic testing will be the same entity that could potentially use the information to identify disease or therapy risks that could in turn be used to restrict or deny future coverage. However, while such patient confidentiality issues represent a significant challenge to the ultimate application of genetic testing, it is generally acknowledged that the potential gains from pharmacogenomics, in terms of patient well-being and cost of healthcare, heavily outweigh the risks. Indeed, the promise of pharmacogenomics is such that society must eventually find a way to ensure that the risk of exploitation does not overshadow the public good that will come from putting such powerful information in the hands of knowledgeable health care providers and those involved in the discovery of new approaches to disease treatment and prevention.

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CHAPTER 63

Pharmacokinetics/Pharmacodynamics in Drug Development

G L Drusano, MD

Developing drugs requires a long, expensive process of discovery and preclinical development followed by clinical trials resulting in the submission of a package of data to a regulatory agency that will ultimately lead to licensure of that product for sale.

The goal of drug development is to find a dose of a drug for a specific indication that attains the desired therapeutic outcome while engendering a low probability of the patient experiencing a toxic event. Pharmacokinetics and pharmacodynamics can straightforwardly lead to attaining this goal. Indeed, in the last one to two decades there has been a marked increase in our understanding of the relationship between drug exposure and response. This is related to wider availability of the appropriate mathematical modeling methodologies. The application of these techniques in the time-line of drug development is presented in Figure 63-1.

The clearest example of employing a pharmacokinetic/pharmacodynamic approach to drug development can be seen in the area of anti-infective agents. Part of the reason for this is that these drugs are unique in that we are not attempting to dock a molecule into a receptor in the human body. Rather, the target of drug action and the site to which we are attempting to bind the drug is a receptor in the pathogen of interest. This has several important consequences.

The first is toxicity. Anti-infective targets are chosen specifically so that they have little sequence homology to similar mammalian targets. A straightforward example is the topoisomerase enzymes seen in bacteria but also in man. The fluoroquinolone antimicrobials have a 100- to 1000-fold difference in the concentrations necessary for microbiological effect relative to activity for topoisomerase targets in man.[1] In contrast, there is often a narrow therapeutic index, for example, between normal human cells and cancerous cells, meaning that oncologic chemotherapy is often (but not always) saddled with considerable toxicity.

The other important consequence is the ease with which pharmacodynamic relationships can be developed both preclinically as well as in clinical trials. The reason is that almost always (Hepatitis C is currently an exception to the rule) one can straightforwardly grow the pathogen of interest *in vitro* and determine a measure of drug exposure that will affect the growth of the pathogen in some standardized way. For example, for viruses, we can measure an EC_{50}, a drug concentration that will cause a 50% downturn in the number of rounds of replication per unit time. For bacteria, we can measure indices such as MICs or MBCs, that are defined as drug concentrations that will keep the bacteria from growing enough over an 18- to 24-hour period to cause turbidity in the growth medium (MIC) or to cause the number of bacteria to be reduced by 1000 fold over the 18–24 hour time frame (MBC). This ability to measure the difficulty a drug will encounter inhibiting or killing different pathogens allows the drug exposure necessary to achieve different endpoints to be normalized across pathogens. In contrast, if one were to try to develop an anti-hypertensive agent, the true between-patient variability in the affinity with which a drug will bind to the receptor cannot currently be measured. Certainly, in the near future, the widespread use of phamacogenomic profiling, looking, for example, for specific single nucleotide polymorphisms (SNPs) or deletions will allow identification of patients likely to respond less well to therapy. Currently, however, this true between-patient variance in receptor affinity is completely unobserved variability.

Creating a Pharmacodynamic Relationship

MEASURE OF DRUG EXPOSURE—The process of creating a pharmacodynamic relationship starts with the idea of linking some measure of drug exposure to the outcome of interest. There are a number of measures of drug exposure that can be employed. Some of the most common are Peak concentration, Area Under the concentration-time Curve (AUC) and Time > Threshold. Many other measures of drug exposure are possible (eg, trough concentrations), but are usually related in some way to those mentioned above.

The critical idea behind which of these metrics is most closely linked to a specific measure of outcome is that the shape of the concentration-time curve may have an impact on the outcome measure. For example, for agents where the range of concentration that mediates minimal effect to that which mediates maximal effect is small, Time > Threshold will be the most useful metric for exposure. That is because higher concentrations will not produce significantly more effect than moderate concentrations. The overall effect will then be maximized by maintaining the drug concentration above the level that produces the degree of effect that is required. In contrast, many drugs are quite concentration-dependent in the effect that they produce. Here, much more effect will be produced at higher concentrations with much less being produced as concentrations decline. This will produce a situation where the total drug exposure will be linked to effect and AUC will be the most useful measure of drug exposure. Peak concentrations may be seen as linked to effect when an irreversible event occurs, such as covalent binding to a receptor that only occurs above a specific concentration. Here, only peak concentrations will produce enough exposure to have the binding occur in the appropriate time frame. This is the rarest situation seen in the development of pharmacodynamic relationships. Peak concentrations can also appear to be linked to outcome when there is a mixture of populations of sensitive and less sensitive targets present. This will be discussed in greater detail below under the topic of suppression of emergence of resistance.

For the development of such relationships for anti-infective agents, the exposure measures are normalized to the measure

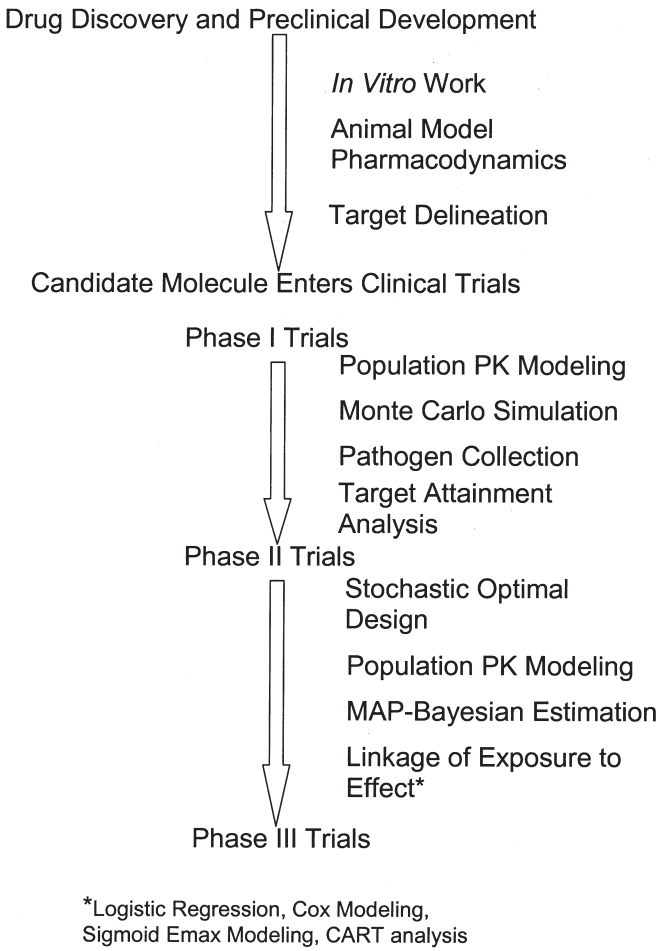


Figure 63-1. Use of pharmacodynamics in the drug development process.

of susceptibility of the pathogen to the drug being studied (eg, MIC, EC_{50}). This produces a hybrid measure that explicitly depends on the drug exposure, but also on the pathogen being studied. So we can now measure Time > MIC, AUC/MIC ratio, or Peak Concentration/MIC ratio.

As an example of the shape of the curve having an impact on the effect developed by drug exposure, the β-lactam antibiotic imipenem/cilastatin was studied in a neutropenic mouse thigh infection model by Fluckiger, Segessenmann, and Gerber.[2] The actual idea that the shape of the curve can affect the endpoint measured was popularized by the laboratory of Craig,[3–5] but arguably the clearest demonstration was by Fluckiger.[2] In this study, the effect of a dose of drug was determined on the number of organisms present at the primary infection site. In parallel, a second cohort of animals received the same drug dose, but on a highly fractionated basis, so that the resultant concentration-time curve had a much lower peak concentration, but remained above the MIC for a much longer time interval. The AUC/MIC ratios developed in the two cohorts were nearly identical. The results are shown in Figure 63-2. The number of organisms killed was much greater when the Time > MIC was longer. This indicates that there was no benefit derived from the high peak concentrations developed in the first group and that keeping the drug concentrations in excess of the MIC was the effect driver in this circumstance.

An example of exactly the opposite linkage can be seen with fluoroquinolone antimicrobials, as well as other agents like aminoglycosides, or the new anti-MRSA agent, daptomycin. For these drugs, there is a clear relationship between drug concentration and the rate of organism kill that is engendered. In this circumstance, AUC/MIC ratio is the exposure variable most closely linked to outcome.

In a study by Louie et al,[6] a mouse thigh infection model study was performed using methodology similar to that described above, but without the massive dose fractionation. An exposure-response curve was described (Fig 63- 3). On the steep part of the curve Q 24 hour, Q 12 hour, and Q 6 hour administration schedules were studied, so that the 24-hour AUC was the same for each group (same AUC/MIC ratio), but that the once daily dosing group had the highest Peak concentrations (and hence Peak concentration/MIC ratio) while the Q 6 hour dosing group attained the longest Time > M IC. When the results for these groups were tested for differences by analysis of variance, no differences could be discerned (Table 63-1). This indicates that for daptomycin, AUC/MIC ratio is the exposure variable most closely linked to outcome.

CHOOSING THE TARGET—In the examples given above, a microbiological endpoint was chosen. This is because we were dealing with animal model systems. It is important to recognize that in the drug development process, there will be a progression from a preclinical stage to the performance of clinical trials to document safety and efficacy.

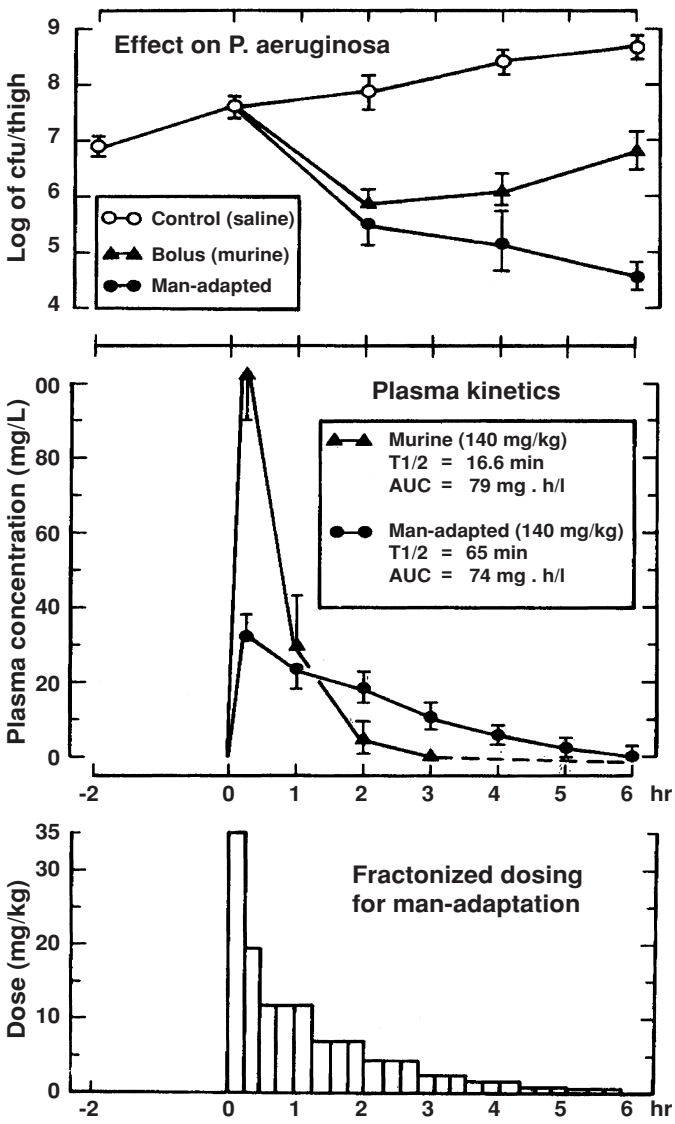


Figure 63-2. Effect of the shape of the concentration-time curve on the ability of imipenem-cilastatin to kill *P aeruginosa* in a mouse thigh infection model. (From Fluckiger U, Segessenmann C, Gerber AU. *Antimicrob Agents Chemother* 1991; 35:1905.)

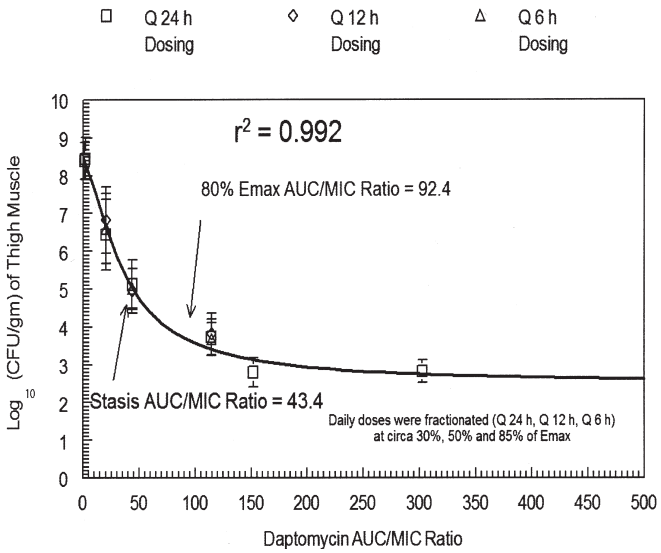


Figure 63-3. Relationship between the 24-h AUC/MIC ratio of daptomycin and log10 CFU of *S. aureus* per gram of thigh muscle (mean ± 1 SD) when the total daily dose of daptomycin is given as one dose in 24 h, two equally divided doses every 12 h, or four equally divided doses every 6 h. The total daily doses of 2.5, 5.6, and 15.0 mg of daptomycin/kg resulted in AUC/MIC ratios of approximately 21, 44, and 115, respectively. The AUC/MIC ratio for a given total daily dose was similar regardless of whether a total daily dose was administered as one, two, or four equally divided doses over 24 h. (From Louie A, Kaw P, Liu W, et al. *Antimicrob Agents Chemother* 2001; 45:845.)

Prior to the inception of clinical trials, animal model and *in vitro* systems are required for the determination of the true pharmacodynamically linked effect variable (eg, AUC/MIC ratio, Time > MIC). After the start of clinical trials, we can examine either clinical or microbiological endpoints. These endpoints can be dichotomous in nature (succeed/fail, eradication/persistence) or can be continuous (microbiological quantitative repetitive sampling from an infection site). The target that is chosen in either of these circumstances will determine, to a great degree, the dose that is required to attain the target.

In the preclinical circumstance, one can examine the ability of a regimen (dose and schedule) to kill organisms at a primary infection site (as above, Figs 63-2 and 63-3). Alternatively, one could examine a mortality endpoint. In either circumstance, the model system could be developed so that the animal was either normal or rendered immunocompromised. In each instance, this will change the interpretation of the endpoint chosen and, in the case of an immunocompromised animal system, will require a larger drug exposure to achieve whatever endpoint is desired. The reason to perform these studies in immunocompromised animals is twofold. First, it is a conservative measure of the drug exposure required to achieve whatever target is desired. It is a more direct measure of "bug versus drug." Second, and perhaps as important, it is much easier to find strains of pathogens that will grow in whatever model is being used. In the presence of the full immune system of the animal, many pathogens will self-clear over the period of observation in the no-treatment control group. This renders the interpretation of the experiment much more difficult.

It is also important to recognize that the animal system being employed should accurately reflect the local pharmacokinetics of the drug for the indication being sought. While a mouse thigh infection model may accurately represent the ability of the drug to kill organisms in a skin/skin structure infection, the lessons learned and exposure targets derived would not be helpful if the drug were going to be studied for a meningitis indication in clinical trials.

This also raises the issue of what endpoint will be chosen. Do we wish merely to shut off organism growth or to kill the organism at the primary infection site to a specific degree (eg, 1 $\log_{10}$ (CFU/g) kill, 2 $\log_{10}$ (CFU/g) kill, 80% of maximal kill). Figure 63-3 demonstrates that an AUC/MIC ratio of 43.4 is required to shut off growth of the organism, whereas attaining 80% of the maximal bacterial kill for this strain of *Staphylococcus aureus* requires a larger exposure, with an AUC/MIC ratio of 92.4. For a relatively uncomplicated skin and skin structure infection, attaining an exposure target that will result in organism stasis is likely all that is required. However, for a complicated skin and skin structure infection, particularly if bacteremia would be likely, an exposure target that would drive some high percentage of the maximal bacterial kill (80–90% of maximal kill) would be more appropriate. This choice of target is crucial to the successful choice of an appropriate drug dose for clinical trial.

SUPPRESSION OF EMERGENCE OF RESISTANCE AS AN ENDPOINT—Until recently, little has been done with suppression of emergence of resistance as an endpoint for the choice of drug dose. The key idea underlying the problem of emergence of resistance is the population burden of bacterial cells at an infection site relative to the inverse of the mutational frequency to resistance. If the population burden exceeds the inverse of the mutation frequency, there will be a high probability (but not a certainty) that organisms bearing a resistance mechanism will already be present. The larger the burden relative to the frequency, the higher will be the probability. This means there will be multiple populations of organisms present at the time that drug therapy is initiated. It is not surprising that the population bearing a resistance mechanism will respond quite differently to the pressure of drug therapy than will the population without this mechanism. Again, as above, the example used will be from the anti-infective literature, but the lessons are clearly applicable in the realm of oncolytic chemotherapy.

In Figure 63-4 Panels A-D, the effect of different doses (including a no-treatment control) of the fluoroquinolone levofloxacin on the total and resistant populations of *Pseudomonas aeruginosa* is displayed.[7] As the effect was determined at multiple time points, it allowed the effect of the drug concentrations on the two populations to be modeled simultaneously for all regimens.[7] This allowed a calculation of dose to maximally amplify the resistant population as well as a dose to hold the number of clones in the resistant population steady. These doses were then studied prospectively over a longer time frame (24 versus 48 hours) as a validation of the modeling result. This is displayed in Figure 63-5.

This is the first prospective validation that a target drug exposure can be derived to suppress the amplification of mutant subpopulations. This makes the point that the choice of the exposure target is flexible and is a choice that should be made with great care if the drug is to achieve the hoped-for results when it enters clinical trials. If the toxicity profile of the drug allows it, a suppression of resistance endpoint may be wise, as it will extend the lifetime of the drug.

CHOOSING A DRUG DOSE FROM PRECLINICAL PLUS PHASE I DATA—Once the appropriate animal or *in*

Table 63-1. *Staphylococcus aureus* Densities in Thigh Muscles of Mice That Were Treated With Various Doses of Daptomycin, Administered in One, Two, or Four Divided Doses

TOTAL DOSAGE (MG/KG)	*Staphylococcus aureus* Densities ($\log_{10}$ (CFU/g) + 1 Standard Deviation) with: 1 DOSE	2 DIVIDED DOSES[b]	4 DIVIDED DOSES[c]	P VALUE[a]
2.5	6.54 ± 0.98	6.83 ± 0.88	6.61 ± 0.93	0.64
5.6	5.12 ± 0.66	4.96 ± 0.59	5.02 ± 0.52	0.73
15.0	3.73 ± 0.48	3.82 ± 0.55	3.68 ± 0.43	0.59

[a]Statistical testing was performed by analysis of variance. A P value of <0.05 was considered statistically significant.
[b]One-half of the single dose was administered at 0 hour and then 12 hours later.
[c]One-quarter the single dose was administered at 0 hour and then 6, 12 and 18 hours later.

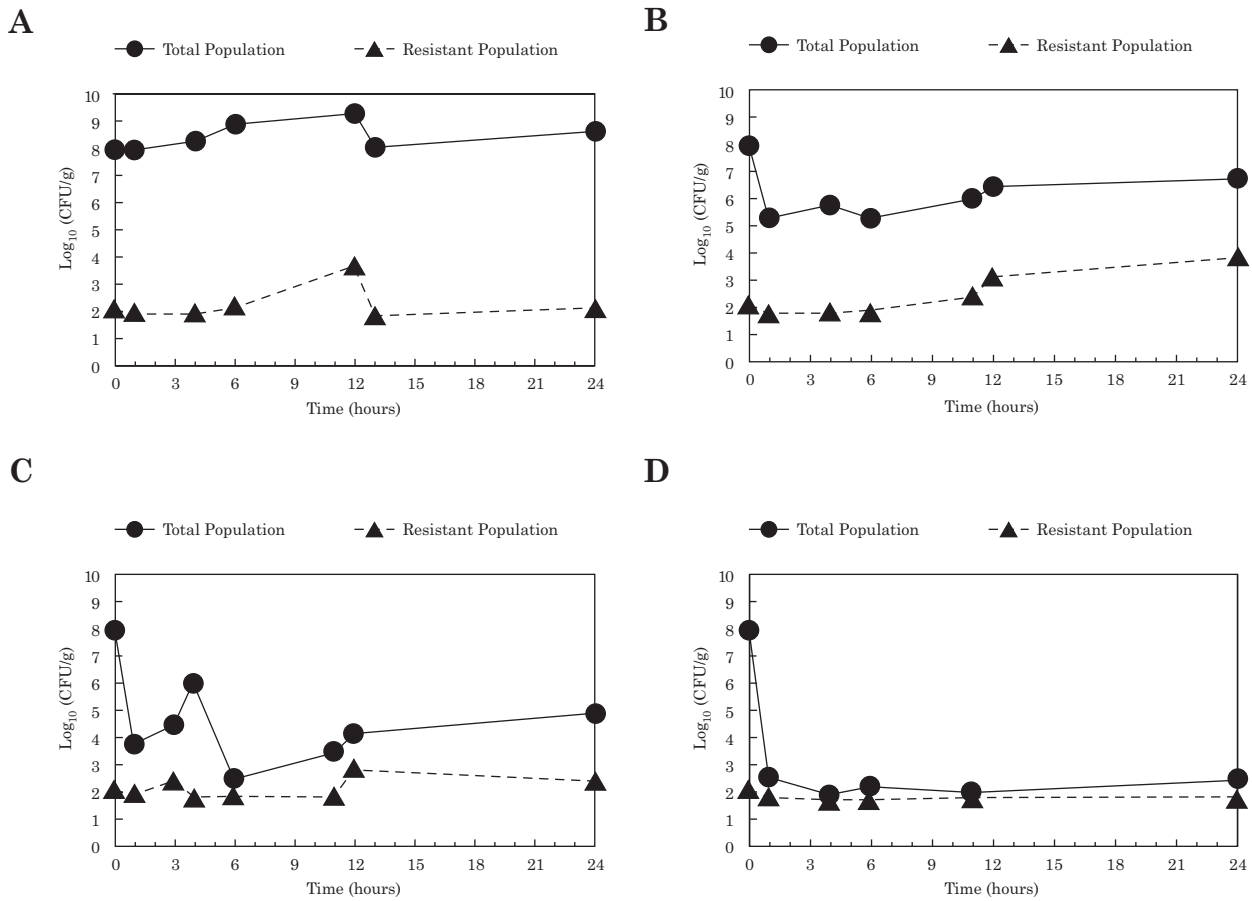


Figure 63-4. Effect of 4 drug doses of levofloxacin on the total and resistant bacterial populations of Pseudomonas aeruginosa over 24 hours. Drug doses were 0, 90, 215, and 600 mg/kg (Figure 63-3, panels A-D, respectively). The 90 mg/kg dose allowed amplification of the resistant population by almost 2 $\log_{10}$ (CFU/g). The 215 mg/kg dose allowed only minimal resistant mutant amplification. (From Jumbe N, Louie A, Leary R, et al. *The Journal of Clinical Investigation* 2003; 112(2):275. Reproduced with permission from the American Society for Clinical Investigation.).

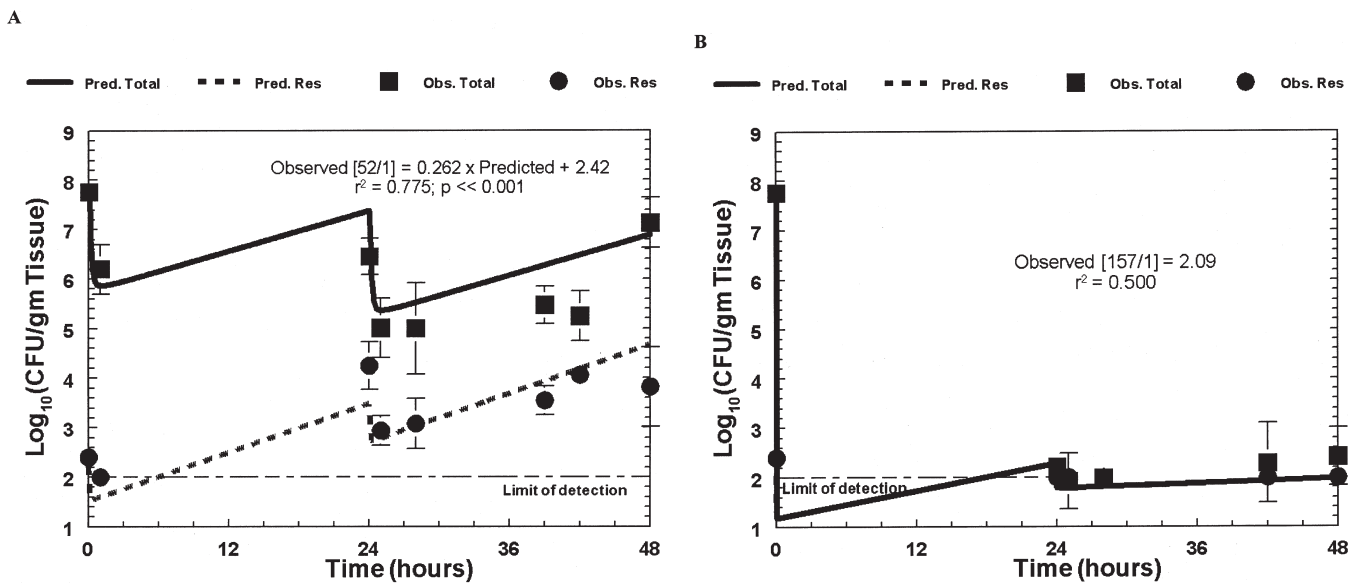


Figure 63-5. Model validation. The emergence of resistance model developed in this study was prospectively evaluated and validated by generating response predictions for doses not previously studied that would (A) encourage selection of resistance or (B) suppress emergence of resistance. An exposure of an AUC/MIC ratio of 157/1 was calculated to prevent emergence of resistance. Experiments were performed to 48, not 24 hours as in the studies performed to generate parameter estimates, using model predicted conditions. Levofloxacin dosing occurred at time 0 and at 24 hours. The lines are model predictions (not best-fit curves). (■) represents experimental measurements of the total population. (•) represents experimental measurements of the resistant subpopulation. The model predicted changes in the resistant mutant population well at both exposures. (From Jumbe N, Louie A, Leary R, et al. *The Journal of Clinical Investigation* 2003; 112(2):275. Reproduced with permission from the American Society for Clinical Investigation.).

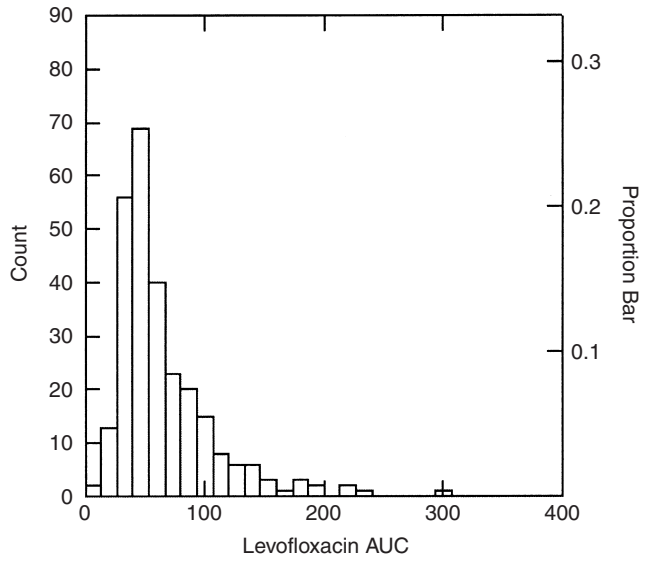


Figure 63-6. The distribution of Area Under the concentration-time Curve (AUC) values for 272 patients receiving 500 mg of levofloxacin for the therapy of community-acquired infections.

vitro models have been chosen and the drug studied in these systems, the linked pharmacodynamic variable will have been elucidated and the exposure target(s) identified for the indications that are to be sought for the drug. A critical issue is how to employ the pharmacodynamic information to allow the "correct" dose of drug to be chosen for clinical trial(s).

The ability of a specific dose of drug to attain the desired exposure target is influenced by a small number of factors. These are (*i*) The true between-patient variability in drug pharmacokinetics; (*ii*) The variability in the MIC of the drug for the pathogens of interest (ie, those pathogens that are likely causes of the diseases for which indications are being sought); (*iii*) The protein binding of the agent being studied. Each of these factors will be examined in turn.

PHARMACOKINETIC VARIABILITY—True between-patient variability in pharmacokinetics clearly exists. The same dose of drug will produce very different drug concentration profiles if given to a large number of patients. We can account for some portion of this variance by measuring covariates such as age, sex, weight, height, creatinine clearance, etc. However, even after examining these and other covariates, there will still be true, residual between-patient variance. Accounting for this variability plays an important role in determining the correct dose for clinical trials. The basic idea is that whatever dose is chosen, it should be adequate to attain the desired exposure target in a very high proportion of the population of interest.

It is important to obtain an idea of the degree of variability of the drug exposure achieved when a fixed dose of drug is administered. Preston et al[8] studied 272 patients with community-acquired infections who received the fluoroquinolone antibiotic levofloxacin. In this study, all patients had a serum creatinine that was <2.0 mg/dl. Figure 63-6 shows the variability in AUC achieved in these patients with a fixed dose of drug. In this relatively normal community-based population there was a >10-fold range of AUCs observed.

It is unusual to have such a rich data set early on in drug development. The usual reality is to have anywhere between 12 and 60 volunteers who have had the drug's pharmacokinetics studied. These study subjects represent a very biased estimator of how the drug will be handled in the population of interest, most of whom will be older and, by definition, sicker than the normal volunteer population. Nevertheless, if these data can be employed to choose a drug dose, it will almost certainly be a conservative choice.

Monte Carlo simulation is a mathematical technique that allows prior knowledge of the central tendency of a parameter and its distribution to be employed to set up a sampling distribution. That is, we can take a large number of samples (eg, 1,000, 10,000, 30,000) from the "known" prior distribution of parameter values. These can be used to calculate Peak concentrations, AUC values, or Time > Threshold. It provides the opportunity to perform large clinical trials "*in silico*." These measures of drug exposure then can be employed to determine how often a specific drug dose will produce an exposure that will attain the exposure target value for a specific MIC.

MICROBIOLOGICAL VARIABILITY—Usually the pathogen(s) of interest for a specific indication have a broad range of values. It is obvious that for whatever range of drug exposures are achieved by a specific dose, it will be more difficult to achieve the exposure target for an organism with a higher MIC value.

Luckily, the determination of the range of MIC values for organisms that are causative pathogens for the indications being studied is relatively straightforward to obtain.

PROTEIN BINDING—As a rule, only non-protein bound drug is active. This has been most clearly seen in two studies, one of bacteria[9] and one of HIV.[10]

Merriken, Briant, and Rolinson[9] examined a group of isoxazolyl penicillins for their activity against *Staphylococcus aureus*. There were 7 molecules studied. Each was chosen because it had the same MIC for the challenge strain of Staphylococcus and had very similar pharmacokinetics, but had very different protein binding that ranged from 30% bound to >97% bound. When examined in a mouse model, the effect of the drug was related to the free fraction of the drug concentration (Fig 63-7).

For HIV, Bilello et al[10] examined a highly bound (ca 90%) HIV-1 protease inhibitor and examined the impact of protein binding *in vitro*. In a transitive logic set of experiments, the impact in free fraction of the major drug binding protein for this agent (α-1 acid glycoprotein) was determined. In Figure 63-8A, it is demonstrated that increasing the amount of binding protein over the physiologic range of 0.5–1.5 mg/ml decreases the free fraction in a quantitative manner. In was also demonstrated (Fig 63-8B) that lower free amounts of drug were associated with less cell-associated drug. Finally, the lower cell-associated

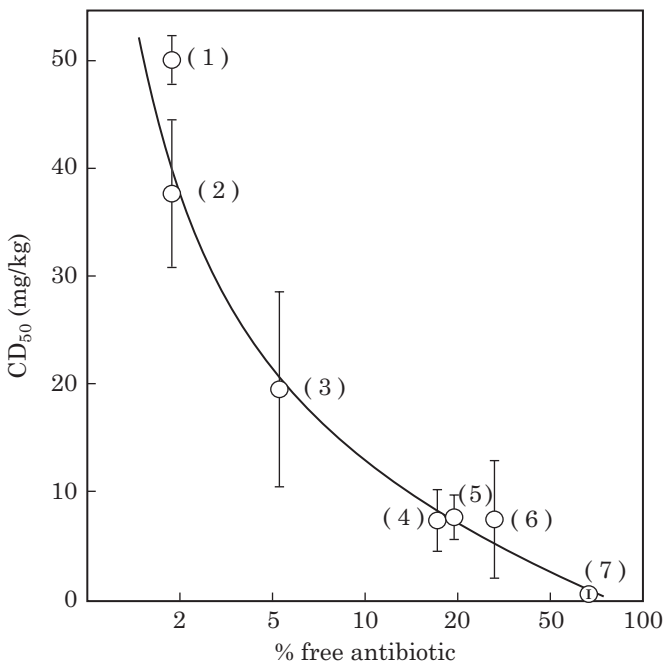


Figure 63-7. The effect of protein binding on the microbiological activity of 7 isoxazolyl penicillins as determined in a mouse model of Staphylococcal intraperitoneal infection. (From Merriken DJ, Briant J, Rolinson GN. *J Antimicrob Chemother* 1983; 11:233.)

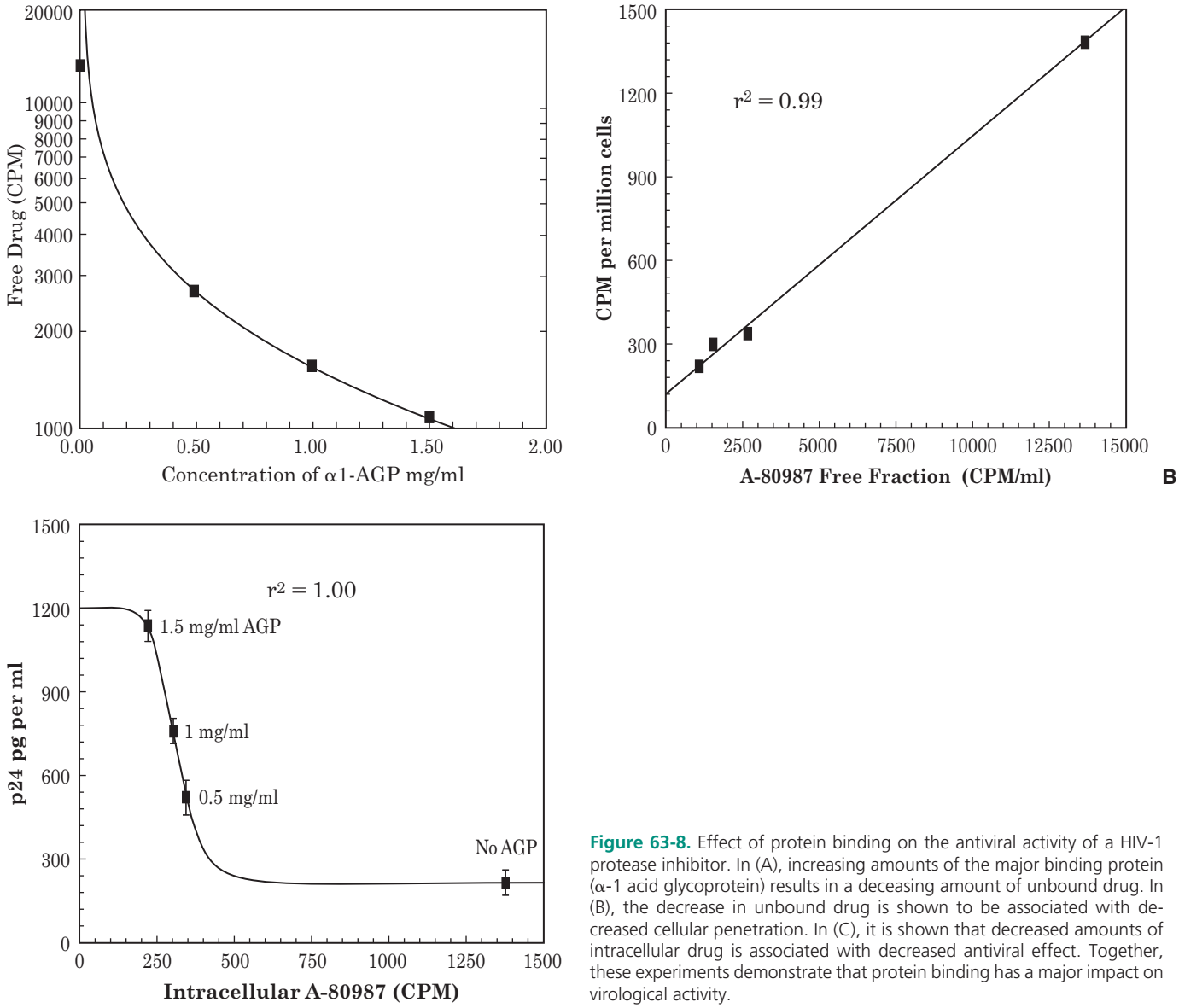


Figure 63-8. Effect of protein binding on the antiviral activity of a HIV-1 protease inhibitor. In (A), increasing amounts of the major binding protein (α-1 acid glycoprotein) results in a deceasing amount of unbound drug. In (B), the decrease in unbound drug is shown to be associated with decreased cellular penetration. In (C), it is shown that decreased amounts of intracellular drug is associated with decreased antiviral effect. Together, these experiments demonstrate that protein binding has a major impact on virological activity.

amounts of drug were shown to produce less antiviral effect, in a quantitative fashion (Fig 63-8C).

Clearly, then, protein binding has a major, quantitative effect on drug effect, particularly in microbiological systems. There are instances when protein binding has a less than anticipated impact on effect or where it appears that there is actually no effect of binding on activity. It is likely (but unproven) that in these instances drug is taken onto its binding effect site from its protein-binding site because of a major difference in K_d for the drug for the two receptors. Even so, when developing a drug and picking an effect target, it is wise to understand the drug binding characteristics and to ascertain the impact of drug binding on the effect that is desired. This is particularly important preclinically, as there may be considerably different binding seen in animal versus man.

INTEGRATING THE SOURCES OF VARIABILITY— Once we have chosen an exposure target, studied pharmacokinetic variability, MIC (or $EC_{50/95}$) variability and the impact of protein binding, the question remains as to how to use this preclinical information to choose dose(s) for clinical trials.

Our group (11–14) developed the use of Monte Carlo simulation to integrate these disparate sources of variability. In the paradigm developed, a population pharmacokinetic study is performed. The measure of central tendency (usually, but not necessarily the mean parameter values) and dispersion (full or major diagonal covariance matrix) are employed to generate a Monte Carlo simulation for specific drug doses. These generated values are then corrected for protein binding, as a function of the measured impact of binding on effect. Then the fraction of the simulated population that attains the desired exposure target is determined for different values of MIC (or $EC_{50/95}$). In so doing, clear breakpoint values for pathogen drug susceptibility can be determined for a specific dose of drug. Because we have information regarding the distribution of MIC (or $EC_{50/95}$) values, the overall response of the population can be determined by taking a weighted average over the product of the range of target attainment rates and MIC (or $EC_{50/95}$) values.

An example of this technique validated with a prospective study was performed with an HIV-1 non-nucleoside reverse transcriptase inhibitor [NNRTI].[14] The target agreed upon was keeping trough free drug concentrations above the EC_{90} of HIV. Preclinical study demonstrated that addition of purified binding proteins to the medium increased the EC_{50} value by 7.6-fold. In addition, other preclinical studies demonstrated that there was approximately a 10-fold change in drug concentration between the EC_{50} and the EC_{90}. Therefore, a 76-fold adjustment was made to the simulated trough concentrations of the drug for doses of 50 mg, 100 mg, and 200 mg. Finally, preliminary preclinical data indicated that different wild-type HIV isolates all had EC_{50} values less than 10 nM. In Figure 63-9A, the target

A

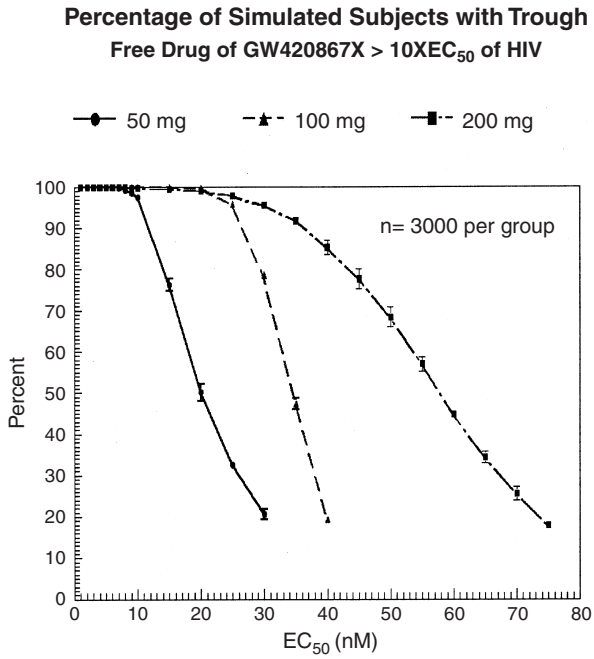
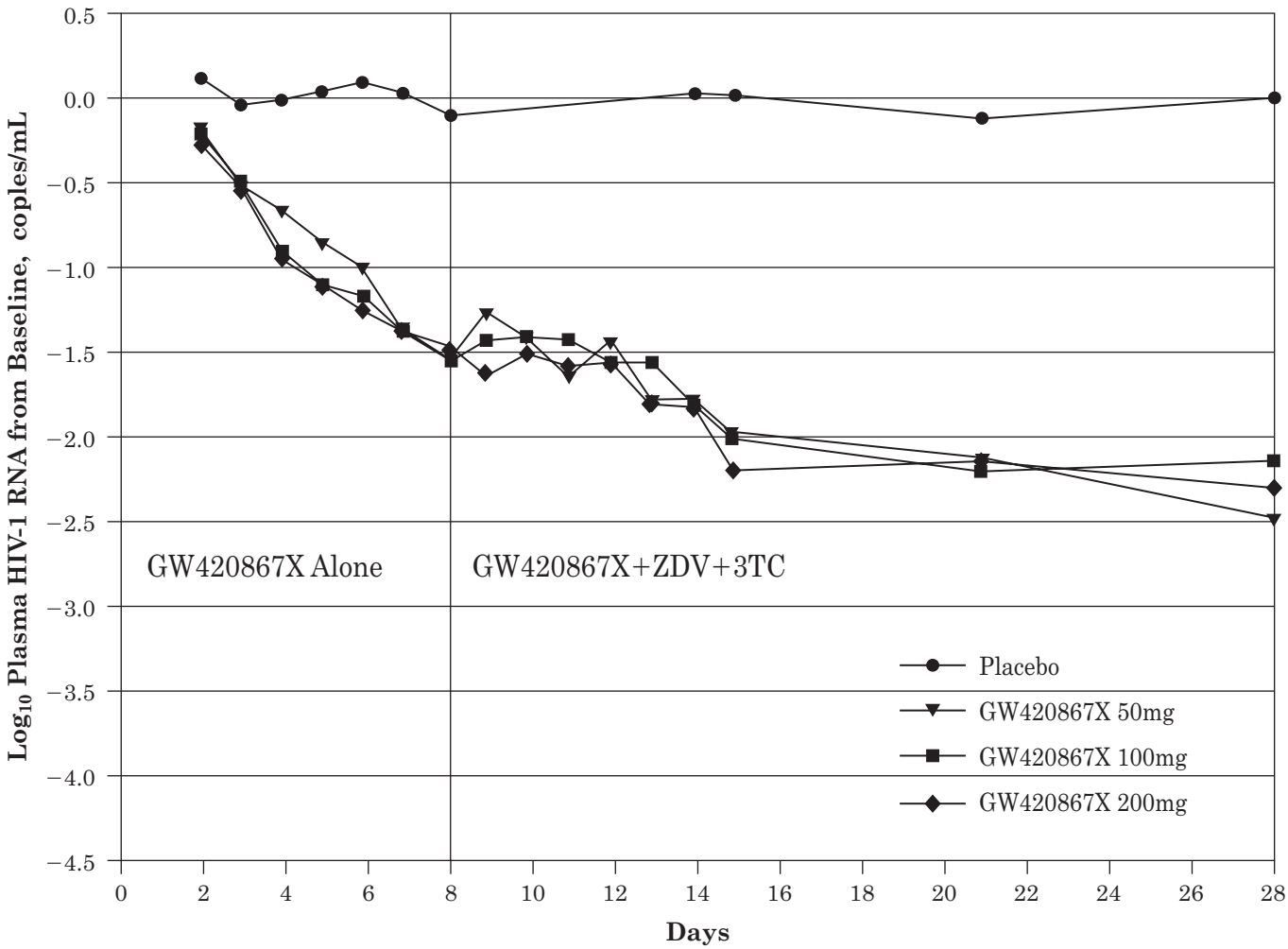


Figure 63-9. In (A), three different doses of an experimental non-nucleoside reverse transcriptase inhibitor keep free drug in excess of the EC_{90} of HIV for the whole dosing interval to the same extent, as long as the EC_{50} is less than 10 nM. As is demonstrated in (B), this leads to equipotent antiretroviral activity in a Phase I/II randomized, double-blind clinical trial.

B



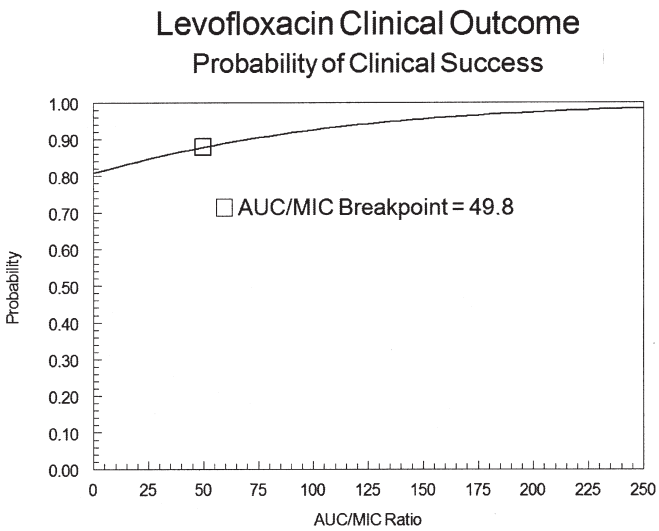


Figure 63-10. The relationship between the AUC/MIC ratio of levofloxacin and the probability of a good clinical outcome in 134 patients receiving this fluoroquinolone for community-acquired infections. Classification And Regression Tree (CART) analysis identified a breakpoint of a total drug AUC/MIC ratio of 50 (free drug AUC/MIC ratio of 35).

attainment rate by EC_{50} values (not determined in the presence of binding proteins) is displayed. It is clear that if the EC_{50} value does not exceed 10 nM, there will be no difference in the target attainment rates for the three doses evaluated.

This analysis resulted in the prediction that no difference in viral load decline would be observed in a clinical trial. This agent was examined in a 60 patient Phase I/II randomized, double-blind trial in which 15 HIV-infected patients were each given one of the doses examined in the Monte Carlo simulation, and 15 patients served as a no-treatment control in this short term trial. The results are displayed in Figure 9B. On the morning of day 8 of the trial (the end of monotherapy), the median viral load decline ranged from 1.48 to 1.52 $\log_{10}$(copies/ml), prospectively validating the predictions.

Other Monte Carlo simulation-based trial predictions have also been prospectively validated.[12,13] This technique where the sources of variability are quantified and integrated is a useful guide to determining drug doses for evaluation in the Phase I/II environment.

PHASE II CLINICAL TRIAL VALIDATION OF DOSE FOR USE IN PHASE III TRIALS

Given the extensive number of patients studied and the possibility for harm if an incorrect dose is chosen for Phase III clinical trial evaluation, it is important to validate the dose(s) chosen by the use of Monte Carlo simulation. In order to do this, it is critical to pay attention to the same sources of variability as in the integration of the preclinical information.

It is important, therefore to have an index of drug exposure for each patient participating in the analysis, a pathogen identified, and an MIC determined to the drug being employed. Finally, it is important to decide upon an endpoint (eg, clinical success/failure, organism eradication/persistence).

The first prospective, multicentered trial of this type was published by Preston and colleagues.[15] Patients were enrolled in 22 centers for the therapy of community-acquired infections (respiratory tract infections, skin and skin structure infections, and urinary tract infections) with a fluoroquinolone antimicrobial (levofloxacin). A sampling scheme was derived using a stochastic D-optimal sampling technique. There were 272 patients who had pharmacokinetic data collected. These data were analyzed employing a non-parametric population modeling technique (NPEM II program of Schumitzky and Jelliffe). Individual estimates of exposure were calculated for each patient by obtaining patient-specific pharmacokinetic parameter values employing Maximum *A-posteriori* Probability (MAP) Bayesian parameter estimation. Of these patients, there were 134 patients with a documented outcome and identified pathogen that had a levofloxacin MIC. For clinical outcome, both Peak/MIC ratio as well as AUC/MIC ratio could be linked to outcome. As there has been considerable preclinical data linking AUC/MIC ratio to fluoroquinolone effect, this relationship will be presented in Figure 63-10. The breakpoint AUC/MIC value, determined by Classification and Regression Tree (CART) analysis, was 49.8. This was for total drug. The free drug value would be 34.9. A mouse thigh infection model developed in our laboratory examined levofloxacin for the therapy of *Streptococcus pneumoniae*.[16] The value for an organism kill of 1 log10(cfu/g) was 29.4 for a free drug AUC/MIC ratio. The free drug AUC/MIC value associated with a good outcome determined in a separate clinical study by Ambrose only for *Streptococcus pneumoniae* for two fluoroquinolones (levofloxacin and gatifloxacin) was 27.2–33.7.[17] All these determinations are in excellent concordance.

What is clear is that it is possible to identify targets for desired drug action preclinically and to bridge between animal and man employing Monte Carlo simulation techniques. Further, it is also clear that these findings are robust. They have been validated in clinical trials. The paradigm for clinical validation is simple. It is set forth in Table 63-2. It is important to obtain good individual-patient estimates of their pharmacokinetic parameter values in order to perform clinical pharmacodynamic analysis. While population modeling allows good estimates of population mean parameter values, the precision with which the values are determined for an individual patient after the MAP-Bayesian step depend explicitly on how much information is present in the samples that have been obtained for *that* patient. This problem can be solved without undue patient invasion (ie, minimizing the numbers of samples) by employing stochastic optimal design techniques.[18–21] Once the patients have been studied, the population values are best attained using population modeling techniques, with patient-specific values determined through MAP-Bayesian estimation. Exposure variables can then be normalized (in the case of anti-infective agents) to some measure of the degree of susceptibility of that patient's pathogen to the drug in question (Peak/MIC ratio, AUC/MIC ratio or Time > MIC). These normalized exposure variables can then be linked to the probability of a good outcome (clinical/microbiological) through use of logistic regression. Breakpoints can be sought through use of CART analysis. If the outcome is a time-to-event, Kaplan-Meier analysis (when a breakpoint is available) or Cox proportional hazards analysis

Table 63-2. Paradigm for the Development of Exposure-Response Relationships

1. Decide on an endpoint
2. Make potency measurements of the cells to be inhibited/killed (MIC/EC_{50}, etc)
3. Obtain drug exposure estimates for patients in these trials
   a. Stochastic Optimal Sampling Design
   b. Population Pharmacokinetic Modeling
   c. MAP-Bayesian parameter determinations for individual-patient exposure estimates
4. Decide on an analytical tool for endpoint analysis (examples only)
   a. Sigmoid-Emax analysis for a continuous endpoint
   b. Logistic regression for dichotomous/polytomous outcomes
   c. Cox proportional hazards modeling (or a fully parametric variant) for time-to-event data
   d. Classification and Regression Tree (CART) analysis for breakpoint determination

(for a continuous variable) can be employed. If the outcome is a continuous variable (eg, viral load determination), some variant of a sigmoid-Emax effect model can be employed to link exposure to effect.

Determination of a pharmacodynamically linked variable pre-clinically with an exposure target combined with a target attainment analysis from Phase I/II data will allow identification of a dose for Phase III trials. Validation of this outcome in a (relatively) small Phase II trial will provide confidence that the dose chosen for large, Phase III clinical trial investigation is optimal for the effect target desired. This will maximize the speed of drug development and minimize drug failure.

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PART 7

Pharmaceutical and Medicinal Agents

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CHAPTER 64

Diagnostic Drugs and Reagents

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Optimum treatment of a patient begins after a physician makes a diagnosis. This process usually begins with a discussion between patient and physician regarding symptoms the patient is experiencing. The physician performs a physical examination of the patient and then decides if further tests are required for diagnosis.

Biological samples such as blood, urine, or tissue biopsy may be required for in vitro analysis that may use chemical reagents and scientific instruments. However, accurate analysis depends on the purity of reagents and proper functioning and calibration of any instrumentation. The United States Pharmacopeia/National Formulary publishes standards for reagents used in testing.

Certain diagnostic procedures require the administration of drugs to the patient for determining the functional status of organs and tissues within the body, in vivo tests. Some diagnostic drugs are not metabolized as they pass through the body; inulin is a classic example of this type of diagnostic drug. Inulin is administered intravenously and filtered by the glomeruli. It is not reabsorbed or secreted by the renal tubules and is excreted unchanged. Measurement of inulin in the urine provides information about the glomerular filtration rate of the kidney, thereby providing information about the status of kidney function. The incidence of adverse drug effects to inulin is very low.

Other drugs must undergo rather extensive processes in the body before they provide the information needed for diagnosis. For example, iopanoic acid is administered orally after consumption of a fat-free meal the evening before the scheduled examination of gallbladder function. Iopanoic acid is absorbed from the gastrointestinal tract, concentrating in the gallbladder. The next morning the patient has an x-ray study of the gallbladder, cholecystography. Iopanic acid is eventually excreted in the feces and urine. Adverse effects from ingestion of iopanoic acid are mild, usually nausea and diarrhea, but allergic reactions may occur.

Cholecystography requires that the drug possesses radiopaque properties. A radiopaque drug absorbs x-rays so that the organ, in this case the gallbladder, can be visualized and distinguished from other structures in the abdomen. Body structures can be examined using radioactive drugs, which provide their own source of ionizing radiation to produce images. Newer techniques using magnetic resonance and ultrasound have been developed that produce images. Some studies may require the administration of drugs, but each imaging modality requires drugs with different physical properties.

The physician's order for any diagnostic test must balance the benefit of the procedure with the risk to the patient. Factors the physician considers before ordering any diagnostic test are: (1) the type of information needed, (2) the sensitivity and specificity of the procedure, (3) potential adverse effects associated with the procedure, (4) concomitant diseases of the patient, (5) current drug therapy of the patient, and (6) cost of the procedure. MF Roizen expressed these concerns by writing, "In this era of cost efficiency, the best method for both patient and practice survival is to perform the tests and assessments that provide more benefit for the patient than risk."[1]

The inter-relationship of these factors may be understood more clearly by examining some specific examples. Generally, in vitro tests may be perceived to be safer than in vivo tests. Obtaining a urine sample for analysis is a simple procedure without adverse effects. However, obtaining a biopsy sample of kidney for examination, an in vivo test, has a greater risk of adverse effects because of the invasive nature of obtaining the sample.

Any in vivo test requiring the administration of a drug possesses several factors that could cause adverse effects. The most serious adverse effect is, of course, an anaphylactic allergic reaction to the drug. Diagnostic drugs that are most likely to cause allergic reactions are those containing protein or iodine. All parenteral drugs used as contrast media for studies utilizing x-rays contain iodine. These drugs are also called contrast agents, radiopaques, or roentgenographic drugs.

Other adverse effects from drugs administered parenterally, chemotoxic effects, are related to factors such as osmolality, viscosity, hypertonicity, inherent toxicity of the drug, route of administration, rate of administration, total dose, concentration of drug, and formulation of the drug. Osmolality of drugs used as contrast media is of particular concern for the radiopaque drugs. High osmolality drugs have a greater risk of producing adverse drug reactions (ADRs) than low osmolality drugs.

Osmolality depends on the number of particles of drug in solution and its molecular size. The first iodinated contrast drugs developed were all ionic monomers, having high osmolality when compared to plasma, about 1500 to 1800 milliosmols (mOsm) per kilogram. They are either sodium or meglumine salts with the anionic portion of the molecule containing a tri-iodinated aromatic ring. These high osmolality contrast agents (HOCA), sodium or meglumine diatriazoate, meglumine iodipamide, and meglumine iothalamate, are also known as ratio 1.5 drugs. This ratio is determined by dividing the number of iodine atoms in the molecule by the number of particles in solution. The chemical structure of sodium diatriazoate contains 3 atoms of iodine and consists of 2 particles in solution, producing a ratio of 1.5. Iothalamate is a representative of 1.5 ratio drugs.

Because of the high incidence of ADRs associated with the HOCAs, lower osmolality contrast agents (LOCA) were developed. These drugs include iohexol, iopamidol, iopromide, and ioversol, which are all nonionic monomeric drugs. In solution these drugs have one particle containing 3 atoms of iodine in the molecule. These LOCAs are known as ratio 3.0 drugs and have an osmolality of 600 to 850 mOsm per kilogram. However, not all ratio 3.0 drugs are nonionic monomers. Ioxaglate sodium

or megluamine is an ionic dimer molecule, also having a ratio of 3.0 (6 iodine atoms divided by 2 particles; and is considered to be a LOCA.

The most recently developed drugs in this group are non-ionic dimers that are nearly iso-osmolar with plasma, about 290 mOsm per kilogram. Iodixanol was the first drug of this type to be approved in the United States. Although dimers have lower osmolality, they have greater viscosity, which may limit their use in some situations, for example, greater difficulty in administration through small arterial catheters.

ADRs associated with contrast media may be described as mild, moderate, or severe. Mild reactions include flushing or feeling of warmth after injection, itchy skin, mild rash, or diaphoresis. Moderate ADRs include extensive rash or hives, nausea, bronchoconstriction, dyspnea, and edema of the larynx. Severe ADRs include hypotension, shock, pulmonary edema, cardiac arrhythmias, nephrotoxicity, respiratory depression and deaths.[2]

Mild to moderate ADRs may be greatly reduced or prevented by pretreating patients sensitive to radiopaque drugs with antihistamines or corticosteroids. The risk of severe ADRs from HOCAs in the normal population is rather low, ranging from 0.025% to 0.1%, and the risk of fatalities is about 10 times lower.[2] The risk of nephrotoxicity, a very serious ADR is much higher in patients with diabetes and pre-existing renal disease. It is estimated that the use of contrast media causes about 10% of the cases of hospital-acquired acute renal failure, which occurs in about 5% to 7% of all hospitalized patients.[3,4] Risk of ADRs associated with contrast media is greatly reduced for all patients by adequately hydrating them using either 0.45% or 0.9% normal saline administered intravenously prior to performing contrast studies.

Risks of all ADRs can be reduced by using low osmolality or iso-osmolar contrast media. However, these agents currently cost about 10 times more than HOCAs and are used for patients categorized as high risk. A randomized, double-blind, prospective study by Aspelin et al reported that use of iodixanol, an iso-osmolar drug, had an incidence of 3% for nephrotoxocity in sample of high-risk patients undergoing coronary angiography compared with 26% in patients who received iohexol, a LOCA.[5]

Diseases associated with increased risk of adverse effects in patients receiving intravascular iodine contrast agents are severe cardiovascular disease, multiple myeloma, diabetes mellitus, homozygous sickle-cell disease, and pheochromocytoma. There are reports of thyroid storm following the use of these drugs in patients with hyperthyroidism. Thyroid testing of patients receiving iodinated contrast media should be delayed for a week or more because levels of iodine may be detected for days or even weeks in some patients after imaging procedures.

Storage conditions may affect solutions containing high concentrations of drug, causing precipitation of the drug in the vial or ampoule. Gentle agitation or mild heating should result in re-solution of the drug. If any particulate remains or if there is a color change in the solution, the drug should be discarded.

Drugs used for magnetic resonance imaging (MRI) also present a risk for chemotoxic ADRs. Many MRI drugs are hyperosmolar and hypertonic compared to plasma, but the volume of drug administered is less than that needed in radiopaque studies. Thus, the osmotic load is much less than the iodine contrast media, producing fewer ADRs. Risk of allergic reactions or sensitivity to MR drugs is low, but remains a concern.

MR images are created when protons present in tissues align themselves in a magnetic field depending on the nuclear magnetic moment to produce a nuclear spin energy state. A second magnetic field is produced by pulsed radiofrequency to induce nuclear resonance. The time it takes for the protons to return to the lower energy state is the relaxation time. The relaxation time varies from tissue to tissue, creating signals that are detected by a receiver coil and analyzed by a computer to produce an image. MR-enhancing drugs must contain one or more unpaired electrons. Currently approved MR drugs (also known as paramagnetic or supramagnetic agents) contain one of the following atoms in their structure: manganese (Mn^{2+}), iron (Fe^{3+}), or gadolinium (Gd^{3+}).

Additional precautions must be followed in patients with deoxygenated sickle erythrocytes, hemolytic anemias, cardiovascular disease, and renal or hepatic impairment.

Ultrasound diagnostic drugs are relatively new agents in diagnostic imaging. The FDA approved the first ultrasound drug, 5% human albumin microspheres, for cardiac imaging in 1995. Ultrasound studies use non-ionizing electromagnetic waves in the low megahertz range. Ultrasound waves produced in a transducer head are projected into a patient and reflected from tissue surfaces back to the transducer, much like radar waves. The transducer receives the ultrasound waves, converts them into signals, which are interpreted by a computer, producing an image.

Ultrasound contrast studies require very small particles, microspheres. Drugs used currently for cardiac studies consist of human albumin or lipid coated microspheres containing perflutren gas. ADRs include headache, dizziness, palpitations, and potential serious cardiopulmonary effects. Protein containing drugs have a higher risk of producing allergic reactions.

Technical advances made in the various modalities used for imaging the human body have been accompanied by the introduction of new drugs to enhance image formation to improving diagnostic information available to physicians. This chapter reviews the radiopaque, magnetic resonance, and ultrasound drugs.

This chapter also includes drugs used frequently to evaluate other physiological states or diagnose diseases by either in vivo *or* in vitro methods, including many self-care diagnostic aids. However, tests for identifying organisms for infectious diseases are not included in this chapter. Readers desiring the most complete information for identification of micro-organisms should refer to *The Manual of Clinical Microbiology,*[6] or *Manual of Commercial Methods in Clinical Microbiology.*[7] This chapter also does not include the many tests that are performed in clinical laboratories or doctors' offices.

Advances in the application computer technology and biotechnology methods have added a great number of diagnostic tests or devices available for patients to use at home. Patients who desire to be more pro-active about their health care have created a growing market for these devices. For example, at one time patients with diabetes mellitus could only monitor blood glucose and urinary ketones, but now they can measure blood glucose, blood ketones, and hemoglobin A1c. Other OTC devices are available to monitor blood cholesterol, predict ovulation, determine pregnancy, detect occult blood in the urine and feces, detect protein and leuckocytes in the urine, and detect the use of illicit drugs. This chapter includes a discussion of selected devices that are used frequently as self-care in vitro diagnostic aids.

DIAGNOSTIC IMAGING DRUGS

ROENTGENOGRAPHIC DRUGS (X-RAY CONTRAST AGENTS)

The discovery of x-rays by Wilhem Conrad Roentgen in 1895 gave physicians a tool that allowed them to view the inside of the body, thus improving their ability to make a more accurate diagnosis of a patient's illness. Physicians were using x-rays and urethral catheters with metal inside them for examining the urinary tract by 1905.[8]

Oral administration of bismuth and barium salts were used to produce images of the gastrointestinal tract, and by 1906, the technique of retrograde pyelography using bismuth subnitrate

or colloidal silver was developed. Toxicities associated with these drugs led to the use of thorium salts (a radioactive element) as imaging agents in 1915. The use of sodium or potassium iodide as a contrast agent was proposed in 1918, but the concentrations needed for good images produced numerous toxicities.[8]

The mid-1920s saw the introduction of compounds composed of pyridine with iodine or arsenic substituents as therapy for infectious diseases, especially syphilis. One of these iodinated pyridine compounds was selectively concentrated and excreted by the kidneys, and it was eventually developed as an imaging agent for the urinary tract. Intravenous examination of the urinary tract using substituted pyridines became an integral part of medical practice by the end of the decade.[8]

Adverse reactions to contrast agents were a significant problem. The search for safer drugs resulted in the development of tri-iodinated benzoic acid compounds that produced better quality images with fewer adverse effects. Development continued to improve the safety profile of these drugs throughout the decade of the 1950s. The first drugs developed were ionic, monomeric salts that had either sodium or meglumine (N-methylglucamine) as the cation. Meglumine salts produce less pain at the site of injection and less vasodilation during arteriography, both advantages; however, they increase urine output, a disadvantage during venography. Sodium salts are less viscous, an advantage in reducing administration problems, but they are more toxic to the blood brain barrier and heart. Efforts to improve benefit to risk profiles for imaging agents led to the use of mixtures of the two salts in varying ratios, depending on the organ system to be visualized.[8]

Although much safer than earlier drugs, the high osmolality of the ionic monomeric contrast agents (HOCA) compared to plasma and their hypertonicity contribute significantly to their adverse effects. Lower osmolality contrast agents (LOCA) were developed in the 1960s and 1970s by creating dimers of ionic monomeric agents or by synthesizing nonionic contrast agents. The newest compounds, which have almost the same osmolality as plasma, are nonionic dimer compounds. The LOCA and iso-osmolality drugs are considerably more expensive than the older agents and are used in patients who are at a greater risk of adverse effects, particularly for patients with renal impairment, diabetes mellitus, and those undergoing *coronary angiography* studies. Patients with multiple myeloma, homozygous sickle-cell disease, and pheochromocytoma are also at higher risk for adverse effects. Iodinated drugs must be used with caution in patients allergic or sensitive to iodine or any other components of the drug.

The drugs in this section are listed in alphabetical order by their generic name because some drugs are used to visualize several organ systems depending on their concentrations. Each drug's description includes the concentration used for each organ system. Only barium sulfate and organic iodine compounds are used as radiopaque drugs.

BARIUM SULFATE

Sulfuric acid, barium salt (1:1); Synthetic or Artificial Barytes

Barium sulfate (1:1)
[7727-43-7] $BaSO_4$ (233.39).

Caution—When Barium Sulfate is prescribed, the title always should be written out in full to avoid confusion with the poisonous barium sulfide or barium sulfite.

Preparation—Barium sulfate precipitates when an aqueous solution containing barium ion is mixed with a solution containing sulfate ion. It also can be obtained by suitable purification of native barium sulfate.

Description—Fine, white, bulky powder, free from grittiness; odorless; tasteless; its suspension in water is neutral to litmus paper.

Solubility—Practically insoluble in water; solutions of acids or alkalies, or organic solvents.

Comments—Primary contrast agent for visualizing the esophagus, stomach, small and large intestines. Barium sulfate is available as either a powder for suspension or suspensions with different concentrations. The particle size in the suspension and the concentration of the final preparation are important determinants in the ability of barium sulfate to adhere to the mucosal wall of the digestive system. High-density preparations (>200% w/v) are preferred for the stomach, medium density (100–200% w/v) for the esophagus, and low density (<100% w/v) for the small intestine. Barium sulfate of medium density is administered as an enema for visualization of the large intestine (colon).[9]

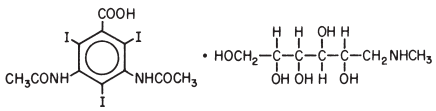
If barium sulfate is used alone, the study is referred to as a single contrast study. Studies using air or carbon dioxide force the particles in the suspension against the mucosal wall for optimum visualization and are referred to as double-contrast studies. Sodium bicarbonate and tartaric acid may be administered with barium sulfate when carbon dioxide serves as the second contrast medium. Barium sulfate is usually used for *fluoroscopy*, but it is also used for *computed tomography* (CT) of the gastrointestinal tract.

Preparations intended for oral use are available in several flavors to improve palatability of barium suspensions. Stabilizers are added to prevent flocculation of the particles, such as gelatin; and, simethicone is added to prevent bubbles from forming during the procedure.[9]

Severe adverse effects are rare. Common adverse effects include bowel disturbances, either constipation or diarrhea. Known contraindications for the use of barium sulfate are intestinal obstruction, perforation of the gastrointestinal tract, tracheoesophageal fistula, and sensitivity to barium sulfate formulations.

DIATRIZOATE MEGLUMINE

Benzoic acid, 3,5-bis(acetylamino)-2,4,6-triiodo-, compound with 1-deoxy-1-(methylamino)-D-glucitol (1:1); Cystografin, Cystografin Dilute, Hypaque Meglumine (30 and 60%), Reno-30, Reno-60, Reno-DIP



1-Deoxy-1-(methylamino)-L-glucitol 3,5-diacetamido-2,4,6-triiodobenzoate (salt)
[131-49-7] $C_7H_{17}NO_5.C_{11}H_9I_3N_2O_4$ (809.13).

Preparation—Diatrizoic acid is reacted with an equimolar quantity of methylglucamine (meglumine), usually in water for injection, to produce a solution of the required concentration.

Description—A clear, colorless solution.

Comments—Different concentrations are used for visualizing several organs. A 60% solution is used for *excretory urography, cerebral angiography, peripheral arteriography, venography operative and postoperative cholangiography, percutaneous transhepatic cholangiography, splenoportography, arthrography, discography, urography,* and enhancement of *computed tomography* of the brain and body. *Retrograde pyelography* is performed using a 30% solution whereas *retrograde cystourethrography* may be performed with either a 30% or 18% solution. Cystografin and Cystografin Dilute are only used for retrograde studies and are not to be injected intravascularly. Reno-DIP, a 30% solution of diatrizoate, may be used for drip infusion *pyelography*, lower extremity *venography*, and *computed tomography* of the brain and body.

Diatrizoate meglumine is contraindicated for use in intrathecal procedures, and must be used with great caution in patients who are allergic or sensitive to diarizoate salts. Severe adverse effects to ionic iodinated contrast agents include inhibition of blood coagulation, acute renal failure, myocardial infarction, and stroke. Patients who have multiple myeloma, pheochromocytoma, or are homozygous for sickle-cell disease are at greater risk for adverse effects. Extreme caution should be used in patients with renal or hepatic impairment or disease. Safety for use in pregnancy has not been established.

DIATRIZOATE MEGLUMINE AND DIATRIZOATE SODIUM

Hypaque-76, Gastrografin, MD-Gastroview, MD-76R, RenoCal-76, Renografin-60

A sterile solution of diatrizoate meglumine and diatrizoate sodium in water for injection, or a sterile solution of diatrizoic acid in water for injection prepared with the aid of NaOH and meglumine. It may contain small amounts of suitable buffers and of edetate calcium disodium or edetate disodium as a stabilizer. When intended for intravascular use, it contains no antimicrobial agents.

Description—Clear, colorless to pale yellow, slightly viscous liquid; may crystallize at room temperature or below.

Comments—Designed to combine the lower toxicity of the meglumine salt with the lower viscosity and higher iodine content of the sodium salt. Two concentrations are in current use. Intravenous products with 76 in the trade name contain 66% of the meglumine salt and 10% of the sodium salt. They are used as contrast agents for *angiocardiography, aortography, angiography, excretion urography, peripheral*

arteriography, *nephrotomography* (RenoCal-76 only), *venography* (Hypaque-76 only), *ventriculography*, and *computed tomography*.

Renografin-60 contains 52% of the meglumine salt and 8% of the sodium salt of diatrizoate. It is indicated for use in *urography, angiography, arteriography, venography, cholangiography, splenoportography, arthrography, discography, and computed tomography*.

A solution containing 66% of diatrizoate meglumine and 10% of diatrizoate sodium (Gastrografin, *Bracco*) is used as a contrast medium for radiographic examination of the GI tract following oral or rectal administration. This preparation is used when the use of barium is not feasible or is potentially dangerous. It may also be used for *computed tomography* studies.

These diatrizoate salt combinations have the same contraindications and warnings as diatrizoate meglumine and daitrizoate sodium. The safety of the oral solution in pregnancy has not been established. It is usually tolerated well; occasionally, diarrhea occurs.

DIATRIZOATE MEGLUMINE AND IODIPAMIDE MEGLUMINE

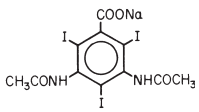
Sinografin

A sterile, aqueous, clear to pale yellow solution of diatrizoate meglumine equivalent to 40% diatrizoic acid and iodipamide meglumine equivalent to 20% iodipamide, containing approximately 38% bound iodine.

Comments—A radiopaque medium indicated for *hysterosalpingography*. Intrauterine administration provides immediate visualization of the uterus and uterine tubes. Any contrast agent spilled into the peritoneal cavity is absorbed within 20 to 60 minutes. Use of this drug is contraindicated during pregnancy, within 6 months of a terminated pregnancy, and within 30 days following curettage or conization. The procedure should not be performed during the menstrual period or if the patient has a genital tract infection. Precautions, adverse effects, and contraindications are similar to those for other iodinated diagnostic agents.

DIATRIZOATE SODIUM

Benzoic acid, 3,5-bis(acetylamino)-2,4,6-triiodo-, monosodium salt; Hypaque Sodium 50% Injection, Hypaque Sodium (powder)



[737-31-5] $C_{11}H_8I_3N_2NaO_4$ (635.90).

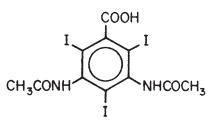
Preparation—Diatrizoic acid is reacted with an equimolar quantity of NaOH, usually in water for injection, to produce a solution of the required concentration.

Comments—A radiopaque agent with uses, profile of toxicity, and precautions similar to those for *Diatrizoate Meglumine*. It contains somewhat more iodine (59.87%) than the meglumine salt (47.01%). Solutions are considerably less viscous than those prepared from diatrizoate meglumine. Diatrizoate sodium if used in *coronary angiography* is more likely to cause serious cardiac arrhythmias than is the meglumine salt.

Indications for the use of diatrizaote sodium include *excretory urography, angioangiography, aortography, cholangiography, hysterosalpingography, splenoportography,* and *computed tomography*.

DIATRIZOIC ACID

Benzoic acid, 3,5-bis (acetylamino)-2,4,6-triiodo-



anhydrous [117-96-4] $C_{11}H_9I_3N_2O_4$ (613.92); *dihydrate* [50978-11-5] (649.95).

Preparation—Derived from benzoic acid by (1) nitration to the 3,5-dinito acid, (2) reduction by means of stannous chloride or other reducing agent to the corresponding diamino acid, (3) iodination with iodine monochloride in acetic acid to the 2,4,6-triiodo derivative, or (4) acetylation of the amino groups by use of acetic anhydride.

Description—White powder; odorless.

Solubility—Very slightly soluble in water or alcohol; soluble in dimethylformamide or alkali hydroxide solutions.

Comments—Radiopaque component of *Diatrizoate Meglumine Injection, Diatrizoate Meglumine and Diatrizoate Sodium Injection, Diatrizoate Sodium Injection,* and *Diatrizoate Sodium Oral Solution*.

ETHIODIZED OIL

Ethiodol

A sterile iodine addition product of the ethyl ester of the fatty acids of poppy seed oil, containing 35.2% to 38.9% organically combined iodine. [8008-53-5] (no molecular weight given).

Preparation—By saponifying poppy seed oil and subjecting the resulting fatty acids to iodination and subsequent esterification with ethanol.

Description—Straw-colored to amber-colored, oily liquid; may have an alliaceous odor.

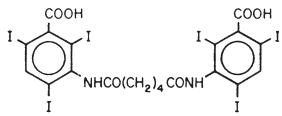
Solubility—Insoluble in water; soluble in acetone, chloroform, or ether.

Comments—A contrast agent used in *hysterosalpingography* and *lymphography*. Contraindications for *hysterosalpingography* are the same as for other iodine contrast agents as well as the following: pregnancy, presence of intrauterine bleeding, pelvic inflammatory disease, cervical erosion, and 30 days after conization.

Contradications for *lymphography* include right-to-left cardiac shunt, advanced pulmonary disease, and patients who have had radiation therapy to the lungs. Subclinical pulmonary embolism may occur that is usually transient in nature. Pregnancy category is C, and it is unknown if ethiodized oil appears in breast milk.

IODIPAMIDE

Benzoic acid, 3,3′-[(1,6-dioxo-1,6-hexanediyl)diimino]bis[2,4,6-triiodo; Cholografin



3,3–(Adipoyldiimino)bis[2,4,6-triiodobenzoic acid]
[606-17-7] $C_{20}H_{14}I_6N_2O_6$ (1139.76).

Preparation—From benzoic acid by (1) nitration to 3-nitrobenzoic acid, (2) reduction by means of stannous chloride or other reducing agent to 3-aminobenzoic acid, (3) iodination with iodine monochloride in acetic acid to the 2,4,6-triiodo derivative, or (4) acylation of the amino group with adipoyl chloride [$ClCO(CH_2)_4COCl$].

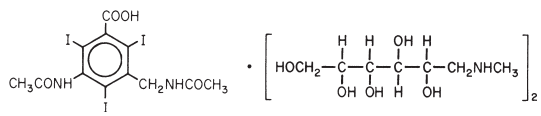
Description—White, crystalline powder; nearly odorless.

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

Comments—Radiopaque component of *Iodipamide Meglumine Injection*.

IODIPAMIDE MEGLUMINE

Benzoic acid, 3,3′-[(1,6-dioxo-1,6-hexanediyl)diimino]bis2,4,6-triiodo-, compound with 1-deoxy-1-(methylamino)-D-glucitol (1:2); Cholografin Meglumine



1-Deoxy-1-(methylamino)-D-glucitol3,3′-(adipoyldiimino)bis[2,4,6-triiodobenzoate] (2:1) (salt)
[3521-84-4] $C_{20}H_{14}I_6N_2O_6.2C_7H_{17}NO_5$ (1530.19).

Preparation—Iodipamide is reacted with a double equimolar quantity of methylglucamine (meglumine), using sufficient water for injection to produce a solution of the required concentration.

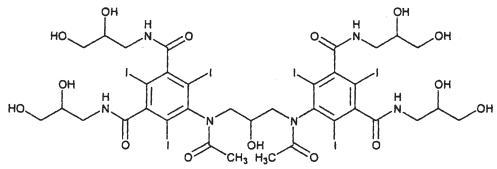
Description—Clear, colorless to pale yellow, slightly viscous liquid.

Comments—For *intravenous cholangiography* and *cholecystography* as follows: visualization of the gallbladder and biliary ducts in the differential diagnosis of acute abdominal conditions; visualization of the biliary ducts especially in patients with symptoms after cholecystectomy; and visualization of the gallbladder in patients unable to take oral contrast media or to absorb media from the gastrointestinal tract. The contrast agent appears in the bile within 10 to 15 minutes after injection, and the biliary ducts are visualized within 25 minutes; the gallbladder begins to fill within 1 hour, maximum filling occurs within 2 to 2.5 hours.

Adverse reactions and contraindications are similar to those common to iodine containing compounds.

IODIXANOL

1,3-Benzenedicarboxamide, 5,5′-[(2-hydroxy-1,3-propane diyl)bis(acetylimino)]bis[*N,N′*-bis(2,3-dihydroxypropyl)-2,4,6-triiodo-; Visipaque



[92339-11-2] $C_{35}H_{44}I_6N_6O_{15}$ (1550.18).

Preparation—Eur Pat Appl EP 108,538 (1984) See *CA* 1984; 101:151,599g,

Description—Melts about 250°–250°; I_2 content 49.1%; a 50% aqueous solution (w/v) d 1.26; viscosity 8.7 cP @ 37°. Osmolality 290 mOsm/kg water, pH 7.2-7.6.

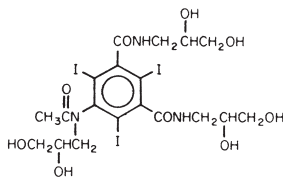
Solubility—Soluble in water.

Comments—A dimeric, isomolar, nonionic, iodine contrast agent used for both intra-arterial and intravenous administration. Intra-arterial Visipaque 320 is used for *angiocardiography (left ventriculography* and *selective coronary arteriography), peripherial arteriography, visceral artiography, and cerebral arteriography*. Visipaque 270 is only approved for *intra-arterial digital subtraction angiography*. Both concentrations are used intravenously for *computer tomography* of the head, and body, and *excretory urography*; Visipaque 270 is also approved for *peripheral venography*.

Iodixanol is isosmolar with plasma and is preferred to the hyperosmolar contrast agents in patients at increased risk for adverse effects, such as acute renal failure. The same warnings and precautions must be taken with iodixanol as with other iodinated contrast agents. Iodixanol is pregnancy category B, and it is not known if it excreted in human milk.

IOHEXOL

1,3-Benzenedicarboxamide, 5-[acetyl(2,3-dihydroxypropyl)amino]-*N,N*-bis(2,3-dihydroxypropyl)-2,4,6-triiodo-, Omnipaque 140, 180, 240, 300, and 350 (Note: The numerical values indicate the concentration of organically bound iodine in mg/mL, not the concentration of drug/mL.)



[66108-95-0] $C_{19}H_{26}I_3N_3O_9$ (821.14).

Preparation—US Pat 4,250,113.

Description—White crystals; melts at about 176°.

Solubility—Soluble in water to form stable solutions.

Comments—A nonionic, water-soluble, radiographic contrast medium used in different concentrations. The lowest concentration, Omnipaque 140, has 140 mg of iodine per mL, and is 1.1 times the osmolality of plasma. Omnipaque 350 has an osmolality that is 3 times higher than plasma. Omnipaque 180, 240, and 300 are indicated for intrathecal use for *myelography* (lumbar, thoracic, cervical, total columnar) and for contrast enhancement in *computed tomography* (CT) for *myelography, cisternography,* and *ventriculography*.

Contraindications for intrathecal use include known hypersensitivity to iohexol. Patients with infections that could cause bacteremia should not undergo *myelography* with iohexol. Intrathecal administration of corticosteroids is contraindicated with iohexol use. In addition to the usual warnings and precautions for use of iodinated contrast agent, the package insert warns about possible idiosyncratic reactions in patients who may have a history of sensitivity to iodine, other contrast agents, bronchial asthma, hay fever, and food allergies.[10] Iohexol is pregnancy category B, and it is not known if it is secreted in breast milk.

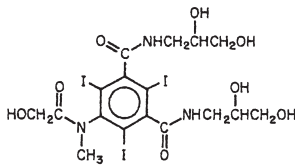
Caution is advised in patients with a history of epilepsy, severe cardiovascular disease, chronic alcoholism, or multiple sclerosis. Drugs that lower seizure threshold, especially phenothiazine derivatives, including those used for their antihistaminic or anti-nauseant properties, are not recommended for use with iohexol. Others drugs to be avoided include monoamine oxidase (MAO) inhibitors, tricyclic antidepressants, CNS stimulants, psychoactive drugs described as analeptics, major tranquilizers, or antipsychotic drugs. Such medications should be discontinued at least 48 hours prior to *myelography*, should not be used for the control of nausea or vomiting during or after *myelography*, and should not be resumed for at least 24 hours after procedure.

Iohexol also may be administered intravascularly and is distributed in the extracellular fluid and excreted unchanged by glomerular filtration. Intravascular administration is used in *computed tomography* imaging of the head and total body as well as for *angiocardiography, arteriography, digital subtraction, peripheral angiography,* and *excretory urography*.

Iohexol may be injected directly into body cavities for a variety of procedures including *arthrography, hysterosalpingography, herniography, voiding cystourethrography, endoscopic retrograde pancreatography,* and *cholangiopancreatography*.

IOMEPROL

1,3-Benzendicarboxamide, *N,N′*- bis (2,3-dihydroxypropyl)-5-[(hydroxyacetyl)methylamino]-2,4,6-triiodo-, Iomeron



[78649-41-9] $C_{17}H_{22}I_3N_3O_8$ (777.09).

Preparation—US Pat 4,352,788.

Description—Crystalline powder; melts about 290°.

Solubility—Very soluble in water or methanol; poorly soluble in ethanol; insoluble in chloroform.

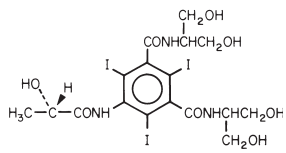
Solution Properties

mg I_2/mL	Conc drug mg/mL	$d^{20}/_4$	$\eta^{20}/_D$	Osmolality 37° (mOsmol/Kg water)
150	303.6	1.166	1.3828	0.27
300	607.3	1.329	1.4327	0.52
400	809.7	1.446	1.4660	0.72

Comments—This drug is available in over 40 countries, but has not been approved for use in the United States by the FDA. It is a tri-iodinated, nonionic contrast agent intended for examination of the brain and liver by *computed tomography*.

IOPAMIDOL

(S)- *N,N′*-bis[2-Hydroxy-1-(hydroxymethyl)ethyl]-2,4,6-triiodo-5-lact-amidoisophtpalamide. Isovue 128, 200, 250, 300, and 370; Isovue-M 200, Isovue-M 300 (Note: The numerical values indicate the concentration of organically bound iodine in mg/mL, not the concentration of drug/mL.)



1,3-Benzenedicarboxamide,(*S*)-*N,N′*-bis[2-hydroxy-1-(hydroxymethyl) ethyl]-5-[(2-hydroxy-1-oxopropyl)amino]-2,4,6-triiodo-,
[60166-93-0] $C_{17}H_{22}I_3N_3O_8$ (777.09).

Preparation—See US Pat 4,001,323.

Description—White, odorless crystals; decomposes at about 300° without melting.

Solubility—Very soluble in water or methanol; soluble in boiling ethanol; practically insoluble in chloroform.

Comments—Only Isovue-M 200 and Isovue-M 300 are used administered by intrathecal injection for *myelography, (lumbar, thoracic, cervical, total columnar,* and *contrast enhancement of CT cisternography* and *ventriculography*. They are nonionic contrast agent that have osmolalities greater than plasma and cerebrospinal fluid and are more hypertonic than plasma and cerebrospinal fluid.

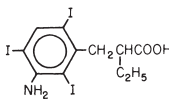
Iopamidol is absorbed rapidly into the blood from the cerebrospinal fluid, following intrathecal administration. It appears in plasma within 1 hour but does not bind to plasma protein. It is excreted by the kidneys and eliminated within 48 hours.

Iopamidol should not be administered with any other drugs, and contraindications and precautions are the same as for other iodine contrast agents. It should be administered with caution in patients with increased intracranial pressure, a history of convulsive disorders, severe cardiovascular disease, chronic alcoholism, or multiple sclerosis and in elderly patients. Other adverse reactions include headache, nausea, and back and leg pain. It is pregnancy category B and not known if it appears in breast milk.

The lowest concentration, iopamidol 128 mg I/mL, has the same osmolality as plasma and is approved for use during *intra-arterial digital subtraction angiography*. Selective *visceral arteriography* and *aortography, pediatric angiocardiography,* and *coronary arteriography* and *ventriculography* are performed using the highest concentration, iopamidol 370 mg I/mL. Iopamidol 250, 300, and 370 mg I/mL are indicated during *excretory urography*, while iopamidol 250 and 300 mg I/mL are used for *computed tomography* of the head and body. *Cerebral arteriography* is performed using Iopamidol 300 mg I/mL, and *peripheral venography* is performed using Iopamidol 200 mg I/mL.

IOPANOIC ACID

Benzenepropanoic acid, 3-amino-α-ethyl-2,4,6-triiodo-, Telepaque



3-Amino-α-ethyl-2,4,6-triiodohydrocinnamic acid.
[96-83-3] $C_{11}H_{12}I_3NO_2$ (570.93).

Preparation—A mixture of *m*-nitrobenzaldehyde, butyric anhydride, and sodium butyrate is heated in xylene to effect a Perkin condensation yielding *m*-nitro-α-ethylcinnamic acid. The acid is reduced with hydrogen in the presence of Raney nickel. The resulting *m*-amino-α-ethylhydrocinnamic acid is iodinated with iodine monochloride in acetic acid solution.

Description—Cream-colored powder; tasteless or nearly so; faint characteristic odor; affected by light; melts with decomposition between 152° and 158°.

Solubility—Insoluble in water; soluble in alcohol, chloroform, or ether; soluble in solutions of alkali hydroxides or carbonates.

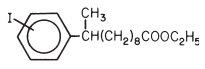
Comments—Administered as oral tablets for *cholecystography* and *cholangiography*. It is absorbed rapidly from the GI tract, concentrated in the gallbladder, and subsequently excreted, approximately two-thirds through the GI tract and one-third through the kidneys. About 50% of an administered dose is excreted within 24 hours and the remainder in about 5 days.

Iopanoic acid has low toxicity, causing nausea, diarrhea, and rarely, dysuria. Hypersensitivity reactions involving the skin and mucous membranes and a systemic serum sickness-type reaction have been reported. It is contraindicated in patients with acute nephritis and uremia, since it is eliminated by the kidneys. It should not be administered when disorders of the GI tract exist that prevent absorption of the drug. Its safety in pregnant women has not been evaluated.

The patient has a fat-free evening meal followed by administration of the drug approximately 14 hours before the time scheduled for *roentgenography*. Immediately after the roentgen examination, the patient is given a high-fat meal, causing the gallbladder to contract via stimulation of the hormone, cholecystokinin from the intestinal mucosa. This permits visualization of the patency of the extrahepatic ducts.

IOPHENDYLATE

Benzenedecanoic acid, iodo-x-methyl-, ethyl ester

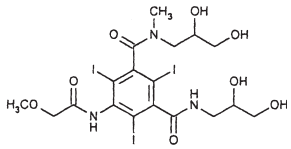


[1320-11-2] $C_{19}H_{29}IO_2$ (416.34).

Comments—*NOTE:* *This drug appears in USP 26 and NF 21 but the manufacturer has discontinued the product. It has been replaced by the low-osmolality nonionic contrast media.*

IOPROMIDE

1,3-Benzenedicarboxamide, *N*, *N*′-bis(2,3-dihydroxypropyl)-2,4,6-triiodo-5-[(methoxyacetyl)amino]-*N*-methyl-, Ultravist 150, 240, 300, and 370



[73334-07–3] $C_{18}H_{24}I_3N_3O_8$ (791.11).

Preparation—US Pat 4,364,921 (1982).

Description—Colorless solid; non-ionic and stable in aqueous solution. Iodine content 48.1%.

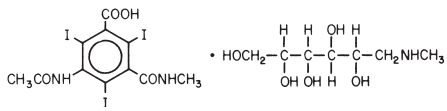
Solubility—Very soluble in water.

Comments—A nonionic, sterile, clear, colorless solution used by intravascular injection. Iopromide 150 mg I/mL is used *for intra-arterial digital subtraction angiography*; the 240I/mL for *peripheral venography;* the 300 mg I/mL for *cerebral arteriography, peripheral arteriography,* and *computed tomography of the head and body,* and *excretory urography;* and the 370 mgI/mL for *coronary arteriography, left ventriculography, visceral angiography, and aortography*.

Adverse effects include pain at injection site and back, nausea, vomiting, chest pain, headache, dizziness, drowsiness, confusion, dyspnea, and altered vision and taste perception in addition to allergic and sensitivity warnings. It is pregnancy category B, and it is not known if it appears in breast milk.

IOTHALAMATE MEGLUMINE

Benzoic acid, 3-(acetylamino)-2,4,6-triiodo-5-[(methylamino)carbonyl]-, compound with 1-deoxy-1-(methylamino)-D-glucitol (1:1); Conray (60%), Conray 30, Conray 43, Cysto-Conray II (17.2%)



[13087-53-1] $C_{11}H_9I_3N_2O_4.C_7H_{17}NO_5$ (809.13).

Preparation—Iothalamic acid is reacted with an equimolar quantity of methylglucamine (meglumine), using sufficient water for injection to produce a solution of the required concentration.

Comments—A radiopaque medium used *parenterally* as a 30%, 43%, or 60% solution for *urography;* as a 30% or 60% solution for *angiography* and *computed tomography;* as a 43% or 60% solution for *venography;* as a 43% solution for *pyelography* and *cystourethrography;* and, as a 60% solution for *cholangiography, arteriography, ventriculography,* and *arthrography*. Cysto-Conray II, a 17.2% solution, is indicated for *cystography* and *cystourethrography*.

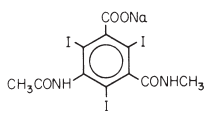
Iothalamate Meglumine is contraindicated in patients with a known allergy or sensitivity to salts of iothalamic acid and should not be used for urography in patients with anuria. Intravenous urography is hazardous to patients with multiple myeloma, anuria, progressive uremia, renal failure, and deaths have occurred. It is pregnancy category B, and it is excreted unchanged in breast milk. Bottle feedings should be used for 24 hours after the drug is administered.

IOTHALAMATE MEGLUMINE AND IOTHALAMATE SODIUM

Comments—*NOTE: Still listed in the USP 26 and NF 21, but the manufacturer discontinued the product.*

IOTHALAMATE SODIUM

Benzoic acid, 3-(acetylamino)-2,4,6-triiodo-5-[(methylamino)carbonyl]-, monosodium salt; Conray 400



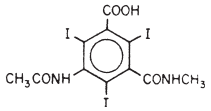
[1225-20-3] $C_{11}H_8I_3N_2NaO_4$ (635.90).

Preparation—Iothalamic acid is reacted with an equimolar quantity of NaOH, using sufficient water for injection to produce a solution of the required concentration.

Comments—For *intravascular angiocardiography, aortography, excretory urography,* and enhancement of *computerized tomography*. It is contraindicated in cerebral angiography, and in patients with sensitivity to iothalamic acid. Its adverse effects and precautions are similar to those for other iodinated diagnostic agents.

IOTHALAMIC ACID

Benzoic acid, 3-(acetylamino)-2,4,6-triiodo-5-[(methylamino)carbony]-



[2276-90-6] $C_{11}H_9I_3N_2O_4$ (613.92).

Preparation—By oxidizing *m*-xylene with potassium permanganate, condensing the resulting isophthalic acid with an equimolar quantity of methylamine, and iodinating with iodine monochloride in acetic acid.

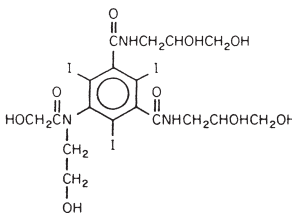
Description—White powder; odorless.

Solubility—Slightly soluble in water or alcohol; soluble in solutions of alkali hydroxides.

Comments—Radiopaque component for *Iothalamate Meglumine Injection, Iothalamate Meglumine and Iothalamate Sodium Injection,* and *Iothalamate Sodium Injection.*

IOVERSOL

1,3-Benzenedicarboxamide, *N,N'*-bis(2,3-dihydroxypropyl)-5-[(hydroxyacetyl)-(2-hydroxyethyl)amino]-2,4,6-triiodo-,Optiray 160, 240, 300, 320, and 350. (Note: The numerical values indicate the concentration of organically bound iodine in mg/mL, not the concentration of drug/mL.)



[87771-40-2] $C_{18}H_{24}I_3N_3O_9$ (807.12).

Preparation—See US Pat 4,396,598.

Solubility—Soluble in water.

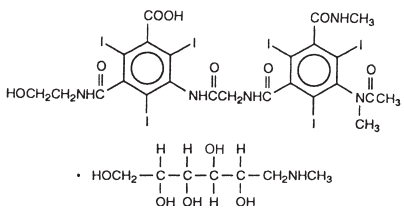
Description—A nonionic, water-soluble, radiographic contrast medium used in different concentrations having osmolalities that range from 1.2 (Optiray 160) to 2.8 (Optiray 350) times that of plasma and are hypertonic under conditions of use.

The lowest concentration of ioversol, 160mg I/mL, is only indicated for *intra-arterial digital subtraction angiography* (IA-DSA). Only the highest concentration of ioversol, 350 mg I/mL, is indicated for *intravenous digital subtraction angiography*. Ioversol 350, 320, 300, and 240 mg I/mL are indicated for *venography, computed tomography of the head and body, and intravenous urography*. Ioversol 350, 320 and 240 mg I/mL are indicated for *peripheral arteriography*; the 320, 300 and 240 mg I/mL for *cerebral arteriography*; the 350 and 320 mg I/mL for *coronary arteriography and left ventriculography*; and the 320 mg I/mL for *visceral and renal arteriography and aortography.*

Caution must be exercised in patients with severely impaired renal function, combined renal and hepatic disease, severe thyrotoxicosis, myelomatosis, or anuria, particularly when large doses are administered. Intravenously administered iodine-containing radiopaque media are potentially hazardous in patients with multiple myeloma or other paraproteinemia, particularly in those with therapeutically resistant anuria. Arterial injection should never be made following the administration of vasopressors, since they strongly potentiate neurological effects. Extreme caution must be used if patient is known or suspected to have pheochromocytoma because a hypertensive crisis could occur. It is pregnancy category B and it is not known if it appears in breast milk.

IOXAGLATE MEGLUMINE AND IOXAGLATE SODIUM

Hexabrix



A mixture of ioxaglate meglumine 39.3% [59018-13-2] $C_{24}H_{21}N_5O_9.C_7H_{17}O_5$ (1464.10) and ioxaglate sodium 19.6% ([67992-58-9] $C_{24}H_{20}I_6N_5NaO_8$ (1290.87)). The structure for the meglumine adduct is depicted above. The other component of Hexabrix is the sodium salt of the benzoic acid moiety of ioxaglate.

Comments—A radiopaque medium containing 32% iodine for *urography, arthrography, angiography, angiocardiography, arteriography, aortography, venography, hysterosalpingography,* and *computerized tomography*. Its precautions, drug interactions, adverse reactions, and clinical procedures are similar to those for other iodine-containing radiopaque agents. It is pregnancy category B and is excreted unchanged in breast milk. Bottle feeding is advised for 24 hours after the administration of the drug.

MAGNETIC RESONANCE CONTRAST AGENTS

The majority of MR contrast agents are gadolinium chelates. These compounds don't cross the intact blood-brain barrier, making them important drugs for evaluating the brain. They are eliminated by passive glomerular filtration through the kidney. Gadolinium, a lanthanide metal, is relatively inert and produces few adverse effects.

Although most MR contrast agents are hypertonic and of higher osmolality than plasma, they have a lower risk of adverse effects, especially renal toxicity, than radiopaque contrast agents. The magnetic field can alter the alignment of the iron in hemoglobin in patients with sickle-cell disease and hemolytic anemias, possibly causing vaso-occlusive effects.

FERUMOXIDES

Ferumoxides; Feridex, Endodorm (as IV injection)

[119683-68-0]

Preparation—See US Pat 4,770,183 (1988).

Description—A colloidal suspension of super paramagnetic cores of non-stoichiometric magnetite coated with dextran. The injection is black to red-brown.

Osmolality – 340 mOsm/Kg, d. = 1.04. *Mag Res Imaging* 1995; 13:661.

Comments—A colloid that is taken up by reticuloendothial cells and used primarily for *visualization of the liver*. It is contraindicated in patients with known allergic or hypersensitivity reactions to parenteral iron, parenteral dextran, parenteral iron-dextran, or parenteral iron-polysaccharide preparations.

Adverse effects include anaphylactic-like reactions, hypotension, acute severe back, leg or groin pain or generalized body pain, dyspnea and other respiratory symptoms, angioedema, and urticaria. It is pregnancy category C, and it is not known if it appears in breast milk.

FERUMOXIL

Ferumoxsil; GastroMARK

Preparation—US Pat 4,554,088 (1985).

Description—Colloidal particles of supermagnetic, non-stoichiometric magnetite coated (bonded to) with siloxane. The injection is a dark brown slightly viscous suspension. Osmolality; 250 mOsm/kg of water.

Comments—A dark brown to orange-brown oral suspension, consisting of silicone-coated particles of supramagnetic iron oxide approximately 0.4 microns that is used to enhance visualization of the bowel.

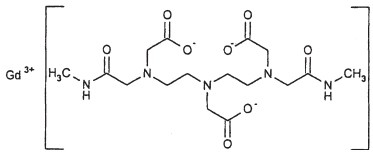
The usual dose of 600 mL, containing 105 mg of iron, is administered orally after a patient has fasted for at least 4 hours. Refrigeration of the drug before use may improve its taste; it should be shaken for at least 1 minute before administration. Absorption of iron from the gastrointestinal tract depends on existing iron stores in each patient and unabsorbed drug is excreted in the feces. Absorbed iron is metabolized by the hematopoietic system, becoming incorporated into hemoglobin in erythrocytes or stored as ferritin. The amount of silicone absorbed or metabolized in humans is unknown.[11]

Ferumoxsil is contraindicated for patients with known or suspected bowel obstruction or perforation and with a known allergy to the drug or any of its components.

Adverse drug reactions include nausea, vomiting, abdominal pain, and diarrhea. Patients who have a history of hiatal hernia, esophageal reflux, nausea, vomiting, abdominal pain and inflammatory bowel disease may not be able to tolerate administration of ferumoxsil. Less frequently seen adverse effects include fever, chills, postoperative ileus, itching, rash, stomatitis, paresthesia of the oral cavity, taste alteration, and edema of the hands and feet. It is pregnancy category B. Iron is known to appear in breast milk, but it is not know if ferumoxsil is excreted in human milk.

GADODIAMIDE

Gadolinium, [5,8-bis(carboxymethyl)-11-[2-(methylamino)-2-oxo-ethyl]-3-oxo-2,5,8,11-tetraazatridecane-13-oato(3-)-, Omniscan, Gd-DTPA-NMA



[131319-48-5] (anhydrous); [122795-43-1] (with water of hydration and coordination).

Preparation—US Pat 4,687,659 (1987).

Description—A non-ionic, low osmolar, paramagnetic chelate.

Injection; (37°, 0.5 *M)* 789 mOsm/Kg water; d = 1.13. Partition coefficient (butanol/water) -2.1.

Solubility—Water soluble.

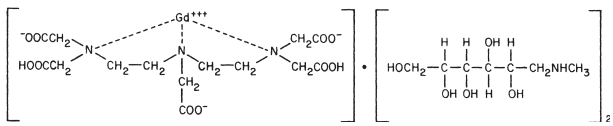
Comments—Gadodiamide injection is a sterile, colorless to slightly yellow, clear, nonionic extracellular enhancing agent for magnetic resonance imaging. It is used to visualize lesions with abnormal vascularity in the brain, spine, and associated tissues. It also is used to detect lesions with abnormal vascularity within the thoracic, abdominal, pelvic cavities, and the retroperitoneal space, but it is not used for cardiac studies.

It should be used with caution in patients with sickle cell anemia because deoxygenated sickle erythrocytes line up perpendicular to the magnetic field in in vitro studies. This phenomenon could cause vaso-occlusive complications. Gadodiamide has not been properly evaluated in other types of hemolytic anemias. It is pregnancy category C, and it is not known if it is excreted in human breast milk.

Gadodiamide should be used with caution in patients who are hypersensitive or allergic to it. Its osmolality is 2.8 times greater than plasma, and it is hypertonic. Adverse reactions most commonly include nausea, headache, dizziness, vasodilation, worsening of migraine headaches, ataxia, and seizures.

GADOPENTETATE DIMEGLUMINE

Gadolinate (2-), [*N,N*-bis[2-[bis(carboxymethyl)amino]-ethyl]glycinato(5-)-, dihydrogen, compound with 1-deoxy-1-(methylamino)-D-glucitol (1:2); Magnevist, Gd-DTPA



[86050-77-3] $C_{14}H_{20}GdN_3O_{10}.2C_7H_{17}NO_5$ (938.00).

Preparation—See US Pat 4,687,659.

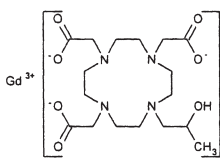
Solubility—Very soluble in water.

Comments—An ionic contrast drug for magnetic resonance imaging (MRI) that detects abnormal vascularity in the brain, head, and neck regions, and in the body, excluding the heart. Adverse reactions most frequently include headache, nausea, coldness at site of injection, and hypotension. Patients with a history of allergy or hypersensitivity-like problems should be monitored closely during the procedure and for several hours after the drug is administered. The drug may cause anaphylaxis, seizures, paresthesias, dizziness, weakness, vomiting, stomach pain, rashes, and urticaria. The drug has an osmolality that is 6.9 greater than plasma and is hypertonic.

Gadopentetate dimeglumine should be used with caution in patients at risk for developing thrombotic syndromes and hemolytic anemias. *In vitro* studies showed that deoxygenated sickle erythrocytes become aligned perpendicular to the magnetic field that may cause vaso-occlusive complications. It is pregnancy category C, and it is not known if it appears in human breast milk but it is excreted in lactating rats.

GADOTERIDOL

Gadolinium, [10-(2-hydroxypropyl)-1,4,7,10- tetraazacyclodecane-1,4,7-triacetato(3-)-N^1,N^4,N^7,N^{10},O^1,O^4,O^7,O^{10}]-, ProHance



[120066-54-8] $C_{17}H_{29}GdN_4O_7$ (558.68).

Preparation—US Pat 4,885,363 (1989).

Description—Non-ionic, low osmolality, paramagnetic chelate. Microcrystalline needles (clumped) from acetone:methanol; melting about 225°. *Inorg Chem* 1991: 30; 1265. ***Injection***: Osmolality at 37°, 630 mOsm/Kg water; d^{25} 1.137.

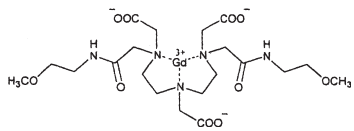
Solubility—(mg/mL) Water 737; methanol 119; 2-propanol 41; DMF 10.1; acetonitrile 6.1; methylene chloride 5.2; ethyl acetate 0.5; acetone 0.4, hexane 0.2; toluene 0.3. At pH 7, log P = −3.68 (octanol/water); −1.98 (butanol/water).

Comments—The injection is a nonionic, clear, colorless to slightly yellow paramagnetic drug used to visualize lesions in the head and neck. It should not be used if discolored, and must be used immediately after being withdrawn into a syringe. Gadoteridol does not cross the intact blood-brain barrier but will appear in lesions with abnormal vascularity, or in areas where the blood-brain barrier is disrupted. It is excreted via glomerular filtration but dosing adjustments haven't been evaluated in patients with renal or hepatic impairment.

Gadoteridol has an osmolality 2.2 times greater than plasma. Its predominate adverse effects are nausea and taste perversion. More severe adverse effects that occur less frequently include facial edema, pain at the injection site, neck rigidity, and vasovagal reactions. It is pregnancy category C, and it is not known if it is excreted in human milk.

GADOVERSETAMIDE

Gadolinium, [8,11-bis(carboxymethyl-14-[2-[(2-methoxy-ethyl)amino]-2-oxoethyl]-6-oxo-2-oxa-5,8,11,14-tetraazahexa-decan-16-oato(3-)]-, OptiMARK



[131069-91-5] $C_{20}H_{34}GdN_5O_{10}$ (661.76).

Preparation—US Pats 5,130,120; 5,137,711; 5,508,388.

Description—Non-ionic, paramagnetic chelate; contains labile water. Log P (butanol/water) −1.93. ***Injection***: Osmolality (37°) 1110 mOsmol/Kg water; d^{25} 1.160

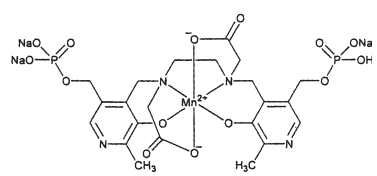
Comments—A nonionic gadolinium chelate of diethyelentriamine pentaacetic acid bismethoxyethylamide used to enhance visualization of abnormal vascularity in the brain, spine and associated tissues, and liver. It is a clear, colorless to slightly yellow solution with an osmolality that is 3.9 times that of plasma.

Gadoversetamide is administered intravenously and is contraindicated in patients known to be allergic to gadolinium or versatamide. It should be used cautiously if patients have sickle cell anemia because deoxygenated erythrocytes align in a perpendicular manner in the magnetic field, which could cause vaso-occlusive complications. It should be used with caution in patients with renal impairment because it is excreted primarily in the urine.

Adverse effects include headache, vasodilation, abnormal taste, dizziness, nausea, parathesia, body pain, and flu-like symptoms. It is pregnancy category C, and nursing women are advised to use bottle feedings for 72 hours after the drug is administered.

MANGAFODIPIR TRISODIUM

Trisodium trihydrogen (*OC*-6-13)-[[*N, N′*-1,2-ethane-diylbis[*N*-[[3-hydroxy-2-methyl-5-[(phosphonooxy)methyl]-4-pyridinyl]methyl]glycinato]](8-)manganate(6-), Teslascan



[140678-14-4] $C_{22}H_{27}MnN_4O_{14}P_2$ (757.32).

Preparation—US Pat 4,933,456 and *Inorg Chem* 1989; 28:447.

Description: Pale yellow, hygroscopic crystals, d 1.537. A 0.01 mmol/mL aqueous infusion is a clear, bright yellow solution, pH 7.5.

Solubility—(g/mL) water (0.46), methanol (0.23); practically insoluble in ethanol, acetone or chloroform.

Comments—A sterile, clear, yellow solution of a complex of paramagnetic manganese and fodipir, a chelating agent that is nearly iso-osmolar with plasma. It is injected intravenously to detect, localize, characterize, and evaluate lesions of the liver.

Mangafodipir trisodium is contraindicated in patients allergic or hypersensitive to manganese, fodipir, or any of the inert ingredients in the drug. Mangafodipir trisodium should be used with caution in patients who cannot tolerate nausea and vomiting and in patients with renal or hepatic impairment because the drug is eliminated via urine and bile.[12]

Common adverse effects include pain at the site of injection, headache, nausea, vomiting, abdominal pain, and generalized body discomfort described as warmth, flushing, pressure, pain, and/or cold. It is pregnancy category C, and the extent of its secretion in milk varies. Nursing women are advised to bottle-feed, but the package insert has no specific time recommendation.

ULTRASOUND CONTRAST AGENTS

Ultrasound agents that are administered intravenously increase the reflectivity of blood and act as echo-enhancing agents because they increase the radiofrequency signal received by the transducers in the ultrasound unit. These drugs must be smaller than the diameter of capillaries, less than 8 μm. The micro-bubbles of gases used for ultrasound studies must be coated to stabilize them or they will collapse and dissolve in blood in less than a second, too short a time for their detection.

Contraindications for intravenous use of ultrasound agents include right-to-left cardiac shunts that could lead to pulmonary emboli formation, and allergic or sensitivity reactions to the drug or its coating.

PERFLUTREN LIPID MICROSPHERES

Propane, octafluoro-, Gaseous component of Definity, Optison

Perfluoropropane, [76-19-7] C_3F_8 (188.02).

Description—The dosage form consists of a sterile suspension of perfluoropropane encapsulated in lipid or protein microspheres.

Comments—A sterile, clear, colorless, non-pyrogenic liquid that after activation in a specialized vial results in an opaque, milky white suspension of perflutren lipid microspheres. It is used in echocardiography to enhance imaging of the left ventricular endocardial borders.

The drug is stored at 2° to 8° C and warmed to room temperature before it is activated in its special mixing vial. The activation reaction requires 45 seconds and must be continuously shaken. The drug should be administered within 5 minutes of activation or the suspension must be re-suspended by hand agitation. The drug is stable for 12 hours after activation and is maintained at room temperature.[13]

The microspheres ranges in size from 1.1 to 43.3 μm. Perflutren gas diffuses out of the microspheres after it is injected and is not metabolized in the body. It could not be detected in the blood or expired air 10 minutes after injection. The lipid microspheres are metabolized to free fatty acid.

Perflutren lipid microspheres are contraindicated in patients allergic or sensitive to perflutren or in patients who have right-to-left cardiac shunts, bi-directional shunts, or transient right-to-left shunts because microspheres could enter the arterial circulation, bypassing filtration and trapping in the capillaries of the lungs.

Common adverse effects include headache, back and renal pain, flushing and feeling of warmth, and nausea. It is pregnancy category B, and studies have not been done to determine if it is excreted in human breast milk.

PERFLUTREN [PROTEIN-TYPE A MICROSPHERES]

Human serum albumin with perflutren, a stable gas, which is chemically Propane, octafluoro-, Optison

Comments—A sterile, nonpyrogenic suspension of human serum albumin microspheres with perflutren that is used in echocardiography to enhance imaging of the left ventricular endocardial borders. The drug is in two distinct layers in a vial, an upper white layer and a lower clear layer, and is stored at temperatures between 2° to 8° C but must not be frozen.

Gentle mixing produces a milky, white, homogeneous**,** opaque suspension that is injected intravenously. If any clear liquid remains after mixing, the drug should not be used. The drug must be injected within 1 minute after formation of the white, opaque suspension.[14]

The microspheres ranges in size from 3.0 to 4.5 μm. Perflutren gas diffuses out of the microspheres after it is injected, producing an acoustic impedance lower than blood. Perflutren is not metabolized in the body, and about 96% is exhaled unchanged from the lungs within 10 minutes of its injection. The human serum microspheres are eliminated after metabolism by the same biological pathways as normal albumin.[14]

Perflutren protein-type A microspheres should not be administered to patients who are allergic or sensitive to blood, blood products, or albumin. This drug must be used with caution in patients who have right-to-left cardiac shunts, bi-directional shunts, or transient right-to-left shunts because microspheres could enter the arterial circulation, bypassing filtration and trapping in the capillaries of the lungs.

Caution must also be used if the drug is to be administered to patients with severe emphysema, pulmonary vasculitis, previous pulmonary emboli, respiratory distress syndrome, or severe liver disease. It is pregnancy category C, and no studies have been done to determine its excretion in human breast milk.

Common adverse effects include headache, nausea, vomiting, flushing and feeling of warmth, pain at the site of injection, dizziness, and altered taste.

NON-IMAGING IN VIVO DIAGNOSTIC DRUGS

Drugs in this category are listed based on the physiological system to be evaluated.

CARDIOVASCULAR SYSTEM

ADENOSINE

See page 1362 for full monograph.

Comments—An endogenous nucleoside that is in all cells of the body. It is a potent peripheral vasodilator used during *myocardial perfusion stress scintigraphy* studies in patients who are unable to exercise. It produces a more reliable and more potent vasodilation than dipyramidole.

Contraindications include allergy or sensitivity to adenosine, second or third degree AV block, sinus node disease, asthma, and other bronchoconstrictive diseases.

Adverse reactions include flushing, chest discomfort, dyspnea, headache, throat, neck or jaw discomfort, gastrointestinal discomfort, dizziness, ST segment depression, first- and second-degree heart block, and hypotension. It is pregnancy category C.

Adenosine has a half-life of less than 10 seconds. Methylxanthines, like theophylline and caffeine, are competitive antagonists that can be used to reverse severe adverse effects when they are administered intravenously.

DOBUTAMINE

See Chapter 70, *Sympathomimetic Drugs* for full monograph.

Comments—Dobutamine is a sympathomimetic amine that produced inotropic and chronotropic effects in the heart. It is used during *myocardial perfusion stress scintigraphy* in patients who can't exercise. It is only used when adenosine or dipyridamole cannot be used as pharmacological stress agents because of dobutamine's severe adverse effects. These effects include chest pain, ST-T segment ECG changes, ventricular ectopy, headache, flushing, dyspnea, and parathesis.

DIPYRIDAMOLE

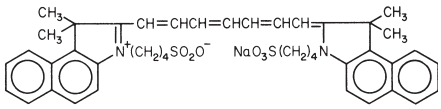
Persantine

Comments—A vasodilator used during *myocardial perfusion stress scintigraphy* as an alternative to exercise in patients who cannot exercise adequately when it is administered intravenously. Dipyridamole indirectly increases of endogenous adenosine by blocking uptake and/or

by inhibiting the enzymes adenosine deaminase and phosphodiesterase.

INDOCYANINE GREEN

1*H*-Benz[*e*]indolium, 2-[7-[1,3-dihydro-1,1-dimethyl-3-(4-sulfobutyl)-2*H*-benz[*e*]indol-2-ylidene]-1,3,5-heptatrienyl]-1,1-dimethyl-3-(4-sulfobutyl)-, hydroxide, inner salt, sodium salt; Cardio-Green



[3599-32-4] $C_{43}H_{47}N_2NaO_6S_2$ (774.98).

Preparation—By reacting 1,1,2-trimethyl-3-(4-sulfobutyl)-1*H*-benz[*e*]indolium hydroxide inner salt (I) with a bis(Schiff base) derived from glutaconic aldehyde. The starting indolium compound (I) is prepared by heating 1,1,2-trimethyl-1*H*-benz[*e*]indole with 4-hydroxy-1-butanesulfonic acid δ-sultone. Details for preparing these tricarbocyanine dyes are provided in US Pats 2,251,286 and 2,895,955.

Description—Dark green, blue-green, olive brown, dark blue, or black powder; odorless or with a slight odor; solutions are deep emerald-green; pH (1 in 200 solution) about 6; unstable in solution. When reconstituted with its diluent, indocyanine remains stable for 8 to 10 hours.

Solubility—Soluble in water or methanol; practically insoluble in most other organic solvents.

Comments—To determine *cardiac output, hepatic function,* and *liver blood flow*. It also has been used to measure *plasma volume* and *regional blood flow* in various organs including the kidneys, eyes, and lungs. Following intravenous injection, the distribution volume is relatively constant among individuals and approximates the plasma volume, because tissue binding is negligible and the fraction of unbound drug in blood is very small. It is so highly bound to plasma proteins, particularly alpha lipoproteins, that it does not distribute extravascularly, and its clearance is not limited by binding.

Indocyanine green should be used with caution in patients allergic or sensitive to it or to iodine because the product contains a small quantity of sodium iodide. Radioactive iodine uptake studies should be delayed for at least 1 week following its use. Its safety in pregnancy has not been established.

ENDOCRINE SYSTEM

Adrenal Gland Function

Both corticotropin (ACTH) and cosyntropin are used to diagnose adrenocortical insufficiency. Cosyntropin may be preferred and/or used as a screening test because it has a lower incidence of allergic or sensitivity reactions and can provide a result within 30 minutes. For a definitive diagnosis, the 24-hour infusion test using corticotropin test is required.

CORTICOTROPIN—page 1439.

Pheochromocytoma Diagnosis

The *overproduction and secretion of catecholamines* from tumors found most often in the adrenal medulla are diagnosed by collecting a 24-hour urine sample and measurement of free or metabolized catecholamines. When the results of this test are equivocal, either clonidine or glucagon may act as aids in the diagnosis.

Clonidine—Clonidine normally suppresses catecholamine level in the plasma, but has little effect in patients with pheochromocytoma.

Glucagon—Glucagon increases circulating catecolamines; phentolamine has also been used in the manner.

Pancreatic Gland Function

The pancreas has both an endocrine and exocrine function. Pancreatic exocrine function tests are described in the gastrointestinal section. An oral glucose tolerance test is used to *diagnose diabetes mellitus*. Devices for measuring blood glucose levels appear in the section on in vitro self-care devices.

TOLBUTAMIDE SODIUM

Orinase Diagnostic

Comments—A single intravenous dose of tolbutaminde sodium is useful in the diagnosis of functioning *insulinomas*. Patients consume a diet of 150 to 300 g of carbohydrates for 3 days before the test. A fasting blood glucose levels is obtained before the injection of tolbutamide sodium. Several blood samples are withdrawn over a period of 180 minutes after the injection.

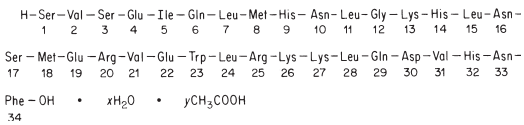
Adverse effects include venospasm, thrombophlebitis, and hypoglycemia, especially in nondiabetic patients. Tolbutamide is contraindicated in patients allergic or sensitive to it, other sulfonylurea drugs, or sulfonamides.

Salicylates and other drugs that produce hypoglycemia should not be administered in the 3 days before the test. It is not recommended for use in pregnant women, and it has a pregnancy category of C. It appears in breast milk, and infants should be temporarily bottle-fed.

Parathyroid Function

TERIPARATIDE ACETATE

L-Phenylalanine, L-valyl-L-seryl-L-α-glutamyl-L-isoleucyl-L-glutaminyl-L-leucyl-L-methionyl-L-histidyl-L-asparaginyl-L-leucylglycyl-L-lysyl-L-histidyl-L-leucyl-L-asparaginyl-L-seryl-L-methionyl-L-α-glutamyl-L-arginyl-L-valyl-L-α-glutamyl-L-tryptophyl-L-leucyl-L-arginyl-L-lysyl-L-leucyl-L-glutaminyl-L-α-aspartyl-L-valyl-L-histidyl-L-asparaginyl-, acetate (salt) hydrate



[99294-94-7] $C_{181}H_{291}N_{55}O_{51}S_2.xH_2O.yC_2H_4O_2$.

Description—A synthetic polypeptide composed of 34 amino acids of the terminal fragment of human parathyroid hormone.

Comments—It is used to distinguish between *hypocalcemia* due to *hypoparathyroidism* and *pseudohypoparathyroidism* but not between these conditions and normal. Adverse effects include headache, nausea, dizziness, leg cramps, and diarrhea. Hypertensive crisis, hypocalcemia convulsions, and tingling of the extremities also have been reported. It is pregnancy category C, and no clinical studies have been done to determine if it is secreted in breast milk.

Pituitary Function

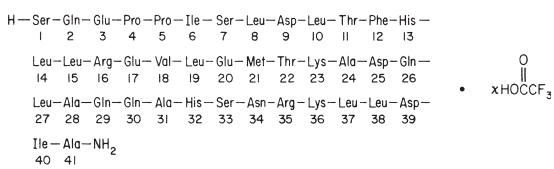
ARGININE HYDROCHLORIDE

See RPS-20, page 1818 for full monograph.

Comments—Intravenous infusion of arginine HCl stimulates the release of growth hormone in patients with competent *pituitary function*.

CORTICORELIN OVINE TRIFLUATE

Acthrel



Corticotropin-releasing factor (sheep), trifluoroacetate salt; CRF, CRH. [121249-14-7] $C_{205}H_{339}N_{59}O_{63}S$ (4670.36).

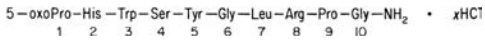
Preparation—See *Science* 1981; 213:1394.

Comments—Approved as an orphan drug for differentiating between the *pituitary gland and ectopic sources of production of ACTH* in patients who have ACTH-dependent Cushing's syndrome. Patients who have primary Cushing's syndrome experience a rise in plasma ACTH and cortisol, whereas patient who have ectopic sources of ACTH do not.

Adverse reactions include flushing of the head and neck, dyspnea, tachycardia, tightness in the chest, hypotension, and decreased blood pressure. It is pregnancy category C and not known if it appears in breast milk.

GONADORELIN HYDROCHLORIDE

Factrel



Luteinizing hormone–releasing factor hydrochloride (LH-RH); [51952-41-1] $C_{55}H_{75}N_{17}O.x$HCl (1182.33 for the free base—the *hydrochloride* may be either the mono- or dihydrochloride or a mixture of the two.)

Preparation—Isolated from the hypothalamus of pigs or sheep. The industrial preparation is described in German Pat 2,213,737. Now available as synthetic luteinizing hormone-releasing factor that is identical to the natural compound.

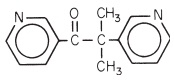
Description—The base is a white to very pale yellowish powder containing not less than 85% active peptide and not more than 6% acetic acid.

Comments—A diagnostic agent used for evaluating *hypothalamic-pituitary gonadotropic* function. The test should be conducted in the absence of other drugs that directly affect pituitary secretion of the gonadotropins, including preparations that contain androgens, estrogens, progestins, or glucocorticoids.

Adverse reactions include headache, nausea, lightheadedness, and abdominal discomfort. Localized swelling and pruritus may occur at the site of injection. Safety for use during pregnancy has not been established.

METYRAPONE

2-methyl-1,2-di-3-pyridinyl-1-propanone; Metopirone



[54-36-4] $C_{14}H_{14}N_2O$ (226.28).

Preparation—Methyl 3-pyridyl ketone is reduced electrolytically to the corresponding pinacol, 2,3-bis(3-pyridyl)-2,3-butanediol; heating with a strong inorganic acid results in dehydration of the pinacol with subsequent rearrangement to form metyrapone. US Pat 2,966,493.

Description—White to light-amber, fine, crystalline powder; characteristic odor; darkens on exposure to light.

Solubility—Sparingly soluble in water; soluble in methanol or chloroform; forms water-soluble salts with acids.

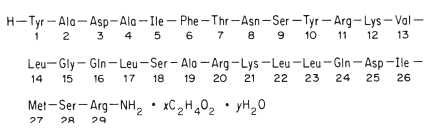
Comments—A synthetic compound that inhibits 11-β -hydroxylation in the biosynthesis of cortisol, corticosterone, and aldosterone. It is used to test for *hypothalamic- pituitary* function in patients suspected of hypopituitarism and Cushing's syndrome. Primary adrenal insufficiency must be excluded before the test is performed. Metyrapone blocks the enzymatic step that leads to cortisol and corticosterone synthesis in normal individuals, and produces an intense stimulation of ACTH secretion, followed by a marked increase in urinary excretion of 17-hydroxycorticosteroids. In patients with abnormal pituitary function, the ability to increase ACTH production is lacking, and no significant increase in 17-hydroxy-corticosteroids is seen.

There are two methods for performing the test. A single dose of metyrapone may be administered at midnight, and a blood sample is taken at 8 o'clock the next morning. A multi-dose test is performed over a 6-day period.

Adverse effects include anorexia, nausea, abdominal discomfort, diarrhea, dizziness, vertigo, headache, sedation, and allergic rash. The drug is contraindicated in patients with adrenal cortical insufficiency. Both hypo- and hyperthyroidism may interfere with the test, causing reduced response to metyrapone. Corticosteroids, estrogen, acetaminophen, and phenytoin alter the results obtained in the test and should not be used during the testing period.

SERMORELIN ACETATE

Somatoliberin (human pancreatic islet), acetate (salt), hydrate; Geref



[114466-38-5] $C_{149}H_{246}N_{44}O_{42}S.xC_2H_4O_2.yH_2O$.

Preparation—See US Pat 4,703,035.

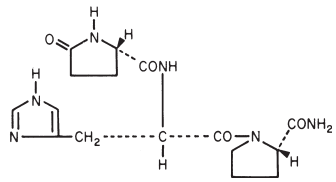
Comments—A diagnostic agent that directly *stimulates the pituitary gland to secrete growth hormone*. It is used in the differential diagnosis of growth hormone deficiency. It may also be used in treatment of *growth hormone deficiency*.

Adverse reactions include irritation at site of injection, warmth, flushing, nausea, vomiting, taste alterations, and chest tightness. No studies are available that evaluate its safety in pregnancy.

Thyroid Function

PROTIRELIN

L-prolinamide, 5-oxo-L-propyl-L-histidyl-;



Thyrotropin-releasing factor [24305-27-9] $C_{16}H_{22}N_6O_4$ (362.39).

Preparation—Protirelin obtained from most mammals appears to be identical and is apparently not species specific. A review of synthetic methods is found in *Methods Enzymol* 1975; 37: 408.

Solubility—Highly purified material is partially soluble in chloroform and very soluble in methanol.

Comments—An adjunct in the diagnostic assessment of *thyroid function* and *pituitary or hypothalamic dysfunction*. It is a synthetic tripeptide believed to be structurally identical to the naturally occurring thyrotropin-releasing hormone produced by the hypothalamus. Following intravenous administration, the $T_{1/2}$ is approximately 5 minutes; TSH levels reach a peak in 20 to 30 minutes and decline slowly over a period of 3 hours to baseline levels.

Adverse effects occur in about 50% of patients and include hypertension or hypotension with or without syncope and breast enlargement. Other reactions include nausea, urge to urinate, flushing, lightheadedness, bad taste, abdominal discomfort, headache, and dry mouth. Safety has not been determined during pregnancy.

THYROTROPIN ALFA

Thyrogen

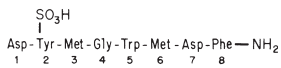
Comments—An adjunct used in determining serum thyroglobulin in patients with well-differentiated thyroid cancer.

GASTROINTESTINAL TRACT

Gallbladder

SINCALIDE

Caerulein, 1-de(5-oxo-L-proline)-2-de-L-glutamide-5-L-methionine; Kinevac



[25126-32-3] $C_{49}H_{62}N_{10}O_{16}S_3$ (1143.27).

Sincalide is the synthetic C-terminal octapeptide of cholecystokinin.

Description—White, lyophilized powder.

Solubility—Very slightly soluble in water; practically insoluble in alcohol.

Comments—A synthetic fragment of cholecystokinin that stimulates contraction of the gallbladder and increases intestinal motility. It is used most frequently during imaging studies such as *cholecystography or ultrasonography* to stimulate the gallbladder to contract and release bile instead of a fatty meals because of its fast action, usually 5 to 15 minutes. It may be used to obtain a *specimen of gallbladder bile for analysis* in conjunction with secretin to *stimulate pancreatic secretion* for analysis. It may also be used to increase movement of barium sulfate through the intestine during *roentgenograpghy or fluoroscopy*.

Adverse reactions include mild, transient, abdominal discomfort and an urge to defecate, and occasional dizziness, flushing, and nausea. It is pregnancy category B and not known if it appears in breast milk.

Liver Function

INDOCYANINE GREEN

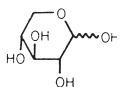
Most evaluations of liver function tests utilize liver enzyme activity. However, liver function and blood flow can be evaluated by the intravenous injection of indocyanine green, an agent *not* taken up by any organ other than the liver. The intrinsic clearance of bound and unbound drug is high, hepatic extraction ratios in man vary from 50% to 80%. It is not metabolized but is eliminated entirely by active uptake into hepatic parenchymal cells. It is transported to bile, excreted in the small intestine, and not reabsorbed; consequently, it imparts a green color to the stool.

Indocyanine green has very low toxicity, is easily analyzed in low concentrations, is not metabolized, and has a plasma-disappearance rate-curve that is nearly exponential. It is injected intravenously in one arm, and 20 minutes later, 6 mL of venous blood is withdrawn from the opposite arm. A sample of serum is read in a photometer at 800 to 810 nm. Retention of 4% of the dye indicates normal liver function, while retention of greater quantities indicates hepatic dysfunction.

Intestinal Absorption

XYLOSE

D-Xylose; Wood Sugar



β-D-Xylopyranose [2460-44-8] $C_5H_{10}O_5$ (150.13).

Preparation—Prepared from corn cobs by distilling with 8% sulfuric acid; *J Am Chem Soc* 1919; 41: 1002.

Description—White, monoclinic prisms or needles melting at about 144°; very sweet taste; pK_a 12.14.

Solubility—1 g in 0.8 mL water; soluble in hot alcohol or pyridine.

Comments—The dextrorotatory form of this 5-carbon monosaccharide (Wood Sugar) is used for evaluating *intestinal absorption* in both adults and children. Malabsorption may occur in any disease that affects the small bowel directly or indirectly, including conditions such as celiac sprue, tropical sprue, lymphoma, small bowel ischemia, blind loop syndrome, short bowel syndrome, Whipple's gastroenteritis, amyloid disease of the gut, Crohn's disease, radiation enteritis, cow's milk protein intolerance (postchallenge), and certain parasitic diseases such as giardiasis, coccidiosis, and ascariasis.

The xylose test indicates the degree impairment in patients with signs and symptoms of malabsorption, and can also be used to monitor or evaluate therapy. Blood and urine samples may be collected, and analyses of these samples provide a better indication of any abnormalities. There are no known contraindications to the use of xylose for the evaluation of intestinal absorption.

Stomach

GASTRIC ACID TEST

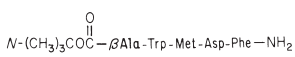
Normal functioning of the gastrointestinal tract depends, in part, on the *ability of the stomach to secrete gastric acid*. The absence of hydrochloric acid in the stomach is essential in diagnosing of pernicious anemia and is frequently associated with gastric cancer. The presence of hydrochloric acid is useful in the diagnosis of certain peptic ulcer conditions. The absence of gastric acid excludes peptic esophagitis as a possible diagnosis in many cases.

The volume of acid secreted by the stomach varies greatly in normal individuals as well as in individuals with pathological states. It is usually important only to establish the presence or absence of free hydrochloric acid in the stomach. The gastric stimulants used for this purpose follow.

HISTAMINE PHOSPHATE—page 1543.

PENTAGASTRIN

L-Phenylalaninamide, *N*-[(1,1-dimethylethoxy)carbonyl]-β-alanyl-L-tryptophyl-L-methionyl-L-α-aspartyl-; Peptavlon



N-Carboxy-β-alanyl-L-tryptophyl-L-methionyl-L-aspartylphenyl-L-alaninamide, *N-tert*-butyl ester [5534-95-2] $C_{37}H_{49}N_7O_9S$ (767.90).

Description—Fine colorless needles; melts at about 230° with decomposition.

Solubility—Soluble in dimethylsulfoxide or dimethylformamide; slightly soluble in alcohol or dilute solutions of ammonia; practically insoluble in water, ether, or benzene.

Comments—A diagnostic agent used to evaluate *gastric acid secretory function*. It is useful in testing for *anacidity* in patients with suspected pernicious anemia, atrophic gastritis, or gastric carcinoma; for *hypersecretion* in patients with possible duodenal ulcer or postoperative stomach ulcer; for the diagnosis of Zollinger-Ellison tumor; and for determining the adequacy of acid-reducing operations for peptic ulcer. Acid secretion is increased within 10 minutes after intradermal injection and reaches a peak in most patients within 20 to 30 minutes, persisting for 60 to 80 minutes. Plasma half-life is reported to be less than 1 minute. Excessive doses may inhibit gastric acid secretion.

It is contraindicated in patients hypersensitive to the drug and should be used with caution in patients with pancreatic, hepatic, or biliary disease. Adverse reactions include abdominal pain, nausea, vomiting, flushing, tachycardia, dizziness, faintness, lightheadedness, drowsiness, blurred vision, and headache. Its use in pregnant women and children has not been studied.

GASTRIC UREASE TEST *(HELIOBACTER PYLORI TEST)*

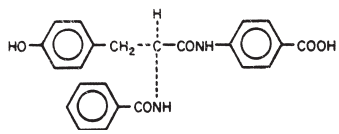
Pytest

Comment—Patients infected with *H pylori* produce gastric urease, an enzyme that releases carbon dioxide from urea. Patients ingest urea that is labeled with radioactive carbon-14 orally. The patient breathes into a device that collects the expired breath and the ^{14}carbon dioxide present in the sample is measured in a liquid scintillation counter.

Pancreas (Exocrine Function)

BENTIROMIDE

Benzoic acid, (*S*)4-[[2-(benzoylamino)-3-(4-hydroxyphenyl)-1-oxopropyl]- amino]-; Chymex



[37106-97-1] $C_{23}H_{20}N_2O_5$ (404.42).

Preparation—See *J Med Chem* 1972; 15: 1098.

Description—White crystals; melts at about 240°.

Comments—Used to diagnose exocrine pancreatic insufficiency and to monitor the adequacy of enzyme replacement therapy in patients with exocrine pancreatic insufficiency. Pancreatic chymotrypsin selectively cleaves para-aminobenzoic acid (ABA) from bentiromide following oral administration. ABA is absorbed rapidly under normal GI function, conjugated by the liver, and excreted in the urine in about 6 hours. If approximately 50% of the ABA content of bentiromide (170 mg in 500 mg) is collected in the 6-hour urine sample, it indicates normal exocrine pancreatic function, gastric emptying, and intestinal and kidney function. This test is a simple, noninvasive test shown to produce reliable, reproducible results in the diagnosis of pancreatic insufficiency.

Adverse effects are transient and relatively infrequent; diarrhea, headache, flatulence, nausea, vomiting, and weakness are the most frequent. Safety and efficacy in children over 6 years have not been established. The drug should not be used during pregnancy or in nursing mothers unless clearly needed. Drugs and foods that are metabolized to primary arylamines, and multiple vitamins should be discontinued at least 3 days prior to the drug's administration.

SECRETIN

SecreFlo

[1393-25-5] $C_{130}H_{220}N_{44}O_{41}$ (no molecular weight was given).

Description—A polypeptide hormone, secreted by the duodenal mucosa and to a lesser extent by the upper jejunal mucosa, which stimulates secretion of water and bicarbonate from the pancreas. As isolated from porcine mucosa and purified, it consists of 27 amino acid units from 12 different amino acids. It has been synthesized (Bodanszky et al, *J Am Chem Soc* 1967; 89:685, 6753). It is the synthetic, C-terminal, octapeptide fragment of cholecystokinin. The hormone supplied for diag-

nostic use is of porcine origin as a sterile, refined, freeze-dried powder, stable for 2 years when stored in its original, unopened vial at 2° to 7° C; it is unstable in solution.

Comments—Used *to diagnosis pancreatic exocrine disease and gastrinoma (Zollinger-Ellison syndrome)*. It may be combined with sincalide as a diagnostic aid for chronic pancreatic function or carcinoma. Intravenous injection of the hormone in persons with normal pancreatic secretion increases the bicarbonate content and volume of secretion from the pancreas. Reduced secretory volume and diminished bicarbonate concentration are signs of pancreatic insufficiency. Reduction is volume only indicates pancreatic duct obstruction while bicarbonate only reductions indicate pancreatic inflammatory disease.

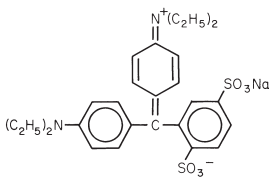
A double-lumen tube is passed through the mouth after a 12- to 15-hour fast, under fluoroscopic guidance so that a proper placement of the proximal tube in the gastric antrum and of the distal tube beyond the papilla of Vater is accomplished. Constant suction is applied to both outlets of the tube throughout the test. After a control period of collection of fluid for 10 to 20 minutes, 0.2 μg of drug is injected intravenously over a period of 1 minute to test for allergic reactions. If none occurs, the full dose of drug is injected. Secretions from the duodenum are collected every 15 minutes for 1 hour and analyzed for volume variations and bicarbonate concentrations.

Secretin is contraindicated in patients with an allergic or sensitivity to the drug and is administered with caution in patients with a history of atopic asthma. It should not be used in patients with acute pancreatitis until the episode has resolved itself.

LYMPHATIC SYSTEM

ISOSULFAN BLUE

Ethanaminium, *N*-[4-[[4-(diethylamino)-phenyl(2,5-disulfophenyl)methylene]-2,5-cyclohexadien-1-ylidene]-*N*-ethyl-, hydroxide, inner salt, sodium salt; Lymphazurin



Colour Index: Sulphan Blue; CI no 42045 (often confused with Patent Blue V, CI no 42051) [68238-36-8] $C_{27}H_{31}N_2NaO_6S_2$ (566.68).

Preparation—By condensation of 4-formylbenzene-1,3-disulfonic acid and *N,N*-diethylaniline. See *Colour Index v4,* 1971.

Description—Violet powder; aqueous solutions are blue, and the color is stable over a wide range of pH if protected from light.

Solubility—Soluble in water (1 in 20); partially soluble in alcohol.

Comments—An adjunct to *lymphography* for visualization of the lymphatic system draining the area in which it is injected. It has no known pharmacological action. Allergic-type adverse effects occur in about 1.5% of patients and include localized swelling and pruritus of the hands, abdomen, and neck. Edema of the face and glottis, respiratory distress, and shock have been reported. These reactions are more likely to occur in patients with a history of hypersensitivity. Its safe use during pregnancy and lactation, as well as in children, has not been established.

NEUROMUSCULAR SYSTEM

The following drugs are used in the *diagnosis of myasthenia gravis*.

EDROPHONIUM CHLORIDE— page 1395.
NEOSTIGMINE METHYLSULFATE—page 1395.

PULMONARY SYSTEM

Bronchial Airway Hyperactivity

METHACHOLINE CHLORIDE— page 1391.

Comments—A parasympathomimetic (cholinergic) agent that is only administered by inhalation for the *diagnosis of bronchial airway hyperactivity* in subjects who do not display symptoms of asthma. Asthmatics are significantly more sensitive to inhaled methacholine chloride than are healthy subjects. The difference in response provides the pharmacological basis for this diagnostic test. It should not be used in patients with epilepsy or cardiovascular, peptic ulcer, or thyroid disease; likewise, it is contraindicated in patients with urinary tract obstruction.

Adverse effects after *inhalation* include headache, throat irritation, lightheadedness, and itching. The safety of the test during pregnancy and lactation and in children under 5 years has not been established.

REPRODUCTIVE SYSTEM

UTERINE CAVITY (SEE DEXTRAN MONOGRAPH page 1322.)

Dextran 70 (32% *W/V*) in Dextrose (10% *W/V*), Hyskon

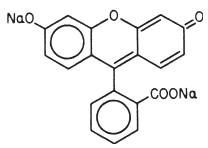
Comments—intended for use as an aid with the hysteroscope in the distension of the *uterine cavity* and in irrigating and visualizing its surfaces.

SPECIAL SENSES

Ophthalmic Diagnostic Aids

FLUORESCEIN SODIUM

Spiro[isobenzofuran-1(3*H*),9′-[9*H*]xanthene]-3-one, 3′,6′-dihydroxy-, disodium salt; Resorcinolphthalein Sodium, Soluble Fluorescein, Uranin, Uranine Yellow



Colour Index: Acid Yellow 73; CI no 45350 [518-47-8] $C_{20}H_{10}Na_2O_5$ (376.28).

Preparation—By heating resorcinol with phthalic anhydride at about 200°. After purifying, the phthalein is dissolved in the required amount of sodium hydroxide solution and evaporated to dryness.

Description—Orange-red, odorless powder; hygroscopic; aqueous solution is strongly fluorescent even in extreme dilution; the fluorescence disappears when the solution is made acid and reappears when the solution is again made alkaline.

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

Comments—Used as a sterile ophthalmic strip impregnated with drug, or as a 2% aqueous solution for the diagnosis of *corneal lesions,* pressure points on the surface of the cornea under contact lenses, and the detection of minute *foreign bodies* embedded in the cornea. A weak solution will not stain the normal cornea, but ulcers or injured epithelium and pressure points will become green and remain so for a time; foreign bodies will appear surrounded by a green ring; loss of substance in the conjunctiva is indicated by a yellow hue. It also reveals defects of the endothelium of the cornea, producing a deep coloration of the abnormal area.

It is particularly important that the preparation be sterile and that no accidental contamination of the solution occurs with *Pseudomonas aeruginosa* because this could cause blindness. Fluorescein is anionic and not compatible with preservatives such as benzalkonium chloride or substances known to be effective against *P aeruginosa,* such as polymyxin B sulfate. It is best used as a unit-dose package. When a sterile ophthalmic strip with fluorescein touches lacrimal fluid in the eye, it releases enough of the highly soluble drug to permit examination of the eye for lesions or injury.

Fluorescein Sodium Injection—[Fluorescite, Ful-Glo, Funduscein] *Comments:* A diagnostic aid in *ophthalmic angiography,* which includes examination of the fundus, evaluation of the iris' vasculature, distinction between viable and nonviable tissue, and observation of the aqueous flow. It is useful in the differential diagnosis of malignant and nonmalignant ocular tumors.

Adverse reactions include cardiac arrest, basilar artery ischemia, severe shock, and thrombophlebitis at the site of the injection. Transient nausea, vomiting, and allergic reactions have been reported in sensitive patients. A strong taste may develop following high dosage.

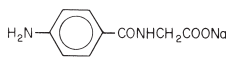
URINARY TRACT

Kidney Function

Measurement of creatinine clearance is used to evaluate the status of kidney function. However, certain aspects of renal function can be accurately determined by the use of other drugs. Glomerular filtration rate can be measured by the renal plasma clearance of inulin, thiosulfate, mannitol, or endogenous creatinine. Inulin clearance is thought to be most reliable, since mannitol is subject to some tubular reabsorption, thiosulfate to some tubular excretion and reabsorption, and endogenous creatinine to some tubular excretion. Effective renal plasma flow and tubular functional capacity can be measured by the use of sodium aminohippurate and iodohippurate. Because of the greater accuracy and facility of chemical methods for the determination of the compound, sodium amminohippurate is considered the drug of choice.

AMINOHIPPURATE SODIUM

Glycine, *N*-(4-aminobenzoyl)-, monosodium salt



Monosodium *p*-aminohippurate [94-16-6] $C_9H_9N_2NaO_3$ (216.17).

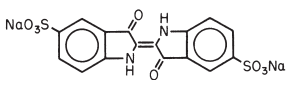
Preparation—p-Aminohippuric acid (PAH) is prepared from *p*-nitrobenzoyl chloride and glycine, and the nitro group is reduced with stannous ion and HCl. The sodium salt of the acid is formed with NaOH and adjusting the pH of the resulting solution to 7 to 7.2 with citric acid. In preparing the injection, the salt is not isolated from the solution.

Comments—To estimate the *effective renal plasma flow* (ERPF) and to measure the functional capacity of the *renal tubular secretory mechanism*. Aminohippurate is distributed throughout the extracellular space after intravenous administration. It is excreted mainly by proximal tubular secretion, although some glomerular secretion occurs. The half-life in patients with normal renal function is 24 minutes. Approximately 90% of the drug represented in plasma concentrations of 10 to 20 μg/mL is extracted from the renal circulation during a single passage through the kidneys; this results in urinary concentrations of 4 to 8 mg/mL. Normal values for ERPF are 675 ± 150 mL/min in men and 595 ± 125 mL/min in women. The maximum capacity of the proximal tubule cells to secrete PAH is reached at plasma levels of 400 to 600 μg/mL. Normal values for *maximum tubular secretory capacity* are 80 to 90 mg/min in both men and women. Conditions that impair renal excretion include cardiac failure, primary vascular disease, and most primary renal diseases.

Adverse effects include nausea, vomiting, cramps, and vasomotor disturbances. These tests are contraindicated in patients on drugs such as diuretics, penicillin, probenecid, or salicylates, which share the same tubular excretory mechanisms, and agents such as procaine, sulfonamides, and thiosulfones, which interfere with the colorimetric analytical procedures. Safety and effectiveness during pregnancy, in nursing mothers, and in children have not been established.

INDIGOTINDISULFONATE SODIUM

1*H*-indole-5-sulfonic acid, 2-(1,3-dihydro-3-oxo-5-sulfo-2*H*-indol-2-ylidene)-2,3-dihydro-3-oxo-, disodium salt; Indigo Carmine, Soluble Indigo Blue



Disodium 3,3′-dioxo[$\Delta^{2,2'}$-biindoline]-5,5-disulfonate; *Colour Index:* Food Blue 1; CI no 73015 [860-22-0] $C_{16}H_8N_2Na_2O_8S_2$ (466.35).

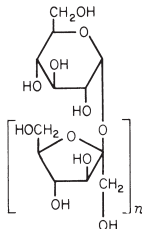
Preparation—Anthranilic acid is treated with chloroacetic acid to form phenylglycine-*o*-carboxylic acid. The latter is fused with KOH or NaOH, and the resulting indoxylacetic acid loses carbon dioxide to form *indoxyl,* which is oxidized by air to *indigo blue*. Indigo carmine is prepared from indigo blue by sulfonating with H_2SO_4 and neutralizing the SO_3H groups with sodium carbonate.

Description—Dusky, purplish blue powder or blue granules with a coppery luster; affected by light; solutions have a blue or bluish purple color.

Solubility—1 g in about 100 mL water; slightly soluble in alcohol; practically insoluble in most other organic solvents.

Comments—Originally used to measure kidney function, but excretion of the dye does not correlate well with renal failure. Currently used to *localize ureteral orifices during cystoscopy and ureteral catheterization* and as a marker dye to identify severed ureters and fistulous communications. It is cleared rapidly from the circulation after intravenous injections; half-life is 4.5 minutes; approximately 10% is excreted by the kidney within 1 hour. Patients with a history of allergy should be tested for sensitivity before the drug is given.

INULIN



[9005-80-5] $C_6H_{11}O_5(C_6H_{10}O_5)_nOH$.

Description—A substance, occurring in some plants of the *Compositae* family, closely allied to starch except that it is a levulan rather than a dextran. It differs from starch in the following particulars: it is colored yellow by iodine, does not gelatinize with water, and is not found in plants in the form of granules having concentric layers. Hydrolysis with acid produces fructose.

Preparation—Isolated from various *Compositae* members, eg, Inula, Taraxacum, Pyrethrum, Lappa.

Comments—It is filtered only by the glomeruli and is neither secreted nor reabsorbed by the tubules. Therefore, it is used as a *diagnostic agent for evaluation of glomerular filtration*. It is considered the most sensitive and accurate method for the measurement of the glomerular filtration rate. Usually, the patient is hydrated with 1000 mL of water followed by 200 mL every 30 minutes until the test is completed; 2 hours following the first intake of water, a control blood sample is taken. Inulin is administered intravenously, and the exact time noted; 1 hour later the bladder is emptied, the urine discarded, the time noted, a blood sample taken, and the time once more noted. Urine and blood samples are collected hourly for 2 hours and analyzed. Normal clearance values are 130 ± 20 mL/min in men and 120 ± 15 mL/min in women. Adverse reactions are infrequent and usually mild.

MANNITOL

See RPS-20, page 1346 for complete monograph.

Comments—Mannitol remains in the extrcellular compartment and undergoes almost no metabolism. It is excreted by the kidney unchanged and may be used to measure the glomerular filtration rate. However, it undergoes some tubular reabsorption and has been replaced by other drugs for this purpose.

MISCELLANEOUS SKIN ANTIGEN TESTS

BENZYLPENICILLOYL POLYLYSINE

Pre-Pen

Penicilloyl polylysine [53608-77-8].

Preparation—From penicillenic acid and polylysine. See *J Exp Med* 1962; 115:803.

Comments—An intradermal *skin test antigen* used to assess the risk of hypersensitivity reactions prior to the administration of penicillin G to adults who have a history of sensitivity to penicillin. It appears to be more sensitive than penicillin G skin tests in detecting penicillin hypersensitivity. This test is of particular value in patients with life-threatening infections for which penicillins are the drugs of choice; those testing positive can be desensitized prior to starting therapy.

Adverse effects include an occasional local inflammatory response, pruritus, erythema, wheal, urticaria, and/or edema. Rarely, these reactions may become generalized with or without some angioneurotic edema, urticaria, dyspnea, hypotension, and/or bronchospasm. Its safety for use in pregnancy has not been established.

CELL-MEDIATED IMMUNITY TESTS

The assessment for *cell-mediated immunity* may involve as many as four different antigen tests to which the patient was

probably exposed to in the past. The following skin antigen tests are used for this purpose and, in some situations, as screening agents for each of the diseases. All tests are performed on the forearm and must be evaluated at a specific time for a positive test reaction. If a positive test is obtained when the drug is used for screening purposes, further testing must be performed for diagnosis or confirmation of the disease.

CANDIDA ALBICANS SKIN TEST ANTIGEN

Candin

Description—A culture filtrate from two strains of *Candida albicans.*

Comments—An intradermal skin test to *evaluate cellular immunity* in patients who may have impaired cellular immunity. Test should be read 24 to 48 hours after injection. Contraindication is a previous allergic response.

COCCIDIOMYCOSIS SKIN TEST ANTIGEN

BioCox, Spherulin

Description—Either a mycelial derivative (BioCox) or a spherule derivative (Spherulin) derived antigen to aid in diagnosing coccidioidomcosis.

Comments—Contraindicated in patients allergic to thimerosal or other mercurial compounds because both products contain thimerosal, and in patients with erythema nodosum. Test should be read at 24 hours and again at 48 hours after injection. Used to *evaluate cellular immunity*.

HISTOPLASMOSIS SKIN TEST ANTIGEN

Histolyn-CYL

Comments—Soluble product from growth of *Histoplasma capsulatum* in the mycelial phase that is administered intradermally. Contraindications include known sensitivity to the drug. Test should be read 48 to 72 hours after injection. Used to *evaluate cellular immunity.*

MUMPS SKIN TEST ANTIGEN; MSTA

Comments—An aqueous suspension of formaldehyde-inactivated mumps virus. Contraindications include known allergic or sensitivity to thimerosal or other mercurial compounds and avian protein because both are used in the product. The test should be read in 48 to 72 hours. Used to *evaluate cellular immunity.*

TUBERCULIN PURIFIED PROTEIN DERIVATIVE

PPD, Tuberculin Skin Test, Aplisol, Tubersol

Comments—Antigen derived from concentrated, soluble growth products of *Mycobacterium tuberculosos or M bovis.* Test area should be read 48 to 72 hours after intradermal injection. Used to *evaluate cellular immunity.*

IN VITRO SELF-CARE DIAGNOSTIC DEVICES

The consumer movement that began in the 1960s added impetus to individuals' desires to be more responsible for their health care. Advances that occurred in computer technology and biotechnology during the 1970s and 1980s led to the marketing of easy to use, accurate, sensitive devices approved by the FDA for self-care monitoring. The most frequently used devices are listed based on the physiological system that they are used to monitor.

BLOOD

ColoCare; EZ Detect

Comments—These test are toilet bowl tests; a paper impregnated with tetramethyl benzidine produces a blue green color if blood is present in the feces. Three consecutive bowel movements are tested. Patients should see their physician if any of the tests are positive. There are no food restrictions except the avoidance of raw or rare cooked meats. The various Hemocult tests (which are not OTC devices) provided by doctors or clinics require that a sample of three consecutive bowel movements be placed on a individual reagent pads and returned for analysis. These tests use guaiac as the reagent and have numerous food restrictions.

Ingestion of drugs, foods, and beverages that are gastric irritants must be avoided during testing because they can produce a false-positive test. Doses of ascorbic acid, vitamin C, over 250 mg can produce a false-negative result and should be avoided.

CHOLESTEROL TESTING

CholesTrak

A capillary finger-stick sample of blood is placed on a reagent pad on a plastic tab. After 2 minutes, the plastic tab is pulled-out and that allows reagent to combine with the sample. The sample move-up a calibrated support by capillary attraction, producing a color. The number on the calibrated scale is compared to a chart included with the test kit to obtain the total serum cholesterol value.

LifeStream

A capillary finger-stick sample of blood is placed on a reagent stick in an automated meter than displays the total serum cholesterol after the test is complete. This test is easier, less prone to error, but the device is more costly, about $120 compared to $12 for the CholesTrak device.

ENDOCRINE

Diabetes mellitus

Monitoring blood glucose levels is the most accurate method for patients who have diabetes mellitus to manage their disease. There are a wide variety of glucose monitors available today, and each has its own test strip. Most devices use a finger-stick capillary blood sample for analysis. The FDA approved several monitors as alternate site testing devices, meaning that a capillary blood sample may be drawn from areas of the body other than fingers. Alternate sites include forearms, upper arms, and thighs, and taking a blood sample is less painful because there are fewer sensory nerves at these sites than in the fingertip. Capillary blood in the fingertip provides a quicker response to rapidly change glucose levels and is preferred for patients who are prone to hypoglycemia. Alternate site meters are also used for fingertip testing.

Cygnus makes the GlucoWatch Biographer that determines blood glucose levels through a transdermal pad that draws a fluid sample through the skin to produce an electro-chemical reaction. Device is very costly, about $200, as are the pads ($2.75 each), which must be replaced every 12 hours. Finger stick measurements are still required to calibrate the device.

Diabetic patients prone to hyperglycemia and ketoacidosis must also measure ketone bodies. Before the introduction of the Precision Extra monitor in 2001, ketones could only be measured in urine sample at home. The Precision Extra monitor has the ability to measure both blood glucose and blood ketones by using two different strips.

The meters are listed by the manufacturer, and some unique features are indicated. Many meters have memories for save readings for comparison at a later date by connecting a data port to a computer.

BLOOD GLUCOSE MONITORS

Ascenia Breeze (*Bayer*): an alternate site meter; holds a disc with 10 strips; Glucometer Dex (*Bayer*): holds a disc with ten test strips; Glucometer Elite (*Bayer*); Glucometer Elite XL (*Bayer*): enhanced memory; Prestige IQ (*Home Diagnostics*); Prestige XL (*Home Diagnostics*); Assure (*Hypoguard*); QuickTek (*Hypoguard*): enhanced memory, downloadable. One Touch Basic (*Lifescan*); One Touch Profile (*Lifescan*): enhanced memory; Sure Step (*Lifescan*); One Touch Ultra (*Lifescan*): alternate site testing. InDuo (*Lifescan/Novo-Nordisk*): combines an insulin pen with a One Touch Ultra meter; LXN; Duet System (*Lifescan/Novo-Nordisk*): also detects glycated fructosamine using a separate strip. Exac Tech RSG (*Medisense*); Precision Extra (*Medisense*): also detects blood ketones using a separate strip; Precision QID (*Medisense*); Sof-Tact (*Medisense*): alternate site testing; large memory, contains strips and lances with meter.

Accu-Chek Active (*Roche Diagnostics*): alternate site testing; Accu-Chek Advantage (*Roche Diagnostics*): voice attachment available; Accu-Chek Compact (*Roche Diagnostics*): has a drum that holds 17 strips; Accu-Chek Complete (*Roche Diagnostics*); Free Style (*Therasense*): alternate site testing.

HEMOGLOBIN A1C TESTING

A1c Now: meter with test strip for measurement.

KETONE TESTING

Acetest : colometric urine test.
KetoStix: colometric urine test.
Precision Extra: meter reads blood ketone levels.

INFECTIOUS DISEASE TESTING

These tests require that a sample of capillary blood from a finger-stick be placed on a pad with reagents, and returned to a laboratory for analysis. Each test has a computer generated random number. The patient calls a toll-free phone number to speak with a trained professional to get the results, and counseling is available.

HIV

Home Access

HEPATITIS C

Hepatitis C Check

OVULATION TESTS

A test stick with monoclonal antibodies is either placed directly in the urine stream or dipped into a sample of urine in a container that *detect leutinizing hormone*. Capillary attraction moves the sample over the test area and a color is produced when the levels of leutinizing hormone reach levels that indicate that ovulation will occur. LH is released about 24 hours before ovulation. The tests come with multiple devices, usually 5 to 9 test sticks, because of the variation that occurs normally in the length of a woman's the menstrual cycle.

Clear Plan Easy Fertility Monitor is a new device that *detects both LH and estrone-3 glucuronide*, a metabolite of estrogen in the urine. It is an automated device programmed to predict fertility in stages ranging from low to high probability.

OVULATION TESTS

Answer 1 Step; Clearplan Easy; CVS brand; Eckerd brand; First Response; Target brand; Walgreen brand

PREGNANCY TESTING

A reagent stick with monoclonal antibodies *for detecting human chorionic gonadotropin (HCG)*, which is only secreted by the corpus luteum can be detected as early as 1 day after a missed menstrual period. The stick is placed in the urine stream or dipped in a same of urine and a positive test result produces a color.

PREGNANCY TESTS

Answer Quick & Easy; Clearblue Easy; Clear Choice; Confirm 1-step; e.p.t.; Quick Stick; First Response 1-Step

Comments—Some chain pharmacies also market their own brand name product as they do for ovulation tests above.

URINARY TESTING

BLOOD

EZ Detect for Hidden Blood in Urine

Comments—A colormetric, urine dipstick test. Users are advised to call their physician if the test is positive or if their symptoms persist after a negative test.

DRUGS OF ABUSE

Dr. Brown's Home Drug Testing System: mail sample; Parents' Alert: mail sample; Parents Home Drug Testing: in home result; QuickScreen A: in home result; American Medical Screening: a 10-drug test card for in home results.

Comments—Some OTC tests provide a result at the time of testing using a dipstick impregnated with reagent to produce a result. Other OTC products containing a random number require a urine sample be sent to a laboratory for analysis. A toll free phone number is provided for obtaining the results.

One OTC test, PDT-90, requires a sample of hair to be returned for analysis.

URINE TESTING FOR INFECTIONS

UTI: a nitrate to nitrite test; AZO Test Strips: a urinary nitrate to nitrite test combined with a dipstick that *detects leuckocyte esterase*, an enzyme produced when leukocytes are release.

Comments—Patients using urinary test kits are advised to see their doctor if the test produces a positive result or if the result is negative but their symptoms persist.

Most bacteria responsible for urinary tract infections convert *urinary nitrates to nitrites*. A dipstick, colorometric test is used.

URINE TESTING FOR PROTEIN

Kidney Screen At Home

Comments—A colormetric, urine dipstick test that *detects albumin*. Users are advised to call their physician if the test is positive or if their symptoms persist after a negative test result.

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CHAPTER 65

Topical Drugs

Chemical agents may be applied to the skin and mucous membranes for localized effects within the skin or membrane. Many of these, such as antibiotics, antiseptics, corticosteroids, antineoplastics, and local anesthetics, belong to distinct pharmacological classes treated elsewhere in this text and are not discussed specifically in this chapter. However, transdermal delivery systems for compounds whose pharmacological activity is discussed elsewhere are outlined briefly from the delivery viewpoint in this chapter. The heterogeneous groups of agents that are not part of a pharmaceutical drug class but nonetheless have effects on epithelial surfaces and are mostly nonselective in action are the primary focus of this chapter.

Those locally acting topical agents that have limited chemical and pharmacological activity generally have a *physical* basis of action. Included in this group are protectives, adsorbents, demulcents, emollients, and cleansing agents. The relative inertness of many of these substances renders them of value as vehicles and excipients. Consequently, many agents in this group are also pharmaceutical necessities and may be treated in Chapter 55.

Topical agents that have general *chemical* reactivity include most astringents, irritants, rubefacients, vesicants, sclerosing agents, caustics, escharotics, many keratolytic (desquamating) agents, and a miscellaneous group of dermatologicals including hypopigmenting and antipruritic agents.

Although the skin (described in further detail in Chapter 37) and other membranes (see Chapter 44 concerning the eye and Chapter 59 concerning absorption across other membranes) differ considerably in structure and function, they exhibit similar absorption profiles for some chemical agents and similar responses to certain physical and pharmacological stimuli. Thus, many of the agents found in this chapter may be applied to other membranes. Nevertheless, it is obvious that many agents, for which there is either contraindication or no rationale for their application to the mucous membranes, may be applied only to the skin.

PROTECTIVES AND ADSORBENTS

In its broadest pharmacological sense a protective is any agent that isolates the exposed surface (skin or other membranes) from harmful or annoying stimuli. Substances that protect by mechanical or other physical means are considered to be protectives. While the surface action of adsorbents and demulcents may impart some protection, demulcents and emollients are placed in separate categories that reflect their primarily dermatological function.

The abridged category of protectives mainly comprises the dusting powders, adsorbents, mechanical protective agents, and plasters.

Dusting Powders

Certain relatively inert and insoluble substances are used to cover and protect epithelial surfaces, ulcers, and wounds. Usually these substances are very finely subdivided powders. They generally absorb moisture and, therefore, also act as cutaneous desiccants. The absorption of skin moisture decreases friction and also discourages certain bacterial growth.

The water-absorbent powders should not be administered to wet, raw surfaces because of the formation of cakes and adherent crusts. Starch and other carbohydrate powders may become doughy with absorption of aqueous-based fluids but also may ferment. Consequently, such powders often contain an antiseptic. Most impalpable powders are absorptive, to some extent. Whether absorption of substances, other than water, contributes to the protection of the skin is uncertain; however, absorption of fatty acids and perspiration constituents along with cutaneous drying, contributes to a deodorant action of such powders. It generally is held that the adsorptive capacity is important to the gastrointestinal (GI) protective action of chemically inert powders taken internally.

Chemically inert dusting powders are not entirely biologically inert, despite the name. When carried into pores or wounds or left upon skin or epithelial surfaces, dusting powders, eg, talc, may cause irritation, granulomas, fibrosis, or adhesions. Even without direct irritation or obstruction of the perspiration, dust can be troublesome.

Absorbable dusting powders (Biosorb, *Ezon*) are available for surgical gloves. This absorbable powder is mixed with 2% magnesium oxide and contains residual amounts of sodium sulfate and sodium chloride. This mixture produces no reaction in tissues and is absorbed completely within a short time. Starch also has drying and absorptive qualities (Fordustin powder; 90 and 24 g). These products, however, can be metabolized by *Candida* and thus can aggravate an infection.

A product containing detranomer (Debrisan) promotes debridement of secreting wounds, including venous stasis and decubitus ulcers, infected traumatic and surgical wounds, as well as infected burns. It consists of hydrophilic spherical beads (0.1–0.3 mm in diameter) of dextranomer. The beads are composed of a three-dimensional network of cross-linked dextran. This network selectively imbibes molecules on the basis of molecular mass (molecules <1000 daltons are imbibed; molecules 1000 to 5000 daltons experience decreased absorption with increasing molecular-weight and molecules >5000 daltons are not imbibed). Four milliliters of water are absorbed for each gram of dextranomer, and absorption is continuous so long as unsaturated beads are in proximity to the wound. This therapy is associated with the rapid and continuous exudate removal from wound surfaces, resulting in a marked reduction in inflammation, edema, and pain, as well as an increase in granuloma tissue formation and reduction in time for wound healing.

Several of the dusting powders are incorporated into ointments, creams, and lotions. They also serve other functions in tablets and other pharmaceutical dosage forms.

BENTONITE—page 1073.
BISMUTH, SUBSALICYLATE—page 1296.
BORIC ACID—page 1083.
CALCIUM CARBONATE—page 1296.
CELLULOSE, POWDERED—see RPS-19, page 1397.
MAGNESIUM STEARATE—page 1087.
TALC—page 1091.
TITANIUM DIOXIDE—page 1293.
ZINC OXIDE—page 1283.

ZINC STEARATE

Octadecanoic acid, zinc salt

Zinc stearate [557-05-1]. A compound of zinc with a mixture of solid organic acids obtained from fats, which consists chiefly of variable proportions of zinc stearate and zinc palmitate. It contains the equivalent of 12.5 to 14.0% of ZnO (81.38).

Preparation—An aqueous solution of zinc sulfate is added to a sodium stearate solution, and the precipitate is washed with water until free of sulfate and dried.

Description—Fine, white, bulky powder, free from grittiness, with a faint characteristic color; neutral to moistened litmus paper.

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

Comments—In *water-repellent* ointments and as a *dusting powder* in dermatological practice for its desiccating, astringent, and *protective* effects. It has been removed from baby dusting powders, owing to accidental, fatal inhalations.

Mechanical and Chemical Protectives

Several materials may be administered to the skin to form an adherent, continuous film that may be either flexible or semirigid, depending on the materials and their formulations, as well as the manner in which they are applied. Such materials may serve several purposes including (1) providing occlusive protection from the external environment, (2) providing mechanical support, and/or (3) serving as vehicles for various medicaments.

The two principal classes of mechanical protectives are the collodions and plasters. Their use is decreasing with the increasing recognition of the importance of air exposure in maintaining a normally balanced cutaneous bacterial flora of low pathogenicity. Also, the mechanical protectives may be somewhat irritating because of interference with normal percutaneous water transport caused by certain oligomers, resins, and other components, especially in plasters. The cerates may be employed similarly to the plasters. Bandages, dressings, new vapor-permeable polymer membranes, and casts also afford mechanical protection and support (see Chapter 108 for additional information). A brief discussion of plasters is included in Chapter 44.

A number of insoluble and relatively inert powders that remain essentially unchanged chemically in the GI tract may possess surface properties that favor their absorption to the GI mucosa. Such materials may offer mechanical protection against abrasion and may even offer slight protection against toxins and chemical irritants. Many such protectives also are adsorbents (charcoal, bismuth compounds, kaolin) or astringents (zinc and bismuth compounds). They are discussed under those categories.

ALUMINUM HYDROXIDE GEL—page 1295.

COLLODION

Contains not less than 5.0%, by weight, of pyroxylin.

Pyroxylin	40 g
Ether	750 mL
Alcohol	250 mL
To make about	1000 mL

Add the alcohol and the ether to the pyroxylin contained in a suitable container, and stopper the container well. Shake the mixture occasionally until the pyroxylin is dissolved.

Description—Clear, or slightly opalescent, viscous liquid; colorless, or slightly yellowish, with the odor of ether; specific gravity between 0.765 and 0.775.

Alcohol Content—22% to 26% of C_2H_5OH.

Comments—Chiefly to seal small wounds, for the preparation of medicated collodions, and to protect nonaffected areas of the skin from topically applied irritants, corrosives, etc.

Caution—*Collodion is highly flammable.*

DIMETHICONE

Simethicone; 360 Medical Fluid; Sentry Dimethicone

[9006-65-9]$(C_2H_6OSi)_n$. A water-repellent silicone oil consisting essentially of dimethyl siloxane polymers (200 series of fluids; see *Silicones,* below).

Preparation—US Pat 2,441,098.

Description—Water-white, viscous, oil-like liquid.

Solubility—Immiscible with water or alcohol; miscible with chloroform or ether.

Comments—Exhibits skin-adherent and water-repellent properties. It is both a *protective* and an *emollient,* for which its Food and Drug Administration (FDA) classification is Category I. Applied to the skin, it forms a *protective* film that provides a barrier to ordinary soap and water and water-soluble irritants. The film may last several hours if the skin is exposed, mainly to aqueous media. The film provides a less effective barrier to synthetic detergents and lipid-soluble materials, such as organic solvents. It should not be applied except in contact dermatoses and dermatoses aggravated by substances that can be repelled by the silicone. It is useful in preventing irritation from ammonia produced by the urine of infants, but it may exacerbate preexisting irritation. The occlusive protection by the silicone is detrimental to inflamed, traumatized, abraded, or excoriated skin and to lesions requiring free drainage. However, applied adjacent to such lesions, it offers protection against irritating discharges and maceration. It practically is harmless and does not sensitize skin, but it does cause temporary irritation to the eyes. It may be incorporated into creams or lotions.

PETROLATUM GAUZE

Petrolated Gauze

Absorbent gauze saturated with white petrolatum. The weight of the petrolatum is 70–80% of the weight of the gauze. It is sterile.

Preparation—By adding, under aseptic conditions, molten, sterile, white petrolatum to dry, sterile, absorbent gauze, previously cut to size, in the ratio of 60 g petrolatum to each 20 g gauze.

Comments—A *protective* dressing; also as packing material for postoperative plugs, packs, rolls, and tampons, and as a wick, drain, or wraparound for tubing. It is claimed that there is no danger of tissue maceration and that no growth of granulation tissue through it occurs.

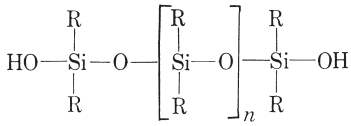
GELATIN SPONGE, ABSORBABLE—page 1337.
KAOLIN—page 1313.
LANOLIN—page 1078.
LANOLIN, ANHYDROUS—page 1077.
MINERAL OIL—page 1308.
MINERAL OIL EMULSION—see RPS-19, page 788.
MINERAL OIL, LIGHT—page 1087.
OLIVE OIL—see RPS-19, page 1400.
PEANUT OIL—page 1072.
PETROLATUM—page 1077.

SILICONES

Polyorganosiloxanes; Silastic; Silicone Rubber

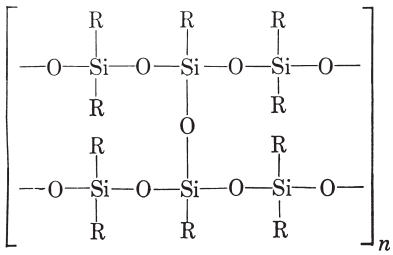
Organosilicon polymers containing chains of alternating oxygen and silicon atoms with substituent organic groups, frequently methyl or phenyl, attached to each silicon atom.

Preparation—May be prepared synthetically by condensing alkylated or arylated *silanols*. Disubstituted *silanediols* $[R_2Si(OH)_2]$ form linear polymers having the general formula.

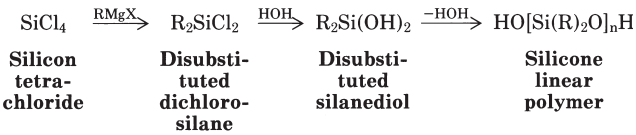


Cross-linked polymers result from condensation of mixtures of substituted silanediols and monosubstituted *silanetriols* $[RSi(OH)_3]$,

represented by the following partial formula where R is a hydrocarbon radical:



One method of preparation involves interaction of silicon tetrachloride with appropriate Grignard reagents to yield alkylated or arylated dichlorosilanes. After hydrolysis to the corresponding substituted silanols, dehydration procedures are used to effect condensation polymerization. The overall reaction, as it involves a disubstituted silanediol, may be represented as



Description—Silicones with a wide range of properties may be produced by varying the molecular weight, tacticity, substituent R groups, R:Si ratios (whether linear, cyclic, or cross-linked polymers), and the degree of cross-linking. Physically, silicones vary from mobile liquids through low-viscosity liquids and semisolids to solids. Linear silicones (liquids to semisolids) have viscosities ranging from 0.65 to 1,000,000 centistokes. Higher-molecular-weight linear silicones form solids. Cross-linked silicones may exhibit gel-like to solid-like properties, depending on the degree of cross-linking and chemical structure of the repeat unit. In general, silicones are odorless, tasteless, water repellent, relatively inert chemically, stable under high and low temperatures, and efficient as antifoam agents.

Solubility—Unmodified silicones are generally insoluble in water, thus they frequently are termed *silicone oils*. However, a water-soluble sodium salt of a simple silicone, *sodium methyl siliconate* [$CH_3Si(OH)_2ONa$], has been marketed.

Comments—Preparations containing silicones have various dermatological uses (see *Dimethicone*) and are used as ingredients of bases for ointments and liniments. In the form of inhalation sprays, silicone preparations have been employed in the treatment of pulmonary edema nvolving frothing of fluid in the upper respiratory tract. They also are used orally as antiflatulent or gastric defoaming agents.

A silicone *bouncing putty* has found acceptance for use as a physical agent in treating conditions requiring finger exercise. The water-repellent properties of the silicones are employed in numerous applications in which drainage of aqueous fluids from surfaces is desirable.

Silicones exhibit low irritation as a result of their surface chemical, physical, and bulk mechanical properties. Consequently, silicone rubbers are component materials in various indwelling catheters and tubes designed for short-time use. Solid implants that incorporate silicone into their composition include nose, chin, and other types of prostheses used in plastic, reconstructive, and orthopedic procedures.

In addition to uses involving antifoaming, water-repellent, and non-irritating characteristics, silicone fluids also are employed to prevent adhesion between components or materials and as release agents. Examples of its usage as a release agent include release of rubber and plastics from molds, food from metal, ice from wings of aircraft and capsules and tablets from molds and dies in which they are fabricated.

Liquid silicones have been used to fill in hypoplastic body areas for cosmetic purposes, although these fluids tend to relocate because of flow under gravity and motion. While the use of silicone fluids in reconstructive breast surgery and similar applications is undergoing reassessment for safety concerns, solid materials continue to be well accepted in biomedical applications.

Higher-molecular-weight (solid) silicone rubbers are used to encapsulate steroid hormones and other drugs intended for chronic implantation. For example, Norplant *(Wyeth-Ayerst)* is a long- term contraceptive implant that incorporates levonorgestrel into silastic-based rods. The steroid is released slowly from the implant over an extended time period to provide approximately 5-yr continuous use.

Silicone-based materials are also an important class of contact lens materials. The silicone polymer is gas permeable, thus enabling oxygen to permeate the contact lens to the cornea. However, silicones are not hydrogels and do not absorb large amounts of water similar to hydrogel-based contact lenses. The materials exhibit minimal if any irritation as a result of surface chemical and physical properties and are comfortable to wear because of the gas permeation and mechanical properties.

ZINC CARBONATE

Smithsonite; Zincspar

[3486-35-9] CO_3Zn (125.38).

Description—White rhombohedroids.

Solubility—Soluble 10 ppm in water at 15°; soluble in dilute acids, alkalies, or solutions of ammonium salts.

Comments—Both for its lubricity and as a drying agent. As a skin protectant it falls into FDA Category I. It is included in commercial topical burn and sunburn products and extemporary protectants.

Occlusive Dressings

Occlusive dressings alter environmental aspects of certain types of wounds that may facilitate healing. While a moist wound environment may be beneficial, there are certain disadvantages. Moisture has been associated with enhanced rates of reepithelialization. Brief increases in the number of inflammatory cells within the wound site may break down cellular debris. While transient increases in bacterial counts have been observed with occlusive dressings, infection usually does not occur, in part as a result of the transitory increased inflammatory cell populations. Dermal and epidermal healing also may be aided by the low-pH and low-oxygen environment. Furthermore, such dressings provide physical protection.

Gas-permeable, synthetic, polymer-based dressings have been developed. These materials provide chemical and physical protection while maintaining a more acceptable microenvironment. Polyurethane-based films that are permeable to oxygen and water vapor include Op-site, Tegaderm, and Bioclusive. Duo-Derm *(Conva Tec)* is a hydrophobic polymer with embedded hydroactive particles that is oxygen- and water-vapor impermeable. Application depends on whether the dressing is self-adherent.

DEMULCENTS

Demulcents (L, *demulcere,* to smooth down) are protective agents that are employed primarily to alleviate irritation, particularly of mucous membranes or abraded tissues. They also often are applied to the skin. They generally are applied to the surface in viscid, sticky preparations that cover the area readily. They also may be medicated. The local action of chemical, mechanical, or bacterial irritants, thereby, is diminished, and pain, reflexes, spasm, or catarrh are attenuated. They also prevent drying of the affected surface. The demulcents may be applied to the skin (lotions, ointments, or wet dressings), GI tract (demulcent drinks or enemas), throat (lozenges or gargles), or corneal membranes (artificial tears and in wetting agents for contact lenses). When demulcents are applied as solid material (as in lozenges or powders), the liquid is provided by secreted or exuded fluids. Demulcents frequently are medicated. In such instances the demulcent may be an adjuvant, a corrective, or a pharmaceutical necessity. Many of the demulcents are also laxatives and are used as such, or they are used with laxatives or antacids for their demulcent and lubricating action.

A variety of chemical substances possess demulcent properties. Among these are the alginates, mucilages, gums, dextrins, starches, certain sugars, and polymeric polyhydric glycols. Mucus itself is a natural demulcent. Certain silicates that form silicic acid on exposure to air or gastric juice and glycerin, although the silicic acid has low molecular weight and relatively low binding power, frequently are placed among the

demulcents. Also the colloidal hydrous oxides, hydroxides, and basic salts of several metals are claimed to be demulcent, but acceptable clinical proof of the claim has not been provided.

The hydrophilic colloidal properties of most demulcents enable them to function as emulsifiers and suspending agents in water-soluble ointments and suspensions. They also retard the absorption of many injections and, thus, may be employed in various depot preparations. Many of the demulcents mask the flavor of medicaments by means of at least three physical phenomena: (1) they apparently coat the taste receptors and render them less sensitive; (2) they incorporate many organic solutes into micelles and, thereby, diminish the free concentration of such solutes; and (3) they coat the surfaces of many particles in suspension. Because of the adhesiveness of the demulcents, they are employed widely as binding agents in tablets, lozenges, and similar dosage forms. Consequently, certain demulcents are discussed in Chapter 55.

ACACIA—pages 1070 and 1072.
AGAR—page 1073.

BENZOIN

Gum Benjamin; Benzoe

The balsamic resin obtained from *Styrax benzoin* Dryander or *Styrax parallelloneurus* Perkins, known in commerce as Sumatra Benzoin, or from *Styrax tonkinensis* (Pierre) Craib ex Hartwich, or other species of the Section *Anthostyrax* of the genus *Styrax,* known in commerce as Siam Benzoin (Fam *Styraceae*).

Sumatra benzoin yields not less than 75.0% of alcohol-soluble extractive, and Siam benzoin yields not less than 90.0% of alcohol-soluble extractive.

Constituents—Siam benzoin contains about 68% crystalline *coniferyl benzoate* [$C_{17}H_{16}O_4$]; up to 10% of an amorphous form of this compound is also present. Some *coniferyl alcohol* (*m-methoxy-p-hydroxycinnamyl alcohol,* mp 73° to 74°) occurs in the free state as well. Other compounds that have been isolated are *benzoic acid,* 11.7%; *d-iaresinolic acid,* 6%; *cinnamyl benzoate,* 2.3%; and *vanillin* 0.3%.

Sumatra benzoin has been reported to contain benzoic and cinnamic acid esters of the alcohol *benzoresinol* and probably also of coniferyl alcohol, free *benzoic* and *cinnamic acids, styrene,* 2 to 3% *cinnamyl cinnamate* (also called *styracin*), 1% *phenylpropyl cinnamate,* 1% *vanillin,* a trace of *benzaldehyde,* a little *benzyl cinnamate,* and the alcohol *d-sumaresinol* $C_{30}H_{48}O_4$.

Description—*Sumatra Benzoin:* Blocks or lumps of varying size made up of compacted tears, with a reddish brown, reddish gray, or grayish brown resinous mass. *Siam Benzoin:* Compressed pebble-like tears of varying size and shape. Both varieties are yellowish to rusty brown externally and milky white on fracture; hard and brittle at ordinary temperatures but softened by heat; aromatic and balsamic odor; aromatic and slightly acrid taste.

Comments—A *protective* application for irritations of the skin. When mixed with glycerin and water, the tincture may be applied locally for *cutaneous ulcers, bedsores, cracked nipples,* and *fissures* of the lips and anus. For throat and bronchial inflammation, the tincture may be administered on sugar. The tincture and compound tincture sometimes are used in boiling water as steam inhalants for their *expectorant* and *soothing action* in acute laryngitis and croup. In combination with zinc oxide, it is used in baby ointments.

Compound Benzoin Tincture [Balsamum Equitis Sancti Victoris, Balsamum Commendatoris, Balsamum Catholicum, Balsamum Traumaticum, Balsamum Vulnerarium, Balsamum Persicum, Balsamum Suecium, Balsamum Friari, Balsamum Vervaini, Guttae Nader, Guttae Jesuitarium, Tinctura Balsamica, Balsam of the Holy Victorious Knight, Commander's Balsam, Friar's Balsam, Turlington's Drops, Persian Balsam, Swedish Balsam, Vervain Balsam, Turlington's Balsam of Life, Balsam de Maltha, Ward's Balsam, Jerusalem Balsam, Saint Victor's Balsam, Wade's Drops, Wound Elixir and Balsamic Tincture]

Preparation—With benzoin (in moderately coarse powder, 100 g), aloe (in moderately coarse powder, 20 g), storax (80 g), and tolu balsam (40 g), prepare a tincture (1000 mL) by Process M, using alcohol as the menstruum. *Alcohol Content:* 74% to 80% C_2H_5OH.

Comments—Especially valuable in acute *laryngitis,* also in croup, when added to hot water and the vapor inhaled. By adding a teaspoonful of the tincture to boiling water in an inhaler and inhaling the vapor, very effective results may be obtained. It also is administered, on sugar, for throat and bronchial inflammation and as a local application, when mixed with glycerin and water, for *ulcers, bedsores, cracked nipples,* and *fissures* of the lips and anus.

CARBOMER METHYLCELLULOSE—see RPS-19, page 1396.
GELATIN—page 1074.
GLYCERIN—page 1081.
GLYCYRRHIZA—page 1064.
HYDROXYETHYL CELLULOSE—page 1074.
HYDROXYPROPYL CELLULOSE—page 1074.

HYDROXYPROPYL CELLULOSE INSERT

Lacrisert

Description—Sterile; translucent; rod-shaped.
Solubility—Soluble in water.
Comments—For administration into the inferior cul-de-sac of the eye. It is used when lacrimation is inadequate or to thicken tear film and prolong the tear-film breakup time, which usually is accelerated in patients with moderate to severe dry-eye states, including conjunctival hyperemia, corneal and conjunctival staining with rose bengal, exudation, itching, burning, foreign body sensation, smarting, photophobia, dryness, and blurred or cloudy vision.

HYDROXYPROPYL METHYLCELLULOSE—page 1074.

HYDROXYPROPYL METHYLCELLULOSE OPHTHALMIC SOLUTION

A sterile solution of hydroxypropyl methylcellulose, of a grade containing 19.0% to 30.0% methoxy and 4.0% to 12.0% hydroxypropoxy groups; may contain antimicrobial, buffering, and stabilizing agents.

Comments—A *wetting solution for contact lenses*. Its demulcent action decreases the irritant effect of the lens on the cornea. It also imparts viscous properties to the wetting solution, which assists the lens in staying in place. The demulcent effect also finds application in ophthalmic decongestants. *Artificial tear* formulations containing this drug may be used when lacrimation is inadequate. A 2.5% solution is used in gonioscopes.

METHYLCELLULOSE—page 1074.

METHYLCELLULOSE OPHTHALMIC SOLUTION

A sterile solution of methylcellulose; may contain antimicrobial, buffering, and stabilizing agents.

Comments—For the same purposes, and in the same manner, as *Hydroxypropyl Methylcellulose Ophthalmic Solution,* above.

PECTIN—page 1313.
POLYETHYLENE GLYCOLS—page 1079.
POLYVINYL ALCOHOL—page 1075.

POLYVINYL ALCOHOL OPHTHALMIC SOLUTION

VasoClear A

A sterile solution of polyvinyl alcohol, which may contain antimicrobial, buffering, and stabilizing agents and other demulcent substances. [9002-89-5] (Polyvinyl alcohol).

Preparation—By partial hydrolysis (*ca* 90%) of polyvinyl acetate.

Description—A white powder that is a linear polymer, —$(CH_2$—$CHOH)_n$—, where the value of n is between 500 and 5000; pH (1 in 25 aqueous solution) between 5 and 8.

Solubility—Soluble in water; insoluble in organic solvents.

Comments—A *wetting solution* for contact lenses. The polyvinyl alcohol has a demulcent action that helps protect the eye from irritation by the contact lens. It also is used in *artificial tears,* employed when there is insufficient lacrimation.

PROPYLENE GLYCOL—page 1082.
SODIUM ALGINATE—page 1073.
TRAGACANTH—page 1076.

EMOLLIENTS

Emollients (L, *emollier,* to soften) are bland, fatty, or oleaginous substances that may be applied locally, particularly to the skin but also to other mucous membranes. Skin usually appears *dry* because of a lack of moisture. Emollients or moisturizers increase the tissue moisture content, thereby rendering the skin softer and more pliable. Increased moisture content in the skin can be achieved by preventing water loss with an occlusive water-immiscible barrier, increasing the water-holding capacity of the skin with humectants, or altering the desquamation of the outermost skin layer, the strateum corneum.

The class of vehicles for emollients providing the range of the greatest moisturizing to the greatest drying effects on the skin include oleaginous bases, anhydrous absorption bases, W/O

emulsions, O/W emulsions, the more-neutral, water-miscible compounds, and, finally, the more-drying gel and solution bases.

Emollients have certain disadvantages. It now is recognized that retention of perspiration below the emollient and exclusion of air render conditions favorable to the growth of anaerobic bacteria. Furthermore, rubbing and massaging during application aids in the spreading of cutaneous bacteria. Consequently, the use of emollients to cover burns and abrasions is diminishing. Some emollients (eg, lanolin, both the hydroxylated and acetylated forms; isopropyl myristate and palmitate; oleyl alcohol and sodium lauryl sulfate) are comedogenic. Other liquid emollients may be used for mild catharsis and for protection against GI corrosives; however, castor oil is hydrolyzed in the gut to the irritating ricinoleic acid and, hence, is employed as an emollient only externally. Orally administered liquid emollients may be aspirated into the trachea and lungs, especially by infants; in the debilitated, such aspiration induces *oil aspiration pneumonia.* This condition also may be induced by emollient nose drops.

The chief use of emollient or moisturizing substances beyond their therapeutic actions is to provide vehicles for lipid-soluble drugs (as in ointments and liniments); hence, many of them are described among the pharmaceutical necessities (Chapter 55). It is widely, but incorrectly, held that such vehicles facilitate the transport through the skin of their active ingredients. On the contrary, when the oil:water partition coefficient is greater than 1.0, the penetration is retarded, and the emollient vehicle prolongs the action of the active ingredient. Emollient substances also are employed in both cleansing and antiphlogistic creams and lotions. Compound ointment bases, creams, and other medicated applications are treated in Chapter 43. Only the simple emollients and important compounded ointments that are used frequently for their emollient actions are listed below.

Animal Fats and Oils

LANOLIN—page 1078.
MINERAL OIL—pages 1087 and 1308.
MINERAL OIL, LIGHT—page 1087.
PARAFFIN—page 1077.
PETROLATUM—page 1077.

RED PETROLATUM

Description—UV-absorbing qualities to 340 nm. It provides a water-protective action because of its petrolatum base.

Comments—Owing to its opacity, it is used as a *sunblock* in creams, ointments, and sticks. It also is used as a *sunshade* with zinc oxide in some formulations and for lip protection (20% petrolatum with 5% *p*-aminobenzoic acid (PABA)).

WHITE OINTMENT—page 1077.
WHITE PETROLATUM—page 1077.
YELLOW OINTMENT—page 1077.

Vegetable Oils

CASTOR OIL—page 1306.
COCOA BUTTER—page 1085.
COCONUT OIL—see RPS-18, page 1317.
CORN OIL—page 1071.
COTTONSEED OIL—page 1072.
OLIVE OIL—see RPS-19, page 1400.
PEANUT OIL—page 1072.
PERSIC OIL—see RPS-18, page 1323.
SESAME OIL—page 1072.

Waxes

CETYL ESTERS WAX—page 1077.
COLD CREAM—page 1078.
HYDROPHILIC OINTMENT—page 1078.
ROSE WATER OINTMENT—page 1078.

Other Emollients

CETYL ALCOHOL—page 1078.
GLYCERIN—pages 758, 1081 and 1423.
PETROLATUM, HYDROPHILIC—page 1078.
ISOPROPYL MYRISTATE—page 1086.

MYRISTYL ALCOHOL

Tetradecyl Alcohol

[112-72-1] $CH_3(C7H_2)_{12}CH_2OH$ (214.38).

Preparation—By reduction of fatty acid esters.

Description—White, crystalline alcohol; specific gravity 0.824; melts at 30°.

Solubility—Insoluble in water; soluble in ether; slightly soluble in alcohol.

Comments—An *emollient* in cold creams.

OLEYL ALCOHOL—page 1075.

SHARK LIVER OIL

The oil extracted from the livers of the *soupfin shark, Galeorhinus zyopterus* or *Hypoprion brevirostris,* both of which are rich in vitamins A and D.

Comments—An *emollient* and *protectant* (FDA classification Category I) used in burn and sunburn ointments.

ASTRINGENTS AND ANTIPERSPIRANTS

Astringents are locally applied, protein precipitants that have such a low cell penetrability that the action essentially is limited to the cell surface and the interstitial spaces. The permeability of the cell membrane is reduced, but the cells remain viable. The astringent action is accompanied by contraction and wrinkling of the tissue and by blanching. The cement substance of the capillary endothelium and the basement membrane is hardened, so that pathological transcapillary movement of plasma protein is inhibited, and local edema, inflammation, and exudation, thereby, are reduced. Mucus or other secretions also may be reduced, so that the affected area becomes drier.

Astringents are used therapeutically to arrest hemorrhage by coagulating the blood (*styptic* action) and to check diarrhea, reduce inflammation of mucous membranes, promote healing, toughen the skin, or decrease sweating.

The principal astringents are

1. Salts of the cations aluminum, zinc, manganese, iron, or bismuth.
2. Certain other salts that contain these metals (such as permanganates).
3. Tannins or related polyphenolic compounds.

Zinc sulfate (0.25%) is the only nonprescription astringent recommended. Acids, alcohols, phenols, and other substances that precipitate proteins may be astringent in the appropriate amount or concentration. However, such substances generally are not employed for their astringent effects, because they readily penetrate cells and promote tissue damage. Strongly hypertonic solutions dry the affected tissues and are often incorrectly called astringents, since protein precipitation also occurs. Many astringents are irritant or caustic in moderate to high concentrations. Consequently, strict attention must be paid to the appropriate concentration. Most astringents are also antiseptics, and many of them are discussed in Chapter 88.

Astringents also possess some *deodorant* properties by virtue of their interaction with odorous fatty acids liberated or produced by action of bacteria on lipids in sweat and by suppressing bacterial growth, partly because of a decrease in pH. The *antiperspirant* effect is the result of both the closure of the sweat ducts by protein precipitation to form a plug and peritubular irritation that promotes an increase in inward pressure on the tubule.

Antiperspirants and deodorants can be applied as aerosols, sprays, pads, sticks, and roll-on liquid, creams, and semisolids for the control of excessive perspiration and body odor. The general adult population secretes between 0.5 to 1.5 L of odorless perspiration a day. The unpleasant odor associated with perspiration is the result of chemical and bacterial

degradation of these skin secretions. Antiperspirants are designed to decrease the flow and/or inhibit the bacterial degradation of skin secretions. Agents most commonly used as antiperspirants include aluminum chlorohydrates, aluminum chloride, buffered aluminum sulfate, and zirconyl chlorohydrates. These agents reduce perspiration 20% to 40% in the general adult population.

Aluminum chlorohydrates are available in a variety of 25% (anhydrous) salt formulations that differ in the ratio of aluminum to chlorine, as well as in complexes with polyethylene glycol or polypropylene glycol. Aluminum chlorohydrates are less acidic than aluminum chloride; thus, they do not stain fabrics in contact with treated skin and maintain antiperspirant activity and antiodor activity by inhibiting growth of gram-negative bacteria on the skin surface.

Buffered aluminum sulfate (8% aluminum sulfate buffered with 8% sodium aluminum lactate) is effective and nonirritating to the skin.

Because of the sarcoid-like granulomas and allergic reactions to aluminum zirconium chlorohydrates, they are not used in aerosol-type antiperspirants. They are used topically as antihydrotics on the axillae in concentrations not exceeding 20%.

Glutaraldehyde (2–10% buffered solution), formaldehyde (5–30% solutions), methenamine (5% stick or 10% solution), and scopolamine hydrobromide (0.025% solution) also are used to treat hyperhidrosis of the planar and plantar surfaces but not axillae surfaces. Deodorants reduce the resident bacteria flora on the skin, thereby inhibiting bacterial decomposition of perspiration.

Commonly used agents include benzalkonium chloride, methylbenzethonium chloride, and neomycin sulfate. The quaternary ammonium chlorides, however, are inactivated by soaps. They can irritate skin at concentrations greater than 1%. Concurrent use of antibiotics may sensitize the individual subject and/or result in the production of resistant bacterial strains.

ALCOHOL—pages 1080 and 1082.

ALUM

Sulfuric acid, aluminum potassium salt (2:1:1), dodecahydrate; Sulfuric acid, aluminum ammonium salt (2:1:1), dodecahydrate; Alumen; Alumen Purificatum; Purified Alum

Aluminum ammonium sulfate (1:1:2) dodecahydrate [7784-26-1]; anhydrous [7784-25-0] (237.14); or aluminum potassium sulfate (1:1:2) dodecahydrate [7784-24-9]; anhydrous [10043-67-1] (258.19).

The label of the container must indicate whether the salt is ammonium alum [$AlNH_4(SO_4)_2 \cdot {}_2O$, 453.32] or potassium alum [$AlK(SO_4)_2 \cdot {}_2O$, 474.38].

Preparation—Prepared from the mineral *bauxite* (a hydrated aluminum oxide) and sulfuric acid, with the addition of ammonium or potassium sulfate for the respective alums. Ammonium alum dominates the market because of its lower cost.

Description—Large, colorless crystals, crystalline fragments, or a white powder; odorless and has a sweetish, strongly astringent taste; solutions are acid to litmus.

Solubility—1 g ammonium alum in 7 mL water, and 1 g potassium alum in 7.5 mL water; both are soluble in about 0.3 mL boiling water, but they are insoluble in alcohol; alum is freely but slowly soluble in glycerin.

Incompatibilities—When alum is dispensed in powders with *phenol, salicylates,* or *tannic acid,* gray or green colors may be developed because of traces of iron in the alum. A partial liberation of its water of crystallization permits it to act as an acid toward *sodium bicarbonate,* thus liberating carbon dioxide. Ammonia is liberated simultaneously from ammonium alum. *Alkali hydroxides and carbonates, borax,* or *lime water* precipitates aluminum hydroxide from solutions of alum. The alums possess the incompatibilities of the water-soluble sulfates.

Comments—A powerful *astringent* in acidic solutions. It is only slightly antiseptic, probably because of bacteriostasis through liberation of acid on hydrolysis. It sometimes is used as a local *styptic,* and frequently is employed in making astringent lotions and douches. It is used especially by athletes to toughen the skin. As an astringent it is used in concentrations of 0.5% to 5%. Some vulvovaginal cleansing and deodorant preparations also contain alum.

Styptic pencils are made by fusing potassium alum, usually with the addition of some potassium nitrate, and pouring it into suitable molds.

Caution—Do not confuse *styptic* pencils with *caustic* pencils ; the latter contain *silver nitrate.*

ALUMINUM ACETATE TOPICAL SOLUTION

Acetic acid, aluminum salt; Liquor Burowii; Burow's Solution
$Al(OCOCH_3)_3$

Yields, from each 100 mL, 1.20 to 1.45 g of aluminum oxide [Al_2O_3, 101.96] and 4.24 to 5.12 g of acetic acid [$C_2H_4O_2$, 60.05], corresponding to 4.8 to 5.8 g of aluminum acetate [139-12-8] $C_6H_9AlO_6$ (204.12). It may be stabilized by the addition of not more than 0.6% of boric acid.

Caution—This solution should not be confused with Aluminum Subacetate Topical Solution, which is a stronger preparation.

Note—Dispense only clear Aluminum Acetate Solution.

Description—Clear, colorless liquid having a faint acetous odor and a sweetish, astringent taste; specific gravity about 1.022; pH 3.6 to 4.4.

Comments—As an *astringent dressing* or as an *astringent mouth wash* and *gargle*. Aluminum acetate is included in preparations to treat athlete's foot, dermatitides, diaper rash, dry skin, poison ivy poisoning, and inflammation of the external ear.

ALUMINUM CHLORIDE

[7784-13-6] AlCl3 · $6H_2O$ (241.43); anhydrous [7446-70-0] (133.34).

Preparation—By heating aluminum in chlorine gas, then dissolving the product in water and crystallizing, or by dissolving freshly precipitated aluminum hydroxide in hydrochloric acid and concentrating to permit crystallization.

Description—White or yellowish white, crystalline powder; deliquescent; sweet, astringent taste; solutions are acid to litmus.

Solubility—1 g in about 0.9 mL water or 4 mL alcohol; soluble in glycerin.

Comments—Extensively employed on the skin as an *astringent* and *anhidrotic;* it is included in some proprietary preparations formulated for this purpose. It is used especially in the treatment of soggy athlete's foot, to promote drying and, hence, to enhance the efficacy of specific antifungal drugs. For ordinary antiperspirant use the basic salt aluminum chlorohydroxide, $Al_2Cl(OH)_5$, is preferable as it is less irritating and causes less deterioration of clothing than does this drug. It may have a special use in the treatment of *hyperhidrosis of the palms, soles, or axillae,* for which a 20% solution in absolute alcohol is used. In the presence of water, it hydrolyzes to aluminum chlorohydroxide and hydrochloric acid, which can cause irritation, especially in fissures, discomfort, and also deterioration of clothing. Concentrations below 15% cause a low incidence of irritation. Consequently, it is essential that the area to be treated is completely dry before application. To protect bedclothes, the treated area is sometimes covered with plastic wrap, but such occlusion of the axillae may result in boils or furuncles. It should not be applied to the axillae immediately after shaving or used where the skin is irritated or broken. Concentrations above 15% are used as *caustics.*

ALUMINUM CHLOROHYDRATES

The hydrate of aluminum chloride hydroxide [1327-41-9] $Al_2Cl(OH)_5$.

Comments—Mainly employed in antiperspirant products, for which they have been rated safe and effective in concentrations of 25% (as anhydride) or less. Since solutions or suspensions are less acidic than those of aluminum chloride, they cause a lower incidence of irritation to the skin.

ALUMINUM SULFATE

Sulfuric acid, aluminum salt (3:2), hydrate; Cake Alum; Patent Alum; Pearl Alum; Pickle Alum; *Papermaker's Alum*

Aluminum sulfate (2:3) hydrate [17927-65-0] $Al_2(SO_4)_3.xH_2O$; anhydrous [10043-01-3] (342.14).

Preparation—By reacting freshly precipitated aluminum hydroxide with an appropriate quantity of sulfuric acid. The resulting solution is evaporated and allowed to crystallize.

Description—White crystalline powder, shining plates, or crystalline fragments; stable in air; odorless and with a sweet, mildly astringent taste; aqueous solution (1 in 20) is acid and has a pH not less than 2.9.

Solubility—1 g in about 1 mL water; insoluble in alcohol.

Comments—A powerful *astringent,* acting much like alum. It is used widely as a *local antiperspirant* and is the effective ingredient in some commercial antiperspirant products. Solutions usually are buffered with sodium aluminum lactate to make them less irritating. It is used for water purification in the *alum flocculation* process. It is a *pharmaceutical necessity* for *Aluminum Subacetate Solution*.

BISMUTH SUBCARBONATE—see RPS-18, page 799.
BISMUTH SUBNITRATE—page 1083.

CALAMINE

Iron oxide (Fe_2O_3), mixt. with zinc oxide; Prepared Calamine; Lapis Calaminaria; Artificial Calamine

Calamine [8011-96-9]; contains, after ignition, not less than 98.0% ZnO (81.38).

Preparation—By thoroughly mixing zinc oxide with sufficient ferric oxide (usually 0.5–1%) to obtain a product of the desired color.

It originally was obtained by roasting a native zinc carbonate, then known as *calamine,* hence, the name. This name also is applied by mineralogists to a native form of zinc silicate, which is not suitable for making medicinal calamine.

Description—Pink powder, all of which passes through a No 100 standard mesh sieve. It is odorless and almost tasteless.

Solubility—Insoluble in water; dissolves almost completely in mineral acids.

Comments—Similar to those of zinc oxide, being employed chiefly as an *astringent* and in *protective* and soothing ointments and lotions for *sunburn, ivy poisoning,* etc. It often is prescribed by dermatologists to give opacity and a flesh-like color to lotions or ointments.

Calamine Lotion [Lotio Calaminae]—*Preparation:* Dilute bentonite magma (250 mL) with an equal volume of calcium hydroxide solution. Mix calamine (80 g) and zinc oxide (80 g) intimately with glycerin (20 mL) and about 100 mL of the diluted magma, triturating until a smooth, uniform paste is formed. Gradually incorporate the remainder of the diluted magma. Finally add calcium hydroxide solution (qs) to make 1000 mL, and shake well. If a more viscous consistency in the Lotion is desired, the quantity of bentonite magma may be increased to not more than 400 mL. *Note: Shake thoroughly before dispensing*. Comments: see *Calamine.*

Phenolated Calamine Lotion [Lotio Calaminae Composita; Compound Calamine Lotion]—*Preparation:* Mix liquefied phenol (10 mL) and calamine lotion (990 mL) to make 1000 mL. Commercial preparations also contain 8.4% isopropyl alcohol and have various other modifications. *Note: Shake thoroughly before dispensing. Comments:* see *Calamine.*

GLUTARAL—page 1628.
METHENAMINE—page 1664.
POTASSIUM PERMANGANATE—see RPS-19, page 1270.
SILVER NITRATE—page 1287.

TANNIC ACID

Gallotannic Acid; Tannin; Digallic Acid; Zibactin Medicated

[1401-55-4]. A tannin usually obtained from nutgalls, the excrescences produced on the young twigs of *Quercus infectoria* Olivier and allied species of *Quercus* Linné (Fam *Fagaceae*).

Description—Yellowish white to light brown amorphous powder, glistening scales, or spongy masses; usually odorless; strong astringent taste; gradually darkens on exposure to air and light.

Solubility—1 g in about 0.35 mL water or 1 mL warm glycerin; very soluble in alcohol; practically insoluble in chloroform or ether.

Incompatibilities—Solutions gradually darken on exposure to air and light through oxidation of phenolic groups to quinoid structures. It is incompatible with most enzymes, gums, salts of many metals, and many other substances.

Comments—On an open sore or denuded surface, it forms a film of protein tannate that acts as a *mechanical protective* that excludes external irritants and infectives and, thus, provides some relief from pain. However, it is not antibacterial and not only does not inhibit the growth of bacteria entrained beneath the film but actually may create favorable conditions for the growth of certain anaerobes. For this reason and also the fact that it is absorbed sufficiently from large denuded areas to cause liver damage, it is no longer used in the treatment of burns and should not be used on any large lesions. Nevertheless, it is incorporated in 8% to 10% concentration in several products to treat ivy or oak poisoning. As a 7% gel it is used on cold sores, fever blisters, and cankers. It is included in 2.16% concentra-tion in a hemorrhoidal preparation and in 4% concentration in a keratolytic product for removing corns, calluses, and warts, these concentrations probably being too low to contribute significantly to the supposed efficacies. In a 25% solution it is used to reduce inflammation and harden skin around ingrown toenails, thus increasing comfort and making nail-cutting easier.

Its content in tea accounts for the use of strong tea as an internal antidote, presumably for the dual purpose of precipitating toxic alkaloids and hardening the surface of the GI mucosa and its mucous layer.

WHITE LOTION

Lotio Alba; Lotio Sulfurata

Zinc Sulfate 40 g

Sulfurated Potash 40 g

Purified Water, a sufficient quantity, to make 1000 mL

Dissolve zinc sulfate and sulfurated potash separately, each in 450 mL of purified water, and filter each solution. Add slowly the sulfurated potash solution to the zinc sulfate solution with constant stirring. Then add the required amount of purified water, and mix.

Note—Prepare freshly and shake thoroughly before dispensing. For further discussion see *Sulfurated Potash.*.

Comments—An *astringent, protective,* and mild *antimicrobial* preparation. The astringency is attributable to the zinc ion. The thiosulfates and polysulfides in it exert antibacterial and antifungal actions. White lotion is used in the treatment of acne vulgaris.

ZINC CAPRYLATE

Zinc Octanoate

[557-09-5] $C_{16}H_{20}O_4Zn$ (351.79).

Preparation—By the methathesis of zinc sulfate and ammonium caprylate.

Description—Lustrous scales; melts about 136°.

Solubility—Sparingly soluble in boiling water; moderately soluble in boiling alcohol.

Comments—In the treatment of *athlete's foot*. The astringency of the zinc decreases inflammation and wetness. The caprylate has a weak antifungal action.

ZINC CHLORIDE

Butter of Zinc

[7646-85-7] $ZnCl_2$ (136.29).

Preparation—By reacting metallic zinc or zinc oxide with hydrochloric acid and evaporating the solution to dryness.

Description—White, or nearly white, odorless, crystalline powder, or as porcelain-like masses, or in molded pencils; very deliquescent; aqueous solution (1 in 10) acid to litmus; solution in water or alcohol usually slightly turbid, but the turbidity disappears on addition of a small quantity of hydrochloric acid.

Solubility—1 g in 0.5 mL water, about 1.5 mL alcohol, or about 2 mL glycerin.

Incompatibilities—Soluble zinc salts are precipitated as zinc hydroxide by alkali hydroxides, including ammonium hydroxide; the precipitate is soluble in an excess of either the fixed or the ammonium hydroxide. *Carbonates, phosphates, oxalates, arsenates,* and *tannin* cause precipitation. The precipitation with sodium borate can be prevented by addition of an amount of glycerin equal in weight to the sodium borate. In weak aqueous solutions, it has a tendency to form the insoluble basic salt by hydrolysis and about one-half its weight of ammonium chloride has been used for the purpose of stabilization. It is very *deliquescent*. It has the incompatibilities of chlorides, being precipitated by *silver* and *lead salts*.

Comments—In high concentrations it is *caustic* and has been used as a caustic agent to treat corns, calluses, and warts. In the low concentrations in which it is marketed it is astringent and mildly antibacterial and probably does not contribute to keratolysis. Although it is used in mouthwashes, the contact time is too short, and only an astringent and not an antibacterial action results.

ZINC OXIDE

Flowers of Zinc; Zinc White; Pompholyx; Nihil Album; Lana Philosophica

Zinc oxide [1314-13-2] ZnO (81.38).

Preparation—By heating zinc carbonate at a low red heat until the carbon dioxide and water are expelled.

Description—Very fine, odorless, amorphous, white or yellowish white powder, free from gritty particles; gradually absorbs carbon dioxide from the air; when strongly heated it assumes a yellow color that disappears on cooling; its suspension in water is practically neutral.

Solubility—Insoluble in water or alcohol; soluble in dilute acids, solutions of the alkali hydroxides, or ammonium carbonate solution.

Incompatibilities—Reacts slowly with fatty acids in *oils* and *fats* to produce lumpy masses of zinc oleate, stearate, etc. *Vanishing creams* tend to dry out and crumble. Whenever permissible, it is advisable to levigate it to a smooth paste with a little mineral oil before incorporation into an ointment.

Comments—Has a mild *astringent, protective,* and *antiseptic* action. In the form of its various official ointments and pastes it is employed widely in the treatment of dry skin and such skin disorders and infections as *acne vulgaris, prickly heat, insect stings and bites, ivy poisoning, diaper rash, dandruff, seborrhea, eczema, impetigo, ringworm, psoriasis, varicose ulcers,* and *pruritus*. It is contained in

some sunscreens. It is included in some vulvovaginal deodorant preparations and in preparations for the treatment of hemorrhoids. It also is used in dental cements and temporary fillings. It is the essential ingredient in *Calamine*.

ZINC PYRITHIONE—see RPS-18, page 1173.
ZINC SULFATE—see RPS-19, page 1271.
ZINC UNDECYLENATE—see RPS-18, page 1237.

IRRITANTS, RUBEFACIENTS, AND VESICANTS

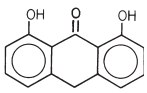
Irritants are drugs that act locally on the skin and mucous membranes to induce, based on irritant concentration, hyperemia, inflammation, and when the action is severe, vesication. Agents that induce only hyperemia are known as *rubefacients*. Rubefaction is produced by increased circulation to the injured area and is accompanied by a feeling of comfort, warmth, and sometimes itching and hyperesthesia. Appropriately low concentrations of directly applied or inhaled vapors of volatile aromatic irritants, such as camphor or menthol, induce a sensation of coolness rather than warmth. When the irritation is more severe, plasma escapes from the damaged capillaries and forms blisters (vesicles). Agents that induce blisters are known as *vesicants*. Most rubefacients also are vesicants in higher concentrations. Certain irritants may be relatively selective for various tissues or cell types, so that hypersecretion of the surface, seborrheic abscesses, paresthesia, or other effects may be noted in the absence of appreciable hyperemia.

Irritants have been used empirically for many centuries, probably even prehistorically. They may be employed for counterirritation, the mechanism of which is poorly understood. A moderate-to-severe pain may be obscured by a milder pain arising from areas of irritation appropriately placed to induce reflex stimulation of certain organs or systems, especially respiratory. Sensory and visible effects of irritation sometimes give patients the assurance that they are receiving effective medication. The rubefacient of choice is simply the applicant of heat, as drugs are much less efficient. Taken internally, many irritants exert either an emetic or laxative action. A few irritants, especially cantharides, on absorption into the bloodstream, irritate the urogenital tract and, consequently, have been dangerously employed as *aphrodisiacs*. Certain irritants also possess a healing action on wounds, possibly the result of local stimulation. Many condiments are irritants. In high concentrations, many irritants even can be corrosive.

ALCOHOL—pages 1080 and 1082.
ALCOHOL, RUBBING—see RPS-19, pages 1264 and 1510.

ANTHRALIN

1,8,9-Anthracenetriol; Dithranol; Dioxyanthranol; Cignolin; Anthra-Derm



1,8-Dihydroxyanthranol [480-22-8] $C_{14}H_{10}O_3$ (226.23).

Preparation—Anthraquinone is sulfonated to the 1,8-disulfonic acid, which is isolated from the reaction mixture and then heated with a calcium hydroxide–calcium chloride mixture to form 1,8-dihydroxy-9,10-anthraquinone, which is reduced with tin and HCl to anthralin.

Description—Yellowish brown, crystalline powder; odorless and tasteless; melts between 175° and 181°.

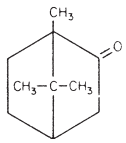
Solubility—Insoluble in water; slightly soluble in alcohol; soluble in chloroform; slightly soluble in ether.

Comments—Although long considered to be an irritant, its principal therapeutic action is the reduction of epidermal DNA synthesis and mitotic activity. It is used in the treatment of *psoriasis, alopecia areata, eczema,* and other *chronic dermatoses*. It usually is used in combination with ultraviolet light and a daily coal tar *bath.* To avoid harmful irritation, medicaments containing it should not be used on the face, scalp, genitalia, or intertriginous skin areas; they should not be applied to blistered, raw, or oozing areas of the skin and should be kept from the eyes, since they may cause severe conjunctivitis, keratitis, or corneal opacity. Renal irritation, casts, and albuminuria may result when the drug is absorbed systemically. The hands should be washed immediately after applying medication. A reversible slight discoloration of the skin may occur.

BENZOIN TINCTURE, COMPOUND—page 1280.

CAMPHOR

2-Camphanone; 2-Bornanone; Gum Camphor; Laurel Camphor



[76-22-2] $C_{10}H_{16}O$ (152.24). A ketone obtained from *Cinnamomum camphora* (Linné) Nees et Ebermaier (Fam *Lauraceae*) (Natural Camphor) or produced synthetically (Synthetic Camphor).

Preparation—Natural crude camphor may be obtained by steam distilling chips of the camphor tree; the crude camphor so obtained is purified, usually by sublimation. One method of producing synthetic camphor starts with *pinene* [$C_{10}H_{16}$], a hydrocarbon obtained from turpentine oil. The pinene is saturated with hydrogen chloride at 0°, forming bornyl chloride [$C_{10}H_{17}Cl$]. On heating the bornyl chloride with sodium acetate and glacial acetic acid, it is converted into isobornyl acetate, which is hydrolyzed subsequently to isobornyl alcohol [$C_{10}H_{17}OH$] and oxidized with chromic acid to camphor. Synthetic camphor resembles natural camphor in most of its properties except that it is a racemic mixture and, therefore, lacks optical activity. When camphor is mixed in approximately molecular proportions with chloral hydrate, menthol, phenol, or thymol, liquefaction ensues; such mixtures are known as *eutectic mixtures*.

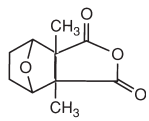
Description—Colorless or white crystals, granules, or crystalline masses or colorless to white, translucent, tough masses; a penetrating, characteristic odor, a pungent, aromatic taste and readily pulverizable in the presence of a little alcohol, ether, or chloroform; specific gravity about 0.99; melts between 174° and 179° and slowly volatilizes at ordinary temperature and in steam.

Solubility—1 g in about 800 mL water, 1 mL alcohol, about 0.5 mL chloroform, or 1 mL ether; freely soluble in carbon disulfide, solvent hexane, or fixed and volatile oils.

Incompatibilites—Forms a liquid or a soft mass when rubbed with *chloral hydrate, hydroquinone, menthol, phenol, phenyl salicylate, resorcinol, salicylic acid, thymol,* or other substances. It is precipitated from its alcoholic solution by the addition of water. It is precipitated from camphor water by the addition of soluble salts.

Comments—Locally, weakly *analgesic,* mildly *analgesic (antipruritic),* and *rubefacient* when rubbed on the skin. The spirit is applied locally to allay itching caused by insect stings. It also is used as a counterirritant in humans for *inflamed joints, sprains,* and *rheumatic* and other *inflammatory* conditions such as colds in the throat and chest. Although the patient may feel improved, the inflammation is not affected. However, reflexly induced local vasoconstriction may mediate a mild nasopharyngeal decongestant effect. When taken internally in small amounts it produces a feeling of warmth and comfort in the GI tract and, therefore, formerly was much used as a *carminative*. Systemically, it is a reflexly active *circulatory* and *respiratory stimulant*. However, its use as a stimulant is obsolete. It also possesses a slight *expectorant* action and is included in some cough-suppressant mixtures. Concentrations above 11% are not safe. Toxicity consists of nausea and vomiting, headache, feeling of warmth, confusion, delirium, convulsions, coma, or respiratory arrest. Camphor is a *pharmaceutical necessity* for *Salicylic Acid Collodion* and *Camphorated Opium Tincture*.

CANTHARIDIN



[56-25-7] $C_{10}H_{12}O_4$ (186.21). The active principle of *Cantharides*.

Preparation—*JACS* 1980; 102:6893.

Description—White platelets.

Solubility—1 g in 40 mL acetone, 65 mL chloroform, 560 mL ether, or 150 mL ethyl acetate; soluble in oils.

Comments—An *irritant* and *vesicant* on skin. As a result of its intradermal vesiculation, it also is employed to remove benign epithelial growths such as warts (particularly the periungual type), molluscum contagiosum, and thick hyperkeratotic lesions without leaving a scar. It usually is applied under occlusive bandages. The vesicle eventually breaks, becomes encrusted, and falls off in 1 to 2 weeks. It is not an aphrodisiac as folklore suggests.

CAPSICUM

The dried ripe fruit of *Capsicum frutescens* Linné, *Solonaceae,* which contains not less than 0.5% of capsaicin [*(E)-N*[4-hydroxy-3-methoxyphenyl]-8-methyl-6-nonaneamide [404-86-4] $C_{18}H_{27}NO_3$ (305.40), which is the active ingredient.

Comments—Its active ingredients are mildly irritant, causing erythema and a feeling of warmth without vesication. Its preparations are used as *counterirritants*.

COAL TAR

Pix Carbonis; Prepared Coal Tar BP; Pix Lithanthracis; Gas Tar

The tar obtained as a by-product during the destructive distillation of bituminous coal.

Description—Nearly black, viscous liquid, heavier than water, with a characteristic naphthalene-like odor and a sharp burning taste; on ignition it burns with a reddish, luminous, and very sooty flame, leaving not more than 2% of residue.

Solubility—Only slightly soluble in water, to which it imparts its characteristic odor and taste and a faintly alkaline reaction; partially dissolved by alcohol, acetone, methanol, solvent hexane, carbon disulfide, chloroform, or ether; to the extent of about 95% by benzene, and entirely by nitrobenzene with the exception of a small amount of suspended matter.

Comments—A *local irritant* used in the treatment of *chronic skin diseases*. Like anthralin, its primary action is to decrease the epidermal synthesis of DNA and, hence, to suppress hyperplasia. Occasionally, it may cause a rash, burning sensation, or other manifestations of excessive irritation or sensitization. Since photosensitization may occur, the treated area should be protected from sunlight. It should be kept away from the eyes and from raw, weeping, or blistered surfaces. Temporary discoloration of the skin may occur.

ICHTHAMMOL

Ammonium Ichthosulfonate; Sulfonated Bitumen; Ictiol; Ichthymall; Ichthyol

[8029-68-3]. It yields not less than 2.5% of ammonia and not less than 10% of total sulfur.

Preparation—By the destructive distillation of certain bituminous schists, sulfonating the distillate and neutralizing the product with ammonia.

Description—Reddish brown to brownish black, viscous fluid, with a strong, characteristic, empyreumatic odor.

Solubility—Miscible with water, glycerin fixed oils, or fats; partially soluble in alcohol or ether. *Incompatibilities:* Becomes granular in the presence of *acids* or under the influence of *heat*. In solution, it is precipitated by acids and *acid salts* as a dark, sticky mass; *alkalies* liberate ammonia; many *metallic salts* cause precipitation.

Constituents—It belongs to a class of preparations containing, as essential constituents, salts or compounds of a mixture of acids designated by the group name *sulfoichthyolic acid,* formed by sulfonation of the oil obtained in the destructive distillation of certain bituminous shales. Sulfoichthyolic acid is characterized by a high sulfur content, the sulfur existing largely in the form of sulfonates, sulfones, and sulfides.

Comments—A *mildly astringent irritant* and *local antibacterial agent* with moderate *emollient* and *demulcent* properties. It is used alone or in combination with other antiseptics for the treatment of skin disorders such as *insect stings and bites, erysipelas, psoriasis,* and *lupus erythematosus* and to produce healing in *chronic inflammations*. It also is used to treat *inflammation* and *boils* in the external ear canal. Medical opinion is divided as to whether this agent is useful. In higher concentrations, irritation is frequent and rashes may develop. It should be kept away from the eyes and other sensitive surfaces. It has been reported to cause hyperepithelialization, an action that would be counterproductive in the treatment of psoriasis.

JUNIPER TAR

Cade Oil

The empyreumatic volatile oil obtained from the woody portions of *Juniperus oxycedrus* Linné (Fam *Pinaceae*).

Description—Dark-brown, clear, thick liquid; tarry odor; faintly aromatic, bitter taste.

Solubility—Very slightly soluble in water; 1 volume in 9 volumes alcohol or 3 volumes ether, leaving a slight, flocculent residue; miscible with chloroform.

Comments—A mildly irritant oil that is employed as a *topical antipruritic* in several chronic dermatological disorders, such as *psoriasis, atopic dermatitis, pruritus, eczema,* and *seborrhea*. Since it is irritant to the conjunctiva and also may cause chemosis of the cornea, care should be taken to keep it out of the eyes. Systemic absorption may result in renal damage.

MENTHOL

Peppermint Camphor

[1490-04-6] $C_{10}H_{20}O$ (156.27). An alcohol obtained from diverse mint oils or prepared synthetically. It may be levorotatory [(−)-Menthol] from natural or synthetic sources, or racemic [(±)-Menthol)].

Preparation—It owes its odor chiefly to menthol, which is obtained from it by fractional distillation and allowing the proper fraction to crystallize or by chromatographic processes. Among numerous methods of synthesis of an optically inactive menthol, the most popular involves the catalytic hydrogenation of thymol (obtained from natural sources or synthesized from *m*-cresol or cresylic acid). The difficulty in the synthesis of (−)-menthol arises from the fact that menthol contains three asymmetric carbon atoms, and there are thus eight stereoisomers, designated as (−)- and (+)-menthol, (−)- and (+)-isomenthol, (−)- and (+)-neomenthol, and (−)- and (+)-neoisomenthol. To obtain a product meeting USP requirements, it is necessary to separate (−)-menthol from its stereoisomers, for which purpose fractional crystallization, distillation under reduced pressure, or esterification may be used. The other stereoisomers differ from the official (−)-menthol in physical properties and possibly to some extent in pharmacological action.

Description—Colorless, hexagonal, usually needle-like crystals or fused masses or a crystalline powder, with a pleasant, peppermint-like odor; (−)-menthol melts between 41° and 44°; (±)-menthol congeals at 27° to 28°.

Solubility—Very soluble in alcohol, chloroform, or ether; freely soluble in glacial acetic acid, mineral oil, or fixed and volatile oils; slightly soluble in water.

Identification—When mixed with about an equal weight of camphor, chloral hydrate, phenol, or thymol, it forms a *eutectic* mixture liquefying at room temperature.

Incompatibilities—Produces a liquid or soft mass when triturated with *camphor, phenol, chloral hydrate, resorcinol, thymol,* or numerous other substances. *Labeling:* The label on the container indicates whether it is levorotatory or racemic.

Comments—In low concentrations, it selectively stimulates the sensory nerve endings for cold and, hence, causes a *sensation of coolness.* Some *local analgesic* effects also accompany this effect. Higher concentrations not only stimulate sensory endings for heat and other pain, but also may cause some irritation. Consequently, there may first be a sensation of coolness, then a slight prickly and burning sensation. The *local analgesia* and *sensation of coolness* are employed in the treatment of insect bites and stings, itching (antipruritic effect), minor burns and sunburn, hemorrhoids, toothache, cankers, cold sores, and sore throat. The local analgesic effect also is the probable basis of the *antitussive* use, although the value of the drug as an antitussive remains unproved. Care must be taken to avoid the inhalation of irritant concentrations. The contribution of a placebo effect to some of these effects cannot be discounted. It is incorporated into *irritant* products used to treat acne vulgaris, dandruff, seborrhea, calluses, corns, warts, and athlete's foot and in vaginal preparations to lessen the sense of irritation. Whatever effects the rubbing of menthol-containing ointment on the chest possesses to relieve pulmonary congestion in colds and allergy are attributable to *counterirritation* and placebo effects. It also is contained in counterirritants for the treatment of muscle aches.

METHYL SALICYLATE—page 1065.

PERUVIAN BALSAM

Peru Balsam; Balsam of Peru; Indian Balsam; Black Balsam

Obtained from *Myroxylon pereirae* (Royle) Klotzsch (Fam *Leguminosae*). Contains from 60% to 64% of a volatile oil termed *cinnamein* and from 20% to 28% resin. Cinnamein is a mixture of compounds, among which the following have been identified: the esters *benzyl benzoate, benzyl cinnamate,* and *cinnamyl cinnamate (styracin)* and the alcohol *peruviol* (considered by some to be identical with the sesquiterpene alcohol *nerolidol,* $C_{15}H_{26}O$) as ester, free *cinnamic acid:* about 0.05% *vanillin;* and a trace of *coumarin*. The resin consists of benzoic and cinnamic acid.

Description—Dark brown, viscid liquid; transparent and appears reddish brown in thin layers; agreeable odor resembling vanilla; a bit-

ter, acrid taste, with a persistent aftertaste and free from stringiness or stickiness. It does not harden on exposure to air; specific gravity, 1.150 to 1.170.

Solubility—Nearly insoluble in water; soluble in alcohol, chloroform, or glacial acetic acid, with not more than an opalescence; partly soluble in ether or solvent hexane.

Comments—A local *irritant* and *vulnerary*. It once was used as a dressing to promote growth of epithelial cells in the treatment of *indolent ulcers, wounds,* and certain *skin diseases,* eg, scabies. It presently is an ingredient in suppositories used in the treatment of hemorrhoids and anal pruritus. Allergic reactions to it occasionally occur. Ointments containing both this and sulfur present a problem in compounding, since the resinous part of the balsam tends to separate. This difficulty may be overcome by mixing the balsam with an equal amount of castor oil prior to incorporating it into the base or, alternatively, by mixing it with solid petroxolin—an ointment vehicle (oxygenated petroleum) consisting of liquid paraffin, oleic acid, and ammoniated alcohol.

PINE TAR

Pix Pini; Pix Liquida; Tar

The product obtained by the destructive distillation of the wood of *Pinus palustris* Miller or of other species of *Pinus* Linné (Fam *Pinaceae*). Usually obtained as a by-product in the manufacture of charcoal or acetic acid from wood. It is a complex mixture of phenolic bodies for the most part insoluble in water. Among these are *cresol, phlorol, guaiacol, pyrocatechol, caerulignol,* and *pyrogallol* ethers. Traces of *phenol* and *cresols* also are present as well as hydrocarbons of the paraffin and benzene series.

Description—Very viscid, blackish brown liquid; translucent in thin layers, but becomes granular and opaque with age; has an empyreumatic, terebinthinate odor, a sharp, empyreumatic taste, and is more dense than water; solution is acid to litmus.

Solubility—Miscible with alcohol, ether, chloroform, glacial acetic acid, or fixed and volatile oils; slightly soluble in water, the solution being pale yellowish to yellowish brown.

Comments—Externally as a mild *irritant* and *local antibacterial* agent in chronic *skin diseases,* especially eczema and psoriasis. Its volatile constituents are claimed to be *expectorant,* but their efficacy is unproven; its inhalations formerly were used for this purpose.

STORAX—page 1090.
TOLU BALSAM—page 1068.

SCLEROSING AGENTS

A number of irritant drugs are of sufficient activity to damage cells but are not so potent as to destroy large numbers of cells at the site of application. Such agents promote fibrosis and are used to strengthen supporting structures, close inguinal rings, etc. The intimal surface of blood vessels may break down under attack by such agents and thus initiate thrombosis, which may be an undesirable side effect. This action is the basis of the use of sclerosing agents in the reduction of varicose veins and hemorrhoids. They can be harmful when used improperly and sometimes even when used with caution.

MORRHUATE SODIUM INJECTION

Scleromate

A sterile solution of the sodium salts of the fatty acids of cod liver oil. It contains 50 mg of sodium morrhuate/mL. A suitable antimicrobial agent, not to exceed 0.5%, and ethyl or benzyl alcohol, not to exceed 3%, may be added.

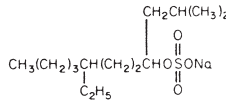
Note—It may show a separation of solid matter on standing. Do not use the material if such solid does not dissolve completely upon warming.

Preparation—By heating cod liver oil with alcoholic sodium hydroxide until completely saponified. After dilution with water the alcohol is removed by distillation. Dilute H_2SO_4 then is added to the aqueous solution, and the liberated organic acids are separated or preferably extracted with a suitable immiscible solvent such as ether. Just-sufficient aqueous NaOH then is added to neutralize the acids. About 20 mg of benzyl alcohol/mL of the Injection usually is added to lessen the pain of injection.

Comments—Formerly, widely used as a *sclerosing* and *fibrosing* agent for obliterating *varicose veins*. Irritants of this type once were employed for closure of hernial rings, fibrosing of uncomplicated hemorrhoids, removal of condylomata acuminata, and in other conditions where the ultimate objective was production of fibrous tissue.

SODIUM TETRADECYL SULFATE

STS; Sotradecol



[139-88-8] $C_{14}H_{29}NaO_4S$ (316.43).

Preparation—One method reacts the corresponding alcohol with $ClSO_3H$ and neutralizes the resulting hydrogen sulfate ester with Na_2CO_3.

Description—White, waxy, odorless solid.

Solubility—Soluble in water, alcohol, or ether.

Comments—A *sclerosing* agent similar in action to sodium morrhuate. It formerly was used widely as a buffered solution in the *obliteration of varicose veins and internal hemorrhoids*. For such purposes, the solution is injected directly into the vein. Injection outside of the vein may cause sloughing. For this reason, the substance is not used to close inguinal rings. The principal untoward effect is pain immediately upon injection, although brief; mild anaphylactoid and idiosyncratic responses rarely occur. Because the substance is an anionic surface-active agent, it also is used as a *wetting agent* to promote spreading of certain topical antiseptics.

CAUSTICS AND ESCHAROTICS

Any topical agent that causes destruction of tissues at the site of application is a *caustic* (or corrosive).

Caustics may be used to induce desquamation of cornified epithelium (*keratolytic* action) and, therefore, are used to destroy warts, condylomata, keratoses, certain moles, and hyperplastic tissues.

If the agent also precipitates the proteins of the cell and the inflammation exudate, there is formed a scab (or eschar), which later is organized into a scar; such an agent is an *escharotic* (or cauterizant). Most, but not all, caustics are also escharotic. Furthermore, certain caustics, especially the alkalies, redissolve precipitated proteins, partly by hydrolysis, so that no scab or only a soft scab forms; such agents penetrate deeply and generally are unsuitable for therapeutic use. Escharotics sometimes are employed to seal cutaneous and aphthous ulcers, wounds, etc. Since most escharotics are bactericidal, it formerly was thought that chemical cauterization effected sterilization; however, sterilization is not achieved always, especially by those agents that remain bound to the protein precipitate. The growth of certain bacteria even may be favored by the chemically induced necrosis and by the protection of the scab.

ACETIC ACID, GLACIAL—page 1083.
ALUM—page 1282.
ALUMINUM CHLORIDE—page 1282.

DICHLOROACETIC ACID

Bichloracetic Acid

$Cl_2CHCOOH$ [79-43-6] $C_2H_2Cl_2O_2$ (128.95).

Preparation—From chloral; *Chem Ind* 1960; 718.

Description—Pungent liquid; boils about 194°.

Solubility—Miscible with water, alcohol, or ether.

Comments—A *cauterizing agent*. It rapidly penetrates and cauterizes skin, keratins, etc. Its cauterizing ability compares with that of electrocautery or freezing. It is used on calluses, hard and soft corns, xanthoma palpebrarum, seborrheic keratoses, ingrown nails, cysts, and benign erosion of the cervix. See also *Trichloroacetic Acid*.

NITRIC ACID, CONCENTRATED

An aqueous solution containing 67% to 71% HNO_3.

Preparation—By oxidation of ammonia.

Description—Fuming liquid; very caustic; characteristic, highly irritating odor; boils at 120°; specific gravity about 1.41.

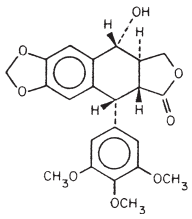
Solubility—Miscible with water.

Comments—A *cauterizing agent* for the immediate sterilization of dangerously infected wounds, such as the bite from a rabid animal; it does not penetrate too deeply and forms a firm eschar.

PHENOL—page 1087.

PODOFILOX

Furo[3′,4′:6,7]naphtho[2,3-*d*]-1,3-dioxol-6(5a*H*)-one, [5*R*-(5α,5aβ, 8aα,9α)]-5,8,8a,9-tetrahydro-9-hydroxy-5-(3,4,5-trimethoxyphenyl)-, Condylox



Podophyllotoxin [518-28-5] $C_{22}H_{22}O_8$ (414.41).

Found in the rhizomes of several species of plants, principally *Podophyllum peltatum* L *Berberidaceae, P emodi,* and *Juniperus virginiana* L *Coniferae*.

Preparation—See *JACS* 1981; 103:6208.

Description—Hydrated crystals; melts about 115° (dec) and about 184° after drying; a number of polymorphic forms exist.

Solubility—Very slightly soluble in water; soluble in alcohol, chloroform, or acetone.

Comments—Actions, uses, and adverse effects are those of *Podophyllum Resin* (below), except that the therapeutic index is greater. It is several times more potent.

PODOPHYLLUM

Mandrake; May Apple

The dried rhizome and roots of *Podophyllum peltatum* Linné (Fam *Berberidaceae*); it yields not less than 5% of podophyllum resin.

Constituents—From 3% to 6% resin along with up to 1% quercetin and podophyllotoxin and peltatin glucosides. At least 16 different compounds have been isolated and characterized. The aglycone *podophyllotoxin* [$C_{22}H_{22}O_8$] is the lactone of 1-hydroxy-2-(hydroxymethyl)-6,7-methylenedioxy-4-(3′,4′,5′-trimethoxyphenyl)-1,2,3,4-tetrahydronaphthalene-3-carboxylic acid. Hydrolytic rupture of the lactone ring yields *podophyllic acid* [$C_{22}H_{24}O_9$], the 2,3-*trans* form of which is *podophyllinic acid,* while the 2,3-*cis* form is *picropodophyllinic acid*.

Although podophyllotoxin has been demonstrated to possess marked caustic, cathartic, and toxic properties, it is believed that not it, but an amorphous *resin,* called *podophylloresin,* is the chief cathartic principle of the drug. However, podophyllotoxin is safer and ultimately likely will replace the crude preparations.

Comments—See *Podophyllum Resin*.

PODOPHYLLUM RESIN

Comments—Supersedes *Podophyllum*. Certain glycosides and polynuclear lactones in the resin interact with tubulin and, thus, interfere with cell cycling and intracellular dynamics such as to cause the eventual death of affected cells. Applied topically, it is corrosive in the region of contact. It mainly is used in the treatment of *condyloma acuminatum* but also that of *juvenile papilloma of the larynx, multiple superficial epitheliomatoses* (basal cell and squamous cell carcinomas), *precancerous keratoses* (seborrheic, actinic, and radiation keratoses), *verrucae fibroids,* and *calluses*. Some pain usually occurs at the site of application; if it is excessive, the drug should be removed with ethyl or isopropyl alcohol. Resin on adjacent normal tissues also should be removed. Pain may be avoided somewhat by treating only a small area of surface at any one time. *It especially is irritating to the eyes and mucous membranes*. Treatment of large surfaces also may result in excessive absorption and systemic effects, such as nausea and vomiting, tachycardia, shallow respiration, leukopenia, thrombocytopenia, renal damage, paralytic ileus, lethargy, stupor, psychotic confusional states, and peripheral neuropathy, including flaccid paralysis. Systemic absorption is enhanced by occlusion. The drug is contraindicated in pregnancy and lactation.

POTASSIUM HYDROXIDE

Caustic Potash; Lye; Potash Lye

[1310-58-3] KOH (56.11); it contains not less than 85.0% K_2CO_3 (138.21).

Caution—Exercise great care in handling, as it rapidly destroys tissues. Do not handle it with bare hands.

Preparation—By electrolysis of a solution of potassium chloride in a diaphragm cell that does not allow liberated chlorine to react with it. It is prepared in the form of sticks, pellets, flakes, or fused masses. Sticks or pellets are made by evaporating a solution of it to a fluid of oily consistency and then pouring the hot liquid into suitable molds in which it solidifies.

Description—White, or nearly white, fused masses, small pellets, flakes, sticks, and other forms; hard and brittle and shows a crystalline fracture; exposed to air it rapidly absorbs carbon dioxide and moisture and deliquesces; melts at about 360 to 380°; when dissolved in water or alcohol or when its solution is treated with an acid, much heat is generated; solutions, even when highly diluted, are strongly alkaline.

Solubility—1 g in 0.9 mL water, 3 mL alcohol, or 2.5 mL glycerin at 25°; very soluble in boiling alcohol.

Incompatibilities—Bases react with *acids* to form salts, liberate alkaloids from aqueous solutions of *alkaloidal salts,* and promote various hydrolysis reactions such as the decomposition of *chloral hydrate* into chloroform and a formate or the breakdown of *salol* into phenol and a salicylate. Only the alkali hydroxides are appreciably soluble in water. Nearly all common *metals* will be precipitated as hydroxides when solutions of their salts are added to solutions of the alkali hydroxides. Certain hydroxides, however, notably those of aluminum, zinc, arsenic, or lead, will dissolve in an excess of sodium or potassium hydroxide.

Comments—A *caustic,* principally in veterinary practice. The end of a stick of potassium hydroxide may be inserted into a section of rubber tubing or wrapped several times with tin foil to avoid cauterizing the fingers of the operator. It is used also as a *pharmaceutical necessity* in several pharmacopeial preparations.

SALICYLIC ACID—page 1288.

SILVER NITRATE

Nitric acid, silver(1+) salt; Argenti Nitras

Silver(1+) nitrate [7761-88-8] $AgNO_3$ (169.87).

Preparation—By the action of nitric acid on metallic silver.

Description—Colorless or white crystals; on exposure to light in the presence of organic matter, it becomes gray or grayish black; pH of solutions about 5.5.

Solubility—1 g in 0.4 mL water, 30 mL alcohol, about 250 mL acetone, slightly more than 0.1 mL boiling water or about 6.5 mL of boiling alcohol; slightly soluble in ether.

Incompatibilities—Easily reduced to metallic silver by most *reducing agents,* including *ferrous salts, arsenites, hypophosphites, tartrates, sugars, tannins, volatile oils,* and other *organic substances*. In neutral or alkaline solutions, precipitated by *chlorides, bromides, iodides, borax, hydroxides, carbonates, phosphates, sulfates, arsenites,* and *arsenates. Potassium permanganate, tannic acid,* and *soluble citrates and sulfates* may cause a precipitate if sufficiently concentrated. In acid solution, only the *chloride, bromide,* and *iodide* are insoluble. *Ammonia water* dissolves many of the insoluble silver salts through formation of the silver diamine complex, $Ag(NH_3)_2^+$.

Comments—Silver ions combine with proteins and cause denaturation and precipitation. As a result, silver ions have *astringent, caustic, bactericidal,* and *antiviral* properties. In low concentrations, silver-denatured protein is confined to the interstitial spaces and the surface of denuded, weeping areas, so that only astringent and antimicrobial effects occur; with higher concentrations, cell membranes are disrupted and caustic effects result. The corroded site will become covered with a scab of silver-protein precipitate.

It is used mainly in podiatry as a caustic to *destroy excessive granulation tissue,* such as *corns, calluses, granuloma pyogenicum,* and *plantar warts; reduce neurovascular helomas; remove papillomas; and cauterize small nerve endings* and *blood vessels*. As an astringent, it is used to treat *impetigo vulgaris* and *pruritus* as well as *indolent ulcers, wounds,* and *fissures*. It also is used as a *styptic,* especially in dentistry.

As an antiseptic, it mainly is employed prophylactically against *ophthalmia neonatorum*. It formerly was applied regularly to burned surfaces because of its high efficacy against both staphylococci and pseudomonas. However, the precipitation of AgCl at the site of application and in dressing depletes plasma chloride and can cause serious electrolyte disturbances; consequently, the drug seldom is used in burn therapy today.

Excessive corrosion at the target site and corrosion from inadvertent application or leakage away from the intended site can occur. Dental cones or pieces of toughened silver nitrate that are accidentally ingested can cause death. Elemental silver from the bioreduction of silver ion may reside permanently at the site of application and cause a bluish-to-black discoloration called argyria. Locally injected sodium thiosulfate sometimes can remove the silver. Nitrate ion absorbed from large, denuded surfaces can cause methemoglobinemia. Only concentrations 0.5% or below should be applied to raw wounds, fresh cuts, or broken skin.

TRICHLOROACETIC ACID

Tri-Chlor

[76-03-9] $C_2HCl_3O_2$ (163.39).

Preparation—Usually by oxidizing chloral hydrate with fuming nitric acid.

Description—Colorless, deliquescent crystals with a slight, characteristic odor; melts at about 58° and boils at 196° to 197°.

Solubility—1 g in about 0.1 mL water; soluble in alcohol or ether.

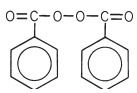
Comments—Precipitates proteins and used as a *caustic* on the skin or mucous membranes to destroy local lesions and for treatment of various dermatological disease. Its chief use is to destroy ordinary warts and juvenile flat warts. It is employed extensively as a precipitant of protein in the chemical analysis of body fluids and tissue extracts, as well as a *decalcifier* and *fixative* in microscopy.

Caution—Trichloroacetic Acid is highly corrosive to the skin.

KERATOLYTICS (DESQUAMATING AGENTS)

The epidermis consists of layers of flat cells, called *stratified squamous epithelial cells*. They are bound together by desmosomes and penetrating tonofibrils, both of which largely consist of keratin. The outer layer of the epidermis (cornified epithelium or stratum corneum) is composed of the collapsed ghosts of the squamous cells (keratinocytes or corneocytes) that are primarily tight networks of keratin and lipoprotein within a matrix of lipid multilayers. Unlike most cellular membranes, the lipids include fatty acids, neutral lipids, ceramides, etc, and are predominantly in the gel (solid-like) state. Certain fungi, especially the dermatophytes, use keratin and, therefore, reside in the stratum corneum in those places where the degree of hydration and the pH are sufficiently high. One way such mycoses may be suppressed is removal of the stratum corneum, a process called *desquamation*. Certain chemical substances, especially among phenols and sulfhydryl compounds, loosen the keratin and thus facilitate desquamation. These substances are called *keratolytics*. Aqueous maceration of the stratum corneum also favors desquamation. In addition to the treatment of epidermophytosis, keratolytics are used to thin hyperkeratotic areas. Most keratolytics are irritant. Irritants also can cause desquamation by causing damage to, and swelling of, the basal cells.

BENZOYL PEROXIDE



[94-36-0] $C_{14}H_{10}O_4$ (242.23); contains 65% to 82% of benzoyl peroxide; also contains about 26% of water for the purpose of reducing flammability and shock sensitivity.

Preparation—Benzoyl chloride is reacted with a cold solution of sodium peroxide.

Description—White, granular powder with a characteristic odor; melts about 104°; *may explode with heat*.

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

Caution (for the drug entity, not the dosage forms)—It may explode at temperatures higher than 60° or cause fires in the presence of reducing substances. Store it in the original container, treated to reduce static charges. Do not transfer it to metal or glass containers fitted with friction tops. Do not return unused material to its original container, but destroy it by treatment with NaOH solution (1 in 10) until addition of a crystal of KI results in no release of free iodine.

Comments—Possesses *mild antibacterial* properties, especially against anaerobic bacteria. It is also mildly irritant, and it exerts moderate keratolytic and antiseborrheic actions. Its principal use is in the treatment of mild *acne vulgaris* (in which it is comedolytic) and *acne rosacea,* but it also is used in the treatment of decubital and stasis ulcers.

It causes stinging or burning sensations for a brief time after application; with continued use these effects mostly disappear. After 1 or 2 weeks of use there may be a sudden excess dryness of the skin and peeling. The drug must be kept away from the eyes and from inflamed, denuded, or highly sensitive skin, such as the circumoral areas, neck, and skin of children. It should not be used in conjunction with harsh abrasive skin cleansers. It can cause contact dermatitis. It can bleach hair and fabrics.

FLUOROURACIL—pages 1573 and 1680.

SALICYLIC ACID

Benzoic acid, 2-hydroxy-, *o*-Hydroxybenzoic Acid

Salicylic acid [69-72-7] $C_7H_6O_3$ (138.12).

Preparation—Mostly by the Kolbe-Schmidt process in which CO_2 is reacted with sodium phenolate under pressure at about 130° to form sodium salicylate, followed by treatment with mineral acid.

Description—White, fine, needle-like crystals or a fluffy, white, crystalline powder; the synthetic acid is white and odorless; sweetish, afterward acrid, taste; stable in the air; melts between 158° and 161°.

Solubility—1 g in 460 mL water, 3 mL alcohol, 45 mL chloroform, 3 mL ether, 135 mL benzene, or about 15 mL boiling water.

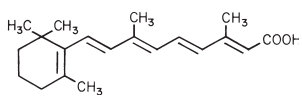
Comments—Used *externally* on the skin, where it exerts a slight *antiseptic* action and considerable *keratolytic* action. The latter property makes it a beneficial agent in the local treatment of certain forms of *eczematoid dermatitis*. It also is included in products for the treatment of *psoriasis,* for which the FDA classification is Category I. Tissue cells swell, soften, and ultimately desquamate. Salicylic Acid Plaster often is used for this purpose. The drug is especially useful in the treatment of *tinea pedis* (athlete's foot) and *tinea capitis* (ringworm of the scalp), since the fungus grows and thrives in the stratum corneum. Keratolysis both removes the infected horny layer and aids in penetration by antifungal drugs. It is combined with benzoic acid in an ointment long known as *Whitfield's Ointment* (see RPS-18, page 1235). It also is combined commonly with zinc oxide, sulfur, or sulfur and coal tar. It is incorporated into mixtures for the treatment of acne, dandruff, and seborrhea, insect bites, and stings and into soaps and vaginal douches, but efficacy remains to be established. In high concentrations it is *caustic* and may be used to remove *corns, calluses, warts,* and other growths.

Collodions or solutions of 17% or higher and other forms above 25% concentration should not be employed if the patient has diabetes mellitus, peripheral vascular disease, or inflammation or infection at the intended site of application. Continuous application of the drug to the skin can cause dermatitis. Systemic toxicity resulting from application to large areas of the skin has been reported. It is not employed internally as an analgesic because of its local irritating effect on the GI tract.

SULFUR, PRECIPITATED—page 1598.

TRETINOIN

Retinoic acid; Retin-A



All *trans*-Retinoic acid [302-79-4] $C_{20}H_{28}O_2$ (300.44).

Preparation—By oxidation of vitamin A aldehyde which may be obtained by oxidation of vitamin A. *Biochem J* 1964; 90:569.

Description—Yellow to light-orange crystals or crystalline powder with the odor of ensilage; should be stored in cold and protected from light and air; melts between 176° and 181°.

Solubility—Insoluble in water; slightly soluble in alcohol; slightly soluble in chloroform; 1 g in 10 mL boiling benzene.

Comments—It is retinoic acid, or so-called *vitamin A acid,* which is formed when the aldehyde group of retinene (retinal) is oxidized to a carboxyl group. It is not known whether retinoic acid has a physiological function, but some authorities consider it to be the form of vitamin A that acts in the skin. This view is supported by the fact that retinol and retinal have very little action on the skin but large systemic doses of vitamin A evoke prominent dermatological changes.

Topically, it causes inflammation, thickening of the epidermis (acanthosis), and local intercellular edema, which leads to some separation of the epidermal cells. Follicular epithelial cells become less adhesive, the stratum corneum loosens, and exfoliation may occur. High concentrations can cause vesiculation. These actions are used in the treatment of *acne vulgaris.* The loosened horny layer makes it easier for the comedo

to rise up and discharge, and the inflammatory response mobilizes white cells that attack the bacteria in the follicle. In the early stages of treatment, the sudden surfacing of obscured preexisting comedones makes it appear that the acne has been exacerbated, but the new comedones do not coalesce into cysts or nodules, and scarring does not occur. The exaggerated stage may last for as long as 6 weeks, after which improvement comes rapidly. Shortly after discontinuation of treatment, relapses readily occur. Deep cystic nodular acne (acne conglobata) or severe cases usually are not improved by the drug.

Various hyperkeratotic conditions are reported to respond to it, responses being sometimes exceptionally dramatic. *Solar* and *follicular keratosis, lamellar ichthyosis, keratosis palmaris* and *plantaris,* and other hyperplastic dermatoses have been treated successfully with the drug. It also has been used in the treatment of some skin cancers. Recent reports indicate that it may somewhat rejuvenate sun-aged skin.

It is an antioxidant and free-radical scavenger. There is some evidence not only that topical applications may provide some protection from actinic and other radiation effects on the skin, including cancer, but that internally it may be protective against carcinogenesis from radiation and carcinogens. Systemically, it does not cause the toxic effects of large doses of vitamin A.

In concentrations of 0.05% to 0.1%, it causes a transient feeling of warmth or mild stinging, and erythema follows. Peeling of the skin may occur. Irritation and peeling are marked more when the concentration exceeds 0.1%. When peeling, crusting, or blistering occur, medication should be withheld until the skin recovers, or the concentration should be reduced. The drug should not be applied around the eyes, nose, or angles of the mouth, because the mucosae are much more sensitive than the skin to the irritant effects. It also may cause severe irritation on eczematous skin. It should not be applied along with, or closely following, other irritants or keratolytic drugs. Exposure to sunlight should be avoided if possible. Both hypo- and hyperpigmentation have been reported, but the conditions appear to be reversible and temporary.

TRICHLOROACETIC ACID—page 1288.

CLEANSING PREPARATIONS

The skin may be cleansed with detergents, solvents, or abrasives, singly or in combination. Among the detergents, the soaps have enjoyed the greatest official status, more through custom than through special merit. The nonsoap detergents became important not only as household hand cleansers, but in dermatological and surgical practice as well. However, because many nonsoap detergents do not decompose in sewage disposal plants, there has been a return to real soap. Some of the antiseptic *soaps* still contain synthetic detergents. Soap interferes with the action of many antiseptics, which is one reason synthetic detergents often are used in antiseptic cleansing preparations. However, synthetic detergents also interact with some antiseptics. Anionic nonsoap skin detergents rarely sensitize the skin and, thus, are prescribed when the user is allergic to soap.

Ordinary soaps tend to be alkaline, with pH ranging from 9.5 to 10.5. Superfatted soaps have a pH in the lower end of the range. Synthetic detergents usually have a pH ≤5.6. Neutral toilet bars contain synthetic detergents. Anionic surfactants and cationic detergents emulsify fats with water as well as assisting in the removal of foreign particulates from the skin, scalp, or hair.

Shampoos are liquid soaps or detergents used to clean the hair and scalp. Both soaps and shampoos often are used as vehicles for dermatological agents.

Many bar soaps contain either triclosan or triclocarban as antiseptics in concentrations that suppress bacterial production of body odors but that effectively are not antiseptic. A number of soaps and shampoos contain keratolytic and antiacne ingredients. Abrasive soaps contain particles of alumina, polyethylene, or sodium tetraborate decahydrate.

It commonly, but erroneously, is believed that soap has an antiseptic action. The promotion of either soap or synthetic detergents alone for the control of acne is unwarranted; antiseptic substances must be added to the cleansing material or be used separately. Quantitative studies of the cutaneous flora before and after cleansing with soap or with other anionic detergents show a negligible antiseptic effect. However, the removal of loose epidermis lessens the likelihood that cutaneous bacteria will be transferred from the skin to other structures. Certain cationic detergents employed in dermatology are antiseptic. Detergents are treated under *Surface-Active Agents*, chapter 39.

The choice of organic solvents to cleanse the skin depends largely upon the nature of the material to be removed. In medical practice ethanol and isopropyl alcohol are the most frequently employed organic solvents. Cleansing creams act both as solvents and as detergents. Other soapless cleansers variously contain petrolatum, vegetable oils, lanolin, high-molecular-weight alcohols, various carbohydrate derivatives, oatmeal, and other ingredients.

ALCOHOL—pages 1080 and 1082.
ALCOHOL, RUBBING—see RPS-19, pages 1264 and 1510.
BENZALKONIUM CHLORIDE—page 1626.
HEXACHLOROPHENE CLEANSING EMULSION—page 1628.
ISOPROPYL RUBBING ALCOHOL—page 1629.
SELENIUM SULFIDE—page 1629.
SODIUM LAURYL SULFATE—page 1075.

TRANSDERMAL SYSTEMS

Transdermal systems are designed to employ the skin as either a rate-controlling barrier to drug absorption or a reservoir for drug absorption. The primary compounds delivered via transdermal systems include estradiol, page 1463; nitroglycerin, page 1359; nicotine, page 1371; clonidine, page 1270; fentanyl, page 1531; scopolamine, page 1408, and testosterone, page 1472.

These drugs are discussed elsewhere, since their pharmacological activity is not primarily skin-related. However, transdermal systems have been developed to deliver salicylic acid for localized therapy in the skin to remove warts (salicylic acid, page 1288).

The underlying principles of percutaneous absorption are discussed in further detail in Chapter 37, while the systems are discussed in Chapter 50. However, transdermal systems may give localized effects within skin because of increased hydration as a result of occlusion, drug metabolism or degradation within the skin, penetration enhancer–associated skin alterations, increased localized bacterial populations, etc.

MISCELLANEOUS DERMATOLOGICALS

Gargles, nasal washes, douches, enemata, etc, generally contain as basic ingredients substances described under other categories in this chapter.

Antiphlogistics include alcohol and several creams and lotions that cool the skin by evaporation. Many antiphlogistic preparations also contain an astringent and a local anesthetic or camphor or menthol.

Commonly employed *antipruritics* also depend to some extent upon local anesthetics and the soothing effect of cooling, although some emollients or demulcents may be included, especially depending upon the cause of the pruritus. The antipruritic properties of phenol preparations largely derive from superficial local anesthesia.

Vulnerary and *epithelizing* properties are attributed to numerous irritants and to several dyes; however, few reliable data exist to support most claims to vulnerary action.

Sunscreens contain aromatic compounds such as aminobenzoic acid, which efficiently absorb the harmful UV rays from the incident sunlight and transmit mainly the less harmful wavelengths, or titanium dioxide, which reflects sunlight from the surface of application. UV light in the spectral range of 290 to 320 nm causes suntan and sunburn; therefore, a sunscreen to prevent tan or burn should have a high molar absorptivity in this range. However, *photosensitization* (ie, the photoactivation of chemicals to make them toxic or allergenic)

may occur with wavelengths as high as 500 nm; consequently, to protect recipients of certain drugs (tetracyclines, sulfonamides, erythromycin, promazine, chlorpromazine, promethazine, psoralens), sunscreens with a broader absorption spectrum are required. An adequately broad spectrum is usually achieved with combinations of sunscreens (eg, dioxybenzone and oxybenzone).

Melanizers are substances that promote the pigmentation of the skin. Most melanizers produce their effect by sensitizing the skin to UV light, so that the effect is principally the same as if the subject had been exposed for a long time to the sun.

This action is termed a *photodynamic action*. The term has been used loosely to include all instances of enhanced sensitivity to light, but in strict definition it is confined to photosensitization in which the participation of oxygen is required. In the photodynamic process, light of wavelengths too long to be ordinarily effective may be used, so that the activating spectrum may be shifted toward longer wavelengths.

Skin bleaches, or *demelanizers,* mostly contain hydroquinone derivatives.

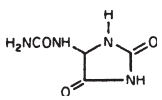
Hair bleaches generally contain peroxides.

There is a large variety of *depilatories* on the market. Many of them are sulfhydryl compounds, especially thioglycollates, which reduce the disulfide bonds of keratin, thus softening the hair to the point where it can be separated easily from the epidermis. Some of the same compounds are used in lower concentrations in hairwaving preparations. There is one drug, minoxidil, an antihypertensive drug, which can *increase hair growth* and *treat baldness*.

Antiperspirants have been included among the astringents.

ALLANTOIN

Urea, (2,5-dioxo-4-imid-azolidinyl)-,



[97-59-6] $C_4H_6N_4O_3$ (158.12).

Preparation—By oxidation of uric acid.

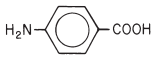
Description—Colorless crystals; melts at 238°.

Solubility—1 g in 190 mL water or 500 mL alcohol; nearly insoluble in ether.

Comments—In World War I it was noticed that maggot-infested wounds seemed to heal better than uninfested wounds, an effect attributed to this drug produced by maggots. It is used topically as a *vulnerary* to stimulate tissue repair in suppurating wounds, resistant ulcers, acne, seborrhea, cold sores, hemorrhoids, and various dermatological infections and psoriasis. It frequently is combined with astringents, keratolytics, coal tar, antiseptics, and antifungal drugs. The silver salt has been used in the topical treatment of extensive burns.

AMINOBENZOIC ACID

Benzoic acid, 4-amino-, PABA



p-Aminobenzoic acid [150-13-0] $C_7H_7NO_2$ (137.14).

Preparation—*p*-Nitrotoluene is oxidized with permanganate to *p*-nitrobenzoic acid, and the nitro group then is reduced to an amino group with iron and hydrochloric acid.

Description—White or slightly yellow, odorless crystals or crystalline 8 powder; melts between 186° and 189°; discolors on exposure to air or light.

Solubility—Slightly soluble in water or chloroform; freely soluble in alcohol or solutions of alkali hydroxides and carbonates; sparingly soluble in ether.

Comments—A *sunscreen*. It absorbs UV light of wavelengths in the region of 260 to 313 nm; its molar absorptivity at 288.5 nm is 18,300. However, it does not absorb throughout the near UV range, so that drug-related photosensitivity and phototoxicity may not be prevented by it, but in combination with benzophenone it does protect against some drug-induced phototoxicities. Nevertheless, in the 260 to 313 nm range, it has the highest protection index of current sunscreen agents.

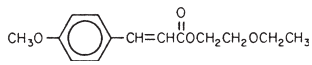
For animal species that do not use preformed folic acid, which contains the *p*-aminobenzoyl moiety, it is a B vitamin. However, man does not use it, and its promotion in vitamin preparations preys on the ignorance of the consumer. It or its potassium salt is promoted as an agent that softens or regresses fibrotic tissue in Peyronie's disease, scleroderma, dermatomyositis, morphea, and pemphigus. The claims for the antifibrotic actions are substantiated poorly, and the actions and uses are not mentioned in major works on pharmacology and therapeutics.

Topically, it is rarely allergenic to recipients, but phototoxicity and photoallergenicity occur. Systemic side effects include nausea, anorexia, fever, and rash.

CETYL ALCOHOL—page 1078.

CINOXATE

Propenoic acid, 3-(4-methoxyphenyl)-, 2-ethoxyethyl ester



[104-28-9] $C_{14}H_{18}O_4$ (250.29).

Preparation—Brit Pat 856,411.

Description—A viscous liquid; may have a slightly yellow tinge; boils about 185°.

Solubility—Practically insoluble in water; miscible with alcohol.

Comments—A *sunscreen* that absorbs UV light at 270 to 328 nm and has a relatively high molar absorptivity (19,400 at 306 nm) but is nonabsorbing throughout the entire offending range of UV light. Consequently, it is used principally in preparations intended to promote tanning rather than to protect against photosensitivity and phototoxicity.

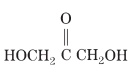
DEXTRANOMER

For the complete monograph, see page 1290.

Comments—For *drying, cleansing,* and *debridement* of exudative *venous stasis ulcers; infected wounds* and *burns;* it is not useful for cleansing nonexudative wounds or lesions. The beads not only absorb water but also proteins, including fibrin/fibrinogen degradation products, and thus prevent encrustation. The beads are poured into the cleansed wound, which is circumscribed with petroleum jelly, and a compress is taped in place to retain the material. Changes may be made up to three or four times a day, as needed. The beads must be removed before skin grafting is attempted. Care must be taken to prevent cross-contamination from patient to patient. On the floor the beads are slippery and thus hazardous.

DIHYDROXYACETONE

Chromelin Complexion Blender



[96-26-4] $C_3H_6O_3$ (90.08).

Preparation—By oxidation of the secondary alcohol group of glycerin.

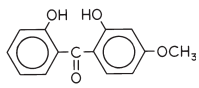
Description—Crystalline powder; fairly hygroscopic; characteristic odor; sweet taste; melts about 77°.

Solubility—*Dimer* (normal form): slowly soluble in 1 part water or 15 parts alcohol. *Monomer* (formed in solution): very soluble in water, alcohol, or ether.

Comments—Interacts with keratin in the stratum corneum to form a dark pigment that simulates the appearance of a suntan. It is incorporated in several *sunscreen* preparations. Since the sunscreen component is usually present in a concentration lower than optimal, such preparations may not provide protection to photosensitive persons. Also used to treat vitiligo.

DIOXYBENZONE

Methanone, (2-hydroxy-4-methoxyphenyl)(2-hydroxyphenyl)-, Solaquin



2,2′-Dihydroxy-4-methoxybenzophenone [131-53-3] $C_{14}H_{12}O_4$ (244.25).

Preparation—By a Friedel-Crafts reaction in which *o*-methoxybenzoyl chloride is added gradually to a mixture of 1,3-dimethoxybenzene, chlorobenzene, and aluminum chloride. The reaction conditions are such that both methoxy groups ortho to the carbonyl bridge in the initial condensation product are demethylated. US Pat 2,853,521.

Description—Off-white to yellow powder; congeals not lower than 68°.

Solubility—Practically insoluble in water; freely soluble in alcohol or toluene.

Comments—A *sunscreen* of intermediate molar absorptivity (11,950 at 282 nm), but it absorbs throughout the UV spectrum and, hence, affords protection not only against sunburn but also against the photodynamic, photosensitizing, and phototoxic effects of drugs. At present, it is marketed in combination with the closely related *Oxybenzone*.

ETHYLHEXYL *P*-METHOXYCINNAMATE

Parsol MCX

Octyl methoxycinnamate [5466-77-3] $C_{18}H_{26}O_3$ (290.40).

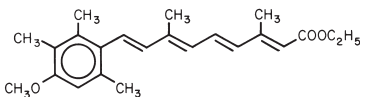
Preparation—US Pat 4,713,473.

Description—High-boiling liquid.

Comments—A *sunscreen* with a narrow absorption band of 290 to 320 nm and a moderate molar absorptivity.

ETRETINATE

2,4,6,8-Nonanetetraenoic acid, 9-(4-methoxy-2,3,6-trimethylphenyl)-3,7-dimethyl-, ethyl ester *(all-E);* Tegison



[54350-48-0] $C_{23}H_{30}O_3$ (354.49).

Preparation—One scheme involves the Wittig condensation of diphenyl 2,3,6-trimethyl-4-methoxybenzylphosphonium chloride and 8-oxo-3,7-dimethyl-2,4,6-octane-trienoic acid (all-*trans*) in the presence of butylene oxide; *Experientia* 1978; 34: 1113.

Description—Crystalline solid melting about 104°.

Solubility—Soluble in alcohol; insoluble in water.

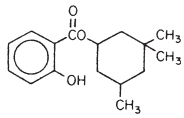
Comments—Although not a topical drug, it is a retinoid closely related to tretinoin and is used only for its dermatological actions; consequently, it is included in this chapter. It is used in the treatment of recalcitrant *psoriasis,* especially the severe, pustular, erythrodermic type. It decreases scaling, erythema, and the thickness of lesions and causes epithelial and dermal cells to redifferentiate to normal cells. Sometimes, dramatic improvement occurs within 2 weeks and complete clearing in 1.5 to 4.5 months. However, relapses are frequent once treatment is discontinued and sometimes even during chronic maintenance. It can be used alone or in low-dose combination with PUVA (psoralen augmented UVA) therapy. The mechanism of action is unknown, but it is undoubtedly like that of vitamin A. Activity resides in the acid metabolite.

Adverse effects occur in more than 75% of recipients. They include chapped lips; peeling of the palms, soles, and fingertips; dryness of the mucous membranes; sore tongue; cheilitis; rhinorrhea; nosebleed; gingival bleeding; loss of hair; nail abnormalities; dry and irritated cornea, sclera, and conjunctiva (50%); epidermal fragility; easy sunburning; and other effects. Occasionally, pseudotumor cerebri, metastatic calcification of ligaments and tendons, and liver dysfunction or necrosis occur. In children and adolescents there may be premature closure of the epiphyses. Plasma cholesterol and triglycerides rise and high-density lipoprotein decreases. The drug is also teratogenic. Adverse effects are less with the low doses used in conjunction with PUVA therapy.

Absorption after oral administration is incomplete. It can be increased by whole milk and other lipid-containing foods. There is a rapid metabolism during which it is deesterified to the acid metabolite. A much slower degradation and conjugation follows, the metabolites being secreted into bile and urine. Nearly all of the circulating drug is bound to plasma lipoproteins, but the active metabolite is bound to albumin. Ultimately, it is taken up into fat, where it may be found even as long as 2 years after the last dose. The apparent elimination half-life is about 120 days. This persistence of drug in the body militates against the use of the drug in fertile women of child-bearing age, since the incidence of congenital defects is high even when conception occurs months after the drug is discontinued. The drug also is excreted into milk; effects in the nursing infant are not known.

HOMOSALATE

Benzoic acid, 2-hydroxy-, 3,3,5-trimethylcyclohexyl ester; ing of Coppertone



Homomenthyl salicylate [118-56-9] $C_{16}H_{22}O_3$ (262.36).

Preparation—US Pat 2,369,084.

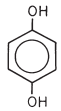
Description—Colorless liquid boiling about 163° at 4 mm.

Comments—A liquid with relatively low molar absorptivity (6720 at 310 nm) and limited absorption in the near ultraviolet range (290–315 nm), so that it is used mainly to *promote tanning*. Photosensitive persons may not be protected from burns and phototoxicity.

HYDROGEN PEROXIDE SOLUTION—page 1628.

HYDROQUINONE

1,4-Benzenediol; *p*-Dihydroxybenzene; Hydroquinol; Quinol; Eldoquin and Eldopaque Forte



Hydroquinone [123-31-9] $C_6H_6O_2$ (110.11).

Preparation—Various processes are employed. One involves reacting a sulfuric acid solution of aniline with manganese dioxide and reducing the resulting *p*-benzoquinone with sodium bisulfite.

Description—Fine, white needles; darkens on exposure to air; melts between 172° and 174°.

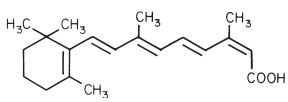
Solubility—1 g in about 17 mL water, 4 mL alcohol, 51 mL chloroform, or 16.5 mL ether.

Comments—A *hypopigmenting* agent employed percutaneously to lighten localized areas of hyperpigmented skin, such as skin blemishes, lentigo, melasma, chloasma, freckles, etc. Its action is temporary, so that it is necessary to repeat the application at frequent intervals. It is a mild irritant, and erythema or rash may develop, which requires discontinuation of the drug. It should not be used near the eyes or in open cuts. It is contraindicated in the presence of sunburn, miliaria, or irritated skin. It is not to be used in children. Ingestion of 1 g results in tinnitus, nausea, vomiting, a sense of suffocation, shortness of breath, cyanosis, convulsions, delirium, and collapse. Death has occurred with ingestion of 5 g. Irritation of the GI tract occurs with oral ingestion. Dermatitis results from skin contact. Corneal staining and opacification have been noted in those exposed for prolonged periods to hydroquinone vapor at concentrations not sufficiently high for systemic effects.

HYDROXYUREA—page 1575 .

ISOTRETINOIN

13-*cis*-Retinoic Acid; Accutane



3,7-Dimethyl-9-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2-*cis*-4-*trans*-6-*trans*-8-*trans*-nonatetraenoic acid [4759-48-2] $C_{20}H_{28}O_2$ (300.44). Differs from tretinoin (vitamin A) only in the configuration of the unsaturation at the α and β carbon atoms, which is *cis rather than trans*.

Comments—Although not a topical drug, it is a dermatological agent and, hence, is described here. Its primary action is to decrease the production of sebum, which lends itself to the treatment of severe *modular* and *cystic acne* (acne conglobata). The size of the sebaceous gland is decreased, and there is a change in the morphology and secretory capacity of the cells (dedifferentiation). Complete clearing of lesions is seen in about 90% of cases. A single course of treatment usually brings about long-lasting, sometimes permanent, remissions.

It also appears to diminish hyperkeratosis and has been reported to be effective in *rosacea,* gram-negative *folliculitis, lamellar ichthyosis, Darier's disease, pityriasis rubra pilaris,* and *keratocanthoma*.

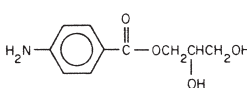
Adverse effects include facial dermatitis, fragile skin, thinning and drying of the hair, reversible cheilitis, and dry skin, mouth, eyes, and conjunctivitis in 25 to 80% of recipients. Peeling of the palms and soles and

sensitivity to sunburn occur in about 5% of users. Urethral inflammation also occurs frequently. Joint pains and exacerbation of rheumatoid arthritis also has been reported to occur in about 16% of patients. Sedimentation rate, serum triglyceride concentration and serum levels of alanine and aspartate transaminases transiently occur in about 25% of users. Vertebral hyperostosis has been noted with the current recommended dose regimen. It was noted originally in patients receiving isotretinoin for various keratinization disorders at higher dosages and for longer periods than those recommended for acne. In spite of the relatively high incidence of side effects, treatment rarely has to be discontinued.

After oral administration, peak blood concentrations occur within 1 to 4 hr. The compound is oxidized to 4-hydroxy-13-*cis*-retinoic acid, which then is glucuronidated and is secreted into the bile. The elimination half-life is 11 to 39 (mean 20) hr. Isotretinoin should not be given during pregnancy or nursing.

LISADIMATE

1,2,3-Propanetriol, 1-(4-aminobenzoate) ester; Escalol 106



Glyceryl *p*-aminobenzoate [136-44-7] $C_{10}H_{13}NO_4$ (211.21).

Preparation—By esterification of aminobenzoic acid with glycerin.

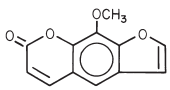
Description—Waxy semisolid or syrup.

Solubility—Insoluble in water, oils, or fats; soluble in alcohol, isopropyl alcohol, or propylene glycol.

Comments—A *sunscreen* that absorbs UV light at 264 to 315 nm and that has a relatively high molar absorptivity (17,197 at 295 nm) but a limited spectrum, therefore used primarily to promote tanning rather than to protect sensitive persons.

METHOXSALEN

7*H*-Furo[3,2-*g*][1]benzopyran-7-one, 9-methoxy-, Ammoidin; 9-Methoxypsoralen; Xanthotoxin; Oxsoralen



[298-81-7] $C_{12}H_8O_4$ (216.19).

Preparation—Occurs naturally in *Psorales coryfolia, Ammi majus, Ruta chalepensis,* and various other plants. It may be synthesized by methods described in *JACS* 1957; 79: 3491, and in US Pat 2,889,337.

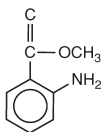
Description—White to cream-colored, odorless, fluffy, needle-like crystals; melts between 143° and 148°.

Solubility—Practically insoluble in cold water, sparingly soluble in boiling water; freely soluble in chloroform; soluble in boiling alcohol, acetone, or acetic acid; soluble in aqueous alkalies with ring cleavage; reconstitution occurs on neutralization.

Comments—A *psoralen melanizer*. It increases the photodynamic pigmentation of skin; it does not induce pigmentation in the absence of UV light or melanocytes. It is used in the treatment of *vitiligo* and to *desensitize to sunlight*. Severe sunburning can occur with topical application; it is customary to protect the surrounding skin with a sunscreen. It also is used in PUVA treatment of *psoriasis, mycosis fungoides,* and *cutaneous T-cell lymphoma;* in these, irradiation activates it to cross-link DNA. It may have value in the PUVA treatment of *alopecia areata, inflammatory dermatoses, eczema,* and *lichen planus*. After oral administration GI upset and central nervous system toxicities, such as vertigo and excitement, also occur. Consequently, the drug should be used orally only under medical supervision. It is additive with other photosensitizing drugs and the furocumarin pigments in carrots, celery, figs, limes, mustard, parsley, and parsnips. It inhibits the metabolism of caffeine.

METHYL ANTHRANILATE

2-Aminobenzoic acid, methyl ester



[134-20-3] $C_8H_9NO_2$ (151.16).

Preparation—A constituent of several essential oils; also, by esterification of anthranilic acid with methyl alcohol.

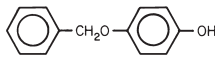
Description—A crystalline substance; melts at 25°.

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

Comments—A *sunscreen,* with the lowest molar absorptivity of all sunscreens (941 at 315 nm); also, it does not absorb throughout the near UV range (absorption band, 290 to 320 nm) and, therefore, is used in combination with other sunscreens or light-protectives. It also is used as a perfume in ointments and cosmetics.

MONOBENZONE

Phenol, 4-(phenylmethoxy)-, Monobenzyl Ether of Hydroquinone; Benoquin



p-(Benzyloxy)phenol [103-16-2] $C_{13}H_{12}O_2$ (200.24).

Preparation—Prepared in various ways. One method involves condensing sodium *p*-nitrophenolate with benzyl chloride to produce benzyl *p*-nitrophenyl ether followed by (1) reduction of nitro to amino, (2) diazotization of amino, and (3) hydrolytic decomposition of the diazonium compound to the corresponding phenol.

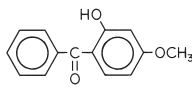
Description—White, odorless, crystalline powder possessing very little taste; melts between 117° and 120°.

Solubility—1 g in >10,000 mL water, 14.5 mL alcohol, 29 mL chloroform, or 14 mL ether.

Comments—A *depigmenting agent* or *demelanizer*. It acts by interfering with the formation of melanin, which is the principal cutaneous pigment. It is recommended only for the final depigmentation in *vitiligo*. It is not recommended for treatment of lentigo, severe freckling, and other types of hyperpigmentation. It is not effective against pigmented moles or malignant melanoma. Its pigment-decreasing action is somewhat erratic. Irritation of varying degrees occurs in a considerable number of patients.

OXYBENZONE

Methanone, (2-hydroxy-4-methoxyphenyl)phenyl-,



2-Hydroxy-4-methoxybenzophenone [131-57-7] $C_{14}H_{12}O_3$ (228.25).

Preparation—Benzoic acid is condensed with resorcinol monomethyl ether by heating in the presence of $ZnCl_2$ or polyphosphoric acid (103% H_3PO_4 equivalent), and PCl_3. US Pat 3,073,866.

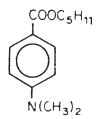
Description—White to off-white powder; congeals not lower than 62°.

Solubility—Practically insoluble in water; freely soluble in alcohol or toluene.

Comments—A *sunscreen* with a high molar absorptivity (20,381 at 290 nm), and it absorbs in both the long and short UV spectrum 270 to 350 nm. Therefore, it serves not only to prevent sunburn but also to protect against the photodynamic, photosensitizing, and phototoxic effects of various drugs. Contact with the eyes should be avoided. At present, it is marketed only in combination with other sunscreens.

PADIMATE A

Benzoic acid, 4-(dimethylamino)-, pentyl ester



[14779-78-3] $C_{14}H_{21}NO_2$ (235.33). A mixture of pentyl, isopentyl, and 2-methylbutyl esters of *p*-aminobenzoic acid.

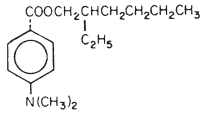
Description—Yellow liquid; faint, aromatic odor.

Solubility—Practically insoluble in water or glycerin; soluble in alcohol, chloroform, isopropyl alcohol, or mineral oil.

Comments—A *sunscreen* of moderate molar absorptivity but relatively narrow UV absorption spectrum (290–315 nm) characteristic of other aminobenzoic acid derivatives.

PADIMATE O

Benzoic acid, 4-(dimethylamino)-, 2-ethylhexyl ester



[21245-02-3] $C_{17}H_{27}NO_2$ (277.41).

Preparation—By the esterification of *p*-dimethylaminobenzoic acid with 2-ethylhexanol in the presence of dry HCl. The product is liberated from the salt by neutralization with base.

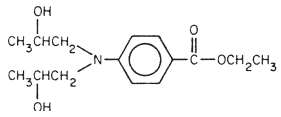
Description—Light-yellow mobile liquid; faint, aromatic odor.

Solubility—Practically insoluble in water, alcohol, or mineral oil.

Comments—See Padimate A.

ROXADIMATE

Benzoic acid, 4-[bis-(2-hydroxypropyl)amino]-, ethyl ester; Amerscreen



[58882-17-0] $C_{15}H_{23}NO_4$ (281.35).

Comments—A *sunscreen* with a limited absorption spectrum (280 to 330 nm) characteristic of *p*-aminobenzoates but a relatively high molar absorptivity. It is used mainly in suntan products.

SODIUM FLUORIDE

Sodium fluoride [7681-49-4] NaF (41.99).

Preparation—By interaction of 40% HF with an equivalent quantity of NaOH or Na_2CO_3.

Description—White, odorless powder.

Solubility—1 g in 25 mL water; insoluble in alcohol.

Comments—A *dental caries prophylactic*. Fluoridation of municipal water supplies is considered a safe and practical public health measure; a concentration of about 1 ppm of fluoride in the water supply results in a 50% to 65% reduction in the incidence of dental caries in permanent teeth. Ingested fluoride is effective only while teeth are being formed. The fluoride is incorporated into tooth salts as fluoroapatite. Excessive intake during development of teeth may cause mottling; hence, mottling of newly erupted teeth is an indication to reduce fluoride intake. Where drinking water contains less than 0.7 ppm of fluoride, dietary supplements for children with unerupted teeth may provide some future protection.

Topical application results in changes only in the outer layers of enamel or exposed dentin. In children, repeated application of a 2% solution of the drug to cleaned teeth results in a 16% to 49% reduction of dental caries; adult teeth are protected to a lesser extent by topical application. Topical application also is used to *desensitize* teeth.

Orally administered, it produces new bone formation in some patients with osteoporosis, especially when calcium and vitamin D (and estrogens in women) are administered concomitantly to facilitate mineralization of the new bone. However, the bone may become brittle.

It removes calcium from tissues and also poisons certain enzymes. Large oral doses may cause nausea and vomiting, which usually can be prevented by taking the substance with food. Pastes, rinses, solutions, and gels for topical applications should not be swallowed.

SODIUM MONOFLUOROPHOSPHATE

Phosphorofluoridic acid, sodium salt

$FPO(ONa)_2$

Disodium phosphorofluoridate [10163-15-2] (143.95).

Preparation—Substantially pure drug is produced by fusing a mixture of sodium metaphosphate and sodium fluoride, in stoichiometric proportion, in a closed vessel from which moist air is excluded.

Description—White to slightly gray, odorless powder.

Solubility—Freely soluble in water.

Comments—Like *Sodium Fluoride,* above, it promotes the replacement of hydroxyapatite by fluoroapatite in the tooth salts and, hence, is used as a *dental prophylactic* against dental caries. It has the advantage over sodium fluoride in that the teeth do not require special preparation before application, it is effective when included in dentifrices, and in dentifrices there is no hazard with respect to local toxicity to the gingivae or systemic intoxication from ingestion.

STANNOUS FLUORIDE

Tin Difluoride; Fluoristan

Tin fluoride (SnF_2) [7783-47-3] (156.69); contains not less than 71.2% Sn_2^+ (stannous tin) and about 24% F^- (fluoride).

Preparation—Stannous oxide is dissolved in 40% HF, and the solution is evaporated out of contact with air.

Description—White, crystalline powder with a bitter, salty taste; melts at about 213°.

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

Comments—Alters the composition and crystalline structure of the hydroxyapatite-like salts that make up the bulk of enamel and dentin, so that the tooth material is more resistant to acidic erosion and dental caries (decay). The substance is applied only topically, so that the tooth substance is only affected in the superficial layers, and it must be applied periodically. It is most effective when applied to the tooth surface after the teeth have been cleaned thoroughly by a dentist. However, there is good evidence that even when incorporated into toothpastes the drug has a retardant effect on the development of dental caries.

TITANIUM DIOXIDE

Titanic Anhydride

Titanium oxide (TiO_2) [13463-67-7] TiO_2 (79.88).

Preparation—By adding ammonia or an alkali carbonate to a solution of titanyl sulfate ($TiOSO_4$). Titanic acid $Ti(OH)_4$ or $TiO(OH)_2$ is precipitated and, after filtration and washing, is dried and ignited.

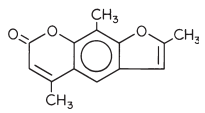
Description—White, amorphous, tasteless, odorless, infusible powder; density about 4; suspension in water (1 in 10) neutral to litmus.

Solubility—Insoluble in water, HCl, HNO_3, or dilute H_2SO_4.

Comments—Its powder has a very high reflectance at visible and UV wavelengths, and, hence, it serves as an excellent white pigment. In ointments or lotions it reflects a very high proportion of incident sunlight, hence, protecting the skin from sunburn and serving as a sunblock. It also is used in cosmetics and as a dusting powder. Topically, it is devoid of toxicity.

TRIOXSALEN

7*H*-Furo[3,2-*g*][1]benzopyran-7-one, 2,5,9-trimethyl-, 6-hydroxy-β,2,7-trimethyl-5-benzofuranacrylic acid, δ-lactone; Trisoralen



[3902-71-4] $C_{14}H_{12}O_3$ (228.25).

Caution—Avoid contact with the skin.

Preparation—2-Methylresorcinol is cyclized with ethyl acetoacetate with the aid of sulfuric acid to 7-hydroxy-4,8-dimethylcoumarin (I). Treatment with allyl bromide in the presence of potassium carbonate transforms I into the 7-allyloxy compound, which, on reacting with acetic anhydride in the presence of *N,N*-diethylaniline and anhydrous sodium acetate, rearranges and esterifies to give the 7-acetoxy-6-allyl compound (II). Bromination of II followed by reaction with sodium methoxide yields trioxsalen. US Pat 3,201,421.

Description—White to off-white, odorless, tasteless crystalline solid; stable in light, air, and heat; melts at about 230°.

Solubility—1 g in 1150 mL alcohol, 84 mL chloroform, or 43 mL methylenedichloride; practically insoluble in water.

Comments—Although not a topical drug, it closely relates to other drugs in this section. It facilitates the action of near UV light to induce melanin (skin pigment) formation. It is used to cause repigmentation in idiopathic *vitiligo* and to **enhance** pigmentation to *increase tolerance to sunlight* or for *cosmetic purposes*. The increased tolerance to sunlight does not occur until enhanced pigmentation has occurred, and the patient must be cautioned that severe sunburning with less than normal exposure can occur early during the course of treatment. The increase in dermal pigment occurs gradually over a period of several days of repeated exposure. Care must be taken to protect the eyes and lips during treatment. The manufacturer's recommended schedule of exposure should be used except at high altitudes, where exposure times should be appropriately reduced.

It is contraindicated in persons with photosensitizing diseases, such as infectious leukoderma, porphyria, or lupus erythematosus, and when photosensitizing drugs are being given. The drug sometimes may cause gastric irritation and emesis. Children under 12 should not take it.

ACKNOWLEDGMENTS–Kristine Knutson, PhD and Lynn K Pershing, PhD are acknowledged for their contributions in previous editions of this work.

CHAPTER 66

Gastrointestinal and Liver Drugs

John E Hoover, BSc Pharm, RPh

The major categories of drugs included in this chapter areantacids, H_2-receptor antagonists, proton pump inhibitors, drugs that enhance mucosal resistance, digestants including pancreatic enzymes, laxatives, antidiarrheals, emetics, antiemetics, prokinetic agents, adsorbents, and miscellaneous drugs. A number of other drugs, used primarily for other indications but also used in the treatment of gastrointestinal (GI) diseases, are not included in this chapter. These include immunosuppressive drugs, anti-inflammatory drugs, immunostimulants and antibiotics.

DRUGS USED TO TREAT ACID PEPTIC DISEASES

Mucosal injury in the acid peptic diseases (ie, gastric ulcer, duodenal ulcer and gastroesophageal reflux disease (GERD)) is mediated by gastric acid. Hydrochloric acid is secreted by parietal cells in the body of the stomach. It is regulated by adjacent endocrine, paracrine, and neurocrine cells. The parietal cell has receptors for acetylcholine (neurocrine), gastrin (endocrine), histamine (paracrine), somatostatin (endocrine), and prostaglandin E_2 (paracrine). Acetylcholine and gastrin both activate calcium channels, albeit different channels. This leads to intracellular accumulation of calcium. Calcium, in turn, stimulates protein kinases that phosphorylate H^+K^+ ATPase, the proton pump. The physiological essence of the proton pump is to exchange extracellular K^+ for intracellular H^+. It is thus the final common pathway of acid secretion. Gastrin and acetylcholine are relatively weak stimuli of the parietal cell. They act primarily through the adjacent enterochromaffin-like (ECL) cell, causing the release of histamine. Histamine is the most potent stimulus of acid secretion and acts as the common mediator. It induces adenylate cyclase, which converts ATP to cyclic AMP (cAMP), which activates the protein kinases. This complex interaction accounts for the well-known phenomenon of potentiation, in which the effect of two or more stimuli is greater than the sum of their additive effects. The converse is also true; histamine antagonists inhibit acid secretion that is stimulated by gastrin and acetylcholine as well as histamine.

There are two types of acid secretion under physiological secretions: (1) meal stimulated, 90% of which is stimulated by gastrin, and (2) basal, which is mostly stimulated by acetylcholine. Meal-stimulated acid secretion is largely regulated by gastrin. Gastrin secretion is modulated by a negative feedback mechanism such that alkalization, ie, feeding, stimulates gastrin release and thus acid secretion, while acidification, ie, discontinuing eating, inhibits gastrin release and shuts down acid secretion. Food stimulates gastrin release by three mechanisms: (1) gastric distention; (2) specific food constituents such as amino acids, protein hydrolysates, ethanol, and calcium; and (3) elevation of gastric pH. Acid is the major inhibitor of gastrin release and thus of acid secretion. Since ingestion of food increases gastric pH, gastrin release is disinhibited and acid secretion continues. As food intake stops, gastric pH falls, gastrin release is inhibited, and acid secretion returns to basal levels. It is in this way that eating regulates acid secretion. Acidification also causes adjacent D cells to release somatostatin, which appears to inhibit acid secretion by direct inhibition of adenyl cyclase in the parietal cell. The major effect of somatostatin, however, is inhibition of histamine release from the adjacent ECL cell.

Basal acid secretion exhibits a circadian rhythm in which gastric secretion is highest at night (approximately at midnight) and lowest in the early morning. This secretion is not paralleled by changes in circulating serum gastrin and is abolished by vagotomy. It appears, therefore, that basal secretion is largely controlled by the vagus nerve and its neurotransmitter, acetylcholine. The importance of basal secretion is twofold:

1. It accounts for the characteristic nighttime awakening with peptic ulcer pain.
2. It serves as the rationale for single nighttime dosing with H_2 receptor antagonists.

In addition to a stimulatory pathway of acid secretion, there is a closely related inhibitory system. This system is activated by prostaglandin E_2 (PGE_2), which appears to act on a membrane receptor that activates an inhibitory protein (GIP) that blocks the histamine activation of adenylate cyclase. An additional function of PGE_2 in the gastric mucosa is to increase bicarbonate and mucus secretion, which enhances mucosal resistance to injury. Thus, the combined effect of PGE_2 is to inhibit acid secretion and increase mucosal protection—yet another example of the constitutive or protective function of the prostaglandins. The inhibition of PGE_2 by nonsteroidal anti-inflammatory drugs (NSAIDs) is the underlying mechanism by which they cause injury. The other major inhibitor of acid secretion is somatostatin.

In general, ulcer disease occurs whenever there is an increase in acid secretion or a decrease in mucosal resistance. Conversely, acid peptic diseases can be treated by either decreasing acid or increasing mucosal resistance. Acid-mediated pain occurs when the gastric pH is below 2. Healing of the acid peptic diseases occurs when the mean 24-hr pH is kept above 3 to 4. The pH can be increased by either neutralizing acid (antacids) or inhibiting gastric secretion (H_2-receptor antagonists or proton pump inhibitors). Mucosal resistance can be increased with prostaglandin analogs.

DRUGS THAT DECREASE ACID

The exact mechanism of gastric acid secretion has yet to be elucidated. It is known that four endogenous substances—acetylcholine, the neurotransmitter of the vagus nerve; gastrin, a systemic hormone secreted by G cells in the antrum of the stomach; histamine, a paracrine hormone secreted by enterochromasin cells in the wall of the stomach; and calcium—all stimulate acid secretion. There are receptors for acetylcholine (muscarinic receptors), gastrin (gastrin receptors), and histamine (H_2-receptors). Calcium may both increase gastrin and act as a second messenger for gastrin and acetylcholine. Histamine probably activates adenylate cyclase, which converts cytosolic ATP to cAMP, which acts as a second messenger. There is some evidence that histamine may act as the common mediator of acid secretion, since it augments acetylcholine- and gastrin-stimulated secretion, and H_2-blockers inhibit both acetylcholine- and gastrin-stimulated secretion.

The final common pathway of acid secretion is the proton pump, Na^+/K^+ ATPase. The physiological essence of Na^+/K^+ ATPase is to exchange K^+ for H^+; H^+ is secreted against a profound concentration gradient of 2,000,000:1 or greater. This acid secretion is stimulated by the sight, smell, and ingestion of food. In addition to the stimulated acid secretion, there is a basal acid secretion that occurs independently of eating. An important feature of basal acid secretion is its diurnal variation, such that acid secretion is low during the day but relatively high at night—generally peaking between 10 PM and midnight. For this reason patients tend to wake up around midnight with dyspepsia and heartburn. It is at this time that gastric pH tends to drop to 1 or 2, since acid secretion is relatively high and is not neutralized by food.

During the day, the food that stimulates acid secretion also neutralizes it, keeping the gastric pH about 4 or 5. The diurnal variation in acid secretion forms the rationale for using H_2-receptor antagonists as a single evening dose in the treatment of gastric and duodenal ulcers.

As discussed above, PGE_2 acts both to inhibit acid secretion and increase mucosal protection. There are other inhibitors of acid secretion. Somatostatin and secretin are probably the most important under physiological conditions.

ANTACIDS

Antacids are drugs that react with hydrochloric acid to form salt and water. This neutralizes acid and, in so doing, raises gastric pH. The most widely used antacids are sodium bicarbonate, calcium carbonate, aluminum hydroxide, and magnesium hydroxide.

Antacids are used widely for the relief of heartburn and dyspepsia, as well as a large variety of nonspecific GI symptoms. The primary role of antacids in the management of acid peptic disorders is relief of pain. For the most part, they are safe, but in patients with compromised renal function, indiscriminate use can lead to alkalosis and other complications.

Antacids usually are used in combination. The differences in mixture account for the relative differences in neutralizing capacity and side effects. It is apparent that the more acid neutralized, the greater the efficacy of the antacid. For practical purposes, however, efficacy is obtained by increasing the gastric pH to 3.5 or greater. This is achieved readily with modern antacids, giving doses of 15 to 30 mL, 1 and 3 hr after meals. Such doses also heal ulcers in 4 to 8 weeks in approximately 80% of patients.

The mechanism of action of antacids is complex. A proposed mechanism is the prevention of back-diffusion of hydrogen ions across the GI mucosa. Fifty percent of the acid in a given amount of gastric juice with a pH of 1.3 can be neutralized by raising the pH to 1.6, 90% by raising the pH to 2.3, and 99% by raising the pH to 3.3. It generally is accepted that raising the gastric pH to approximately 4 prevents stress ulcer, which is thought to be mediated by acid back-diffusion. Another action of antacids is to prevent the conversion of gastric pepsinogen to pepsin, the active form. This is a proteolytic enzyme thought to mediate tissue injury in ulcer disease. Pepsinogens are inactivated irreversibly at pH 5 and inactivated at pH 7. It thus may be necessary to raise the pH to 5 to achieve the maximum benefit from antacids. Antacids also may enhance cytoprotection in the stomach. Finally, antacids may confer a therapeutic benefit by inactivating bile salts, which are thought to reflux from the duodenum into the stomach and play some role in acid peptic disease.

There are differences in the types of antacids in terms of their cation content, neutralizing capacity, duration of action, side effects, and cost. These must be considered when choosing an antacid for therapeutic use.

NEUTRALIZING CAPACITY—Antacids are compared quantitatively in terms of acid-neutralizing capacity (ANC), defined as the number of milliequivalents of hydrochloric acid required to maintain 1 mL of an antacid suspension at pH 3 for 2 hr *in vitro*. The rate of neutralization varies according to the degree of comminution, crystal form, precipitants used, and presence of reactive suspending agents. Consequently, the ANC and rate of neutralization of various antacids differ enormously. For example, 5 mL of aluminum hydroxide suspension (Amphojel) will neutralize 6.5 mEq of acid in 60 min, whereas a similar volume of aluminum hydroxide–magnesium hydroxide suspension (Delcid) will neutralize 42 mEq in the same period of time.

DOSING INTERVAL—An ideal antacid should be rapid in onset and provide a continuous buffering action. Antacids with a rapid onset include magnesium hydroxide, magnesium oxide, and calcium carbonate; those with an intermediate onset, magaldrate and magnesium carbonate; and those with a slow onset, magnesium trisilicate and the aluminum compounds. The duration of buffering action is determined largely by when the antacid is administered; if administered while food is in the stomach, the buffering action will last for 2 hr. An additional dose 3 hr after meals will extend the buffering time by 1 hr. Therefore, the ideal dosing interval is 1 and 3 hr after meals and at bedtime.

THE PATIENT—Certain patients by nature of their underlying disease may be at increased risk of antacid toxicity. For example, patients with heart failure may be at risk from excess sodium intake. Most available antacids are low in sodium and thus the presence of edema or heart failure precludes the use only of sodium bicarbonate. Patients with renal failure should not use magnesium-containing antacids, because of the possibility of hypermagnesemia, or sodium bicarbonate, which may cause systemic alkalosis. While patients with renal failure are sometimes given aluminum-containing antacids for their phosphate-lowering effect, there is increasing concern about aluminum neurotoxicity in such patients.

SIDE EFFECTS—A systemic antacid, such as sodium bicarbonate, is soluble and readily absorbed. It can cause electrolyte disturbances and alkalosis. The so-called nonsystemic antacids, such as aluminum-, calcium-, and magnesium-containing antacids, form relatively insoluble compounds in the GI tract. It is not true, however, that such compounds are not absorbed. Toxicity occurs as the result of systemic absorption of all of these antacids. Ingestion of large amounts of calcium carbonate can lead to hypercalcemia, alkalosis, and renal failure with so-called milk-alkali syndrome. Magnesium-containing antacids can cause both diarrhea and hypermagnesemia. Prolonged treatment with aluminum-containing antacids can cause phosphate depletion and, eventually, osteoporosis and osteomalacia as well as neurotoxicity. All of the toxicities of the nonsystemic antacid are more common and more serious in patients with renal failure.

ALUMINUM CARBONATE GEL, BASIC—see RPS-20, page 1221.

ALUMINUM HYDROXIDE GEL

Colloidal Aluminum Hydroxide; Amphojel; Alternagel

Aluminum Hydroxide [21645-51-2] $Al(OH)_3$ (78.00); a suspension each 100 g of that contains the equivalent of 3.6 to 4.4 g of aluminum oxide [Al_2O_3 = 101.96] in the form of aluminum hydroxide and hydrated oxide.

It may contain peppermint oil, glycerin, sorbitol, sucrose, saccharin, or other suitable flavors, and it may contain suitable antimicrobial agents.

Preparation—One process for the preparation of this type of aluminum hydroxide is as follows:

Dissolve 1000 g of $Na_2CO_3 \cdot 10H_2O$ in 400 mL of hot water and filter. Dissolve 800 g of ammonium alum in 2000 mL of hot water and filter into the carbonate solution with constant stirring. Then add 4000 mL of hot water and remove all gas. Dilute to 80,000 mL with cold water. Collect and wash the precipitate and suspend it in 2000 mL of purified water flavored with 0.01% peppermint oil and preserve with 0.1% of sodium benzoate. Homogenize the resulting gel.

The principal property desired is a very fine particle size to achieve large surface and thus maximum adsorption capacity.

Description—White, viscous suspension, from which small amounts of water may separate on standing; translucent in thin layers; affects both red and blue litmus paper slightly but is not reddened by phenolphthalein.

Incompatibilities—The use of Aluminum Hydroxide Gel and similar materials to reduce the GI problems accompanying use of tetracyclines has resulted in complexation with decreased absorption of the antibiotic.

Comments—Used primarily as an antacid in the management of *peptic ulcer, gastritis,* and *esophagitis*. It also is used as a skin protectant and mild astringent. It is a relatively weak antacid and does not elevate gastric pH sufficiently to inhibit pepsin activity. Aluminum hydroxide does not have significant demulcent properties. Although aluminum hydroxide is a nonsystemic antacid, significant amounts are absorbed in patients with renal failure. Aluminum hydroxide is excreted as the phosphate. This provides the basis not only for the occasional use of aluminum hydroxide for the treatment of *phosphate nephrolithiasis,* but also is the cause of the phosphate depletion syndrome sometimes observed after chronic administration. There is increasing concern that aluminum absorption may lead to dementation. The major advantage of aluminum hydroxide is that no systemic alkalosis is produced. Aluminum compounds decrease the absorption of certain drugs, such as tetracyclines. It also interferes with the defoaming action of simethicone. These compounds are also constipating.

BISMUTH SUBSALICYLATE

Basic Bismuth Subsalicylate; Pepto-Bismol

[14882-18-19] $C_7H_5BiO_4$ (362.11).

Solubility—Practicaly insoluble in water or alcohol; soluble in alkali; decomposed by hot water.

Comments—The principal ingredient in a popular over-the-counter (OTC) product employed for *indigestion, nausea,* and *diarrhea*. As an antidiarrheal agent it shows good activity versus *Salmonella* but less activity versus *Escherichia coli*. As an antiulcer drug, it seems to increase the rate of healing of peptic ulcers. It also reduces active intestinal secretion induced by *E coli* and *Vibrio cholerae*. This is thought to be due to antiprostaglandin activity by the subsalicylate component. It is used also as an antibiotic for the prophylaxis of traveller's diarrhea and amoebiasis. It also is used to treat the common form of gastritis and duodenal ulcer caused by *Helicobacter pylori*. In this circumstance, it is used in combination with an antibiotic (usually amoxicillin and/or metronidazole) and an H_2-blocker or proton pump inhibitor, but it is effective when given alone.

Bismuth subsalicylate has several properties aside from its effect on *H pylori* that may account for its efficacy in the treatment of ulcer disease. It forms a glycoprotein-bismuth complex with mucus that may create a protective barrier against acid peptic digestion. Furthermore, it may stimulate PGE_2, which in turn stimulates mucus and bicarbonate secretion. Finally, it may stimulate epidermal growth factor, which may enhance healing of ulcers.

Adverse Effects—Most ingested bismuth subsalicylate is excreted in feces as bismuth sulfide. However, small amounts are absorbed, and plasma levels are detectable. Encephalopathy has been reported with other bismuth salts. Its use is not recommended in patients with renal failure. The toxicity of long-term therapy is uncertain. Since this agent is a salicylate, it may cause ringing of the ears if taken with aspirin. Bismuth subsalicylate causes a temporary darkening of the stool and tongue. The darkening of the stool mimics melena and may mistakenly suggest GI bleeding.

CALCIUM CARBONATE

Mylanta; Titrilac

Calcium carbonate (1:1) [471-34-1] $CaCO_3$ (100.09).

Preparation—By double decomposition of calcium chloride and sodium carbonate in aqueous solution. Its density and fineness are governed by the concentration of the solutions; heavy and light forms are available on the market.

Description—Fine, white, microcrystalline powder, without odor or taste, and stable in air; aqueous suspension is practically neutral to litmus.

Solubility—Practically insoluble in water (its solubility in water is increased by the presence of any ammonium salt and by the presence of carbon dioxide; alkali hydroxide reduces its solubility); insoluble in alcohol; dissolves with effervescence in dilute acetic, hydrochloric, or nitric acids.

Comments—A rapidly acting *antacid*. It is used in the treatment of dyspepsia and heartburn and as an add-on treatment of gastritis, peptic ulcer disease, and esophagitis. Precipitated calcium carbonate also is employed in dentifrices and is a pharmaceutical necessity for Aluminum Subacetate Solution and antacid oral suspension dosage forms.

Adverse Effects—Although calcium carbonate is classified as a *nonsystemic* antacid, long-term therapy with large doses may cause systemic alkalosis and hypercalcemia (milk-alkali syndrome) in patients with renal failure. The salt reacts with hydrochloric acid in the stomach to form calcium chloride, which is largely (90%) insoluble. However, a proportion of the calcium (7–19%) is absorbed. Calcium is constipating. For this reason, calcium and magnesium antacids often are alternated in therapy or given in fixed combination.

Calcium-containing antacids cause *acid rebound*—an increase in acid secretion that occurs after the neutralizing effect occurs. Calcium-containing antacids are used for the prevention, not treatment, of osteoporosis. The goal of therapy is to maintain, rather than restore, bone mass. Large doses, ie, 1000 to 1500 mg, as elemental calcium daily are required in order to prevent or slow the progression of osteoperosis.

CALCIUM HYDROXIDE TOPICAL SOLUTION—page 1084.
CALCIUM PHOSPHATE, DIBASIC—page 1338.
DIHYDROXYALUMINUM SODIUM CARBONATE—see RPS-20, page 1221.

MAGNESIUM HYDROXIDE

Milk of Magnesia; Rolaids

[1309-42-8] $Mg(OH)_2$ (58.32).

Preparation—By precipitation using aqueous solutions of magnesium chloride or sulfate and sodium hydroxide. US Pat 3,127,241. A method for preparing it in various particle sizes is described in US Pat 3,232,708.

Description—White, very fine, bulky powder; slowly absorbs carbon dioxide on exposure to air.

Solubility—Practically insoluble in water or in alcohol; dissolves in dilute acids.

Comments—As a laxative and an antacid (although at usual doses it does not have enough neutralizing capacity to be defined as an antacid). Magnesium hydroxide is a mild cathartic that usually produces bowel movements in 1/2 to 6 hr. It probably acts by altering intestinal motility. It should not be used in patients with vomiting or abdominal pain.

It is not recommended, although frequently used as an antacid. As with other magnesium-containing compounds, it should not be used in patients with impaired renal function.

MAGNESIUM OXIDE

Magnesia; Light Magnesia; Calcined Magnesia; Heavy Magnesium Oxide; Heavy Magnesia; Heavy Calcined Magnesia; Uro-Mag and Mag-Ox 400

[1309-48-4] MgO (40.30)

Preparation—Light or heavy magnesium carbonate is exposed to red heat, whereupon CO_2 and H_2O are expelled, and light or heavy magnesium oxide is left. The density of the oxide also is influenced by the calcining temperature; high temperatures yielding more compact forms.

Description—Very bulky white powder, known as light magnesium oxide, or a relatively dense white powder, known as heavy magnesium oxide. Readily absorbs moisture and carbon dioxide when exposed to air.

Solubility—Practically insoluble in water to which, however, it imparts an alkaline reaction; insoluble in alcohol, soluble in dilute acids.

Comments—An effective, fairly long-acting, nonsystemic antacid. Since in water it is converted to the hydroxide, its biological properties are the same as those of the hydroxide. It is sometimes employed as a cathartic.

Light magnesia is preferable to heavy for administration in liquids, because being a finer powder, it suspends more readily.

Table 66-1. The Relative Onset and Duration of Action, Sodium Content, Acid Neutralizing Capacity (ANC), and Potential Adverse Effects of Common Single-Entity Antacids

ANTACID	ONSET OF ACTION	DURATION OF ACTION	SODIUM (MG/UNIT)	ANC[a]	ADVERSE EFFECTS[b]
Aluminum carbonate gel	Slow	Short	0.12	12	AFGI
Aluminum hydroxide gel	Slow	Prolonged	<2.5	16	AFGI
Calcium carbonate	Fast	Prolonged	<2.3	10	ABCEH
Magnesium carbonate	Intermediate	Prolonged	—	20/g	BD
Magnesium hydroxide	Fast	Short	0.12	14	BD
Magnesium oxide	Fast	Short	—	21	BD
Sodium bicarbonate	Fast	Short	88	12/g	CEJ

[a] ANC per capsule, tablet, or 5-mL suspension unless otherwise indicated.
[b] A, constipation; B, laxation; C, hypercalcemia; D, hypermagnesia; E, metabolic alkalosis; F, neurotoxicity in renal failure; G, osteomalacia and osteoporosis; H, renal calculi; I, phosphorus depletion; J, swelling of feet.

MAGNESIUM TRISILICATE

Hydrated Magnesium Silicate

Magnesium silicate hydrate [39365-87-2] $2MgO{\cdot}3SiO_2{\cdot}xH_2O$; *anhydrous* [14987-04-3] (260.86). A compound of magnesium oxide and silicon dioxide with varying proportions of water. It contains not less than 20% magnesium oxide [MgO = 40.30] and not less than 45% silicon dioxide [SiO_2 = 60.08].

Preparation—By precipitating a solution of sodium silicate of the proper composition [$Na_4Si_3O_8$, or having a ratio of Na_2O to SiO_2 of 1:1.5] with a solution of magnesium chloride or sulfate.

Description—Fine, white, odorless, tasteless powder, free from grittiness; its suspension is neutral or only slightly alkaline to litmus.

Solubility—Insoluble in water or alcohol; readily decomposed by mineral acids, with liberation of silicic acid.

Comments—A nonsystemic *antacid* and *adsorbent*. As an antacid, it has a slow onset of action and is relatively weak; as a single entity it does not meet current pH requirements for nonprescription antacids. It is available only in combination with other antacids. Approximately 5% of the magnesium and 7% of the silicate may be absorbed. Therefore, a number of cases of siliceous nephrolithiasis have been reported following chronic use. Large doses may cause diarrhea due to the action of the soluble magnesium salts on the GI tract.

SODIUM BICARBONATE

Carbonic acid monosodium salt; Baking Soda; Sodium Acid Carbonate; Brioschi; Neut

Monosodium carbonate [144-55-8] $NaHCO_3$ (84.01).

Preparation—May be produced by the ammonium-soda process, or *Solvay process,* as it is usually called. In this process, CO_2 is passed into a solution of common salt in ammonia water, sodium bicarbonate is precipitated, and ammonium chloride, being much more soluble, remains in solution. The ammonium chloride solution is heated with lime, whereby the ammonia is regenerated and returned to the process.

Description—White, crystalline powder; odorless and with a saline and slightly alkaline taste; solutions freshly prepared with cold water without shaking are alkaline to litmus paper; alkalinity increases as the solutions stand or are agitated or heated; stable in dry air, but slowly decomposes in moist air.

Solubility—1 g in 12 mL water; with hot water it is converted into carbonate; insoluble in alcohol.

Comments—Widely employed as an antacid, especially by the laity, despite its many disadvantages. Sodium bicarbonate reacts with HCl to produce CO_2, thus giving rise to epigastric distress and eructation. Although the onset of action is rapid, the duration of action is short. In the treatment of systemic acidosis, it is specific in that the salt is composed of the two ions essential to correct this condition.

It is used locally on the skin in the form of a moist paste or a solution. In this form, it is an effective antipruritic. The salt also is an ingredient of many effervescent mixtures, alkaline solutions, douches, etc.

Sodium bicarbonate is absorbed readily. Prolonged therapy with large doses will produce systemic alkalosis. Moreover, chronic therapy along with milk or calcium may precipitate the milk-alkali syndrome in patients with renal failure. Even moderate amounts may expand plasma volume, increase blood pressure, and lead to edema. Therefore, it may be hazardous in patients with renal insufficiency, hypertension, or cardiac failure.

ANTACID MIXTURES

Antacids are used commonly in combination in order to

1. Combine fast- and slow-reacting antacids to obtain a product with a rapid onset and relatively even, sustained action.
2. Lower the dose of each component and minimize the possibility of certain adverse effects.
3. Use one component to antagonize one or more side effects of another component (eg, laxation vs constipation).

The antacid substances listed in Table 66-1 are employed extensively in the preparation of antacid mixtures. Indeed, they are the principal ingredients in almost 100 OTC antacid preparations, including chewable tablets, suspensions, and gels. For example, examination of 78 antacid mixtures reveals that 72% are composed of aluminum hydroxide and magnesium hydroxide alone or with simethicone, 12% of aluminum hydroxide and either magnesium trisilicate or magnesium carbonate, 11% of magnesium oxide and/or calcium carbonate with simethicone, and 5% of magaldrate with simethicone. Simethicone is not an antacid. It is used in antacid combinations to defoam gastric juice to decrease the incidence of gastroesophageal reflux. It does not decrease the antacid requirement.

The acid neutralizing capacity (ANC) of the suspensions closely approximates that of the tablets, but in general their neutralizing capacity tends to be greater because tablets go into solution less well. Gaviscon is listed in Tables 66-2 and 66-3, although it is not used in peptic ulcer disease and the ANC of its regular preparation does not qualify it as an antacid. Its unique formulation produces a foam that floats on the stomach contents. When acid reflux occurs, the foam precedes the stomach contents into the esophagus and protects the mucosa from further irritation. Hence, it is formulated specifically for acid reflux.

H_2-RECEPTOR ANTAGONISTS

There are three types of histamine receptors. The second of these mediates acid secretion by the gastric parietal cells and is inhibited by the H_2-receptor blocking drugs (Black et al. *Nature* 1972; 236:385). The identification of this receptor and its modulation introduced an era of pharmacology and led to the awarding of the Nobel prize to Dr Black. The H_2-receptor antagonists are histamine analogs. They consist of ring structures with side chains. While the rings and the side chains differ among compounds, they all have in common a nitrogen either in the ring or immediately adjacent to the ring and a nitrogen on the side chain that is recognized by the receptor.

The H_2-receptor antagonists are designer drugs developed as the result of the intentional modification of the histamine structure in an effort to find analogs with a higher binding affinity than histamine for the H_2-receptor. Such compounds would displace histamine and thus act as competitive inhibitors. The first such substance was burimamide, but it was only effective when given intravenously. The next substance was metiamide, effective both orally and intravenously but abandoned because it caused agranulocytosis. Finally, in 1977, cimetidine was approved by the Food and Drug Administration (FDA). It quickly became the number-one-selling drug in the world. It contains a substituted imidazole ring like that in histamine. Subsequently, ranitidine, a substituted furan ring, and famotidine and nizatidine, substituted thiazoles, were approved.

The H_2-receptor antagonists are a remarkably safe group of drugs. The list of adverse reactions is long, but the incidence is low. Among the side effects associated with all four drugs are headache, dizziness, malaise, myalgia, nausea, diarrhea, constipation, rashes, pruritus, and impotence. It has been said that

Table 66-2. Composition, Sodium Content, and Neutralizing Capacity of Some Proprietary Antacid Suspensions

	CONTENT (MG/5 ML)				
	$AL(OH)_3$	$MG(OH)_2$	$CACO_3$	NA	ANC[a]
PRODUCT	(PER 5 ML)				
Alternagel	0	0	0	0	0
Gaviscon	31.7	137[b]	0	13	1
Gelusil	200	200	0	0.7	12
Gelusil-II	400	400	0	1.3	24
Maalox	225	200	0	1.4	13.3
Maalox TC	600	300	0	0.8	28.3
Mylanta	200	200	0	0.68	12.7
Mylanta II	400	400	0	1.14	25.4
Riopan Plus	0	540[c]	0	>0.1	15

[a] Acid-neutralizing capacity (in milliequivalents).
[b] Magnesium carbonate.
[c] Magaldrate.

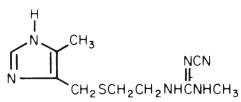
dementation and bradycardia are more common with intravenous cimetidine (especially in elderly patients), but the evidence supporting this contention is not convincing. A mild cardiotoxicity may be more common with famotidine. Impotence is said to occur more commonly with large IV doses of cimetidine, but again, the data supporting this are less than convincing. Mild hepatotoxicity has been seen with all of the compounds, probably more commonly with ranitidine. Overall, the incidence of side effects is so low that they are of little practical importance.

The major safety issue relates to drug interactions. Cimetidine binds to part of the cytochrome P-450-dependent mixed-function oxidase system. Some of the properties of the H_2-receptor antagonists are compared in Tables 66-4 and 66-5.

CIMETIDINE

Guanidine, *N*″-cyano-*N*-methyl-*N*′-[2-[[(5-methyl-1*H*-imidazol-4-yl)-methyl]thio]ethyl]-, Tagamet

[51481-61-9] $C_{10}H_{16}N_6S$ (252.34)



Preparation—Methods of synthesis of analogs of histamine capable of functioning as H_2-receptor antagonists of the type of cimetidine are described in German Pats 2,344,779 and 2,344,833 (se *CA* 1974; 80: 146167h, 146168j). In one of these methods a substituted guanidine such as $CH_3NHC(:NCN)SCH_3$ is refluxed with a histamine-related imidazole, as $NH_2CH_2CH_2SCH_2Z$ (in which Z is a methylimidazole), in methyl cyanide to produce the product $N{=}CHNH(CH_3)C{=}CHCH_2CH_2SCH_2Z$.

Description—White to off-white, crystalline powder; unpleasant odor; melts 141° to 143°; pK_a 6.8

Solubility—1 g in about 200 mL water, 18 mL alcohol, 1000 mL chloroform; insoluble in ether.

Comments—A competitive inhibitor of H_2-receptors. It is used for the acute treatment of gastric ulcer, duodenal ulcer, and gastroesophageal reflux. It also is used in the maintenance treatment of the above conditions and the treatment of pathological hypersecretory conditions such as Zollinger-Ellison syndrome and systemic mastocytosis. It is used for the long-term treatment of gastroesophageal reflux, but tachyphylaxis undermines its use in this condition. Studies also suggest that cimetidine is effective in both prevention and treatment of stress ulcers.

Cimetidine competitively inhibits H_2-receptors of parietal cells, reducing gastric acid secretion. This reduction occurs under basal conditions as well as when gastric acid secretion is stimulated by food. The oral administration of 800 mg of cimetidine reduces nocturnal gastric acid output by 80% over an 8-hr period, with no effect on daytime acid secretion. The gastric pH is raised to 5 or higher for at least 21/2 hr. Administered orally after a standard meal, 300 mg of cimetidine inhibits gastric secretion by 50% during the first hour and by 75% during the subsequent 2 hr.

Cimetidine is absorbed rapidly and well after oral administration, with a relative bioavailability of 70%. A small portion of the drug is metabolized on its first pass through the liver. It is 19% bound to serum proteins; the volume of distribution is 1.5 L/kg; 48% is excreted unchanged; elimination half-life ranges from 2 to 3 hr; mean serum concentration is 500 ng/mL, and mean peak blood level is 1440 ng/mL.

Cimetidine has been reported to reduce hepatic metabolism of drugs that are metabolized primarily by cytochrome P-450, thereby delaying elimination and increasing blood levels of these drugs. Therefore, cime-

Table 66-3. Composition, Sodium Content, and Neutralizing Capacity of Some Proprietary Antacid Chewable Tablets

	CONTENT (MG/TABLET)				
	$AL(OH)_3$	$MG(OH)_2$	$CACO_3$	NA	ANC[a]
PRODUCT	(PER UNIT)				
Di-Gel	282[b]	85	0	<5	9
Gaviscon	80	20[c]	0	18.4	0.5
Gelusil	200	200	0	0.8	11
Gelusil-M	300	200	0	1.3	12.5
Gelusil-II	400	400	0	2.1	21
Maalox No 1	200	200	0	0.7	8.5
Maalox No 2	400	400	0	1.4	18
Maalox Plus	200	200	0	0.8	11.4
Maalox TC	600	300	0	0.5	28
Mylanta	200	200	0	0.77	11.5
Mylanta II	400	400	0	1.3	23
Tums	0	500	0	<5	20

[a] Acid-neutralizing capacity (in milliequivalents).
[b] Magnesium carbonate.
[c] Aluminum hydroxide and magnesium carbonate.

Table 66-4. Comparison of H_2-Receptor Antagonists

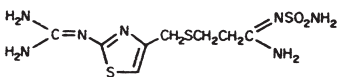
CHARACTERISTIC	CIMETIDINE	FAMOTIDINE	NIZATIDINE	RANITIDINE
Relative potency	1	20–50	4–8	4–8
Equivalent dose	1600 mg	40 mg	300 mg	300 mg
Bioavailability	60–80%	40–50%	50–60%	90–100%
Time to peak concentration (hr)	1–2	1–3	1–3	1–3
Serum half-life (hr)	1.5–2.5	2.5–4	2–3	1–2

tidine should be used with caution in patients on *warfarin-type anticoagulants, phenytoin, beta-adrenergic-blocking agents, lidocaine,* and *theophylline*; cimetidine reduces the hepatic metabolism of these substances, delays their elimination, and increases their blood levels. The half-life of benzodiazepines is also increased in patients taking cimetidine. A decrease in serum digoxin may occur in patients taking both digoxin and cimetidine.

Adverse reactions are usually mild and transient; diarrhea, muscular pain, dizziness, and rash have been reported in a few patients. A few cases of headache, ranging from mild to severe, have been reported. Reversible arthralgia, myalgia, and exacerbation of joint symptoms in patients with preexisting arthritis are observed on rare occasions. Gynecomastia has been reported in about 4% of patients with hypersecretory conditions receiving large doses; in all others the incidence was 0.3 to 1%. A few cases of reversible confusional states in elderly or severely ill patients have been observed in patients receiving IV cimetidine. Small increases in plasma creatinine and serum aminotransferase enzymes have been reported; all of these cleared when the drug was withdrawn. Interstitial nephritis also has been reported. The safe use of cimetidine in pregnant women or nursing mothers has not been established.

FAMOTIDINE

Propanimidamide, *N*′-(aminosulfonly)-3-[[[2-((diaminomethylene)-amino]-4-thiazolyl]methyl]thio-, Pepcid



[76824-35-6] $C_8H_{15}N_7O_2S_3.HCl$ (337.43)

Preparation—Synthesized from *S*-(2-aminothiazol-4-ylmethyl)isothio-urea, 3-chloropropionitrile, and benzoylisothiocyanate in 9 steps. Belg Pat 882,071.

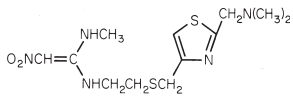
Description—White to pale yellow, crystalline solid, melting at 163 to 164°.

Solubility—Freely soluble in glacial acetic acid; slightly soluble in methanol; very slightly soluble in water; practically insoluble in ethanol. At 25°, in water, $pK_a$is 7.1.

Comments—An inhibitor of H_2-receptors. It is recommended for the short-term treatment of acute duodenal ulcer, gastric ulcer, and gastroesophageal reflux. It also is indicated for maintenance therapy of duodenal ulcer and management of pathological hypersecretory conditions, such as Zollinger-Ellison syndrome and multiple endocrine adenomas. Tachyphylaxis compromises its long-term use. Famotidine is absorbed incompletely. Bioavailability of oral doses is 40% to 45%; this may be increased slightly by food or decreased slightly by antacids. After oral doses, peak plasma levels occur in 1 to 3 hr; the peak plasma level is not altered by chronic administration, and elimination half-life is 2.5 to 3.5 hr. It is eliminated largely unchanged by the renal route (65–70%), and the remainder (30–35%) by metabolic routes. The only metabolite identified is the *S*-oxide. Thus, famotidine should be used in a lower dosage and at longer dosing intervals in patients with severe renal insufficiency. Adverse reactions reported to occur in more than 1% of patients include headache (4.7%), dizziness (1.8%), constipation (1.2%), and diarrhea (1.7%). Other adverse reactions reported include fever, asthenia, fatigue, palpitations, nausea, vomiting and abdominal distress, anorexia, dry mouth, liver enzyme abnormalities, thrombocytopenia, orbital edema, pain, arthralgia, paresthesias, psychic disturbances (depression, anxiety, decreased libido, hallucinations, insomnia, and somnolence), bronchospasm, alopecia, acne, pruritus, rash, and flushing. Although reproductive studies in laboratory animals revealed no evidence of impaired fertility or harm to the fetus, safety in pregnancy or in nursing mothers has not been established.

NIZATIDINE

1,1-Ethenediamine, *N*-[2-[[[2-[dimethylamino)methyl]-4-thiazolyl]-methyl]thio]ethyl]-*N*′-methyl-2-nitro-, Axid.

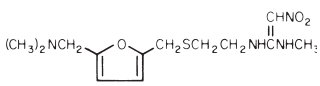


[76963-41-2] $C_{12}H_{21}N_5O_2S_2$ (331.45)

Comments—A reversible inhibitor of H_2-receptors. It is used in the treatment of acute duodenal ulcer, gastric ulcer, and gastroesophageal reflux and maintenance of duodenal ulcer. It often is used for maintenance of gastroesophageal reflux, but tachyphylaxis compromises that use. After oral administration of 100 and 300 mg, peak plasma concentrations of 700 to 1800 μg/L and 1400 to 3600 μg/L, respectively, occur within 0.5 to 3 hr; plasma concentrations after 12 hr are less than 10 μg/L. Elimination half-life is 1 to 2 hr; plasma clearance, 40 to 60 L/hr; and volume of distribution, 0.8 to 1.5 L/kg. More than 90% of an oral dose is excreted in the urine within 12 hr; 60% as unchanged drug. Therefore, it should be used in reduced dosage in patients with severe renal insufficiency. Adverse reactions include somnolence, sweating, and urticaria. Hepatocellular injury, ventricular tachycardia, decreased libido, gynecomastia, and thrombocytopenia have been reported but are rare. Safety and efficacy in children has not been established.

RANITIDINE

1,1-Ethenediamine, *N*-[2-[[[5-[(dimethylamino)methyl]-2-furanyl]methyl]thio]ethyl]-*N*′-methyl-2-nitro-, Zantac



[66357-35-5] $C_{13}H_{22}N_4O_3S$ (314.40).

Preparation—See US Pat 4,128,658.

Description—White solid melting about 70°.

Table 66-5. Duodenal Ulcer Healing Rates and Acid Suppression with Antisecretory Drugs

		SUPPRESSION OF	
	4-WK HEALING RATE (%)	NOCTURNAL ACIDITY	24-HR ACIDITY
Lansoprazole, 30 mg qam	92–100	90	92
Omeprazole, 20 mg qam	75–97	88	90
Cimetidine, 800 mg qhs	80	79	48
Cimetidine, 300 mg qid	74	68	65
Famotidine, 40 mg qhs	82	94	64
Famotidine, 20 mg bid	67		
Ranitidine, 300 mg qhs	84	90	68
Ranitidine, 150 mg bid	79	70	68

Comments—A substituted furan derivative. It is an H_2-receptor antagonist indicated for the short-term treatment of duodenal ulcer and the management of hypersecretory conditions such as Zollinger-Ellison syndrome and systemic mastocytosis. The pharmacokinetic profile of ranitidine is similar to that of cimetidine. Oral absorption appears to be variable and decreased if given concurrently with antacids; bioavailability after an oral dose of 150 mg is approximately 50% (range 40–88%); 15% is bound to plasma protein; volume of distribution is 1.4 L/kg; 30% of the administered dose is excreted unchanged; elimination half-life ranges from 2.5 to 3 hr; serum concentrations vary from 36 to 94 ng/mL; and mean peak blood levels are 440 to 545 ng/mL. Ranitidine lacks a predictable dose/response relationship. For example, 75, 100, and 150 mg of ranitidine inhibit nocturnal gastric acid output by 95%, 96%, and 92%, respectively. Interactions with warfarin, benzodiazepines, fentanyl, metoprolol, nifedipine, and acetaminophen have been reported. Pharmacologic tolerance occurs rapidly with ranitidine. It loses 50% of its activity to suppress acid within 1 week.

Adverse reactions include headache, malaise, dizziness, constipation, nausea, abdominal pain, and rash. Decreased white blood cell and platelet counts also have been reported. Increases (up to five times the upper limit of normal) in serum aminotransferases and gammaglutamyl transpeptidase have been noted. Rare cases of hepatitis also have been reported. In normal volunteers, ALT was increased at least twice the pretreatment levels in 6 of 12 subjects given 100 mg four times a day, intravenously, for 7 days and in 4 of 24 subjects given 50 mg four times daily, intravenously, for 5 days. This dose-related effect, however, is not associated with hepatotoxicity. With respect to use in pregnancy and lactation, studies in rats and rabbits have revealed no evidence of impaired fertility or harm to the fetus. Nevertheless, it should not be used in pregnancy unless needed. Ranitidine is secreted in milk; therefore, it should not be used in nursing mothers unless absolutely necessary.

PROTON PUMP INHIBITORS

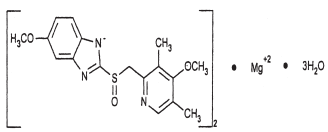
The final common pathway in gastric acid secretion is the *proton pump*—an H^+/K^+ ATPase. The physiological essence of this enzyme is the exchange of hydrogen ion for potassium ion. Thus, hydrogen is secreted by the parietal cell into the gastric lumen in exchange for potassium. The proton pump inhibitors lansoprazole and omeprazole belong to a new class of antisecretory drugs called substituted benzimidazoles. The prototype, omeprazole, is an irreversible inhibitors of the proton pump. It has a plasma half-life of 0.5 to 1 hr, but its duration of action is greater than 24 hr, reflecting the time required to generate new H^+/K^+ ATPase. The proton pump inhibitors should be taken prior to meals. This is because, in the resting state, the proton pump resides on the inner membrane of secretory vesicles within the parietal cell. When the cell is activated by eating (or by pharmacological stimulus), the inner membrane of the vesicle is externalized and becomes the outer; ie, the secretory membrane, of the secretory villus. The physiological importance of this is that the proton pump inhibitors are prodrugs that need to be protonated, and this can occur only when the proton pump is externalized and secreting acid. Thus, these drugs are more potent when taken prior to meals and when taken orally. They also are absorbed more effectively in the morning and thus should be dosed approximately 30 min prior to breakfast.

The proton pump inhibitors are used for the short-term treatment of acid peptic disease, gastroesophageal reflux, gastric ulcer, duodenal ulcer, and Zollinger-Ellison syndrome and for maintenance treatment of GERD. The therapeutic advantages of the proton pump inhibitors over the H_2-receptor antagonists are a faster healing rate, a higher healing rate, and the ability to heal patients who have not been helped by H_2-receptor antagonist therapy.

There are numerous side effects of the proton pump inhibitors, but they occur infrequently. Headache, diarrhea, abdominal pain, dizziness, rash, and constipation are seen with about the same frequency as seen with H_2-blockers, ie, 1% to 5%. Of some concern with the use of proton pump inhibitors is an elevation of serum gastrin. The elevations are 1.5- to 4-fold—about twice that seen with H_2-blockers. Gastrin is a trophic hormone that causes enterochromaffin cells to proliferate in rats. These cells produce histamine and are the precursor to carcinoid tumors in rats. The effect in rats is almost certainly mediated through gastrin rather than from a carcinogenic effect of the drug itself, since the tumors do not occur after antrectomy, a situation that precludes an increase in serum gastrin. Human studies have shown only a slight increase in the enterochromaffin cell population with chronic use of proton pump inhibitors. Carcinoid tumors have not been reported in human subjects using omeprazole. Nevertheless, there is an increased incidence of carcinoid tumors in patients with pernicious anemia, a condition that also is associated with hypergastrinemia. The FDA initially warned against prolonged use of omeprazole. Long-term studies, however, support the view that omeprazole is safe and efficacious for long-term (10+ years) treatment of ulcer disease. Some of the properties of the proton pump inhibitors are shown in Tables 66-5 and 66-6.

ESOMEPRAZOLE MAGNESIUM

1*H*-Benzimidazole, 5-methoxy-2-[(*S*)-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-, magnesium salt, trihydrate; Nexium



[217087-09-7] $C_{34}H_{36}MgN_6O_6S_2.3H_2O$ (767.17).

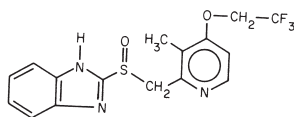
Preparation—see *Omeprazole,* page 1301.

Description—The *S*- enantiomer of *omeprazole.* The acidic form is a white to off-white crystalline powder from acetonitrile, melting about 156°. Mg salt is a white powder; $[\alpha]_D^{20}$ − 128.2 c = 1, methanol).

Solubility—(Acidic form); freely soluble in ethanol or methanol; slightly soluble in acetone or 2-propanol; very slightly soluble in water. (Mg salt); slightly soluble in water. Stability is a function of pH; at pH 6.8 (phosphate buffer) the half-life is about 19 hrs at 25° and 8 hrs at 37°.

LANSOPRAZOLE

1*H*-Benzimidazole, 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl-, Prevacid



[103577-45-3] $C_{16}H_{14}F_3N_3O_2S$ (369.36).

Table 66-6. Antisecretory Effects of Proton Pump Inhibitors

	LANSOPRAZOLE 30 MG			OMEPRAZOLE 20 MG	
	BASELINE	DAY 1	DAY 5	DAY 1	DAY 5
Mean 24-hr pH	21	3.6	4.9	2.5	4.6
Mean nighttime pH	1.9	2.6	3.8	2.2	3.0
% time pH > 3	18	51	72	30	60
% time pH > 4	12	41	66	19	51

Preparation—See US Pat 5,374,730 (1994).

Description—White to off-white, odorless crystals melting about 166° (180° decomposition).

Solubility—Freely soluble in DMF; soluble in methanol; slightly soluble in ethyl acetate, acetonitrile, or methylene chloride; very slightly soluble in ether; insoluble in water or hexane. Degrades in aqueous solution, and rate increases with decreasing pH. At 25°, $t_{1/2}$ = 0.5 hr at pH 5 and 18 hr at pH = 7.

Comments—A proton pump inhibitor. Like all proton pump inhibitors, it is a lipophilic weak base that is unstable in acid. It is administered as enteric-coated, acid-resistant granules that are released in the neutral-alkaline environment of the small intestine. The nonencapsulated granules can be suspended in apple juice or sprinkled in apple sauce to be taken orally or through a nasogastric tube. It is indicated for the short-term treatment of acute duodenal ulcer, gastric ulcer, and erosive esophagitis. It also is indicated for maintenance treatment of healed idiopathic duodenal ulcer, erosive esophagitis, and pathological hypersecretory states such as Zollinger-Ellison syndrome.

It is a prodrug that requires protonation for activation. Thus, it is most effective given 30 to 60 min prior to a meal. Peak concentration occurs at approximately 1.7 hr. The plasma elimination half-life is 1.5 hr, but because it is an irreversible inhibitor of the proton pump, its acid inhibitory effect is greater than 24 hr. On a molar basis, it is approximately 30% to 35% more potent than omeprazole, with the equivalent doses being lansoprazole 30 mg and omeprazole 40 mg.

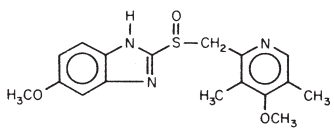
Like other proton pump inhibitors, it is very effective in healing acid peptic disease with 4-week healing rates for duodenal ulcer of approximately 95%, 8-week healing rates for gastric ulcer of 95%, and 8-week healing rates for gastric ulcer of 95%, and 8-week healing rates for erosive esophagitis of 95%.

Adverse reactions occurring in more than 1% of patients include abdominal pain (1.8%), diarrhea (3.6%), and nausea (1.4%), but only diarrhea occurs with a higher frequency than with placebo. The initial concern about carcinoid tumors seen in male rats treated with high doses for prolonged periods has not been borne out in clinical studies. While there is an increase in serum gastrin levels and hyperplasia of enterochromaffin-like cells, dysplasia and carcinoids have not been seen in other animal species or man after several years of continuous treatment.

Lansoprazole is metabolized through the CYP3A and CYP2C19 isozymes. Studies have not shown significant interactions with commonly used drugs, except a 10% increase in theophylline clearance. This interaction appears to be of no clinical significance. Lansoprazole, however, should not be administered with ketoconazole, which requires low pH for absorption. The pregnancy category is B.

OMEPRAZOLE

1*H*-Benzimidazole, 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-, Prilosec



[73590-58-6]$C_{17}H_{19}N_3O_3S$(345.42).

Preparation—US Pat 4,255,431.

Description—White crystals melting about 156°; pK_a (pyridine-N) 4.0, (imidazole-N) 8.7.

Solubility—1 g in about 8000 mL water or 25 mL alcohol.

Comments—In the treatment of acid peptic disorders. It is approved for the short-term treatment of duodenal ulcer, severe or poorly responsive gastroesophageal reflux, and hypersecretory conditions such as Zollinger-Ellison syndrome, systemic mastocytosis, and multiple endocrine adenomas. It is also effective in the prevention of NSAID ulcers and their complications. While not approved for that use, it appears to be as effective as misoprostol and has fewer side effects. It is now thought that, with the exception of NSAID-induced and *H pylori*–induced ulcers, the acid peptic diseases are lifelong diseases that require a lifetime of therapy. Long-term studies have demonstrated efficacy in the prevention of recurrence of reflux esophagitis and duodenal ulcer. The current trend in practice is to use proton-pump inhibitors as both initial and maintenance therapy; the so-called black-box precaution for long-term use of omeprazole has been removed and it was never placed on lansoprazole, the subsequently approved proton pump inhibitor.

Omeprazole, because of its acid lability, is given as a delayed-release capsule. Absorption occurs in the small bowel, with peak plasma levels occurring at 0.5 to 3.5 hr. Peak plasma levels and area under the concentration-time curve (AUC) are approximately proportional to dose in the therapeutic range. Bioavailability is 30% to 40%. Plasma half-life is 0.5 to 1 hr with total body clearance of 500 to 600 mL/min. Protein-binding is approximately 95%. Two plasma metabolites have been identified: hydroxyomeprazole and its corresponding carboxylic acid. The metabolites have virtually no antisecretory activity. Most of the drug is eliminated as metabolites in the urine. Dosage adjustment is not needed for patients with impaired renal function.

The antisecretory effect of omeprazole occurs within 1 hr, with maximum effect occurring within 2 hr. Inhibition of secretion remains at about 50% at 24 hr and lasts approximately 72 hr. The prolonged effect, beyond that expected for a drug with a short half-life, is due to irreversible binding to the H^+/K^+ ATPase. The inhibition of acid secretion peaks in 3 to 4 days and lasts for 3 to 5 days after discontinuing treatment. Omeprazole, at therapeutic doses of 20 to 40 mg causes an 80% to 95% decrease in 24-hr intragastric acidity.

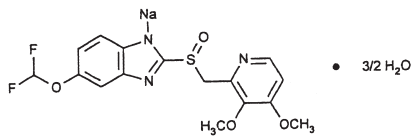
Duodenal ulcer healing occurs in 80% to 95% of patients at 4 weeks and greater than 95% at 8 weeks. Reflux esophagitis healing occurs in 8 weeks in approximately 80% of patients.

Adverse reactions reported to occur in more than 1% of patients include headache (6.9%), diarrhea (3.0%), abdominal pain (2.4%), nausea (2.2%), dizziness (1.5%), vomiting (1.5%), rash (1.5%), constipation (1.1%), asthenia (1.1%), and back pain (1.1%). The previous concern about the development of carcinoid tumors after long-term treatment is not justified after several years of clinical studies; in fact, such tumors have not been reported, other than in patients with Zollinger-Ellison syndrome and the multiple endocrine adenoma syndrome, Type C. These patients are predisposed to the development of gastric carcinoid tumors.

Omeprazole prolongs the elimination of diazepam, warfarin, and phenytoin. Clinical interactions have been seen with cyclosporine, disulfiram, and benzodiazepines. Omeprazole also inhibits the absorption of pH-dependent drugs such as ketoconazole and it should not be used during pregnancy.

PANTOPRAZOLE SODIUM

1*H*-Benzimidazole, 5-(difluoromethoxy)-2-[[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl] -, sodium salt, hydrate(2.3); Protonix



[164579-32-2] $C_{16}H_{14}F_2N_3NaO_4S.11/2H_2O$ (432.37).

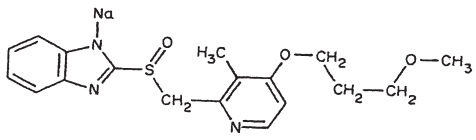
Preparation—*J Med Chem,* 1992; 35: 1049 and US 4,758,579 (1986).

Description—(Acid form) weakly amphoteric, white to off-white solid melting about 136° (dec); pK_{a1} 3.92, pK_{a2} 8.19. (Salt) Off-white solid decomposing about 130°.

Solubility—(Salt) Freely soluble in water; slightly soluble in pH 7 phosphate buffer; insoluble in hydrocarbon solvents. Solution stability is pH dependent with degradation increasing with decreasing pH. At pH 5, $t_{1/2}$ is 2.8 hrs and 220 hrs at pH 7.8. The pH of the injection is 9 to 10.

RABEPRAZOLE SODIUM

1*H*-Benzimidazole, 2[[[4-(3-methoxypropoxy)-3-methyl-2-pyridinyl]methyl]sulfinyl]- , sodium salt; Pariprazole, Aciphex



[117976-90-6] $C_{18}H_{20}N_3NaO_3S$ (381.42).

Preparation—US Pat 5,045,552 (1991).

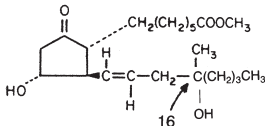
Description—(Acid form) White crystals from methylene chloride\ether melting about 100° (dec). Sodium salt occurs as white crystals from ether melting about 140° (dec). Stability is a function of pH, with rapid decomposition in acid medium.

Solubility—Very soluble in water or methanol; freely soluble in ethanol, chloroform or ethyl acetate; insoluble in ether or hexane.

DRUGS THAT ENHANCE MUCOSAL PROTECTION

MISOPROSTOL

Prost -13-en-1-oic acid, (11α, 13*E*)-(±)-11,16-dihydroxy-16-methyl-9-oxo-, methyl ester; Cytotec



[59122-46-2]$C_{22}H_{38}O_5$(382.54).

Preparation—*J Med Chem* 1957; 20:1152.

Description—Pale yellow oil. It is a mixture of the (±)-*R* and (±)-*S* forms with reference to carbon atom no 16.

Solubility—1 g in 2500 mL of water or 100 mL of alcohol.

Comments—In the prevention of NSAID gastropathy. A prostaglandin E_1 analog, it differs from the naturally occurring compound in that it is more water soluble and has a longer half-life. It both inhibits gastric acid secretion and increases mucosal resistance. Its inhibition of acid secretion, however, may not be sufficient to cause a therapeutic effect. Misoprostol probably derives its therapeutic benefit in the GI tract by increasing mucus and bicarbonate secretion by the gastric epithelium by increasing epithelial regeneration and by enhancing mucosal blood flow, thus enhancing mucosal protection.

Misoprostol is used for the prevention of gastric injury by NSAIDs. Controlled studies demonstrate that doses of 100 μg four times a day, 200 μg four times a day, and 200 μg twice a day are effective in preventing gastric injury induced by NSAIDs and reducing the incidence of severe complications by approximately 50%. It is superior to H_2-blockers in preventing gastric ulcers but not duodenal ulcers. It is superior to sucralfate in preventing both gastric and duodenal ulcers and superior to H_2-receptor antagonists in preventing gastric ulcer.

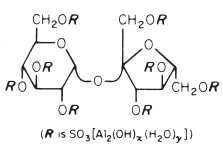
It is not yet clear which patients should receive misoprostol routinely for prophylaxis of NSAID-induced injury or under what circumstances misoprostol is cost effective. The patients at greatest risk for NSAID injury are patients with a previous history of ulcer disease, the elderly, patients with concomitant debilitating disease, and patients on multiple drug therapy. It is becoming common practice to treat all such patients prophylactically.

Misoprostol is also effective in the treatment of gastric ulcer, duodenal ulcer, and stress ulcer but is not approved for these uses, presumably because it has more side effects and no therapeutic advantage over H_2-blockers or proton pump inhibitors. Side effects from misoprostol have, to some extent, limited its use. At a dosage of 200 μg four times a day, more than 30% of patients have diarrhea. This appears to be lower with 100 μg four times a day, which should be the initial dose. It has no effect on GI hormones (gastrin, motilin, somatostatin, and vasoactive intestinal peptide) and no effect on gastric motility.

Misoprostol, because it causes uterine contractions, is contraindicated in pregnancy. It is rapidly (T_{max}, 12 min) and extensively absorbed. It has a terminal half-life of 20 to 40 min, with 80% being recovered in the urine. Dosage adjustment is not needed in patients with renal impairment. There is no effect on hepatic mixed-function oxidase systems, and no drug interactions are known. Misoprostol does not inhibit the therapeutic benefit of NSAIDs in rheumatoid arthritis.

SUCRALFATE

α-D-Glucopyranoside, β-D-fructofuranosyl-, octakis(hydrogen sulfate), aluminum complex; Carafate



[54182-58-0] $C_{12}H_mAl_{16}O_nS_8$ (*m* and *n* are approximately 54 and 75, respectively, giving an average molecular mass of about 2086 daltons).

Preparation—See US Pat 3,432,489.

Description—White powder; pK_a between 0.43 and 1.19.

Solubility—Practically insoluble in water; soluble in fixed alkali or acids.

Comments—Approved for short-term (8-week) therapy of duodenal ulcers and, at reduced dosage, for maintenance therapy of duodenal ulcer. Clinical reports indicate that 1 g four times a day for 4 weeks will heal 73% to 92% of duodenal ulcers. Antacids may be prescribed as needed for pain relief. Sucralfate is absorbed minimally from the GI tract. The mechanism by which sucralfate accelerates healing of duodenal ulcer remains to be defined fully. It reduces acid secretion by approximately 50%, and this is probably its most important effect. It also forms an ulcer-adherent complex with proteinaceous exudate at the ulcer site; this complex covers the ulcer site and protects it against further attack by acid, pepsin, and bile salts. Animal studies suggest that sucralfate also enhances local prostaglandin synthesis, which would increase mucosal protection by stimulating mucus and bicarbonate secretion. Whatever the mechanism, sucralfate is effective in healing ulcers. There are no known contraindications. Nevertheless, it should not be used during pregnancy or in nursing mothers unless clearly needed. Since sucralfate is an aluminum salt of a sulfated disaccharide, it may prevent absorption of tetracycline, phenytoin, H_2-blockers, warfarin, or digoxin if the drugs are given simultaneously; giving the drugs 2 hr apart minimizes these effects. Adverse effects occur in approximately 5% of patients; constipation is most common (2.2%). Other adverse effects include diarrhea, nausea, gastric discomfort, indigestion, dry mouth, rash, pruritus, back pain, dizziness, sleepiness, and vertigo.

PROKINETIC DRUGS

Prokinetic drugs enhance GI motility and are used in the treatment of gastroesophageal reflux disease (GERD), gastroparesis, and constipation. GI motility is regulated through a complex integration of the autonomic nervous system, the enteric nervous system, and GI hormones. Each organ, ie, the esophagus, stomach, small intestine, and colon, have both integrated physiological regulation as well as unique regulation for each organ. The features that are unique to each organ are poorly understood, and many of the specific receptors have not been identified. Thus, the drugs tend to have a broad range of activity, with the beneficial and adverse effects mimicking each other. It is important to realize that in disorders of gastric emptying, oral drug absorption may be impaired or delayed, and thus IV therapy may be needed to the initial treatment.

BETHANECHOL CHLORIDE

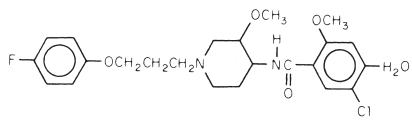
For the full monograph, see page 1390.

Comments—A parasympathemimetic that stimulates muscarinic receptors. It increases lower esophageal sphincter pressure and as such reduces nocturnal gastroesophageal reflux. It also increases contractions in the fundus and antrum of the stomach but does not trigger migratory motor activity. Thus, it does not enhance gastric emptying and is not a true prokinetic drug.

It is indicated for the treatment of acute postoperative and postpartum urinary retention in the absence of obstruction of the urinary tract.

CISAPRIDE

Benzamide, *cis*-4-amino-5-chloro-*N*-[1-[3-(4-fluorophenoxy)propyl]-3-methoxy-4-piperidinyl]-2-methoxy-, monohydrate; Propulsid



[81098-60-4] $C_{23}H_{29}ClFN_3O_4.H_2O$ (483.97).

Preparation—See US Pat 5,665,884 (1997).

Description—White to off-white powder melting about 110°.

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

Comments—It stimulates acetylcholine release from enteric nerves and acts as a direct smooth muscle stimulant. It also appears to be a serotonin 4 (5-HT_4) agonist and 5-HT_3 antagonist. It has effects along the entire GI tract. It increases lower esophageal sphincter pressure and also enhances esophageal peristalsis. It thus has a beneficial effect in GERD by increasing lower esophageal sphincter pressure and by increasing acid clearance from the esophagus.

Cisapride increases gastric liquid and solid emptying with a reduction of duodenogastric reflux. Thus, it has potential benefit in patients with disorders of gastric emptying such as diabetic gastroparesis.

It also has prokinetic effects on the jejunum and colon that account for its sometimes beneficial effect in patients with constipation but also its major side effect of diarrhea.

Cisapride is indicated for the symptomatic treatment of noctural heartburn but is used widely for gastroparesis, and constipation.

Peak plasma levels are achieved within 2 hr of the usual oral dose of 10 mg. The use of cisapride often is limited by the development of diarrhea, which occurs in 10% to 20% of patients. Tachyphylaxis occurs within a few months of continuous use.

Cisapride is metabolized by the CYP3A4 isoenzyme system. Drugs that inhibit this enzyme, such as fluconazole, ketoconazole, traconazole, miconazole, clarithromycin, and erythromycin elevate cisapride blood levels, which can lead to serious cardiac arrhythmias including ventricular tachycardia and torsades de pointes. Deaths have been reported. Pregnancy category is C. The FDA has restricted the use of cisapride due to cardiac effects.

ERYTHROMYCIN

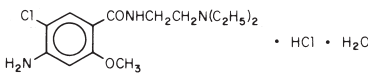
For the full monograph, see page 1653.

Comments—While widely used as an antibiotic, it is apparent that low-dose erythromycin also has prokinetic activity. It is a motilin agonist causing premature migratory motor-complex activity when used at doses of 1 to 2 mg/kg. Interestingly, at high doses, it does not have significant prokinetic activity. Tachyphylaxis, a problem common to all prokinetic drugs, is a significant problem with erythromycin as well.

It has no approved indication for the treatment of gastroparesis but is used widely. It appears to be especially helpful when used IV for acute gastroparesis. It must not be used in conjunction with cisapride.

METOCLOPRAMIDE HYDROCHLORIDE

Benzamide, 4-amino-5-chloro-*N*-[2-(diethylamino)ethyl]-2-methoxy-monohydrochloride, monohydrate; Reglan



[54143-57-6]$C_{14}H_{22}ClN_3O_2.HCl.H_2O$

Preparation—See *Arch Pharm* 1980; 313:297.

Description—White crystals melting about 185° with decomposition.

Solubility—Soluble 1 g in about 0.7 mL of water, 3 mL of alcohol, or 55 mL of chloroform. A 10% aqueous solution has a pH of about 5.5.

Comments—A substituted benzamide with dopaminergic activity. Its prokinetic activities are limited to the proximal gut, and as such it is used for the prophylaxis of *vomiting* associated with *cancer chemotherapy;* relief of symptoms associated with *acute* and *recurrent diabetic gastroparesis;* it also is used as adjunctive therapy in patients with gastroesophageal reflux. When treating diabetic gastroparesis, it should be used IV until some gastric emptying is restored to ensure absorption.

In addition to its ability to stimulate the gut, it also has enteric cholinergic properties, apparently sensitizing intestinal smooth muscle to the action of acetylcholine rather than acting directly on cholinergic receptors. The drug is not effective in motion sickness. The use of metoclopramide is limited by two factors—a narrow therapeutic index and tachyphylaxis that usually occurs within 6 weeks.

DIGESTANTS

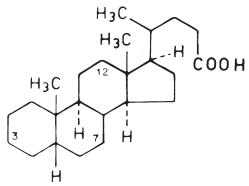
Bile Acids

Bile is composed of a variety of substances, but only the bile salts (salts of the native bile acids) are therapeutically important. When given by mouth the bile salts are absorbed from the intestine and reexcreted by the liver in the bile, thus, entering the same cyclic process (enterohepatic circulation) as endogenous bile salts. They are of little value in promoting the absorption of fats and fat-soluble vitamins from the GI tract but are useful in the dissolution of gallstones and in the treatment of primary biliary cirrhosis and, perhaps, steatohepatitis or fatty liver.

Bile, a viscid, bitter, alkaline (pH 7.8) fluid, isotonic with serum and yellowish brown to golden yellow in color, is excreted by adults at the rate of 500 to 1100 mL per 24 hr. The principal organic constituents are bile acids (as salts), bile pigments, cholesterol, lecithin, and mucin. The principal inorganic constituents are water, sodium, calcium, copper, iron, magnesium, potassium, bicarbonate, phosphate, and sulfate.

The bile acids, present as the sodium salts of a mixture of acids, are divided into two groups: primary (derived from cholesterol) and secondary (derived from primary bile acids). The bile salts are conjugated through peptide linkages to glycine or taurine. The primary bile salts are taurine or glycine conjugates of cholic acid and chenic acid; the secondary bile salts are taurine and glycine conjugates of deoxycholic and lithocholic acids.

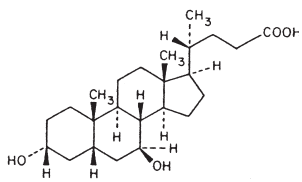
The predominant bile acids represented in bile are cholic, chenic, deoxycholic, and lithocholic. The structural relationships among these and their parent molecule, 5b-cholanic acid, are shown below. The synthetic dehydrocholic acid is included for comparison.



These bile acids combine with phospholipid to solubilize cholesterol and fatty acid in the intestine as mixed micelles. In so doing, they solubilize lipids and promote the absorption of fats, cholesterol, and the fat-soluble vitamins. The major clinical use of bile acids, however, is the dissolution of cholesterol gallstones and the treatment of primary biliary cirrhosis.

URSODIOL

Cholan-24-oic acid, (3α,5β,7β)-3,7-dihydroxy-, Ursodeoxycholic Acid; Actigall; Urso



[128-13-2]$C_{24}H_{40}O_4$ (392.58).

Preparation—For the isolation, see *J Biochem (Japan)* 1927; 7:505.

Description—Platelets, melting about 203°; $pK_a \approx 5$.

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

Comments—A naturally occurring bile acid that is found in small amounts in man and in large amounts in bear (hence the name *urso*). It is the 7β epimer of chenodeoxycholic acid—an important primary bile acid in man. It reduces the cholesterol saturation of bile by inhibiting HMG-CoA reductase, the rate-limiting enzyme in cholesterol synthesis. It is indicated for the dissolution of radiolucent (ie, cholesterol) gallstones and the treatment of primary biliary cirrhosis. It also is used in primary sclerosing cholangitis, chronic active hepatitis and nonalcoholic steatohepatitis (fatty liver), but without proved therapeutic benefit.

Ursodiol is 90% absorbed in the small bowel. Upon absorption, it enters the portal circulation and then is extracted by the liver, where it is conjugated with glycine or taurine and finally secreted into bile and ultimately back into the intestine. This intrahepatic recirculation of ursodiol ultimately results in some replacement of endogenous bile acids such that after about 3 weeks of therapy, ursodiol makes up about 60% of the total bile acid pool. Since the total bile acid pool also is increased, cholesterol more readily can be solubilized, and cholesterol gallstones are dissolved gradually. Once ursodiol is conjugated, little change occurs in the liver or intestine. Small amounts of 7-ketolithocholic acid or lithocholic acid are formed but mostly lost in the feces. This is helpful since larger amounts of lithocholic acid are hepatotoxic. There is also some deconjugation of ursodiol in the intestine. The resultant free ursodiol is reabsorbed and subsequently reconjugated in the liver.

Clinical trials with ursodiol in the treatment of primary biliary cirrhosis have shown a retardation of disease progression and delay in the need for liver transplantation.

Urosodiol reduces the amount of fat in the liver in patients with nonalcoholic steatohepatitis and by implication should reduce the progression of cirrhosis. That, however, has neither been proved nor is it known whether life expectancy is altered.

Clinical trials also have demonstrated that gallstone dissolution occurs in about 30% of patients with gallstones less than 20 mm in diameter treated for up to 2 yr. Patients with larger stones or with nonvisualizing gallbladders on oral cholecystogram rarely dissolve their stones. However, patients with floating stones less than 0.5 cm in diameter have a greater than 50% chance of dissolution.

MALT EXTRACT—page 1076.

PANCREATIC ENZYMES

Pancreatic enzymes are approved for the treatment of malabsorption secondary to pancreatic insufficiency caused by chronic pancreatitis, pancreatectomy, and cystic fibrosis. They also have been advocated for the treatment of chronic pancreatitis and pancreatic fistulae. Pancreatic enzyme preparations consist of mixtures of lipase, amylase, and protease.

Lipase hydrolyzes dietary triglycerides at the alpha position, forming two molecules of fatty acid and a molecule of β-monoglyceride. In so doing, the large triglyceride molecule is converted into three smaller molecules that can be incorporated in mixed bile acid micelles for solubilization and transported in the intestine.

Amylase is an α-1,4-glucosidase that splits straight-chain polyglucosides (the amyloses in dietary starch) into maltose and maltotriose. These subsequently are cleaved into glucose by intestinal brush-border disaccharidase enzymes and absorbed.

Protease is a mixture of proteolytic enzymes—trypsin, chymotrypsin, and elastase—that cleaves peptide bonds in the center of proteins and polypeptides. The hydrolytic products of these enzymes are amino acids and oligopeptides. The amino acids are absorbed directly, while the oligopeptides are split further by brush-border enzymes or intracellular enzymes before being transported in the portal circulation to the liver.

The treatment of malabsorption is the usual indication for pancreatic enzymes. The major manifestation of pancreatic malabsorption is steatorrhea—a voluminous, malodorous stool that is light in color and laden with fat that is not being absorbed. Clinical steatorrhea does not occur until pancreatic lipase output is less than 10% of normal. Thus, the lipase content of the pancreatic enzyme replacement preparation is the critical factor in the treatment of steatorrhea. Approximately 28,000 U of lipase should be delivered during the 4-hr postprandial period.

Only a few preparations have sufficient lipase to be effective (Table 66-7 for enzyme contents). Because lipase is inhibited irreversibly below pH 4, the enzyme preparations either have to be enteric coated or need to be given with sodium bicarbonate supplementation to avoid inactivation. The new microsphere preparations, Creon, Entolase-HP, Pancrease MT16, and Zymase, appear to have the most bioavailability. The usual dose is 3 capsules prior to each meal. When using Viokase (8 tablets), Cotazyme (6 capsules), or Ilozyme (4 capsules), adjuvant therapy with an H_2-receptor antagonist or proton pump inhibitor may be needed to ensure bioavailability. Dosing is generally 2 to 3 tablets or capsules with each meal but should be adjusted to alleviate steatorrhea.

The treatment of abdominal pain in patients with chronic pancreatitis is complex and controversial. Many of the patients have chronic pain syndrome with narcotic addiction.

An important component of pain management in these patients is withdrawal from pain medications that in themselves may be perpetuating the pain. Once this is done, correction of mechanical problems, ie, drainage of pseudocysts and the correction of duct stenosis, is essential. If pain persists, there is evidence that large doses of pancreatic enzymes will decrease pain in these patients. The rationale for this treatment is that *resting* the pancreas will allow it to heal.

Pancreatic enzymes inhibit cholecystokinin, which stimulates pancreatic secretion when food reaches the duodenum. Putting the pancreas to rest presumably eliminates the pain that occurs when the pancreas is actively secreting. The effective components of the pancreatic enzymes for relieving pain are the serine proteases (trypsin, chymotrypsin, and elastase). Patients with idiopathic chronic pancreatitis appear to respond better than patients with chronic alcoholic pancreatitis.

Finally, pancreatic enzymes also have been advocated for the treatment of pancreatic fistulae and for the reduction and frequency of attacks of acute recurrent pancreatitis. To date, there are no controlled studies to support this type of therapy.

LACTASE

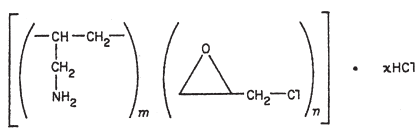
Lactaid; Lactrase

Preparation—A β-D-galactosidase isolated from *Aspergillus oryzae* (caplets) or *Kluyveromyces lactis* (drops).

Comments—The enzyme lactase hydrolyzes lactose—the sugar found in milk—into two simple sugars: glucose and galactose. It is indicated for patients with symptomatic lactose deficiency manifested by abdominal cramps, bloating, flatuluence, and diarrhea following the ingestion of dairy products. Its only known side effect is allergy. Diabetics should be aware that the glucose formed through degradation by lactase will be absorbed and, in effect, increase their sugar intake. Lactase drops are used for the treatment of milk prior to ingestion; adding 10 to 15 drops to a quart of milk reduces the lactose by 90% to 99%. Caplets are to be taken with meals that contain dairy products.

SACROSIDASE

β-Fructofuranosidase; Sucraid



[85897-35-4]

Table 66-7. Pancreatic Enzymes

NAME	FORMULATION	ENZYME CONTENT[a,b]
Cotazyme	Powder in capsules	L, 8000; P, 30,000; A, 30,000
Cotazyme S	Enteric-coated spheres in capsules	L, 8000; P, 30,000; A, 30,000
Creon 10	Enteric-coated microspheres in capsules	L, 8000; P, 13,000; A, 30,000
Creon 25	Enteric-coated microspheres in capsules	L, 25,000; P, 62,500; A, 74,700
Ku-zyme	Capsules	L, 1200; P, 6 mg; A, 30 mg
Pancrease	Enteric-coated microspheres in capsules	L, 4000; P, 25,000; A, 30,000
Pancrease MT 4	Enteric-coated microtablets in capsules	L, 4000; P, 12,000; A, 12,000
Pancrease MT 10	Enteric-coated microtablets in capsules	L, 10,000; P, 30,000; A, 30,000
Pancrease MT 16	Enteric-coated microtablets in capsules	L, 16,000; P, 48,000; A, 48,000
Viokase	Tablets	
Powder (1/4 tsp.)	L, 8000; P, 30,000; A, 30,000	

[a] L, lipase; P, protease; A, amylase.
[b] Expressed in USP units. USP units (*in vitro* test method) indicate digestive capacity such that 1000 units of lipase digests 3.5 g of fat, 1000 units of protease digests 1 g of protein, and 1000 units of amylase digests 1 g of starch.

Preparation—A β-D-fructofuranoside fructohydrolase obtained from baker's yeast (*Saccharomyces cerevisiae*).

Description—An enzyme of reported molecular weight between 97 and 140 kDa.

Comments—Sacrosidase is used in the treatment of congenital sucrase-isomaltase deficiency (CSID) as it hydrolyzes sucrose (in the gut) into its elements, glucose and fructose.

LAXATIVES

Laxatives are drugs that either accelerate fecal passage or decrease fecal consistency. They work by promoting one or more of the mechanisms that cause diarrhea.

Constipation has different meanings for different people but, in general, refers to stools that are too small, too infrequent, or too difficult to expel. Patients also may describe it as a sense of incomplete evacuation. None of these definitions is easy to quantify, and the normal range is wide. Normal stool weight is largely a function of diet. Thus, stools generated by the Western diet, which tends to be low in undigestible fiber, weigh 100 to 200 g a day, while stools in Africa tend to weigh 400 to 500 g a day. Similarly, the frequency of stools varies greatly and is largely a function of the diet. It is said that normal stool frequency varies from three stools a day to three a week. There are few studies to determine what really is normal, but in the Western world, it is believed that fewer than five stools a week is abnormal. Another definition is a change to lower frequency than usual for a particular individual.

Since constipation is a symptom rather than a disease, medical evaluation should be undertaken in patients who develop constipation. The wide availability and marketing of OTC laxatives have the potential to preclude appropriate diagnosis. The most common cause is irritable bowel syndrome, but constipation may be associated with neurogenic diseases, systemic diseases, and pharmacological causes. All of these may require primary treatment independent of symptomatic treatment with laxatives. Bowel disease, *per se,* other than irritable bowel syndrome usually does not cause constipation.

Laxatives are divided into several categories as a function of their mechanism of action.

Stimulant laxatives, such as bisacodyl, phenolphthalein, and senna, work by various mechanisms including inhibition of absorption, enhancement of secretion, and effects on motility. In general, these laxatives have the most toxicity and are less physiological in their actions.

Saline laxatives, such as magnesium citrate and sodium phosphate, exert an osmotic effect that increases the water content and volume of stool.

Hyperosmotic laxatives, such as lactulose, exert an osmotic effect, leading to water secretion into the intestine.

Bulk-forming laxatives consist of polysaccharides and cellulose derivatives that are undigestible (Table 66-8). Because they absorb water, they increase the bulk of stool and, in so doing, provide a physiological stimulus to defecation. They also may inhibit bile acid absorption, with subsequent effects on water absorption and secretion by the intestine.

Lubricant laxatives, such as mineral oil, allow easier passage of a stool because of an oil coating. They may also inhibit colonic reabsorption of water.

Emollient laxatives, such as docusate sodium, are surfactants that facilitate mixture of water and lipid soluble substances to soften stool. They also stimulate water secretion in the GI tract.

Patients who use laxatives should be reminded of the following points: laxatives are not for long-term use; if they are not effective after 1 week, a physician should be consulted. Laxative products that contain more than 15 mEq (345 mg) of sodium, more than 25 mEq (975 mg) of potassium, or more than 50 mEq (600 mg) of magnesium in the maximum daily dose should not be used if kidney disease is present. Phenolphthalein preparations should be discontinued if a rash appears. Saline laxatives should not be given orally to children under 6 or rectally to infants under 2 yr of age; mineral oil should not be given to children under 6 yr of age. Dioctyl sodium sulfosuccinate should not be used with mineral oil. To be effective, enemas and suppositories must be administered properly. *Laxatives should not be used to relieve GI symptoms of unknown cause.*

Although occasional use of a laxative is relatively harmless, depletion of fluids and electrolytes can result from their chronic use. Mineral oil should be given at bedtime to minimize its interference with the absorption of fat-soluble vitamins. In addition, aspiration of mineral oil may result in chronic pneumonitis; consequently, it is contraindicated in patients with disorders of gastric or esophageal emptying. Even the soft, bulk-forming laxatives have been reported to cause enteric obstruction in an occasional patient with inflammatory or neoplastic strictures of the gut.

Stimulant Laxatives

The *stimulant laxatives* have multiple actions on the intestine. These include stimulation of motor activity and effects on water reabsorption and secretion. What they have in common is the ability to increase the amount of water in the stool and the ability to decrease colonic transit time. The more commonly employed agents are the anthraquinone laxatives, *cascara sagrada* and *senna;* the diphenylmethane derivatives, *phenolphthalein* and *bisacodyl;* and *castor oil.*

The *anthraquinone-containing laxatives,* such as cascara and senna, are used widely. The active glycosides are absorbed in the small intestine, circulated through the portal system and into the general circulation and excreted in the bile, urine, saliva, colonic mucosa, and in the milk of lactating women. These glycosides stimulate Auerbach's plexus to increase peristalsis. They usually act within 6 to 12 hr of ingestion. The *diphenylmethane derivatives,* such as phenolphthalein and bisacodyl, have similar pharmacological actions; they stimulate sensory nerves in the colonic mucosa to initiate reflex peristalsis. Phenolphthalein is usually active within 6 to 8 hr after administration; bisacodyl results in a smooth, formed stool within 6 to 10 hr after oral administration and 15 to 60 min after rectal administration. *Castor oil* is classified as a stimulant laxative because lipolysis in the

Table 66-8. Composition and Dose of Some Bulk Laxatives

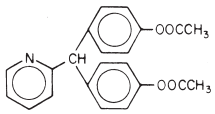
PRODUCT	ACTIVE INGREDIENT	AMOUNT OF FIBER (G/UNIT DOSE)	USUAL ADULT DOSE[a]
Citrucel Orange Flavor	Methylcellulose	2 g	1 tbs
Fiberall Powder	Polycarbophil	2.2 g	1 tsp
Fiberall Fiber Wafers	Psyllium	2.2 g	1 wafer
FiberCon	Polycarbophil	0.5 g	2 tablets
Hydrocil Instant	Psyllium	3.5 g	1 packet
Metamucil Regular	Psyllium	3.4 g	1 tsp
Metamucil Sugar Free Orange	Psyllium	3.4 g	1 packet
Perdiem Fiber	Psyllium	4 g	1 tsp
Serutan	Psyllium	2.5 g	1 tsp

[a] Teaspoonful and tablespoonful quantities are rounded unless otherwise stated.

small intestine liberates ricinoleic acid, a short-chain fatty acid that stimulates peristalsis and inhibits the absorption of water and electrolytes from the small intestine. *Glycerin,* in the form of suppositories, promotes defecation by stimulating the rectal mucosa; it also acts to lubricate and soften inspissated fecal material. The stimulant laxatives have many characteristics in common; they increase intestinal motility leading to abdominal cramps, increase mucus secretion and increase fluidity of the stool. Intensity of effect is related to dosage, but effective doses vary markedly from one individual to another.

BISACODYL

Phenol, 4,4′-(2-pyridinylmethylene)bis-, diacetate (ester); Dulcolax



4,4′-(2-Pyridylmethylene)diphenol diacetate (ester) [603-50-9] $C_{22}H_{19}NO_4$ (361.40).

Caution—Avoid inhalation and contact with the eyes, skin, and mucous membranes.

Preparation—2-Pyridinocarboxaldehyde is condensed with phenol with the aid of a suitable dehydrant such as sulfuric acid, and the resulting 4,4′-(2-pyridyl)diphenol is esterified by treatment with acetic anhydride and anhydrous sodium acetate. US Pat 2,764,590.

Description—White to off-white, crystalline powder in which particles having a longest diameter smaller than 50 μm predominate; melts between 131° and 135°.

Solubility—1 g in >10,000 mL water, 210 mL alcohol, 2.5 mL chloroform, or 275 mL ether.

Comments—A stimulant laxative that acts directly on sensory nerve fibers in the colonic mucosa to increase peristalsis throughout the large intestine. It is administered either orally or rectally for constipation and for evacuation of the bowel prior to surgery, proctoscopy, or radiological examination. It is usually effective overnight or within 6 to 10 hr. Bisacodyl provides satisfactory cleansing of the bowel, obviating the need for an enema. Side effects usually are limited to abdominal cramps. Continued use of the suppository may cause rectal irritation. There are no contraindications to the use of bisacodyl, except for an acute surgical abdomen.

CASANTHRANOL—see RPS-20, page 1231.

CASCARA SAGRADA

Nature's Remedy; ing of Peri-Colace; Sacred Bark; Chittem; Dogwood; Bear-berry; Bitter Bark

The dried bark of *Rhamnus purshiana* De Candolle (Fam *Rhamnaceae*).

Constituents—The following active principles have been reported: *Aloe-emodin* (1,8-dihydroxy-3-hydroxymethylanthraquinone), *chrysophanic acid* (1,8-dihydroxy-3-methylanthraquinone), *iso-emodin* (3,5,8-trihydroxy-2-methylanthraquinone), *methylhydrocotoin* (2,4,6-trimeth oxybenzophenone), and *purshianin,* a glycoside-forming red-brown crystal melting about 237°. Cascara also contains several resins, one of which is very bitter and gives a bright-red color with potassium hydroxide solution, which can be used to test stools in patients suspected of laxative abuse.

Comments—A widely used cathartic. It is used for relief of transient constipation. Its precise mechanism of action is unknown. It has very little action on the small intestine but promotes peristalsis in the large intestine. The action of cascara is mild and is unaccompanied by cramping. A therapeutic dose causes a single evacuation of the bowel in approximately 8 hr. The stool may be solid or semifluid. Prolonged ingestion frequently results in melanosis coli, which regresses after cascara sagrada is discontinued. It should not be given to lactating mothers, since it is excreted in breast milk.

CASTOR OIL

Emulsoil; Neoloid; Purge

The fixed oil obtained from the seed of *Ricinus communis* Linné (Fam *Euphorbiaceae*).

Preparation—By cold expression and subsequent clarification of the oil by heat. It consists chiefly of glycerides of ricinoleic and isoricinoleic acids. The purgative action has been attributed to hydrolysis of ricinolein in the intestine, ricinoleic acid being produced. The seeds contain two principles, *ricin,* a very poisonous albumin (150 mg toxic *per os*), and *ricinine,* a poisonous base (1,2-dihydro-4-methoxy-1-methyl-2-oxonicotinonitrile). Because of the presence of these toxic substances, the seeds are definitely poisonous.

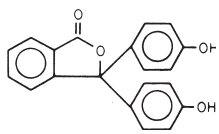
Description—Pale yellowish or almost colorless, transparent, viscid liquid with a faint, mild odor and a slightly acrid and usually nauseating taste; specific gravity between 0.945 and 0.965.

Solubility—Soluble in alcohol; miscible with dehydrated alcohol, glacial acetic acid, chloroform, or ether.

Comments—Used internally as a *laxative* and externally as an *emollient*. The oil is bland and soothing to the skin. Castor oil is metabolized to ricinoleic acid, which stimulates water secretion in the intestine while decreasing glucose absorption. It also stimulates colonic motility. When administered orally it produces one or more copious stools within 2 to 6 hr after ingestion. It is used frequently to empty the GI tract prior to proctoscopy or x-ray studies of the GI tract and to threaten children. It should not be used in the therapy of acute constipation. Chronic use is not recommended, since absorption of nutrients may be reduced.

PHENOLPHTHALEIN

1(3*H*)-Isobenzofuranone, 3,3-bis(4-hydroxyphenyl)-,



3,3-Bis(*p*-hydroxyphenyl)phthalide [77-09-8] $C_{20}H_{14}O_4$ (318.33).

Preparation—A mixture of phenol, phthalic anhydride, and sulfuric acid is heated at 120° for 10 to 12 hr. The product is extracted with boiling water, the residue dissolved in dilute NaOH solution, filtered, and precipitated with acid.

Description—White or faintly yellowish white, crytalline powder; odorless and stable in air; melts no lower than 258°.

Solubility—Practically insoluble in water; 1 g in about 15 mL alcohol or about 100 mL ether.

Comments—It was one of the most widely used of the *cathartic* drugs, it is the base of many proprietary laxatives (Table 66-9). Classified as a stimulant cathartic, although the precise mechanism of action is unknown. It tends to act longer than other laxatives because it enters the enterohepatic circulation and is reexcreted in bile into the intestine. It acts within 4 to 8 hr after ingestion. In susceptible individuals, phenolphthalein may cause allergic reactions, including Stevens-Johnson syndrome and lupus erythematosus. The skin lesions may persist for months after discontinuing the drug. Deaths have been attributed to allergy to this drug. It also may cause a Bartter's-like syndrome with hy-

Table 66-9. Composition of Some Laxative Mixtures

	CONTENT (MG) PER CAPSULE OR TABLET				
PRODUCT	DOCUSATE[a]	CASANTHRANOL	PHENOLPHTHALEIN	OTHER	DOSE
Correctol Tab	100 (Na)				1–2 tabs
Dialose Plus	100 (K)	30			1 cap bid
Extra Gentle Ex-Lax	75 (Na)		65		1–2 tabs
Feen-A-Mint	100 (Na)		65		1–2 tabs
Natures Remedy	100 (Na)			100[b]; 150[c]	1–2 tabs
Peri-Colace	100 (Na)	30			1–2 caps
Phillips' LaxCaps	83 (Na)		90		1–2 caps

[a] Na, sodium; K, potassium.
[b] Aloe.
[c] Cascara sagrada.

peraldosteronism and hypokalemia. Phenolphthalein colors an alkaline urine red, and small portions may appear in the urine after oral ingestion. It also is used as an indicator in volumetric analysis. This reaction forms the basis of a test in which KOH is used to detect phenolphthalein in the stools of laxative abusers. The drug has been discontinued.

SENNOSIDES

ex-lax; Senokot

A natural complex of anthraquinone glycosides found in senna, isolated from *Cassia angustifolia* as calcium salts, contains 55% to 65% of the calcium salts.

Description—Brownish powder; pH (mixture 1 g/10 mL water) between 6.3 and 7.3

Comments—A *laxative*. Evacuation of the bowels occurs 8 to 10 hr after oral administration.

Saline (Hyperosmotic) Laxatives

A number of magnesium and sodium salts in the form of citrates, sulfates, phosphates, and tartrates are used as *saline laxatives*. These cations and anions are at most only slightly absorbed from the GI tract. Consequently, when given orally in hypertonic solutions, they draw water from the tissues into the intestine, increase peristalsis, and induce a profuse, watery stool. This traditional explanation for the mechanism of action of saline laxatives has been questioned. Indeed, several studies indicate that different mechanisms, independent of osmotic effect, are responsible for the laxative properties of these salts. For example, it has been shown that magnesium stimulates release of endogenous cholecystokinin-pancreozymin, a hormone that causes the accumulation of fluid and electrolytes within the human small intestine. The laxative action of magnesium-containing salts, therefore, may result from their ability to diminish the net absorption of fluid and electrolytes.

The choice of saline laxative usually is based on cost and palatability. There are, however, situations in which the injudicious use of a saline laxative results in serious adverse effects. As much as 20% of the magnesium ion may be absorbed after oral administration of a magnesium salt. In patients with impaired renal function, toxic concentrations of the ion can accumulate. Laxatives that contain sodium are contraindicated in individuals with edema and congestive heart failure. Chronic use of saline laxatives also may result in excessive dehydration. Other contraindications are mentioned in the respective monographs.

MAGNESIUM OXIDE—page 1296.

MAGNESIUM SULFATE

Sulfuric acid magnesium salt (1:1), heptahydrate; Bitter Salts; Epsom Salts

Magnesium sulfate (1:1) heptahydrate [10034-99-8] $MgSO_4.7H_2O$ (246.47); *anhydrous* [7487-88-8] (120.36).

Preparation—Magnesium sulfate can be prepared by neutralizing sulfuric acid with magnesium carbonate or oxide, but it also may be obtained directly from natural sources. In the form of a double salt with alkali metals, it occurs abundantly in several mines, and these comprise a large source of the salt. It also is produced in large quantities from the magnesium salts occurring in the brines used for extraction of bromine. The *liquors* after the removal of bromine are treated with calcium hydroxide, thus precipitating magnesium as the hydroxide. Sulfur dioxide and air are passed into an aqueous suspension of the magnesium hydroxide, yielding magnesium sulfate.

$$Mg(OH)_2 + SO_2 + 1/2O_2 \rightarrow MgSO_4 + H_2O$$

Description—Small, colorless crystals, usually needlelike, with a cooling, saline, and bitter taste; effloresces in warm, dry air; at 100° it loses 5 molecules of its water; aqueous solution is neutral to litmus.

Comments—An effective and widely employed *saline laxative*. The laxative action probably results from two factors: (1) magnesium sulfate is not absorbed from the GI tract and, thus, draws water into the lumen of the bowel to make an isotonic solution and (2) the magnesium ion stimulates the release of cholecystokinin-pancreozymin, which causes an accumulation of fluid and electrolytes within the small intestine. It is the increased volume that promotes the motor activity of the bowel. If dissolved in iced water, its nauseous taste is not so perceptible as when water at ordinary temperature is used; it may be disguised further by the use of orange juice.

SODIUM PHOSPHATES

Phosphoric acid, disodium salt, heptahydrate; Dibasic Sodium Phosphate; Disodium Orthophosphate; Disodium Hydrogen Phosphate; Secondary Sodium Phosphate; Fleet Enema, Phospho-Soda

Disodium phosphate heptahydrate [7782-85-6] $Na_2HPO_4.7H_2O$ (268.07); *anhydrous* [7558-79-4] (141.96).

Preparation—From *bone phosphate* or *bone ash,* obtained by heating bones to whiteness, which consists chiefly of tribasic calcium phosphate. The mineral *phosphorite,* which is a tribasic calcium phosphate, also is used. The finely ground phosphatic material is digested with sulfuric acid, the mixture then is leached with hot water, neutralized with sodium carbonate, and the sodium phosphate is crystallized from the filtrate.

Description—Colorless, or white, granular salt; effloresces in warm, dry air; solutions are alkaline to litmus and phenolphthalein (pH about 9.5).

Solubility—1 g in 4 mL water; very slightly soluble in alcohol.

Comments—One of the most palatable of the *saline laxatives.* It also is used in the form of the oral solution (see below) as an *antihypercalcemic.* Its major use, however, is for diagnostic procedures such as proctoscopy, colonoscopy, or barium enema.

Caution—This phosphate should not be confused with tribasic sodium phosphate, which is very alkaline and has a caustic action.

SODIUM PHOSPHATES ENEMA

Fleet Enema

Comments—A *laxative* administered as an enema primarily in preparation for surgery, endoscopy, or x-ray. It should not be used in the presence of abdominal pain, nausea, or vomiting.

SODIUM PHOSPHATES ORAL SOLUTION

Sodium Phosphates Oral Solution; Fleet Phospho-Soda Sodium Phosphates

Comments—An orally administered saline *laxative* used primarily in preparation for surgery, endoscopy, or x-ray. It is usually effective overnight or within 1 hr if taken before meals. It should not be used in patients with abdominal pain, nausea or vomiting.

Bulk-Forming Laxatives

The bulk-forming laxatives (Table 66-8) include a wide range of natural and semisynthetic polysaccharides and cellular derivatives that are only partially digested. The undigested portions are hydrophilic and swell in the presence of water to form a viscous solution or gel. The resultant changes in bowel wall tension and intraluminal pressure promote transit. Other mechanisms also may be involved. For example, bile-salt metabolism may be altered, leading to a choleretic effect. The bulk-forming laxatives have become the mainstay of the management of irritable bowel syndrome, which is manifested typically by alternating diarrhea and constipation, lower abdominal pain, abdominal bloating, and a sense of incomplete evacuation. They are particularly useful in this condition because they not only relieve constipation but also, because of their hydrophilic property, decrease diarrhea. Although used widely for the treatment of irritable bowel syndrome, there is little convincing evidence of their efficacy. This may be because of the variability of this syndrome and the lack of objective parameters to measure efficacy. They also are used for symptomatic treatment of acute diarrhea and for symptomatic treatment of inflammatory bowel disease such as ulcerative colitis and Crohn's colitis. They may be useful for the continued treatment of diverticular disease or in situations when it is desirable to maintain a soft stool, such as after anorectal surgery. They can ease the discomfort of bowel movements in the postoperative period.

Bulk-forming laxatives usually exert a laxative effect in 12 to 24 hr but may require as much as 3 days. Each dose of laxative should be taken with a full glass of water. These drugs interact and combine with other drugs, such as salicylates, digitalis, etc. Consequently, they should not, as a general rule, be taken with

other drugs. For the most part, they are safe. They are devoid of systemic side effects but may increase flatulence. Rare cases of intestinal and esophageal obstruction have been reported. It is important, therefore, to take these agents with large volumes of liquid, at least one glass with each dose. They are contraindicated in patients with known esophageal or intestinal obstruction. The dosing of these agents is highly variable and needs to be adjusted to the individual patient.

CARBOXYMETHYLCELLULOSE SODIUM—page 1073.
METHYLCELLULOSE—page 1074.

PSYLLIUM

Metamucil; Perdiem; Serutan

Description—Various preparations from the outer portions of the clean, dried, ripe seeds of *Plantago psyllium* Linné or *indica*. Known commercially as French Psyllium Seed. The seed are small, dark, odorless, and tasteless, and the ground hulls form a mucilaginous mass with water.

Comments—These are mild laxatives, mostly used in irritable bowel syndrome. They are pharmacologically inert but absorb water, thus increasing the bulk of the stool and producing a physiological stimulus for evacuation. They also are used in diarrheal states such as inflammatory bowel disease to increase the bulk and consistency of the stool. They are contraindicated in the presence of partial or complete obstruction anywhere in the GI tract.

POLYCARBOPHIL

Acrylic Acid-Divinyl Glycol Copolymer; Fiberall; Noveon

Polycarbophil [9003-97-8]; polyacrylic acid cross-linked with divinyl glycol.

Preparation—Acrylic acid and divinyl glycol (1,5-hexadiene-3,4-diol) are copolymerized in a hot salt slurry using azobis [methylpropionitrile] as the initiator. US Pat 3,202,577.

Description—White to creamy white granules with a slight, characteristic, esterlike odor; contains a maximum of 1.5% water.

Solubility—Swells but is insoluble in water; insoluble in most organic solvents.

Comments—A pharmacologically inert substance that has the capacity to bind free fecal water. Hence, it is used in diarrheal disorders to decrease the fluidity or looseness of stools. Orally adminstered, polycarbophil exerts its most marked hydrosorptive action only on reaching the slightly acid or alkaline medium of the small intestine and colon. Polycarbophil also is used as a bulk-forming laxative. This hydrophilic polyacrylic resin is indigestible and nonabsorbable and binds more water than other laxatives of this type. Polycarbophil is reported to have no effect on digestive enzymes, and is thus metabolically inactive. The only adverse effect noted is a sense of fullness and bloating in some patients; this can be minimized by giving smaller doses at shorter intervals. This compound contains calcium, which may interact with tetracycline. It is contraindicated in bowel obstruction or fecal impaction.

Lubricant Laxatives

The *lubricant laxatives* (mineral oil and vegetable oils) lubricate the intestinal tract, soften the fecal contents, and facilitate the passage of feces. The many untoward effects induced by mineral oil, such as *lipid pneumonitis, lipoid avitaminosis A,* foreign-body reactions in the intestinal mucosa, and anal leakage all argue against their use.

COTTONSEED OIL—page 1072.

MINERAL OIL

Liquid Paraffin; Liquid Petrolatum; White Mineral Oil; Heavy Liquid Petrolatum

A mixture of aliphatic hydrocarbons obtained from petroleum. It is indigestible and thus has limited absorption.

Preparation—After removing the lighter hydrocarbons from petroleum by distillation, the residue is again subjected to distillation at a temperature between 330° and 390°, and the distillate treated first with H_2SO_4, then with NaOH, and afterward decolorized by filtering through bone black, animal charcoal, or fuller's earth. The purified product is again chilled, to remove paraffin, and redistilled at a temperature above 330°. In some instances the H_2SO_4 treatment is omitted.

Description—Colorless, transparent, oily liquid, free or nearly free from fluorescence; tasteless and odorless when cold and develops not more than a faint odor or petroleum when heated; specific gravity between 0.860 and 0.905; kinematic viscosity not less than 38.1 centistokes at 37.8°.

Solubility—Insoluble in water or alcohol; miscible with most fixed oils, but not with caster oil; soluble in volatile oils.

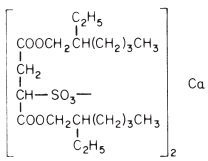
Comments—Used internally as a *laxative.* When taken internally, mineral oil, by virtue of its ability to soften fecal contents and retard the absorption of water, is a mild laxative. It is probably harmless in occasional laxative doses but, if taken continuously in large amounts, may impair appetite, reduce the absorption of fat-soluble vitamins, and possibly be absorbed to an extent sufficient to cause recognizable changes in the liver and mesenteric lymph nodes. It should not be used when abdominal pain, nausea, or vomiting is present. The adverse effects, especially lipid pneumonia, argue against its use as a laxative, especially in children or the elderly.

Fecal Softeners

The fecal softeners represent the most recent approach to the management of constipation and fecal impaction. Substances included in this category are *surface-acting* or *wetting* agents, which are nonabsorbable and relatively nontoxic. Their action is attributed to their surface-active property; by lowering surface tension they permit the intestinal fluids to penetrate the fecal mass more readily and, thus, produce soft, easily passed stools. However, agents such as dioctyl sodium sulfosuccinate have been shown to increase mucosal cAMP and alter ion transport in a manner similar to that of the bile acids. Thus, cAMP-mediated active anion secretion may account for the increased accumulation of luminal fluid. The relative importance of these two mechanisms remains to be determined.

DOCUSATE CALCIUM

Butanedioic acid, sulfo-, 1,4-bis(2-ethylhexyl) ester, calcium salt; Bis(2-ethylhexyl) *S*-Calcium Sulfosuccinate; Dioctyl Calcium Sulfosuccinate; Surfak



[128-49-4] $C_{40}H_{74}CaO_{14}S_2$ (883.22).

Preparation—*Docusate Sodium* (below) is dissolved in 2-propanol and reacted with a methanolic solution of calcium chloride. US Pat 3,035,973.

Description—White, amorphous solid with the characteristic odor of octyl alcohol; free of the odor of other solvents.

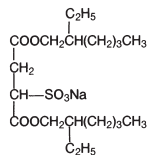
Solubility—1 g in 3300 mL water, <1 mL alcohol, <1 mL chloroform, or <1 mL ether.

Comments—A *fecal-softening* agent useful in *preventing constipation* or in patients for whom laxative therapy is undesirable or contraindicated. It does not increase GI motility and, therefore, may be used in patients in whom cathartic medication is contraindicated. Except for occasional mild, transitory, cramping pains, dioctyl calcium sulfosuccinate is free from side effects and contraindications. It is used also as an emulsifying, wetting, and dispersing agent for external preparations.

DOCUSATE POTASSIUM—see RPS-20, page 1233.

DOCUSATE SODIUM

Butanedioic acid, sulfo-, 1,4-bis(2-ethylhexyl) ester, sodium salt; Dioctyl Sodium Sulfosuccinate; Colace



Sodium 1,4-bis(2-ethylhexyl) sulfosuccinate [577-11-7] $C_{20}H_{37}NaO_7S$ (444.56).

Preparation—Several patents have been issued covering the preparation of this compound. In general, maleic anhydride is treated with 2-ethylhexanol to produce dioctyl maleate, which then is reacted with sodium bisulfite under conditions conducive to saturation of the olefinic bond with simultaneous rearrangement of the bisulfite to the sulfonate structure.

Description—White, waxlike, plastic solid with a characteristic odor suggestive of octyl alcohol; usually available in the form of pellets.

Solubility—1 g slowly in about 70 mL water; freely soluble in alcohol or glycerin.

Comments—A surface-active agent used in the management of constipation and painful anorectal conditions. It is not a laxative but is used to soften the stools in such conditions as anal fissures and postoperative anal pain such as occurs after hemorrhoidectomy. It is also useful for constipation in geriatric, pediatric, and obstetric patients. However, 1 or 2 days of treatment may be necessary before an effect is observed. Although its action is attributed to its *detergent* or *wetting* properties, it does increase mucosal cAMP in a manner similar to that of bile acids, and this may increase fluid and electrolyte secretion into the intestine. As a pharmaceutical aid, it is used as an emulsifying, wetting, and dispersing agent in formulations for external use.

Laxative Combinations

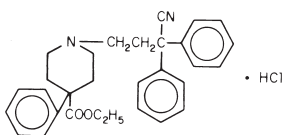
There are many laxative products available to the public (OTC) that contain more than one type of laxative. For example, a product may contain both an emollient (stool softener) and a stimulant laxative. In general, combination products are more likely to cause adverse effects because of the multiple ingredients, especially when the separate ingredients are used in full dose. In addition, laxative combinations do not offer any advantage over products that contain only one type of laxative. The composition of some of the more commonly used laxative combinations, available in either capsule or tablet form, is shown in Table 66-9.

ANTIDIARRHEALS

Diarrhea is the manifestation of many illnesses. Its etiology includes infections (viral, bacterial, fungal, parasitic), irritable bowel syndrome, inflammatory bowel disease (ulcerative colitis, Crohn's disease and others), toxins (food poisoning and pseudomembranous colitis), drugs, surreptitious laxative abuse, neuroendocrine tumors, secretory tumors (villous adenoma), malabsorption syndromes (celiac sprue, lactase deficiency, motility disorders, diverticular disease, and ileostomy. Treatment should be directed to the underlying cause. Nevertheless, it is occasionally necessary to use antidiarrheals for convenience or for conditions for which there is no primary treatment, eg, ileorectal anastomosis and ileoanal pull-through surgery. The most commonly used antidiarrheals are anticholinergics, opoid narcotics, meperidine congeners (diphenoxylate), and loperamide.

DIPHENOXYLATE HYDROCHLORIDE

4-Piperidinecarboxylic acid 1-(3-cyano-3,3-diphenylpropyl)-4-phenyl-, ethyl ester, monohydrochloride; ing of Lomotil



Ethyl 1-(3-cyano-3,3-diphenylpropyl)-4-phenylisonipecotate monohydrochloride [3810-80-8] $C_{30}H_{32}N_2O_2.HCl$ (489.06).

Preparation—Ethyl 4-phenylisonipecotate (prepared as described under *Meperidine Hydrochloride* except omitting the final step of *N*-methylation), is condensed with 2,2-diphenyl-4-bromobutyronitrile by refluxing in toluene using either an excess of the ester or another suitable dehydrobrominating agent. US Pat 2,898,340. Combined with atropine subject.

Description—White, odorless, crystalline powder; pH (saturated solution) about 3.3; melts between 220° and 226°.

Solubility—Sparingly soluble in alcohol or acetone; slightly soluble in water or isopropyl alcohol; freely soluble in chloroform; practically insoluble in ether or solvent hexane.

Comments—A synthetic congener of meperidine that inhibits excessive GI propulsion by slowing intestinal motility. It is *effective as adjunctive therapy* in the management of diarrhea associated with gastroenteritis, irritable bowel, acute infections, food poisoning, and side effects of some drugs. It also is useful in the control of intestinal transit time in patients with ileostomies or colostomies and after ileoanal pull-through surgery.

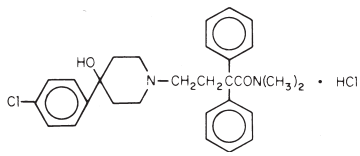
Caution should be used in patients with ulcerative colitis and pseudomembranous colitis who are at increased risk of developing toxic megacolon. Also, it may prolong infectious diarrhea.

In high dosage (40–60 mg) it can produce morphine-like euphoria and prevent withdrawal symptoms in narcotic addicts, but in the recommended dosage range for antidiarrheal therapy no evidence for addiction liability has been reported. The available dosage forms contain a subtherapeutic dose of 0.025 mg of atropine sulfate and a 2.5-mg dose of the hydrochloride. Atropine sulfate decreases GI transit after acumulative dosage and also, because of side effects, discourages usage of excessive amounts, thereby minimizing abuse.

Side effects are usually minor and include nausea, sedation, vertigo, vomiting, pruritus, skin eruption, insomnia, and abdominal cramps. Numbness of the extremities, headache, blurring of vision, swelling of gums, and general malaise also have been reported. The drug is contraindicated in patients with cirrhosis or advanced liver disease and in children under 2 yr. Laboratory studies demonstrate that it inhibits microsomal enzymes. Therefore, it should be used with caution in patients on barbiturates, tranquilizers, and alcohol, because the activity of these drugs may be potentiated by diphenoxylate. Concurrent use with monoamine oxidase inhibitors (MAOIs) may, in theory, precipitate a hypertensive crisis.

LOPERAMIDE HYDROCHLORIDE

1-Piperidinebutanamide, 4-(4-chlorophenyl)-4-hydroxy-*N*,*N*-dimethyl-α, α-diphenyl-, monohydrochloride; Imodium



4-(*p*-Chlorophenyl)-4-hydroxy-*N*,*N*-dimethyl-α,α-diphenyl-1;piperidinebutyramide monohydrochloride [34552-83-5] $C_{29}H_{33}ClN_2O_2.HCl$ (513.51).

Preparation—4-Bromo-2,2-diphenylbutyric acid is converted in a series of reactions to dimethyl(tetrahydro-3,3-diphenyl-2-furylidene) ammonium bromide, which is reacted with *p*-chlorophenyl-4-piperidinol to produce loperamide. US Pat 3,714,159; *J Med Chem* 1973; 16:782.

Description—White to faintly yellow, amorphous or microcrystalline powder; melts about 222°.

Solubility—Slightly soluble in water; soluble in alcohol.

Comments—A synthetic agent used for the control and symptomatic relief of *acute nonspecific diarrhea* and *chronic diarrhea* associated with ileoanal pull-through surgery. It also is used for *reducing the volume of discharge* from ileostomies. Caution should be used in patients with ulcerative colitis, Crohn's colitis, and pseudomembranous colitis who are at increased risk for toxic megacolon. Also, loperamide may prolong the course of infectious diarrhea. Plasma levels are highest 5 hr after oral administration. The elimination half-life is 10.8 hr, with a range of 9.1 to 14.4 hr. Unchanged drug remains below 2 ng/mL after the intake of a 2-mg capsule. Most of the drug is excreted in the feces. The safe use of this agent during pregnancy, by nursing mothers, infants and children, has not been established. Adverse effects are minimal and usually self-limiting. Abdominal pain or discomfort, constipation, drowsiness, dizziness, dry mouth, nausea and vomiting, and tiredness have been reported. Hypersensitivity reactions have been reported. Loperamide should be discontinued if abdominal distention occurs or if other untoward symptoms develop in patients with ulcerative colitis.

EMETICS

An *emetic* is a drug that induces vomiting. They may act directly by stimulation of the *chemoreceptor trigger zone* located in the area postrema of the medulla oblongata, (eg, apomorphine, morphine, hydrogenated ergot alkaloids, and digitalis glycosides),

or they may act reflexly by irritant action on the GI tract (eg, copper sulfate, mustard, sodium chloride, and zinc sulfate). They also may produce stimulation of the vagus (eg, veratrum). It should be remembered that a nasogastric tube is a safer and more efficient tool for emptying the stomach. Emetics should not be used in patients who are unconscious or semicomatose or in whom coma is expected imminently. They should not be used in patients with severe heart disease or advanced pregnancy. They are contraindicated in debilitated patients and in poisoning caused by corrosive or petroleum products.

EMETINE HYDROCHLORIDE—see RPS-20, page 1549.
SODIUM CHLORIDE—page 1341.

ANTIEMETICS

Nausea and vomiting are among the most frequent symptoms of both GI and systemic disease. They may be induced by drugs and frequently occur after surgery and radiation therapy, during pregnancy, with GI tumors, and as the result of certain types of motion in sensitive persons. Useful agents are found among the following six groups:

1. *Antipsychotics* (phenothiazines and butyrophenones) act at the chemoreceptor trigger zone (CTZ) to block dopaminergic emetic receptors excited by apomorphine.
2. *Antihistaminics* provide relief from motion sickness through an action on the vestibular apparatus.
3. *Anticholinergics* in combination with *d*-amphetamine and scopolamine are most effective against motion sickness (mechanism unknown).
4. *Cannabinoids* are especially useful in the emesis from cancer chemotherapy.
5. 5-HT_3-receptor antagonists such as ondansetron block both peripheral and central 5-HT_3 receptors and are especially effective against the emetogenic effects of chemotherapy.
6. *Other agents,* such as trimethobenzamide and metoclopramide, block dopamine receptors in the CTZ, whereas diphenidol depresses the vestibular apparatus.

Centrally acting antimetics, such as trimethobenzamide, the phenothiazines, and similar agents, should not be used for the treatment of uncomplicated vomiting in children because the extrapyramidal symptoms that often occur with these agents may be confused with the CNS signs of an undiagnosed primary disease responsible for the vomiting, eg, Reye's syndrome or other encephalopathy.

The phenothiazine antiemetics are capable of potentiating CNS depressants (eg, anesthetics, opiates, alcohol, etc).

Adverse reactions include

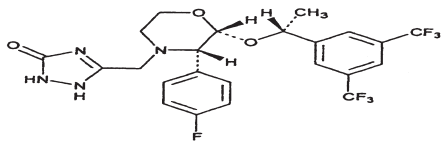
Phenothiazines (aliphatic)—Drowsiness, orthostatic hypotension, ocular changes, anticholinergic effects, extrapyramidal reactions (dystonia, akathisia, parkinsonian syndrome, dysarthria), hypersensitivity reactions, amenorrhea, reversal of epinephrine pressor effect, enhancement of CNS depressant drugs, gynecomastia, lactation, hyperglycemia, hypoglycemia, and glycosuria.
Antihistaminics—Drowsiness, lightheadedness, blurred vision, dryness of the mouth, and urinary retention.
Anticholinergics—Glycosuria, drowsiness, excitement or hallucinations, dryness of the mouth, mydriasis, blurred vision, and urinary retention.
Cannabinoids—Cardiac disorders, drug dependence, hypertension, mania, or depressive states or psychoses.
5-HT_3-receptor antagonists—Constipation, rash, and seizures.

Since drowsiness is common to most of these agents, patients should be cautioned not to drive or operate hazardous machinery while on these drugs.

Persistent vomiting results in loss of hydrochloric acid, alkalosis and dehydration, which in turn may precipitate further vomiting. Hence, a fluid electrolyte therapy may be necessary after vomiting has been present for some time.

APREPITANT

3*H*-1,2,4-Triazol-3-one, 5-[[(2*R*,3*S*)-2-[(1*R*)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1 ,2-dihydro-, Emend



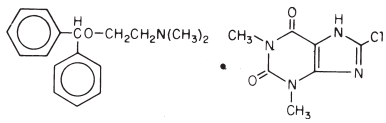
[170729-80-3] $C_{23}H_{21}F_7N_4O_3$. (534.43).

Preparation—US Pat 5,719,147 (1998).
Description—White to off-white crystals.
Solubility—Practically insoluble in water, sparingly soluble in ethanol or 2-propanol; slightly soluble in acetonitrile.

CHLORPROMAZINE—page 1511.

DIMENHYDRINATE

1*H*-Purine-2,6-dione, 8-chloro-3,7-dihydro-1,3-dimethyl-, compd. with 2-(diphenylmethoxy)-*N*,*N*-dimethylethanamine (1:1); Dramamine



8-Chlorotheophylline, compound with 2-(diphenylmethoxy)-*N*,*N*-dimethylethylamine (1:1) [523-87-5] $C_{17}H_{21}NO.C_7H_7ClN_4O_2$ (469.97); contains 53–55.5% of diphenylhydramine ($C_{17}H_{21}NO$), and 44–47% of 8-chlorotheophylline ($C_7H_7ClN_4O_2$).

Preparation—By interaction of diphenhydramine, a base, with 8-chlorotheophylline, an acid, in isopropyl alcohol.

Description—White, crystalline, odorless powder; melts between 102° and 107°.

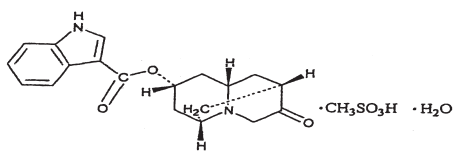
Solubility—Slightly soluble in water; freely soluble in alcohol or chloroform; sparingly soluble in ether.

Comments—An *antihistaminic* compound that is a combination of diphenhydramine (Benadryl) and 8-chlorotheophylline. The latter contributes little, if anything, to its action as an antiemetic or an antihistaminic agent. It is employed chiefly as an *antinauseant* in *motion sickness.* It also has been used with success in the management of the vertigo associated with Ménière's syndrome and radiation sickness. Mild sedation commonly attends it use. See this page. Because of its sedating properties, patients should be cautioned about driving or operating machinery.

DIPHENHYDRAMINE HYDROCHLORIDE—page 1545.
FLUPHENAZINE HYDROCHLORIDE—page 1512.

DOLASETRON MESYLATE

1*H*-Indole-3-carboxylic acid, (2α, 6α, 8α, 9aβ)-octahydro-3-oxo-2,6-methano-2*H*-quinolizin-8-yl ester, monomethanesulfonate salt; Anzemat



[115956-13-3] $C_{19}H_{20}N_2O_3.CH_4O_3S$ (420.48).

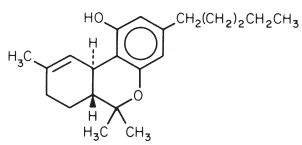
Preparation—US Pat 4,906,755 (1990) and Eur Pat Appl 266,730 (1988).

Description—White to off-white crystalline solid melting about 278°.

Solubility—Freely soluble in water and propylene glycol; slightly soluble in ethanol or normal saline.

DRONABINOL

6*H*-Dibenzo[*b*,*d*]pyran-1-ol, (6a*R*-*trans*)-6a,7,8,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-, Delta-9-tetrahydrocannabinol; Marinol



[1972-08-3]$C_{21}H_{30}O_2$ (314.47)

Preparation—The Δ^1-3,4-*trans* isomer (Δ^9-THC) is the major active component of marijuana (hashish). For the isolation refer to *J Am Chem Soc* 1964; 86:1646; for synthesis, *ibid* 1974; 96:5860.

Description—Viscous, oily liquid; see *J Pharm Sci* 1973; 62:1601 for stability under various conditions of storage.

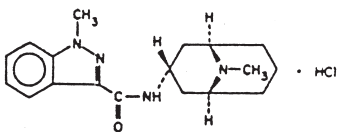
Solubility—Insoluble in water; soluble in 1 part of alcohol or acetone, 3 parts of glycerol; soluble in fixed oils. Stability of parental solutions; *J Pharm Sci* 1972; 61:1106.

Comments—Commonly known as delta 9-THC, it is an orally active cannabinol and one of the active ingredients of marijuana. As such, it may be habit forming. It is especially useful for cancer chemotherapy–induced nausea and vomiting. It is thought to act centrally. Following oral administration dronabinol has systemic bioavailability of 10% to 20%. Its onset of action is 0.5 to 1 hr, with a peak effect at 2 to 4 hr. The drug undergoes extensive first-pass metabolism. Numerous metabolites have been identified, including 11-hydroxytetrahydrocannabinol, which appears in the plasma in about the same concentration as the parent substance. Within 72 hr after oral administration, approximately 50% of the administered dose is excreted in the feces and 15% in the urine, either unchanged or as a metabolite.

Patients may experience mood changes, hallucinations, mental depression, nervousness, and tachycardia followed by bradycardia. Because of its effects on mental status, patients should be warned not to drive, operate machinery, or make judgment decisions. Thus, strict patient compliance to dosage prescribed must be emphasized, and the amount prescribed limited to that required for a single cycle of chemotherapy. Tachyphylaxis occurs to most of its effects but not its appetite-stimulating effect. Withdrawal symptoms consisting of irritability, insomnia, and restlessness occur within 12 hr of abrupt withdrawal.

GRANISETRON HYDROCHLORIDE

1*H*-Indazole-3-carboxamide, endo-1-methyl-*N*-(9-methyl-9-azabicyclo[3.3.1]non-3-yl-, Kytril



[107007-99-8] $C_{18}H_{24}N_4O.HCl$ (348.88).

Preparation—European Pat Appl. 200,444.

Description—White tufts melting about 291°.

Solubility—Very soluble in water or normal saline.

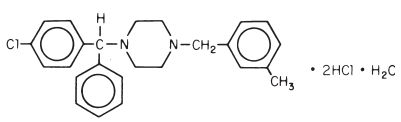
Comments—An injectable, selective 5-hydroxytryptamine (5-HT_3) receptor; 5-HT_3 receptors are located peripherally in vagal nerve terminals and centrally in the CTZ. It is indicated to control nausea and vomiting associated with cancer chemotherapy. It is effective in preventing emesis and nausea when used with cisplatin, carboplatin, and cyclophosphamide. It may also be co-administered with dexamethasone. Total clearance is reduced in patients with hepatic impairment due to metastasis, but dosage adjustment is not necessary.

Principal adverse effects are headache (14%), asthenia (5%), somnolence (4%), diarrhea (4%), and constipation (3%).

HYDROXYZINE HYDROCHLORIDE—pages 1491 and 1548.
HYDROXYZINE PAMOATE—page 1492.

MECLIZINE HYDROCHLORIDE

Piperazine, 1-[(4-chlorophenyl)phenylmethyl]-4-[(3-methylphenyl)methyl]-, dihydrochloride, monohydrate; Antivert; Bonine



[31884-77-2] $C_{25}H_{27}ClN_2.2HCl.H_2O$ (481.89); *anhydrous* [1104-22-9] (463.88).

Preparation—Meclizine is formed by condensing *N*-(*m*-methylbenzyl) piperazine with *p*-chlorobenzhydryl chloride in the presence of triethylamine. The purified base is dissolved in a suitable solvent and converted to the dihydrochloride by a stream of hydrogen chloride.

Description—White or slightly yellowish, crystalline powder; slight odor; tasteless; melts between 217° and 224°, with decomposition.

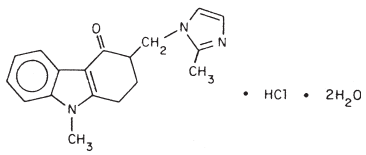
Solubility—Practically insoluble in water and ether; freely soluble in chloroform; slightly soluble in alcohol.

Comments—A long-acting antihistaminic effective in the prevention or treatment of *nausea, vomiting,* and *dizziness* associated with motion sickness. It may be effective in *vertigo* associated with diseases affecting the vestibular system. The antiemetic activity starts within 60 min and lasts for 8 to 24 hr. Like other antihistamines, it may cause drowsiness and other side effects, such as blurred vision, dryness of the mouth, and fatigue. Patients should be cautioned about driving and operating machinery. The action of a single dose can persist for 9 to 24 hr. Use of the drug in pregnancy or in women who may become pregnant is contraindicated. Because it has some anticholinergic activity, it should not be used in patients with asthma, glaucoma, or prostatic enlargement.

PERPHENAZINE—page 1514.

ONDANSETRON HYDROCHLORIDE

4*H*-Carbazol-4-one, (±)-1,2,3,9-tetrahydro-9-methyl-3- [(2-methyl-1*H*-imidazol-1-yl)methyl]-, monohydrochloride, dihydrate; Zofran



[103639-04-9] $C_{18}H_{19}N_3O.HCl.2H_2O$ (365.86).

Preparation—US Pat 4,695,578.

Description—White crystals melting about 180°; pK_a 7.4.

Solubility—1 g dissolves in 3 mL of water.

Comments—A selective 5-HT_3-receptor antagonist. Such receptors are present in vagal nerve terminals and in the CTZ of the area postrema of the brain. It is not clear whether it acts peripherally, centrally, or both. Ondansetron is indicated for the prevention of nausea and vomiting associated with cancer chemotherapy. It appears that cytotoxic chemotherapy such as cisplatin is associated with release of serotonin from enterochromaffin cells in the small intestine. It is speculated that serotonin triggers vomiting through 5-HT_3 vagal receptors that activate the vomiting reflex.

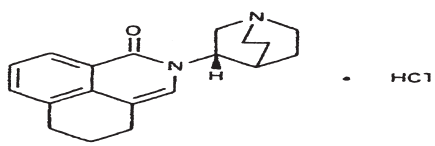
Ondansetron is metabolized extensively; only 5% of unchanged compound is recovered in the urine. It initially undergoes hydroxylation of the indole ring, followed by glucuronidation or sulfation. The mean elimination half-life is approximately 4 to 5 hr but increases with age. Plasma protein binding is 70% to 75%.

Ondansetron is effective in reducing emesis in both cisplatin- and cyclophosphamide-based chemotherapy. Using a visual analog scale (0 to 100), global satisfaction is increased from 10.5 to 96 after single-day cisplatin therapy and from 52 to 100 after single-dose cyclophosphamide therapy.

The most common side effects of ondansetron are diarrhea (22%) and headache (16%). Other adverse reactions after multiple-day therapy include constipation, elevated liver enzymes, rash, bronchospasm, tachycardia, angina, hypokalemia, and seizures. Akathisia and dystonia, seen with metoclopramide, do not occur with ondansetron.

PALONOSETRON HYDROCHLORIDE

1*H*-benz[*de*]isoquinolin-1-one, (3a*S*)-2,3,3a,4,5,6-hexahydro-2-[(3*S*)-3-quinuclidinyl- , monohydrochloride; Aloxi



[135729-62-3] $C_{19}H_{24}N_2O.HCl$ (332.87).

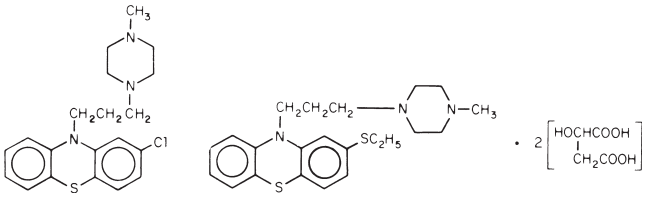
Preparation—*J Med Chem,* 1993;36: 2645 and *Medicinal Research Rev,* 1997;17: 163

Description—White to off-white crystalline powder from 2-propanol/ether, melting above 270°; pK_a 10.4.

Solubility—Freely soluble in water; soluble in propylene glycol; slightly soluble in ethanol or 2-propanol.

PROCHLORPERAZINE

10*H*-Phenothiazine, 2-chloro-10-[3-(4-methyl-1-piperazinyl)propyl]-, Chlorazine; Compro



[58-38-8]$C_{20}H_{24}ClN_3S$ (373.94).

Preparation—A toluene solution of 1-(3-chloropropyl)-4-methylpiperazine and 2-chlorophenothiazine is refluxed with sodamide for several hours. After filtering and distilling off the toluene, the prochlorperazine is obtained by short-path distillation under high vacuum.

Description—Clear, pale yellow, viscous liquid; sensitive to light.

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

Comments—A piperazine-type phenothiazine with actions, uses and limitations similar to those of *Prochlorperazine Maleate.* However, prochlorperazine, as the base, is administered rectally.

PROCHLORPERAZINE EDISYLATE

10*H*-Phenothiazine, 2-chloro-10-[3-(4-methyl-1-piperazinyl)propyl]-, 1,2-ethanedisulfonate (1:1); Prochlorperazine Ethanedisulfonate; Compro

[1257-78-9] $C_{20}H_{24}ClN_3S.C_2H_6O_6S_2$ (564.13).

For the structure of the base, see *Prochlorperazine.*

Preparation—*Prochlorperazine* is dissolved in a suitable solvent and treated with an equimolar portion of 1,2-ethanedisulfonic acid. The salt precipitates.

Description—White to very light yellow, odorless, crystalline powder; solutions are acid to litmus.

Solubility—1 g in about 2 mL water or about 1500 mL alcohol; insoluble in ether or chloroform.

Comments—Same actions and uses as Prochlorperazine Maleate except that it may be administered IM. Parenteral therapy usually is reserved for the treatment of severe nausea and vomiting, for the immediate control of acutely disturbed psychotics, or for patients who cannot or will not take oral medication. It should not be used in children with uncomplicated vomiting of unknown etiology. See *Prochlorperazine Maleate*.

PROCHLORPERAZINE MALEATE

10*H*-Phenothiazine, 2-chloro-10-[3-(4-methyl-1-piperazinyl)propyl]-, (*Z*)-2-butenedioate (1:2); Compro

[84-02-6] $C_{20}H_{24}ClN_3S.2C_4H_4O_4$ (606.09).

For the structure of the base, see *Prochlorperazine.*

Preparation—By the method described for *Prochlorperazine Edisylate* except that maleic acid is employed instead of ethanedisulfonic acid, and it is employed in double equimolar quantity in relation to the prochlorperazine base.

Description—White or pale yellow, practically odorless, crystalline powder; saturated solution is acid to litmus.

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

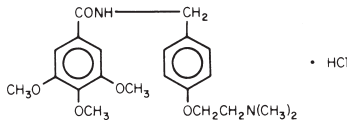
Comments—An *antiemetic, antipsychotic,* and *tranquilizing agent.* It is an effective *antiemetic* in the control of mild or severe nausea and vomiting due to a variety of causes, such as early pregnancy, anesthesia, surgery, and radiation therapy. Safety in pregnancy has not been established. There are reports of prolonged jaundice, extrapyramidial signs, hyperreflexia or hyporeflexia in newborns whose mothers have received phenothiazines. Nevertheless, Compazine is used widely in pregnancy and has a long track record of safety. It, however, is not approved for this usage. It should not be used in children with uncomplicated vomiting of unknown etiology. The drug is also an *effective antipsychotic.* Beneficial results ascribed to its action include reduction in psychomotor agitation and excitement, diminished aggressiveness and destructiveness, mitigation of hallucinations and delusions, and a general calming effect. As a *tranquilizing agent,* it is possibly effective in mild mental disorders in which anxiety, tension, and agitation predominate.

Adverse reactions include *drowsiness, dizziness, amenorrhea, skin reactions, hypotension, cholestatic jaundice, neuromuscular (extrapyramidal) reactions, motor restlessness, dystonias, pseudoparkinsonism, persistent tardive dyskinesia,* and *contact dermatitis.* Children with acute infections (chickenpox, CNS infections, measles, gastroenteritis) or dehydration are more susceptible to neuromuscular reactions, particularly dystonias; such patients should be kept under close supervision. This agent may mask signs of overdosage of toxic drugs or obscure diagnosis of conditions such as intestinal obstruction or brain tumor. Adverse drug reactions can be minimized by periodically evaluating the dosage employed by patients on long-term therapy.

PROMETHAZINE HYDROCHLORIDE—page 1545.
THIETHYLPERAZINE MALATE—see RPS-20, page 1237.
THIETHYLPERAZINE MALEATE—see RPS-20, page 1237.

TRIMETHOBENZAMIDE HYDROCHLORIDE

Benzamide, *N*-[[4-[2-(dimethylamino)ethoxy]phenyl]methyl]-3,4,5-trimethoxy-, monohydrochloride; Tigan



[554-92-7] $C_{21}H_{28}N_2O_3.HCl$ (424.92).

Preparation—4-[2-(Dimethylamino)ethoxy]benzylamine is condensed with 3,4,5-trimethoxybenzoyl chloride by refluxing in an inert solvent. The resulting trimethoxybenzamide may be converted to the hydrochloride by dissolving it in a suitable solvent and treating with HCl. The starting amine may be prepared in various ways, eg, by condensing sodium *p*-aminomethylphenoxide with 2-chloro-*N,N*-dimethylethylamine.

Description—White crystalline powder; slight phenolic odor; melts between 186° and 190°.

Solubility—1 g in 2 mL water, 59 mL alcohol, 67 mL chloroform, or 720 mL ether.

Comments—A dimethylaminoethanol derivative indicated for the control of *nausea* and *vomiting*. Its safety in pregnancy has not been established, but trimethobenzamide frequently is used in this situation. Its antiemetic potency is about 1/10 that of chlorpromazine when given subcutaneously and 1/4 that of the latter when given orally. Minor side effects that have been reported include drowsiness, vertigo, diarrhea, and local irritation. In patients with acute febrile illness, encephalitides, gastroenteritis, dehydration, and electrolyte imbalance (especially children and the elderly and debilitated), CNS reactions, such as opisthotonos, convulsions, coma, and extrapyramidal symptoms, have been reported, but it is not certain that these effects were in all cases due to use of the drug. Therefore, caution should be exercised when trimethobenzamide hydrochloride is used in these conditions. Drowsiness can occur, and patients should be cautioned about driving and operating machinery. The use of the injectable form of the drug in children, the suppositories in premature or newborn infants, and the use of the drug in patients hypersensitive to it are contraindicated. Also, suppositories should not be used in patients known to be sensitive to benzocaine or similar types of local anesthetics. Parkinson-like symptoms have been reported. Blood dyscrasias, blurred vision, coma, seizure, depression, diarrhea, drowsiness, muscle cramps, and jaundice also have been reported. A blanket warning on the label, relating to Reye's syndrome does not seem to be justified, but still should be considered.

ADSORBENTS

Adsorbents are chemically inert powders that have the ability to adsorb gases, toxins, and bacteria. The fine state of subdivision of these inert powders confers high adsorptive capacity upon them. However, in the complex milieu of the GI secretions, physical (van der Waals) adsorbents are more likely to be selective for surface-active substances such as bile salts than for bacterial toxins and other noxious substances. Consequently, only certain materials that possess chemical adsorptive properties lend themselves effectively to detoxification and to the adsorption of gases resulting from abnormal intestinal fermentation. Such substances are kaolin and activated charcoal. It is doubtful that either is an effective adsorbent in the lower GI tract, since passage through the upper tract saturates and deactivates these agents.

Many of the nonsystemic antacids may serve as internal protectives and adsorbents, especially after regeneration in the alkaline small intestine. Magnesium trisilicate is claimed to exert a protective action in the stomach by virtue of released silicic acid, which acts more as a demulcent than as a solid protective. *Antacids* commonly are combined with kaolin or other adsorbents.

BISMUTH SUBNITRATE—page 1083.

ACTIVATED CHARCOAL

Actidase; Charcoal Plus DS; Medicinal Charcoal

The residue from the destructive distillation of various organic materials, treated to increase its adsorptive power.

Preparation—Formerly, a product named *Carbo Ligni* or *Wood Charcoal* was produced by burning wood out of contact with air; the residue obtained consisted of nearly pure carbon. Charcoal made by this process was variable in its adsorptive powers, frequently being entirely devoid of such properties. It was found that the adsorptive powers of charcoal could be increased tremendously by treating it with various substances such as steam, air, carbon dioxide, oxygen, zinc chloride, sulfuric acid, phosphoric acid, or a combination of some of these substances, at temperatures ranging from 500 to 900°. This treatment is referred to as activation, the activating agent presumably removing substances previously adsorbed on the charcoal and, in some instances at least, breaking down the granules of carbon into smaller ones having a greater total surface area. It has been estimated that 1 mL of charcoal, finely divided, possesses a total surface of approximately 1000 m^2.

In addition to wood, many other substances are used as sources of charcoal, including sucrose, lactose, rice starch, coconut pericarp, bone, blood, various industrial wastes, etc. As many different activated charcoals are available for various purposes, one should be certain to use only the medicinal variety for medicinal purposes.

Description—Fine, black, odorless, and tasteless powder, free from gritty matter.

Solubility—Insoluble in water or the other known solvents.

Comments—Used for the acute treatment of poisoning—primarily as an emergency *antidote* in many forms of poisoning. It is the emergency treatment of choice for virtually all drugs and chemicals. Charcoal capsules also are used for the relief of flatulence and the discomfort of abdominal gas, but there is little evidence that it is effective for this purpose.

Industrially, it is used in large quantities in chemical and pharmaceutical manufacturing as a decolorizer.

KAOLIN

Light Kaolin; White Bole; China Clay; Kaolin-Pectin Suspension

A native hydrated aluminum silicate; powdered and freed from gritty particles by elutriation.

Preparation—Kaolin is distributed widely in nature. Most kaolin deposits, however, are contaminated with ferric oxide (hence the red color of ordinary clay) and some other impurities, such as calcium carbonate, magnesium carbonate, etc. To render kaolin suitable for pharmaceutical use, it has to be purified by treatment with hydrochloric acid or sulfuric acid, or both, then washed with water.

Kaolin of a high degree of purity, directly suitable for pharmaceutical use without acid purification, has been mined in the state of Georgia. England has large deposits of a fine grade of kaolin. The kaolin from these deposits is freed of coarse particles by elutriation or screening. Kaolin is essentially a colloid, and the *colloid kaolin* on the market differs only from ordinary kaolin in that it contains a larger percentage of fine particles and is prepared by special screening.

Description—Soft, white or yellowish white powder, or lumps; characteristic earthy or clay-like taste and, when moistened with water, becomes darker and develops a pronounced clay-like odor.

Solubility—Insoluble in water, cold diluted acids, or solutions of the alkali hydroxides.

Comments—Either alone or as *Kaolin Mixture with Pectin* (see below) it is used medicinally as an *adsorbent.* It is perhaps of value in the treatment of *diarrhea* caused by agents capable of being adsorbed; eg, the diarrhea of food poisoning or dysentery. Kaolin also has been used in the treatment of chronic ulcerative colitis, but it is doubtful whether any adsorptive capacity is retained by the time the preparation reaches the colon. Externally, kaolin has some use as a poultice, dusting powder, and an ingredient of toilet powders.

MAGNESIUM TRISILICATE—page 1297.

PECTIN

A purified carbohydrate product obtained from the dilute acid extract of the inner portion of the rind of citrus fruits or from apple pomace. It consists chiefly of partially methoxylated polygalacturonic acids.

Pectin yields not less than 6.7% of methoxy groups and not less than 74.0% of $C_6H_{10}O_7$ (galacturonic acid), calculated on the dried basis.

Pectin may be standardized to the convenient "150 jelly grade" by addition of dextrose or other sugars, and it may contain sodium citrate or other buffer salts. Such pectin is not suitable for medicinal use.

Description—Coarse or fine powder, yellowish white in color, almost odorless, and with a mucilaginous taste.

Solubility—Almost completely soluble in 20 parts of water at 25°, forming a viscous, opalescent, colloidal solution that flows readily and is acid to litmus; insoluble in alcohol or diluted alcohol and in other organic solvents; dissolves in water more readily if first moistened with alcohol, glycerin, or simple syrup or if first mixed with 3 or more parts of sucrose.

Incompatibilities—Precipitated from solution by an excess of *alcohol. Metals,* particularly the heavy metals, form insoluble derivatives. In the presence of *alkalies,* pectin undergoes progressive hydrolysis resulting in a demethylation followed by a splitting of the glycosidic linkages of the galacturonic acid units. *In cold acid solution* it is more stable; prolonged heating of such a solution causes hydrolysis. Liquefaction of pectin pastes may be due to a hydrolysis that accompanies growth of certain types of *mold.*

Comments—A protective used for the treatment of diarrhea in infants and children. The unchanged molecules of the polygalacturonic acids may have an adsorbent action in the intestine.

DRUGS USED FOR THE TREATMENT OF INFLAMMATORY BOWEL DISEASE

The major inflammatory diseases of the bowel are ulcerative colitis, which is confined to the colon, and Crohn's disease, which most often involves the terminal ileum and colon but can involve the entire GI tract. The etiologies are not known, but the injury in both diseases appears to be the consequence of an immune-mediated inflammatory reaction. Thus, therapy consists of anti-inflammatory agents (salicylates) and immunosuppressents (corticosteroids, azathioprine, methotrexate, cyclosporine, and monoclonal antibodies). The goals of therapy are to maintain nutrition, maintain a good quality of life, and prevent the development of cancer. There are two components to therapy—treatment of acute flareups and maintenance of remission.

CORTICOSTEROIDS—Corticosteroid therapy is used for acute flareups of moderate-to-severe Crohn's disease or ulcerative colitis. Dosing is generally started high (ie, prednisone 40 mg or equivalent per day) and tapered as the disease goes into clinical remission. At the same time, maintenance therapy is started with salicylates or immunosuppressents. Corticosteroids are ineffective in maintenance therapy and because of their side effects are contraindicated as maintenance therapy.

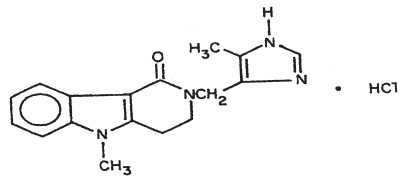
SALICYLATES—Sulfasalazine, the first of the salicylates, was developed in the 1930s for the treatment of rheumatoid arthritis. It subsequently was noted that patients with associated ulcerative colitis benefitted, and in the 1960s, placebo-controlled clinical trials confirmed that benefit. Later, it was noted that most of the severe adverse reactions to sulfasalazine occurred in slow acetylators of sulfapyradine and that 5- aminosalicylic acid (5-ASA) was the active moiety. Subsequently prodrugs and slow-release drugs consisting of 5-ASA and 4-ASA were developed that could deliver salicylate to the distal intestine. Olsalazine consists of two molecules of 5-ASA joined by an azo bond that is split by azo reductase liberated by colonic bacteria. Mesalamine is 5-amino-2-hydroxybenzoic acid that is enteric-coated to dissolve at approximately pH 6 to 7 in the small intestine and colon.

Despite considerable research, the mechanism of action of salicylates is only partially understood. Speculated actions include attenuation of various cytokines including interferon-γ and tumor necrosis factor, inhibition of chloride secretion, inhibition of HLA-DR expression, inhibition of adhesion molecules, inhibition of leukotriene B_4 synthesis, and scavenging of reactive oxygen species. Whatever the mechanism,

salicylates are used widely for the initial treatment of mild disease and as the mainstay of maintenance therapy. Pentasa, because of its release throughout the GI tract, has theoretical advantages for the treatment of Crohn's disease involving the small intestine.

ALOSETRON HYDROCHLORIDE

1*H*-Pyrido[4,3-*b*]indol-1-one, 2,3,4,5-tetrahydro-5-methyl-2-[(5-methyl-1*H*-imidazol-4-yl)methy l]-, monohydrochloride; Lotronex



[122852-69-1] $C_{17}H_{18}N_4O.HCl$ (330.82).

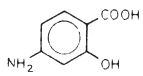
Preparation—EP306323 (1989) and US 5,360,800(1994).

Description—White to beige solid melting about 290°.

Solubility—(mg/mL of solvent); water (61); 0.1*N* HCl (43); pH 6 phosphate buffer (0.3); pH 8 phosphate buffer (0.1).

AMINOSALICYLIC ACID

Benzoic acid, 4-amino-2-hydroxy-, PAS; Paser



4-Aminosalicylic acid [65-49-6] $C_7H_7NO_3$ (153.14).

Caution—Under no circumstances use a solution if its color is darker than that of a freshly prepared solution.

Preparation—From *m*-aminophenol by a modification of the Kolbe-Schmitt reaction, which involves heating the phenol under pressure with a source of carbon dioxide such as ammonium carbonate or potassium bicarbonate.

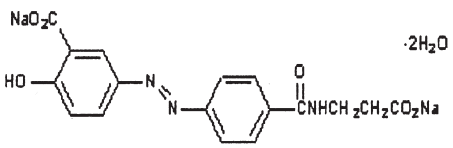
Description—White, or nearly white, bulky powder: darkens on exposure to light and air; odorless, or has a slight acetous odor; melts between 135° and 140° with decomposition; pH (saturated aqueous solution) between 3 and 3.7.

Solubility—1 g in about 600 mL water and about 21 mL alcohol; slightly soluble in ether.

Comments—See *Aminosalicylate Sodium* for *antitubercular* actions, uses, adverse effects, and pharmacokinetics. It is also used to lower blood lipids; it can lower the low-density lipoproteins (and cholesterol) by 15% to 20% and the very-low-density lipoproteins (and tri glycerides) by 25%. It is used mainly in the treatment of *familial* hypercholesterolemia. The drug impairs absorption of cholesterol. The incidence of GI disturbances and of crystalluria is greater than with the sodium salt. A preparation of aminosalicylic acid stated to have much of its irritant impurities removed by recrystallization with ascorbic acid (PAS-C, *Hellwig*) is reported to induce a lesser incidence of GI side effects. Aminosalicylic acid can cause systemic acidosis in children. The urine should be alkalinized.

BALSALAZIDE DISODIUM

Benzoic acid, *(E)*-5-[[4-[[(2-carboxyethyl)amino]carbonyl]phenyl]a zo]-2-hydroxy-, disodium salt, dihydrate; Colazal



[150399-2-6] $C_{17}H_{13}N_3Na_2O_6.2H_2O$ (437.32).

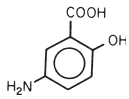
Preparation—US 4,412,992 (1983) and *Chem Abstr* 1978; 88: 69623x.

Description—(Acid) crystals from ethanol, melting about 255°; (salt, dihydrate) stable, odorless, non-hygroscopic, orange to yellow crystalline powder; melts above 350°.

Solubility—Freely soluble in water or normal saline; sparingly soluble in methanol or ethanol; practically insoluble in all other solvents.

MESALAMINE

Benzoic acid, 5-amino-2-hydroxy-, Asacol ; Canasa; Pentasa; Rowasa



[89-57-6] $C_7H_7NO_3$ (153.13).

Preparation—By reduction of *m*-nitrosalicylic acid with zinc dust or iron and HCl or by electrolytic reduction.

Description—Creamy white to off-white powder melting at about 280° (decomposition). Darkens on exposure to light.

Solubility—Soluble in dilute mineral acids and fixed bases; slightly soluble in water; more soluble in hot water.

Comments—*Asacol* and *Pentasa* are indicated for the treatment of mildly to moderately active ulcerative colitis and for the maintenance of remission of ulcerative colitis. The oral preparations are enteric-coated for slow release. Approximately 20% is absorbed, as is the case with suppositories and rectal suspensions. *Rowasa* suspension enema is indicated for treatment of mild to moderately active distal ulcerative colitis and proctitis. Suppositories are indicated for active ulcerative proctitis. Remission rates in mild-to-moderate ulcerative colitis vary from 30% to 65%. Numerous trials using mesalamine as maintenance therapy in ulcerative colitis have shown a 1-yr reduction in relapse from approximately 70% to 20%.

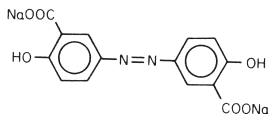
The mesalamines are less effective in Crohn's disease, but *Pentasa* has been shown to be effective at high dose (4 g/day) in ileal and ileal-colonic Crohn's disease.

The choice of salicylate depends on the anatomical extent of disease. *Pentasa,* which is released throughout the GI tract, is theoretically preferable for Crohn's disease involving the small bowel; however, none of the drugs has been shown to be effective in patients with proximal disease.

The most common side effects are diarrhea (2–3%), headache (2%), nausea (1–2%), abdominal pain (1–2%), and rash, but it is unusual to have to discontinue therapy because of adverse reactions.

OLSALAZINE SODIUM

Benzoic acid, 3,3′-azobis[6-hydroxy-, disodium salt; Dipentum



[6054-98-4] $C_{14}H_8N_2Na_2O_6$ (346.21).

Preparation—5-Nitrosalicylic acid is esterified with methanesulfonyl chloride, and the resultant sulfonated nitro compound is reduced with hydrogen and palladium to the amine, which is then diazotized and coupled with methyl salicylate under alkaline conditions. After acidification, this yields the dimethyl ester of the title compound with one hydroxyl group sulfonated. Boiling with sodium hydroxide and adjusting the pH to 6 affords the product.

Description—Yellow crystals melting about 240°.

Solubility—Soluble in water and DMSO; practically insoluble in ethanol, chloroform or ether.

Comments—Indicated for the maintenance of remission of ulcerative colitis in patients intolerant to sulfasalazine. Less than 1% of olsalazine is absorbed. The remaining 99% reaches the colon, where it is converted to mesalamine. It thus has the highest bioavailability of the salicylates, and one comparative study has shown it to be more effective than mesalamine. Its major side effect is diarrhea, which occurs in 3 to 5% of patients.

SULFASALAZINE

For the full monograph, see page 1633.

Comments—Poorly absorbed from the small intestine, so that the major portion of drug passes into the colon, where bacterial enzymes release both 5-aminosalicylic acid and sulfapyridine from the drug. It has a suppressive effect on *ulcerative colitis,* which is not defined precisely. The local antibacterial effect of sulfapyridine in decreasing anaerobic bacteria may not be significant because of systemic absorption. The 5-aminosalicylate inhibits arachidonic acid cascade, both cyclooxygenase and lipoxygenase pathways. Most important may be the inhibition of leukotriene B_4 production by PMNs.

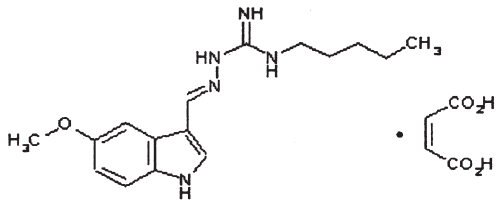
Since some sulfapyridine is absorbed from the colon, this drug has the toxic potential of *Sulfapyridine.* Adverse effects mostly occur when

plasma levels exceed 50 μg/mL of sulfapyridine. Heinz-body and acute hemolytic anemias occur, so that the hematological status of the patient must be monitored regularly. Folic acid absorption also is impaired by the drug. Toxic epidermal necrolysis has been reported. If the initial dose does not exceed 2 g/day, the toxic potential is said to be minimized without seriously compromising therapeutic action. It imparts a yellow color to alkaline urine. Iron compounds decrease its absorption, the therapeutic significance of which is unknown. There have been a few instances in which sulfasalazine exacerbated ulcerative colitis. Desensitization has been used when reinstitution is required in patients with hypersensitivity.

Relapses occur in about 33% of cases, so that continuous prophylactic use often is advocated. However, after a year of continuous successful suppression, the relapse rate is about the same as when no prophylaxis is used.

TEGASEROD MALEATE

Hydrazinecarboximidamide, 2-[(5-methoxy-1*H*-indol-3-yl)-methylene]-*N*-pentyl-, (2*Z*)-2-butenedioate salt (1:1); Zelnorm



[189188-57-6] $C_{16}H_{23}N_5O.C_4H_4O_4$ (417.46).

Preparation—US 5,510,353 (1996).

Description—Off-white to white crystalline powder. Base melts about 155°.

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

IMMUNOSUPPRESSANTS—Azathioprine (page 1563) and its metabolite, 6-mercaptopurine (page 1579), have been demonstrated to be effective in the management of Crohn's disease. Patients usually are started on a low dose of 50 mg a day, gradually increased to 1.5 to 2.5 mg/kg a day or until the patient is slightly lymphopenic. The therapeutic effects are not seen until after 3 to 6 months. There has been some debate about the role that immunosuppressive therapy should play in Crohn's disease, but the trend has been to make it the mainstay of long-term treatment. There is some evidence that immunosuppressive therapy may be helpful in healing the fistulas of Crohn's disease.

The efficacy of azathioprine in the management of ulcerative colitis also has been demonstrated.

The limiting factor in the use of immunosuppressives is their toxicity, in that they commonly cause severe leukopenia. These drugs must be monitored very carefully and should be used only in compliant patients. Other toxicities include pancreatitis, allergic reactions, and infectious complications in 7% of patients. Neoplasms have been reported, but probably only histiocytic lymphoma of the brain is associated with the drug.

CYCLOSPORINE

For the full monograph, see page 1590.

Comments—There is increasing experience with both IV and oral cyclosporine in patients with severe Crohn's disease or ulcerative colitis. It initially is given IV at a dose of 4 mg/kg/day and then maintained at 5 to 8 mg/kg/day for 2 to 3 months, during which time immunosuppressive therapy with azathioprine or 6-mercaptopurine is started. Long-term use is precluded by nephrotoxicity.

INFLIXIMAB

Remicade

Description—A chimeric IgG1K monoclonal antibody with an approx mol wt of 149,000 Daltons. It is composed of human constant and murine variable regions.

Comments—It binds to human tumor necrosis factor alpha (TNFα), an inducer of proinflammatory cytokines such as IL-1 and IL-6. TNFα also enhances leukocyte migration, activates neutrophils, and induces acute phase reactants. Its activity is increased in Crohn's disease and correlates with disease activity. Treatment with this agent reduces infiltration of inflammatory cells and TNFα production in inflamed areas of intestine. It has been shown to reduce symptoms, reduce disease activity, and improve quality of life after a single IV dose in patients with Crohn's disease who have failed other therapy.

Infliximab is indicated for the treatment of moderate to severe Crohn's disease resistant to conventional therapy and in patients with enterocutaneous Crohn's fistulas.

It is given by IV infusion at 5 mg/kg. It has a terminal half-life of 9.5 days. The volume of distribution is increased by concomitant corticosteroid therapy. Up to two courses of therapy may be given at 2- and 4-month intervals.

It has been associated with hypersensitivity reactions including urticaria, dyspnea, and hypotension. Medications for treatment of hypersensitivity reactions should be on hand when infusing infliximab. Autoimmune reactions including a lupus-like syndrome with positive anti-dsDNA antibodies also may occur. Lymphomas have also been reported. Since Crohn's patients and patients on long-term immunosuppressive therapy are predisposed to develop lymphoma, the significance of the reported cases is uncertain. Adverse reactions occur in approximately 85% of patients and include headache, nausea, upper respiratory infections, abdominal pain, fever, rash, and vomiting—each occurring in more than 5% of patients.

METHOTREXATE

For the full monograph, see page 1580.

Comments—While not approved for the management of Crohn's disease or ulcerative colitis, it has been used and appears to be effective in inducing and maintaining remission in approximately 40% of patients. Like immunosuppressive therapy, it takes 3 to 6 months to obtain the full benefit. The major limiting factor in its use is its toxicity.

DRUGS USED FOR THE TREATMENT OF CHRONIC VIRAL HEPATITIS

Immunostimulation is used to treat chronic hepatitis B and C. Approximately 10% to 15% of patients who become infected with the hepatitis B virus develop chronic disease, manifested by chronic hepatitis, cirrhosis, and hepatocellular carcinoma. The reasons that patients develop chronic disease are uncertain. In some parts of the world, southeast Asia for example, almost 90% of infants born to hepatitis B–positive women will become chronically infected. When the disease is acquired at an older age, chronic disease is less likely to occur. Serum interferon levels are decreased in many patients with chronic hepatitis B. This may be secondary to the virus transfecting chromosome-9 at the site that codes for interferon. Interferon is antiviral because of two properties—it stimulates the synthesis of 2,5-A synthetase, which inhibits viral replication, and it induces the HLA major histocompatibility antigens on the hepatocyte surface so that they can become the target of cytotoxic T cells. The demonstration of interferon deficiency in chronic hepatitis B is the rationale for its use in that disease. It induces remission in about half the patients with a relapse rate of 2% to 3% a year. It is not known if it prevents hepatocellular carcinoma in such patients.

Approximately 85% of patients with hepatitis C become chronically infected. Approximately half of these patients will develop chronic hepatitis and cirrhosis. Once cirrhosis develops, hepatocellular carcinoma occurs at a rate of 2% to 3% a year. The mechanism of persistence probably relates to the development of mutants known as quasispecies that escape immune detection. Interferon trials for non-A, non-B hepatitis trials were started prior to the discovery of the hepatitis C virus. It was learned subsequently that most of the patients indeed had hepatitis C and that the drug induced remission in approximately 20% of these patients, with relapse occurring in about half of these patients by 1 yr. It subsequently has been learned that the standard pulse dosing of interferon at 3 MUs SQ tid induces mutations in the hepatitis C virus that may predispose to drug resistance. Thus, it is more common to treat patients with 3 MUs a day for 6 months to 1 yr.

INTERFERON ALFA-2B

Intron A

See also page 1577.

Comments—The alpha interferons are a family of proteins of MW 15,000 to 27,600 that are secreted by lymphocytes in response to viral infections. They bind to cellular proteins and exert a number of effects including induction of certain enzymes such as 2,5 A synthetase, which inhibits viral replication; inhibition of cell proliferation; and immunemodulating activity including expression of HLA major histocompatibility antigens that become the targets of cytotoxic T lymphocytes. Recent data indicate that interferons also may be anti- inflammatory, antifibrinogenic, and anticarcinogenic.

Interferon alfa at a dose of 5 MU a day is indicated for the treatment of chronic hepatitis B, which is continued for 6 months. There is frequently a flareup of the liver disease at 12 to 14 weeks, when the hepatitis e antigen converts to e antibody. This generally signals the end of viral replication and a positive response to treatment. Patients with decompensated liver disease manifested by ascites, encephalopathy, or coagulopathy should not be treated except under special, controlled circumstances, because of the high risk of fatal side effects, especially bacterial peritonitis with sepsis.

Side effects are common with interferon alfa-2b. Those seen in more than 10% of patients include fever (45%), headaches (45%), myalgias (40%), depression (40%), asthenia (20%), rigors (25%), fatigue (20%), arthralgias (20%), nausea (25%), diarrhea (15%), and alopecia (15%). Irritability, insomnia, abdominal pain, pruritus, retinitis, peripheral neuropathy, seizures, rash, and inflammation at the injection site also are seen. Thyroid dysfunction in the form of either hyper- or hypothyroidism occurs in approximately 1% of patients and has been irreversible in some. TSH monitoring prior to therapy and at 1 month is recommended, especially in women. Anemia, leukopenia, and thrombocytopenia occur in 10 to 30% of patients and may require dose modification or temporary discontinuance. Leukopenia is the rate limiting toxicity with interferon (IFN). CBCs are recommended at 2- to 4-week intervals to monitor patients. Despite the long list of side effects and their rather high frequency, therapy almost always can be completed. It should not, however, be used in patients with decompensated liver disease.

Indicated for the treatment of chronic hepatitis B and C, interferon alfa-2a and interferon alfacon-1 for the treatment of chronic hepatitis C. While the interferons are indicated for the treatment of patients 18 yr of age or older with compensated liver disease, it is now routine to treat all hepatitis C patients who are infected, including those with acute hepatitis C. Treatment of acute hepatitis C has reduced the rate of developing chronic disease from approximately 80% to 85% to 10% to 15%.

Initial studies for the treatment of chronic hepatitis C were done using SQ doses of 3 MU tiw for 3 to 6 months. Sustained remission rates of 15 to 20% were obtained. The pulse dosing initially used with alpha interferon was designed to reduce the toxicity. Pharmacokinetic data, however, show that serum levels are not sustained. Peak serum concentration occurs 3 to 12 hr after injection. The elimination half-life is 2 to 3 hr, and serum levels are undetectable after 16 hr. Hepatitis C replication rates are in the trillions a day, with viral half-life of approximately 5 hr. Thus, there is a pharmacokinetic/pharmacodynamic mismatch that ends up increasing the replication rate of the virus above baseline. It also was learned that such dosing increased the mutation rate, potentially leading to the formation of immune-evading quasispecies.

Subsequent studies have used 5 MU for 6 to 12 months and have doubled the sustained remission rate. It appears, however, that the optimum initial dose is 10 MU. Current studies using 10 MU a day for a few days followed by 5 MU a day for 6 to 12 months have shown promise of increasing the sustained remission rate even further. Furthermore, studies with pegelated interferon—a sustained-release form given once a week—have shown promise of even higher sustained remission rates with less toxicity.

RIBAVIRIN IN COMBINATION WITH INTERFERON ALFA-2B

Rebetron

Comments—A guanosine analog that has antiviral activity against respiratory syncytial virus but not hepatitis B or C virus. However, in combination with alpha interferon, it increases the sustained remission rate in chronic hepatitis C. It is packaged as interferon alfa-2b 3 million units/vial and ribavirin (Rebetol) capsule, 200 mg. It is indicated for the retreatment of chronic hepatitis C in both naive patients and those who have not responded to interferon therapy or who have relapsed after prior treatment with alpha interferon. In a large multicenter study, combination therapy for 24 weeks achieved a sustained virological response of 31%, compared with 6% for interferon alone (3 MU SC tiw).

DRUGS THAT DISSOLVE GALLSTONES

See *Bile, Bile Acids, and Bile Salts*, page 1303.

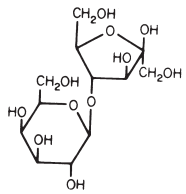
MISCELLANEOUS GASTROINTESTINAL DRUGS

Several drugs with diverse actions on the GI tract are included in this section. They range from the empirical carminative *peppermint spirit* to the novel gallstone dissolution agent *ursodiol* and the well-established *diphenoxylate hydrochloride–atropine sulfate* antidiarrheal combination. Carminatives are substances that were at one time used to relieve gaseous distention of the stomach or intestines. Many carminative volatile oils are used as flavoring agents.

ANISE OIL—page 1064.
CAMPHOR—page 1284.
CARDAMOM OIL—page 1064.
CARDAMOM SEED—page 1064.
CHLOROBUTANOL—page 1059.
CHLOROFORM—page 1085.

LACTULOSE

D-Fructose, 4-*O*-β-D-galactopyranosyl-, Cholac



4-*O*-β-D-Galactopyranosyl-D-fructofuranose [4618-18-2] $C_{12}H_{22}O_{11}$ (342.30).

Preparation—Lactulose (a disaccharide containing 1 molecule of galactose and 1 molecule of fructose) may be prepared by epimerization of lactose (a disaccharide containing 1 molecule of galactose and 1 molecule of glucose) in a lime water medium. *J Am Chem Soc* 130; 52:2101.

Description—White powder; melts at about 169°; levorotatory; reduces Fehling's solution; yields galactose and fructose on acid hydrolysis. The commercially available syrup is a pale yellow to yellow, viscous, sweet liquid; each 15 mL contains 10 g of lactulose (and less than 2.2 g galactose, less than 1.2 g lactose, and 1.2 g or less of other sugars).

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

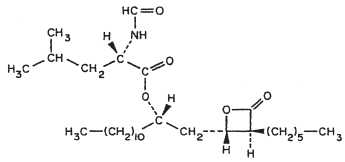
Comments—A disaccharide containing 1 molecule of galactose and 1 molecule of glucose. It is used to reduce blood ammonia levels in patients with portal-systemic encephalopathy. It improves the patients' mental state and EEG patterns but does not alter the course of the underlying liver disease. The action of lactulose, which is absorbed poorly after oral administration, depends on its breakdown by colonic bacteria to carbon dioxide, lactic acid, and small amounts of acetic and formic acids, which acidify the contents of the colon. The acidic environment converts ammonia to ammonium ion ($NH4^+$), which cannot be absorbed. It also favors diffusion of ammonia from blood into the colon. The osmotic laxative action of lactulose and/or its metabolites then expels the trapped ammonium ions from the colon. Therapy with lactulose is reported to reduce blood-ammonia levels by 25% to 50% and effect a favorable clinical response in about 75% of patients. Lactulose is poorly absorbed, with only 3% appearing in the urine in 24 hr.

Lactulose may produce gaseous distention with flatulence or belching and abdominal discomfort such as cramping in about 20% of patients. Excessive dosage produces diarrhea but some degree of diarrhea (2–4 loose stools per 24 hr) is needed for its maximum therapeutic effect. Nausea and vomiting have been reported infrequently.

Lactulose syrup contains some monosaccharides and should be used with caution in diabetics. Concomitant use of neomycin with lactulose may result in elimination of colonic bacteria that are essential for the required degradation of lactulose and thus prevent acidification of the colon. Other laxatives should not be used, especially during the initial phase of therapy, because loose stools falsely may suggest that lactulose dosage is adequate. Lactulose does not alter the course of the underlying liver disease, for which other therapy may be required. The safety of lactulose syrup during pregnancy and the effect on the mother and fetus have not been evaluated.

ORLISTAT

Leucine, *N*-formyl-, [2*S*-[2α(*R),3β]]-1-[(3-hexyl-4-oxo-2-oxetanyl)methyl]dodecyl ester; Xenical**



[96829-58-2] $C_{29}H_{53}NO_5$ (495.74).

Preparation—*J Biol Chem,* 1997; 272: 867 and *J Med Chem,* 2003;46:4209.

Description—The tetrahydro derivative of *lipstatin* which is isolated from the fermentation broth of *Streptomycin toxytricini.* White to off-white crystalline powder melting about 43°; $[\alpha]^{20}_{D}$ − 32° (c = 1, $CHCl_3$).

Solubility—Practically insoluble in water; freely soluble in chloroform; very soluble in methanol or ethanol.

SIMETHICONE

Gas-X; Mylicon; Phazyme

Simethicone [8050-81-5]; a mixture of fully methylated linear siloxane polymers containing repeating units of the formula $[M(CH_3)_2SiO]_n$, stabilized with trimethylsiloxy end-blocking units of the formula $[(CH_3)_3SiOM]$, and silicon dioxide.

Description—Translucent, gray, viscous fluid; specific gravity between 0.964 and 0.984; refractive index between 1.400 and 1.410; viscosity (25° ± 0.1°) not less than 300 centistokes.

Comments—An agent with defoaming action that is supposed to relieve gas in the GI tract. It is used as adjunctive therapy in conditions in which gas is a problem, such as *postoperative gaseous distention, air swallowing, functional dyspepsia, irritable colon,* and *diverticulosis.* It also is used in antacid combinations to defoam gastric juice, to decrease the tendency to gastroesophageal reflux; however, it does *not* decrease the antacid requirement. It has yet to be proved that simethicone has any therapeutic benefit. It is thought to be physiologically inert and devoid of toxicity.

CHAPTER 67

Blood, Fluids, Electrolytes, and Hematological Drugs

Blood is a unique tissue. As a tissue, it can be withdrawn from the body, and an extensive array of its parts can be separated for use in therapy. As a circulating body fluid, blood serves a vital set of physiological functions. A large number of drugs exert useful specific actions directed at maintaining or restoring these functions.

The reader is referred to Chapter 31 for a basic discussion of hematology and blood banking technology.

The responsibility for promulgating and administering federal regulations applicable to blood and blood products is that of the Food and Drug Administration (FDA), Bureau of Biologics. The applicable regulations are found in the *Code of Federal Regulations, 21 CFR 273.3*. Standards also are set by the American Association of Blood Banks and the World Health Organization (WHO).

WHOLE BLOOD AND BLOOD COMPONENTS

Blood serves many vital functions and also reflects the condition of other body tissues. Even though whole blood does not normally come into direct contact with noncirculating cells other than the vascular endothelium, electrolytes and many small organic compounds found in plasma freely exchange with both the lymph and the interstitial fluid. Thus, the composition of blood is an important indicator of cellular ion and metabolic status. Plasma is the vehicle for the transport of most nutrients to, and many wastes from, the tissues. Plasma transports drugs, often in combined, or bound, form; plasma is therefore an important factor in determining the effectiveness of drugs (Chapter 57). The proteins in plasma are involved importantly in the regulation of the hydration of the tissues by virtue of osmosis resulting from the impermeability of the vascular endothelium to most of the protein. Some of the plasma proteins are involved intimately in the clotting of blood and, therefore, in its conservation.

The erythrocytes are involved especially with oxygen and carbon dioxide transport. Leukocytes play major roles in the defense against infection (see Chapter 60), and platelets exert a variety of important functions in hemostasis and response to injury.

USES FOR BLOOD AND BLOOD COMPONENTS— The many physiological functions of blood derive from the specific roles of its many parts; in addition to the formed elements there are more than 80 discrete proteins in plasma. When whole blood has been lost, as by hemorrhage, whole blood is required for replacement. However, the use of whole blood to overcome a deficiency of a single part constitutes a dissipation of the other useful parts.

In most instances, the administration of a single component in concentrated form elicits a far better response than the administration of that component as whole blood. Furthermore, by using the specific parts of the blood, the supply of blood can be used more economically; the net result is the use of the components of a single donation for several purposes.

The number of products now available is increasing but is still short of the number of known parts of blood. For example, the red cells can be made available for the treatment of anemia, albumin for the treatment of shock, immune globulins for the prophylaxis of certain infectious diseases, granulocytes for granulocytopenia, and platelets for thrombocytopenia. These, and other important available blood components, are discussed in the following sections.

In the United States, the collection, processing, preservation, and distribution of blood and its separated components are performed by a wide variety of enterprises. For the purpose of this discussion, however, the important fact is where and how blood and its components are made available for the use of patients and the public at large. The main channels for dispensing blood services and blood products are

1. Blood centers and blood banks. These provide a wide array of services that reach the patient on prescription, usually through a hospital blood bank or transfusion service. The major services include the provision of whole blood, separated red cells, platelets, granulocytes, cryoprecipitated Factor VIII, single-donor plasma, and fresh frozen plasma. These usually are referred to as blood and blood components. They are distinguished by the fact that they are prepared locally in the blood center and dispensed in the form of individual units identified by the donor.
2. The pharmaceutical manufacturer and the pharmacy. This applies to the products of plasma fractionation, which are prepared by pharmaceutical manufacturers from large lots of pooled human plasma and are, therefore, subject to biological control regulations separate from those applying to simple units of blood and its components.
3. Public-health agencies and large blood centers. These may dispense directly to physicians or even to individual patients under certain circumstances.

TRANSMISSION OF INFECTION—The use of blood and its components is accompanied by some risk of transmission of serum hepatitis cytomegalovirus, human immunodeficiency viruses, Epstein-Barr virus, herpes simplex, infectious mononucleosis, syphilis, malaria, Chagas' disease, etc. This risk is different depending on which part of the blood is used and, also, on how it was prepared.

In the case of units of whole blood and blood components prepared and distributed by blood banks and blood centers, the degree of risk depends on the ability to detect the infectious agent in donor blood. Rapid progress is being made in this area. However, it probably will be some time, if ever, before the risk will reach zero; ie, before the absolute safety of donor blood can be assured. Still, the risk may be diminished or indeed eliminated by suitable processing treatments. Thus, immune globulin prepared by the ethanol-water fractionation procedure is free of virus even without specific viricidal treatment.

Human Albumin carries no risk of virus transmission, as a result of heating the solution to 60°C for 10 hr. Therefore, it is likely that any product that can be heated at 60°C for 10 hr will have a greatly diminished, if not zero, risk of viral transmission. Unfortunately, very few products can withstand such rigorous treatment, and other means have been sought to inactivate viruses, but with less than complete success. These include irradiation with ultraviolet light, cathode rays, and chemical treatment with various substances such as β-propiolactone. None of these methods, as presently used, can be relied on to inactivate completely all viruses that might be present, although they diminish the risk associated with use of the material.

In short, except for certain products such as albumin and immune globulin, which are known to be free of virus, most blood derivatives must be assumed to involve a risk of virus transmission, and this risk must be weighed against the medical consequences of withholding the product.

WHOLE BLOOD

Blood may be collected for human use only from persons who are certified by a physician as being free of transmissible disease, as far as can be determined from the donor's personal history, physical examination, etc. Unfortunately, in mass donations (eg, bloodmobiles) these examinations and certifications tend to be hasty and limited. The usual amount drawn is 500 mL. The blood is collected into an anticoagulant solution. A sample of blood is collected at the time of bleeding and subjected to serological and virological tests.

The use of the anticoagulant mixtures known as ACD and CPD extends the useful life of the red cells with the result that, following storage under proper conditions, the blood can be used with safety for a period of 21 days after collection. The addition of adenine to CPD solution (to make CPDA-1) increases the shelf life by another 14 days, thus enabling a useful storage time of 35 days. The use of these solutions has extended greatly the flexibility of hospital and community blood banks. However, with heparin the shelf life is much shorter, the official expiration time being 2 days.

If whole blood is used, it is handled carefully and stored in the cold without further processing or testing, except for occasional observation to detect evidence of hemolysis or contamination.

BLOOD COMPONENTS

Blood collection agencies—blood centers and blood banks—provide an array of blood services to the areas they serve. These include providing whole blood and several blood components prepared in the center from fresh donor blood. Blood components are made from single units of blood without opening or breaking the sterility of the plastic-bag system in which the blood originally was collected. These components thus are individualized with respect to the donor; if greater amounts are required than those available from one donor, multiple units are used. In addition to whole blood, components commonly available are CPD or CPDA-1 red blood cells, frozen red blood cells, saline-washed red blood cells, leukocyte-free red blood cells, granulocyte concentrate, platelet concentrate, cryoprecipitated antihemophilic factor, fresh frozen plasma, and liquid plasma.

WHOLE BLOOD

Blood that has been drawn from suitable human donors under rigid aseptic precautions. It contains citrate ion (acid citrate dextrose or citrate phosphate dextrose or citrate phosphate dextrose with adenine) or heparin as an anticoagulant. Preparations are designated ACD Whole Blood, CPD Whole Blood, CPDA-1 Whole Blood, or Heparinized Whole Blood according to the anticoagulant used. Whole blood from which the antihemophilic factor has been removed is designated Modified Whole Blood (see below).

Description—Deep-red, opaque liquid from which the corpuscles readily settle, on standing for 24 to 48 hr, leaving a clear, yellowish, or pinkish, supernatant layer. If the blood has been drawn soon after the donor has eaten, it may, on standing, acquire a layer of fatlike material near its surface. A deep-pink or red color in the plasma or a purplish tint at the surface of the cell portion usually indicates that the blood is unsatisfactory for use.

Comments—The natural replenisher for lost blood and hence indicated when there has been hemorrhage or traumatic blood loss of over 20% of the blood volume. When the blood loss is small, it is not essential that all of the lost blood be replaced, except in persons with high oxygen demand (eg, thyrotoxicosis, beri-beri) or in anemia. Consequently, some practitioners may replace only part of the lost blood and make up the remainder of the deficit with a saline, hetastarch, or dextran solution. In hemorrhagic shock, some medical opinion holds that the entire volume deficit should not be repaired by whole blood alone because of erythrocyte aggregation and sludging, and a dextran also sometimes is added concomitantly, to suppress not only erythrocyte aggregation but also platelet aggregation, since intravascular clotting sometimes is a complication. Adverse effects of whole blood include reactions from improperly matched blood, passive transfer of allergies, serum hepatitis and other infections, volume overload in improperly monitored administration, and increased viscosity of the circulating blood. Stored whole blood is nearly devoid of platelets and also may be deficient in Factors V and VII, so that clotting and coagulation defects may occur after massive transfusions.

WHOLE BLOOD MODIFIED

Single-donor whole blood from which antihemophilic factor (USP definition) or one or more other, nonerythrocyte components have been removed. Components and plasma may be removed either by sedimentation methods or by continuous separation devices; after selective separation, the plasma is reunited with the erythrocytes.

Comments—The uses are determined, in part, by the health of both the donor and recipient and the reason for removal of the component(s). If the reason for component-pheresis is to remove an adverse component, such as leukocytes in a leukemia or lymphocytes in an autoimmune disorder, the modified whole blood is returned autologously to the donor. If, instead, the donor is healthy and pheresis is conducted to provide a heterologous source of the component(s) for therapeutic purposes, the residual modified whole blood may be used for the same purposes as *Whole Blood,* provided that the volume to be transfused is small enough so as not to cause, by dilution, a clinically significant deficit of the corresponding component(s) in the recipient.

GRANULOCYTE CONCENTRATE

A single-donor concentrate of leukocytes obtained either by separation from sedimented whole blood or by pheresis with a continuous- or intermittent-flow centrifuge. The granulocytes (and entrained lymphocytes) are resuspended in the plasma of the recipient. The component should be used within 24 hr of collection.

Comments—Heterologously in patients with severe leukopenia, usually that which results from cancer chemotherapy or other adverse drug reactions.

LYMPHOCYTES FROZEN

A single-donor frozen concentrate of lymphocytes obtained by differential sedimentation from whole blood or from the removal of lymph from the thoracic duct. The cells are cooled at a rate of 3.5/min. DMSO is added to a 5% concentration when the temperature reaches 0°. Reconstitution requires careful thawing and repeated washout of DMSO. Viable cells are quantified from the uptake of radiothymidine into phytohemagglutinin-stimulated suspensions.

Comments—Investigationally in the treatment of neoplastic diseases, as exchange replacement for lymphocytes pheresed from the blood of patients afflicted with certain thymocyte-mediated autoimmune disorders, and as a diagnostic agent in specialized *in vitro* assessments of immune function.

SINGLE-DONOR PLASMA

Human Plasma

The liquid portion of a single unit of ACD, CPD-, or CPDA-1 whole blood, the separation of which was accomplished within the expiration

time of the whole blood. It is stored at 1 to 6°; it may be stored for 5 days beyond the dating period of the whole blood from which it was separated (26 and 40 days if from CPD- or CPDA-1 whole blood, respectively). The ABO compatibility is that of the donor whole blood. One unit is 220 to 250 mL.

Description—Straw-colored transparent fluid that may sometimes exhibit a slight opalescence.

Comments—Mostly for *volume replenishment* in the treatment of *shock*, especially after severe burns, in which plasma protein loss is considerable. It is used occasionally as a source of the stable coagulation Factors II, VII, IX, and X, and thus can be used to treat hemophilia B. ABO compatibility is desirable but is not a prerequisite to use.

SINGLE-DONOR PLASMA FREEZE DRIED

Human Plasma Freeze-Dried

Single-donor plasma that has been cryodesiccated. If Fresh Frozen Plasma is the source of the cryodesiccate, the plasma may be designated an Antihemophilic Plasma. The expiration time of the reconstituted plasma is that of *Single-Donor Plasma*.

Comments—If the desiccate is made from *Fresh Frozen Plasma,* see the monograph; if made from Frozen Plasma, see *Single-Donor Plasma*.

SINGLE-DONOR PLASMA FRESH FROZEN

Human Plasma, Fresh Frozen; Antihemophilic Plasma

Single-donor human plasma frozen within 6 hr of collection and stored at a temperature of −20° or lower (preferably below −30°). The frozen plasma shall not be stored beyond 12 months. As a source of coagulation factors, the expiration time of thawed fresh frozen plasma is 24 hr; as a volume replenisher, the expiration time is that of Single-Donor Plasma. ABO compatibility is that of the donor whole blood. One unit is 200 to 250 mL.

Description—Light yellow to deep cream in color. When viewed microscopically, a reticulated structure without evidence of fusion may be seen.

Comments—Indicated especially for the treatment of *multiple coagulation factor deficiencies* (since the labile coagulation Factors V and XIII are preserved in fresh frozen plasma), such as those that occur in cases of massive transfusion with stored blood, after heparinization in disseminated intravascular coagulation, or in liver disease, and for *hemophilia*. The preparation also may be used as *Single-Donor Plasma* (above), although such use is unnecessarily expensive. It is the plasma of choice in patients with thrombotic thrombocytopenic purpura. It also is of value in patients with deficiencies of immunoglobulin and/or complement. Serum hepatitis virus is not killed by freezing.

SINGLE-DONOR PLASMA FROZEN

Human Plasma Frozen

Single-donor plasma that has been frozen within the expiration time of the liquid plasma but longer than 6 hr after removal from the donor. The expiration time of the thawed plasma is that of *Single-Donor Plasma.*

Comments—See *Single-Donor Plasma.*

PLATELET CONCENTRATE

Platelets taken from plasma obtained by whole-blood collection, by plasmapheresis or by plateletpheresis, from a single, suitable, human donor of whole blood; or from a plasmapheresis donor; or from a plateletpheresis donor. One unit of platelet concentrate consists of not less than 5.5×10^{10} platelets suspended in a specified volume of the original plasma. (See USP for collection procedure.)

Preserved platelets can be reinfused successfully into recipients suffering from platelet deficiency. Platelets obtained by plateletpheresis must be used within 24 hr of collection, because the open system allows bacterial contamination. Although the official expiration time is only 72 hr, it now is possible to store platelets for up to 120 hr, and it is likely that methods to preserve them for a longer period will be devised in the near future.

Comments—To arrest or prevent bleeding resulting from thrombocytopenia or thrombopathy. In platelet deficiency consequent to disseminated intravascular coagulation and thrombocytopenic purpura (in which a type of intravascular coagulation occurs), the platelets must be coadministered with heparin. When thrombocytopenia is caused by immune destruction, the administration of platelets mostly is futile because of rapid destruction of the added platelets. Likewise, in drug-induced thrombocytopenia, the effects of the platelets mostly are voided unless the drug is discontinued, preferably in advance. Platelets can be used in the priming of extracorporeal circuits, but they may be subjected to faster destruction in the circuit than endogenous platelets. The half-life of platelets is about 1 to 2 days.

RED BLOOD CELLS

Human Red Blood Cells; Red Cell Concentrate

Red cells of whole human blood, separated from plasma by centrifuging or subsidence during the dating period of the blood from which they are derived, but not later than 21 days after the blood is drawn if the anticoagulant solution is ACD or CPD solution; if acid citrate dextrose adenine solution has been used as anticoagulant, such preparation may be made within 35 days therefrom; if heparin is used, the expiration time is 48 hr. The expiration dates are valid only if the hematocrit does not exceed 80% and the seal is unbroken. Preparations are designated CPD Red Cells, CPDA-1 Red Cells, or Heparinized Red Cells, according to the anticoagulant used.

Description—Dark red when packed and may show a slight creamy layer on the surface and a small supernatant layer of yellow or opalescent plasma. Resuspended human blood cells is a dark-red fluid.

Comments—A *blood replenisher* in any condition in which the primary deficiency in the blood is of the erythrocytes. Thus, they are used in the emergency treatment of a number of the anemias that formerly were treated with whole-blood transfusions. They also may be returned to the donor by autologous transfusion after plasmapheresis or apheresis of other components. Human blood cells are not suitable alone as a replacement fluid in hemorrhage, but they may be employed in cases where chronic blood loss is not too great to decrease appreciably the plasma volume and plasma protein content. Each unit of concentrate preferably is mixed with 50 to 100 mL of 0.9% NaCl injection to decrease the viscosity. Lactated Ringer's injection is contraindicated because it provides enough calcium to initiate coagulation; dextrose injection is contraindicated because it causes hemolysis. The half-life is about 4 weeks but varies considerably depending on the recipient.

RED BLOOD CELLS FROZEN

Red Blood Cells (Human) Frozen; Red Cells Fresh Frozen

A preparation in which human red cells are suspended in a glycerol solution and frozen at temperatures ranging from −80 to −120°. There are two types of preparations: one that uses a low concentration of glycerol and rapid freezing and the other, which uses a high concentration of glycerol and slow freezing. The expiration time is 3 years. Before use, the suspension is thawed and the glycerol medium is replaced with a physiological solution. At this stage the preparation is designated Deglycerolized Red Cell Concentrate. The expiration time of the thawed preparation is 24 hr.

Comments—By freezing erythrocytes immediately or shortly after withdrawal, both ATP and 2,3-diphosphoglyceric acid (2,3-DPG) are preserved better than in the classical preparation and storage methods, and frozen erythrocytes have better oxygen-transport capacity. Therefore they especially are suited for use in newborn and premature infants and in older patients with excessive oxygen demands. Because of their single-donor origin they are used especially for autologous transfusions. They also are used when there is a rare blood requirement, in elective gynecological and cardiac surgery, hemodialysis, and kidney transplantation. They essentially are free of irregular antibodies and plasma proteins and hence are useful in patients with allergic, febrile reactions to saline-washed red cells or with nocturnal hemoglobinuria. Since there are few surviving leukocytes, the risk of graft-versus-host response is diminished. The freeze-thaw procedure removes senescent erythrocytes, thus leaving a younger population of cells with a longer survival time in the recipient. The postthaw washing procedure greatly decreases the risk of serum hepatitis and pyrogenic reactions to debris from leukocytes and platelets. Frozen red cells are very expensive.

RED BLOOD CELLS LEUKOCYTES REMOVED

Red Cell Concentrate, Leukocyte-Poor

A single-donor red cell concentrate that contains less than 25% of the original leukocytes. The expiration time is that of *Red Blood Cells* and is determined by the type of anticoagulant used. The hematocrit usually ranges from 0.7 to 0.8.

Comments—Mostly for autologous transfusion in leukemic individuals in whom a reduction in circulating leukocytes is imperative. May be used in heterologous erythrocyte replenishment if the original donor blood was normal (ie, donor blood served as a source of therapeutic leukocytes). Because the preparation has fewer pyrogenic leukocyte fragments than does Red Blood Cells, febrile reactions are less severe and less frequent.

RED BLOOD CELLS SALINE WASHED

Red Cell Concentrate, Washed

A single-donor red-cell concentrate in which most of the plasma, leukocytes, and platelets have been removed within 24 hr of transfusion by

one or more washes with an isotonic saline solution. The hematocrit usually lies between 0.7 and 0.8.

Comments—Washing may be employed for five purposes: (1) to remove adverse components in specific disorders (eg, lymphocytes and/or immune globulins in certain autoimmune disorders, Rh factors in alloimmunity, anticoagulation factors in certain bleeding disorders, thyroid hormone in thyroid storm, etc; in such instances, the erythrocytes are to be reinfused into the donor; (2) to reduce the risk of blood-transmissible infections (not malaria); the erythrocytes are intended for heterologous transmission; (3) to remove citrate in citrated blood when the volume to be transfused is large and the intended recipient has a liver dysfunction in which citrate cannot be tolerated; (4) to decrease the intensity of heterologous transfusion reactions in emergency situations in which out-of-group (nonmatched) blood must be used; or (5) to decrease the incidence and severity of febrile transfusion reaction caused by fragments of leukocytes and platelets.

PLASMA EXPANDERS AND INTRAVENOUS FLUIDS

PROTEIN AND COLLOID SOLUTIONS

Hemorrhage and shock result in loss of blood volume, which, if carried beyond a certain critical point, leads to circulatory failure. Replacement of the plasma proteins or injection of a substance having similar osmotic properties will restore the blood volume at least temporarily, so that circulation of oxygen to the tissues may be maintained. Many substances have been employed for this purpose: *whole blood,* which in certain situations is ideal, but is not always immediately available; *plasma,* which is quite effective, but is unstable in the liquid form, relatively cumbersome in the dry form, involves injection of salt and water, which is in some cases undesirable, and, finally, cannot readily be rendered free of pathogenic viruses; *serum albumin,* the protein in the plasma that functions to control blood volume and polysaccharides, such as *dextrans* and *hetastarch*.

Physiologically, the most clearly established role of albumin appears to be its water-retaining (osmotic) capacity. It is due chiefly to plasma albumin that the water of the plasma, instead of diffusing into the tissues, is retained in the bloodstream, maintaining the volume of blood that is necessary for effective cardiac output and circulation. Albumin, although it comprises less than 60% of the plasma proteins, by virtue of having the lowest molecular weight of these proteins contributes 80% of their osmotic effect. Another highly important property of albumin is its capacity to bind various chemical substances, including certain ions, some hormones, and numerous drugs.

Methods have been devised for preparing human plasma albumin more than 99% pure. Unlike most plasma proteins, it is extraordinarily stable. It does not require desiccation or continuous refrigeration and, therefore, can be kept on hand as a 25% sterile solution, ready for instant use. Separation of the albumin leaves the remaining plasma proteins as by-products. It is possible to derive many specific pharmaceutical agents from one blood donation, enabling more efficient use of a given quantity of blood.

ALBUMIN HUMAN

Normal Human Serum Albumin; Albuminar; Albutein; Plasbumin; Buminate

Human albumin is a sterile, nonpyrogenic preparation of serum albumin, obtained by fractionating blood, plasma, serum, or placentas from healthy human donors and tested for absence of hepatitis B surface antigen. It is prepared by a process ensuring safety for intravenous use. The albumin content is not less than 96% of the total protein. The solution contains 5 or 25 g of albumin, respectively, corresponding to 100 or 500 mL of normal human plasma. It may contain sodium acetytryptophanate alone or with sodium caprylate as a stabilizing agent. The sodium content is not less than 130 mEq/L and not more than 160 mEq/L. No antimicrobial agent is added. It meets the requirements of tests for limit of heme, heat stability, and pH. Solutions are heated in final containers at 60° for 10 hr to kill any pathogenic organisms that may be present. The storage temperature is indicated on the label. The solution is not to be used if it is turbid or there is a sediment.

Description—Moderately viscous, clear, brownish fluid; practically odorless; may develop a slight granular or flaky deposit during storage. When dried, has a slight-yellow to deep-cream color.

Comments—Serves as an emergency agent for restoration of blood volume in the treatment of *shock* or *hemorrhage*. It especially is indicated when blood loss exceeds 20% of blood volume. If albumin is administered in hypertonic concentrations, it will abstract water from interstitial and intracellular fluids and increase blood volume by an amount more than the volume administered; in isotonic concentration it will expand blood volume only by an amount equal to the volume added. Each gram of albumin holds about 18 mL of water in the bloodstream. Because its action depends on the availability of tissue water, hypertonic albumin should not be used in severely dehydrated patients without simultaneous administration of saline or dextrose solutions.

It has been used in protein replacement therapy when serum protein levels are low because of excessive loss, as in extensive burns and nephrosis, certain skin diseases, and other conditions, or because of inadequate formation of proteins resulting from nutritional disturbances, cirrhosis, or other causes. However, the value of albumin in the therapy of chronic nephritis or cirrhosis is less impressive than in acute hypoalbuminemia. Hyperoncotic albumin solutions may be used to cause transient diuresis in edematous patients or in those undergoing renal dialysis. It also is used in the treatment of hyperbilirubinemia and erythroblastosis fetalis to increase the binding capacity for bilirubin.

Low salt content and the high stability of the single protein component present make *salt-poor* albumin the agent of choice in certain types of protein replacement therapy, bearing in mind the following limitations: Albumin does not, in any sense, replace red cells and, therefore, should not be used in hemorrhagic shock except as an emergency remedy. It lacks the other proteins contained in plasma, hence is not an adequate agent for treatment of deficiencies of specific plasma proteins (eg, fibrinogen, prothrombin) such as occur in acute hepatitis or burns. It does not replace lost fluids and therefore must be given with ample quantities of crystalloid solution when used in dehydrated patients, as noted above. Chills, fever, urticaria, and perturbations of respiration and blood pressure sometimes occur. Albumin is contraindicated in congestive heart failure. Large doses should not be given in severe anemia, in low cardiac reserve, and in the absence of hypoalbuminemia.

ANTIHEMOPHILIC FACTOR—page 1326.

PLASMA PROTEIN FRACTION

Human Plasma Protein Fraction; Plasmanate; Plasma Plex; Plasmatein; Protenate

A sterile solution of selected proteins derived from the blood plasma of healthy adult human donors. It contains 4.5 to 5.5 g of protein/100 mL, of which about 83 to 90% is albumin and the remainder is alpha and beta globulins. It contains no antimicrobial agent but may contain suitable stabilizers. The expiration time is 5 years if the storage temperature is 2° to 10°, 3 years if 11° through 29°, the time not to include 1 year of storage at the manufacturing plant at 5°.

Preparation—By a process similar to that by which albumin is made. The product resembles plasma from which certain unstable globulins have been removed, including gamma globulin and certain lipoproteins. The solution is treated by heating at 60° for 10 hr to reduce the risk of virus transmission. The solution is isotonic with normal plasma and is isotonic with respect to diffusible ions, the major ions being sodium and chloride.

Description—Transparent, nearly colorless or slightly brownish liquid; nearly odorless; may develop a slight granular or flaky deposit during storage.

Comments—Indicated, like albumin, as a substitute for plasma in treating nonhemorrhagic *shock*. It also is a convenient source of protein for intravenous nutrition. Because it does not contain any clotting factors, it is not a substitute for fresh plasma in treating hemorrhagic states. The plasma half-life is about 27 days.

Untoward effects are uncommon; they include nausea, vomiting, and increased salivation. Care must be exercised to prevent circulatory overload, especially in nonhypovolemic patients. Solutions of this fraction should not be mixed with other intravenous fluids, either in the bottle or in the tubing.

PLASMA EXTENDERS (VOLUME EXPANDERS)

Much effort has been expended in the search for nontoxic substances, not of human origin, which might be used in an emergency to restore blood volume. It should be emphasized that these substances are in no sense substitutes for plasma; following their emergency use, plasma or blood must be replaced as rapidly as possible. Some substitutes, however, have favorable actions on the rheology of blood and on platelet adhesiveness, hence sometimes may be administered along with blood or plasma just for these effects. Furthermore, in some kinds of hypovolemic shock, the plasma actually is not lost from the vascular tree but is sequestered in various vascular beds. In these situations, it is not necessary to give plasma, because repair of the fictive volume deficit with a plasma extender will mobilize some of the plasma back into the circulation. Even plasma proteins lost into interstitial spaces return by way of the lymph. In hypovolemia, from dehydration or adrenal insufficiency, appropriate electrolyte or dextrose solutions are indicated.

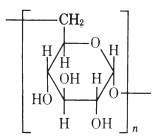
Volume expansion (plasma extension) clearly is not indicated unless the pulmonary arterial wedge pressure (PAW), an approximation of the pulmonary venous pressure, is below 12 torr. It is advisable to give a test injection (about 200 mL) of isotonic saline or dextran solution. If the PAW rises only slightly but cardiac output more substantially, further plasma extension is indicated; if PAW rises sharply but cardiac output does not, plasma extension is redundant, and treatment must be directed toward improving cardiac function. In volume expansion, the endpoint is usually 16 torr (rarely 18 torr), and further expansion will tend to cause pulmonary edema.

Volume expanders also are used to prime extracorporeal circuits.

ALBUMIN—pages 423 and 1321.

DEXTRAN 40

Gentran 40; 10% LMD; Rheomacrodex



Dextran 9004-54-0 $(C_6H_{10}O_5)_n$; a polymer of glucose, with an average mol wt of about 40,000 in which the glucosidic linkages are predominantly of the $\alpha(1\rightarrow6)$ type.

Preparation—Sucrose is subjected to the action of the bacterium *Leuconostoc mesenteroides* B 512, and the crude, high-molecular-weight dextran thus formed is hydrolyzed and fractionated to an average molecular weight of about 40,000 as measured by light-scattering techniques. US Pat 2,644,815.

Description—White, amorphous powder that is odorless and tasteless; 10% solution in 5% dextrose in water darkens slightly over a long storage period as with other dextrose-containing solutions; darkening is accelerated by increased ambient temperatures.

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

Comments—As an isotonic solution to prime pumps or improve flow in surgery requiring *cardiopulmonary bypass*. It has the property of lowering the viscosity of blood and improving flow; in part the improvement in flow is the result of hemodilution. For this reason, 10% of dextran 40 in isotonic saline solution or 5% dextrose is superior to dextran 40 in whole blood. Dextrans decrease platelet adhesiveness. This property is used for *prophylaxis of thrombosis and thromboembolism during and after surgery* and occasionally to decrease coagulopathies in the shock-lung syndrome. Otherwise, it seldom is used in shock, because of the short duration in the body (2–4 hr) and also because of frequent adverse effects.

The size of the molecule is such that the polysaccharide is filtered in the glomeruli more rapidly than larger macromolecules, such as dextran 70 or 75. As the filtrate is concentrated in the renal tubules, it sometimes may become too viscid to flow, and renal damage can ensue. For this reason many surgeons prefer to prime their bypass with other solutions. Renal failure, severe congestive heart failure, severe coagulation disorders, hypervolemia, hypersensitivity, and severe dehydration contraindicate use of this substance. It can cause allergic reactions. It interferes with the cross-matching of blood, especially when enzymatic methods are used. It also interferes with some tests of renal and hepatic function and with assays for blood sugar in which acid hydrolysis is used.

DEXTRAN 70

Gentran 70; Macrodex

Dextran 9004-54-0 $(C_6H_{10}O_5)_n$; a polymer of glucose with an average mol wt of about 70,000, in which the glucosidic linkages are predominantly of the $\alpha(1\rightarrow6)$ type. For the structural formula see *Dextran 40*.

Preparation—As described for *Dextran 40* except that the hydrolysis and fractionation are adjusted to yield a product of average mol wt of about 70,000.

Description—Fine, white, amorphous powder; odorless and tasteless; stable in light and very hygroscopic; commercial grades usually contain about 5% water.

Solubility—Freely soluble in hot water or dimethyl sulfoxide; insoluble in alcohol or ether.

Comments—A plasma expander for the prevention or treatment of *hypovolemic shock*. The macromolecule is contained within the plasma and hence retains fluid in the vascular bed by osmosis. Hypertonic solutions cause the dehydration of tissues, the abstracted water being added to the plasma. For this reason it is useful in the treatment of *toxemia of pregnancy* and *nephrosis*. Although dextran 70 solution is inferior to plasma, it has the advantage that refrigeration is not required and the solution does not have to be prepared immediately before use. Thus, it may be kept ready for use in emergency vehicles, field kits, etc. It is also less expensive than plasma. Like plasma, it is inferior to whole blood as replacement when hypovolemia is due to hemorrhage. When hypoproteinemia exists, it should not be used in place of plasma. It decreases platelet adhesiveness and hence increases clotting time. In some uses this may be a disadvantage, although hemorrhage occurs mainly in the presence of clotting disorders. In some types of shock the effect on platelet adhesiveness is an advantage, because shock-induced coagulopathies will be attenuated. Its anticoagulant effect can be useful clinically; it has been shown to be equal to dicumarol in *preventing thrombosis* after femoral neck fractures and major pelvic surgery. A solution also is used to distend the uterus for hysteroscopy and to irrigate the cavity. It also is used in artificial tears.

A small part of dextran 70, corresponding to the low-molecular-weight molecules, is excreted during the first 1 or 2 days. The remainder is taken up by the reticuloendothelial system and is metabolized later, which requires approximately 10 days.

Side effects include mainly allergic reactions (fever, hypotension, hives, angioedema, bronchospasm, and anaphylaxis). The substance may interfere with cross-matching of blood if unsuitable dilutions of erythrocytes and serum are used. The drug is contraindicated when there is hypersensitivity, severe coagulation disorders, severe congestive heart failure, and hypervolemia.

DEXTRAN 75

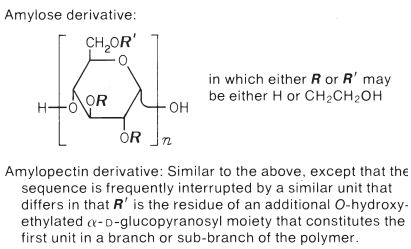
Gendex 75; Macrodex

Chemistry, Preparation, Description, Solubility—See *Dextran 70* (above); read 75,000 in place of 70,000.

Comments—See *Dextran 70,* above. Dextran 75 is not used as an aid to hysteroscopy.

HETASTARCH

Starch 2-hydroxyethyl ether; Hespan



[9005-27-0]. Consists of more then 90% amylopectin that has been treated with ethylene chlorohydrin so that an average of 7 to 8 of the hydroxyl groups occurring in every 10 D-glucopyranose units of the starch polymer have been converted to 2-hydroxyethoxy groups. The molecular mass is about 450,000 daltons.

Comments—A 6% solution is osmotically equivalent to a 5% albumin solution. In the blood, it abstracts some water from interstitial and intracellular fluids, thus expanding the blood volume somewhat in

excess of the volume infused. The expansion persists for 1 to 1 1/2 days. Hetastarch is used in the prevention and treatment of *hypovolemic shock*. It also is used as a suspension medium for leukapheresis.

It does not cause the coagulation abnormalities that does dextran nor does it interfere with the cross-matching of blood. There is general but not complete agreement that it is less likely than dextran to cause anaphylaxis and other allergic manifestations (fever, chills, urticaria, pruritus). The incidence of anaphylactoid reactions is stated to be less than 0.1%.

Elimination has complex kinetics, mainly because of heterogeneity in molecular size and linkage. About 40% of molecules with molecular masses below 50,000 daltons is eliminated in the urine in 1 day, 64% in 8 days, 90% in 41 days, and 100% in 48 days. Larger molecules are taken up by the reticuloendothelial system and degraded by amylase. There is a compound half-life: 90% is eliminated with a half-life of 17 days; the remainder, 48 days.

SINGLE-DONOR PLASMA—page 1319.

BALANCED ELECTROLYTE SOLUTIONS

RINGER'S INJECTION

Isotonic Solution of Three Chlorides

A sterile solution of sodium chloride (8.6 g), potassium chloride (0.30 g), and calcium chloride (0.33 g) in 1 L of solution prepared with Water for Injection. It contains approximately 147.5 mEq of sodium, 4.0 mEq of potassium, 4.5 mEq of calcium, and 156 mEq of chloride ion per liter; antimicrobial agents are not present.

Description—Colorless, odorless solution with a salty taste; pH between 5.0 and 7.5.

Comments—Theoretically superior to *Sodium Chloride Injection* as a *fluid and electrolyte replenisher* in that it supplies the three important cations of the extracellular fluid. However, in actual practice, the addition of potassium and calcium increases only slightly the therapeutic value of an isotonic sodium chloride solution. Neither potassium nor calcium is present in sufficient concentration to render it useful for the repair of deficits of these ions. Further, while administration of large volumes would result in minimal distortion of the cation composition of the extracellular fluid, like *Sodium Chloride Injection,* it would alter acid-base balance. It frequently is used to prime pumps for cardiopulmonary bypass in heart surgery. It also may be applied topically for the purposes of irrigation.

LACTATED RINGER'S INJECTION

Hartmann's Solution

A sterile solution of calcium chloride, potassium chloride, sodium chloride, and sodium lactate in water for injection. It contains no antimicrobial agents. The calcium, potassium, and sodium contents are approximately 2.7, 4, and 130 mEq/L, respectively.

Description—pH 6.0 to 7.5.

Comments—See *Ringer's Injection*. Except for the concentration of lactate and absence of bicarbonate, the composition of this injection closely approximates that of the extracellular fluids. It is employed as a *fluid and electrolyte replenisher*. The lactate ultimately metabolizes to bicarbonate and thus has an alkalinizing effect in the body; in persons with normal cellular oxidative activity, this requires 1 to 2 hr to be fully effective. It is inappropriate in the treatment of lactic acidosis. The absence of bicarbonate from the solution stabilizes the calcium, which sometimes tends to precipitate as calcium carbonate from heated solutions that contain bicarbonate.

MISCELLANEOUS FLUIDS

Miscellaneous Parenteral Fluids—There are at least 69 commercially available parenteral fluids, some of which differ only slightly and others considerably from one or more of those described in the foregoing sections. Excellent summary tables of the composition, names, and manufacturers of these products may be found in *AMA Drug Evaluations* and *Drug Facts and Comparisons* (listed under *Intravenous Nutritional Therapy*). *AMA Drug Evaluations* also provides a useful table of peritoneal solutions.

Miscellaneous Oral Electrolyte Solutions—Oral solutions containing 2 to 2.5% dextrose, 75 to 90 mEq/L sodium, and 20 mEq/L potassium have become widely used in lieu of intravenous solutions for the treatment of dehydration from diarrhea, especially in infants and children. *WHO Oral Rehydration Salts* contains 90, 20, 80, and 30 mEq/L of sodium, potassium, chloride, and bicarbonate, respectively, and 20 g/L of dextrose when reconstituted. *Maintenance/prevention solutions* contain 45 to 50 mEq/L of sodium but about the same potassium, base, and dextrose concentrations as the rehydration solutions.

DEXTROSE INJECTION

Injection of Glucose

A sterile solution of dextrose in water for injection. It contains 95 to 105% of the labeled amount of $C_6H_{12}O_6.H_2O$. It contains no antimicrobial agents.

Preparation—The strength of the solution may vary from 2.0, to 5, 10, 20, 25, or 50%. Quantities that are administered may vary from 100 mL to 1000 mL or more. With such large amounts being administered, a hospital will require considerable quantities of this solution daily, and many shortcuts have been developed for its manufacture. It is general practice to prepare concentrated solutions and then to dilute these with water for injection, thus saving an immense amount of labor and time, particularly in the filtration operation.

Care should be exercised in the selection of dextrose, since the sugar itself may be a source of pyrogens, and extreme care must be observed throughout the preparation of the dextrose injections to prevent contamination, for the conditions are practically ideal for the development of bacteria and, therefore, pyrogens.

Weaker solutions may be sterilized in an autoclave without producing any change in color, but with the more concentrated solutions there is greater possibility of producing a slight change in color on sterilization with high temperatures. Consequently, sterilization by filtration often is resorted to in these cases.

The pH of dextrose solutions is lowered on heating. Nevertheless, buffers seldom are added directly to the solution during its preparation since this is often the cause of discoloration and the buffering capacity diminishes after the solution stands for a period of time. When buffers are desired, they should be dispensed separately so that the physician may add the buffer extemporaneously when the preparation is to be administered. Dextrose solutions should be tested for mold.

Note—Antimicrobial agents are prohibited, since such large quantities of dextrose are administered at one time that excessive doses of the antimicrobial agent would thus be given.

Description—Clear, colorless solution with a pH of 3.5 to 6.5, determined on a portion of injection diluted with water, if necessary, to a concentration of not more than 5% of dextrose.

Comments—The most extensively used injection in hospital practice. Dextrose provides a readily metabolizable nutrient. During periods of inanition, intravenous injection of isotonic solution of dextrose *provides both fluid and carbohydrate*. Each 25 g of dextrose provides about 85 cal. A 20% to 50% solution may be infused into a high-flow vein as a source of calories in total parenteral nutrition. A 50% solution is given in insulin or suspected insulin-coma. A 20% to 50% solution, with or without insulin, is used in hyperkalemia to move potassium intracellularly. Body protein is spared, and starvation-ketosis and acidosis are prevented. It also is employed for parenteral fluid therapy when it is desired to supply water unaccompanied by electrolyte. In the body, the dextrose is converted slowly to glycogen or metabolized, thus leaving the water component of the injection without an osmotic component; the final result is the same as if water were given, but without the hemolysis that accompanies intrave-nous infusions of water. The injection also provides a suitable *vehicle for the slow intravenous infusion* of numerous drugs.

Dextrose usually is administered intravenously as a 5% solution that is isoosmotic with body fluids. Subcutaneous injection is less desirable, since such solutions are irritating and can cause local necrosis. In addition, such solutions cause temporary sequestration of extracellular electrolyte in the subcutaneous depot, and anuria, oliguria, and circulatory collapse can result. If the subcutaneous route is to be employed, *Dextrose and Sodium Chloride Injection* should be used.

When administered rapidly intravenously, hypertonic solutions of dextrose cause cellular dehydration that may be of benefit in the treatment of *cerebral edema, shock,* and *circulatory collapse. However, Dextrose and Sodium Chloride Injection is preferred*. Hypertonic solutions of dextrose also are administered intravenously to initiate *osmotic diuresis*. Dextrose in the glomerular filtrate in excess of that which can be reabsorbed by the renal tubule causes excretion of an osmotic equivalent of water. Additional quantities of extracellular electrolyte also escape renal tubular reabsorption during the osmotic diuresis.

Hyperglycemia and glycosuria may result, depending on the infusion rate and metabolic status. Because of both the dilution of extracellular fluid and endocellular movement of potassium during glucose uptake, hypokalemia may be a consequence. Reactive hypoglycemia may result from the abrupt termination of administration.

DEXTROSE AND SODIUM CHLORIDE INJECTION

Sodium Chloride and Dextrose Injection

A sterile solution of dextrose and sodium chloride in water for injection. It contains 95 to 105% of the labeled amount of $C_6H_{12}O_6.H_2O$ and of NaCl. It contains no antimicrobial agents.

Preparation—This title may include a highly concentrated solution for use as a sclerosing agent or much weaker solutions to be used in a manner similar to the use of 5 or 10% dextrose solution. This may be a mixture of equal parts of isotonic sodium chloride solution and isotonic dextrose solution, or it may represent 5% dextrose in isotonic sodium chloride solution. Both of these should be prepared according to the suggestions given for the preparation of *Dextrose Injection*.

Description—Clear, colorless solution with a pH of 3.5 to 6.5, determined on a portion of injection diluted with water, if necessary, to a concentration of not more than 5% dextrose.

Comments—To provide dextrose as a nutrient (see above) in a medium that does not hydrate the tissues, or it may be employed as a source of isotonic sodium chloride, or both. When hypertonic solutions of dextrose are employed in cerebral edema or in hydrated states, isotonic sodium chloride in the injection prevents a delayed rebound hydration. Since dextrose, alone, cannot be given safely by the subcutaneous route (see *Dextrose Injection*), this is the preferred preparation.

FRUCTOSE INJECTION—page 1692.

ANTIBODIES AND ISOAGGLUTININS

Human plasma contains antibodies of various types, which are concentrated almost entirely in Fractions II and III. Some of these occur naturally, others arise as a result of infection or are stimulated by artificial immunization.

The serum of all human beings contains antibodies (agglutinins or isoagglutinins) that react with those principal blood-group factors (agglutinogens) that the individual does *not* possess (Table 67-1).

Thus, for example, 45% of the population of the *US* possesses the blood-group O factor in their red cells, and agglutinins against the A and B factors in the plasma. Should the whole blood or cells of a Group A individual be injected into a Group O patient, the anti-A agglutinins of the patient will clump the cells received and usually will destroy (lyse) them, causing a serious reaction in many cases, even if the volume of cells injected is as low as 50 mL.

The importance of establishing the blood group of anyone either giving or receiving whole blood is therefore obvious. This is done by mixing a specimen of the cells of the subject with the serum of a selected individual whose group is known; for example, if the cells of an untyped donor are clumped by the serum of a known Group B subject, but not by the serum of a known Group A subject, the donor evidently belongs to Group A.

In practice, anti-A isoagglutinins obtained from selected group B subjects, and anti-B isoagglutinins from similarly selected Group A subjects, have for years provided highly effective reagents for identification of the blood groups. It has been demonstrated that administration of small quantities of the specific blood-group substances A or B (which can be obtained from red blood cells or, in larger quantities, from other animal tissues) to individuals having the corresponding isoagglutinins will induce a tremendous rise in titer of the agglutinin. In this fashion, extremely potent blood-grouping sera have been prepared in ample quantities. It is also possible to produce blood-grouping sera as a by-product of ethanol fractionation of plasma.

In practice (see Chapter 31), it is customary not only to determine the blood group of a donor and recipient of a blood transfusion, but to *cross-match* the cells of the donor with the serum of the patient and *vice versa*, to detect any otherwise unpredictable incompatibility in the bloods of the two individuals. This extra precaution is invaluable, not only for the purpose indicated but also as a final check against mistaken identity of the specimens. Numerous other precautions are involved in correct blood grouping, so that it has become a highly specialized technique that should only be performed by a qualified technician.

Table 67-1. Blood-Group Factors

BLOOD GROUPS (CELLS)		
FACTORS PRESENT	FREQUENCY IN POPULATION	ISOAGGLUTININS (PLASMA)
O	45%	Anti-A and Anti-B
A	41%	Anti-B
B	10%	Anti-A
AB	4%	None

THE Rh FACTOR—A much rarer antibody occurs in a small proportion of individuals as a result of injection of so-called *Rh-positive blood* or absorption of such blood across the placenta during pregnancy in gravid females. This *Rh factor* actually consists of at least nine different factors, any one or several of which may be present in the red cells of a given individual. Isoagglutinins reacting with these factors do not occur normally in humans, but appear only as a result of accidental *immunization* of individuals with a type of Rh factor which they do not possess. Actually, the blood of about 85% of Western Europeans or Americans contains one or two of the commonest of these factors, which also are the most potent as antigens. Therefore, in general practice it is customary and quite permissible to classify individuals simply as either *Rh-positive* or *Rh-negative.* The technique of Rh typing is essentially like that of blood grouping.

Like anti-A and anti-B blood-grouping serum, the principal source for Rh-typing serum is the blood of human donors who, by chance or intention, have become hyperimmunized to one of the Rh factors. One of the commonest sources is the blood of Rh-negative women who have borne several Rh-positive infants, absorbed their Rh factor, and thereby became sensitized. Another source is Rh-negative individuals who have been transfused with Rh-positive blood. Injection of small amounts of Rh substance in the latter individuals will induce very high antibody titers, rendering them suitable donors of hyperimmune serum for typing purposes. The danger of mismatched transfusion in such individuals is actually decreased, since they become extremely easy to identify.

BLOOD-GROUPING AND TYPING SERUMS

BLOOD-GROUP SPECIFIC SUBSTANCES A, B, AND AB

A sterile, isotonic solution of the polysaccharide–amino acid complexes that are capable of reducing the titer of the anti-A and anti-B isoagglutinins of group O blood. The blood-group specific substance A is prepared from hog gastric mucin, and the blood-group specific substances B and AB are prepared from the glandular portion of horse gastric mucosa. Blood-Group Specific Substances A, B and AB contains no preservative.

Description—Clear solution, which may have a slight odor due to the preservative; pH 6.0 to 6.8.

Comments—Added to group O blood as a *neutralizer of isoagglutinins*, and hence it makes the blood reasonably safe for transfusions into patients whose blood is of another group. It also may be used to condition plasma. However, conditioned plasma that contains immune anti-A and anti-B agglutinins may cause reactions. Furthermore, it must not be forgotten that blood from group O donors who previously have received conditioned group O blood may contain A and B isohemagglutinins. Such blood is dangerous to use in universal donation unless it is conditioned with blood group specific substances A and B.

ANTI-A BLOOD-GROUPING SERUM

Derived from high-titered serums of humans, with or without stimulation by the injection of group-specific red cells or substances. It agglutinates human red cells containing A antigens; ie, blood groups A and AB (including subgroups A_1, A_2, A_3, A_1B, and A_2B). It may contain a suitable antibacterial preservative.

Description—Clear or slightly opalescent fluid unless artificially colored, when it has a blue or blue-green color. The dried product is light yellow to deep cream color, unless artificially colored as indicated for liquid serum, and microscopically has a honeycomb-like structure.

ANTI-B BLOOD-GROUPING SERUM

Derived from high-titered serums of humans, with or without stimulation by the injection of group-specific red cells or substances. It agglutinates human red cells containing B antigens; ie, blood groups B and AB (including subgroups A_1B and A_2B). It may contain a suitable antibacterial preservative.

Description—Clear or slightly opalescent fluid unless artificially colored, when it has a yellow color. The dried product is light yellow to deep cream color, unless artificially colored as indicated for liquid serum, and microscopically has a honeycomb-like structure.

ANTI-RH BLOOD-GROUPING SERUMS

Blood Grouping Serums Anti-D, Anti-C, Anti-E

Derived from the blood of humans who have developed specific Rh antibodies. Anti-Rh Blood-Grouping Serums are free from agglutinins for A or B antigens and from alloantibodies other than those for which claims are made in the labeling. They may contain suitable antimicrobial agents.

Two varieties of Anti-Rh Grouping Serums are recognized: (1) complete *(saline-agglutinating)* serums, which specifically agglutinate human red blood cells in saline TS, and (2) incomplete *(blocking)* serums, which agglutinate human red blood cells only in a medium containing protein or other macromolecular substances, which may be furnished in an accompanying diluent. Complete serums commonly are designated *For saline tube test,* and the incomplete serums are designated *For slide or modified (rapid) tube test.* In liquid form, the latter contain, as additives, the required micromolecular substances.

The left-hand column of Table 67-2 lists the designations of the most commonly used anti-Rh blood-grouping serums, and the right-hand column lists the blood factor(s) with which each serum specifically reacts. The designations used in an alternative system of nomenclature are indicated parenthetically.

Comments—As diagnostic agents.

IMMUNE GLOBULINS

Adult blood contains antibodies specific for various infectious agents to which the individual has built up a resistance. In pooled normal plasma used for fractionation some of these are in high enough concentration to have a protective action. This is usually true of measles and poliomyelitis antibodies. Antibodies from adult plasma will protect against the disease if given after exposure. In certain other conditions, it is possible to select individuals with already detectable antibody levels and, by injection of an appropriate vaccine, to raise their antibody level to very high titers, much as described above for blood grouping and Rh typing sera. This practice has been employed mainly in the production of pertussis hyperimmune globulin for the treatment or prophylaxis of whooping cough.

Table 67-2.

SERUM	ANTIGEN(S) REACTING
Anti-D (Anti-Rh_0)	D (Rh_0)
Anti-C (Anti-rh`)	C (rh`)
Anti-E (Anti-rh`)	E (rh`)
Anti-CD (Anti-Rh_0`)	D (Rh_0), C (rh`)
Anti-DE (Anti-Rh_0`)	D (Rh_0), E (rh`)
Anti-CDE (Anti-Rh_0`)	D (Rh_0), C (rh`), E (rh`)
Anti-c (Anti-hr`)	c (hr`)
Anti-e (Anti-hr`)	e (hr`)

During the fractionation of plasma, most of the antibodies are concentrated into a single fraction (Fraction II); electrophoretically the proteins in this fraction are characterized as gamma globulins. Isolated immune globulins, dispensed as a 16% solution, represent a concentration of most antibodies approximately 25 times greater than that in plasma. As a result, they have been found useful in the prophylaxis of certain infectious diseases, including measles, infectious hepatitis (not to be confused with serum hepatitis), and poliomyelitis.

The usefulness derives from the immunity conferred by the *added* antibody. However, since the added antibody is metabolized slowly and therefore disappears, the immunity is passive, and lasts only so long as the concentration of antibody is above an effective level, usually from 1 to 2 months. Thereafter, the recipient once again becomes susceptible to infection. Alternatively, and particularly when exposure to infection can be ascertained with reasonable accuracy, as in measles, a modifying dose of antibodies may be administered.

While failing to prevent active infection, the added antibody lessens the severity of the disease, and patients respond to the infection by producing antibodies of their own. This production of antibodies persists for long periods thereafter, thus conferring long-lasting immunity.

Immune globulin is administered intramuscularly; it cannot be used intravenously. Reactions are uncommon and, when they do occur, chiefly are local and usually mild. Another source of gamma globulin is the blood from normal human placentas. Application of the methods of processing immune globulin from human blood, however, has made possible the preparation of a similar globulin from placentas.

Immune Globulin and immune globulins for *hepatitis B, pertussis, rabies, Rh_o(D), tetanus, cytomegalovirus, respiratory syncytial virus,* and *varicella-zoster* are described in Chapter 89.

IMMUNE SERA

Various biological products obtained from the blood of humans or animals and used for their prophylactic or therapeutic effects, eg, antitoxins, immune sera, and immune globulin, are discussed in Chapter 89.

AGENTS AFFECTING BLOOD COAGULATION

The clotting of blood is a very important process (see Chapter 31). It depends on the existence of a complex system of reactions involving plasma proteins, platelets, tissue factor, and calcium ion. This system normally is in a state of balance known as hemostasis, referring to the spontaneous arrest of bleeding. However, if a factor is defective or absent, as is the case in hemophilia, a hemorrhagic tendency exists that can lead to major hemorrhage under certain circumstances. In hemophilia, the defect is congenital. Other defects, often transient, may arise as the result of disease or malnutrition. Under certain circumstances, the reverse situation is encountered. Hypercoagulability—an abnormal tendency for the blood to clot—can be very serious, leading to thrombosis.

BLOOD-CLOTTING PROTEINS

The inherited coagulation disorders associated with bleeding affect 1 in 10,000 to 15,000 persons, except von Willebrand's disease (VWD), which may affect up to 1% of the population. These diseases are usually the result of either qualitative or quantitative defects in a single plasma protein. In hemophilia

A, plasma levels of Factor VIII are decreased, and in hemophilia B, plasma levels of Factor IX are diminished. VWD is due to an abnormality in the Factor VIII–von Willebrand Factor (VWF) complex that is required for normal platelet adhesion. In its most common form, VWD is associated with mild, mucocutaneous bleeding such as bruising, epistaxis, and menorrhagia. There are also various acquired disorders that result in excessive bleeding, including vitamin K deficiency, liver disease, or circulating antibody inhibitors to Factor VIII that can occur with age, autoimmune disease, postpartum, or in previously transfused hemophilic patients. The principal treatment is replacement therapy of the deficient factor by use of blood products derived from normal people or animals or recombinant coagulation proteins. The activity of the various coagulation factors is expressed in units, referring to the activity found in 1 mL of fresh plasma pooled from normal donors.

ANTIHEMOPHILIC FACTOR

Humate P

A sterile, purified, lyophilized concentrate of human antihemophilic factor prepared from the Factor VIII–rich cryoprotein fraction of human venous plasma.

Preparation—Precipitated by glycine from a solution of AHF-rich first precipitate from pooled normal human plasma. After treatment to lower the content of glycine and inactive proteins, a solution of the active fraction is pasteurized by heating to 60°C for 10 hr in aqueous solution.

Description—White or grayish, to yellow, amorphous substance dried from the frozen state; colorless or opalescent when reconstituted with the diluent provided. One unit is the activity in 1 mL of pooled human plasma less than 1 hr old.

Comments—The coagulation defect in classical hemophilia (hemophilia A) is predominately a deficit of the coagulation Factor VIII, called antihemophilic factor (AHF). In severe hemorrhage in the patient with hemophilia A, it is used as a cryoprecipitate or concentrate, or in fresh plasma or whole blood, as required *to terminate hemorrhage* or to prevent hemorrhage in surgery or consequent to various procedures in which bleeding may occur. The concentrate generally is preferred to plasma or whole blood, since the AHF titers of blood and plasma are quite variable, but in VWD the cryoprecipitate (below) is more effective. Although the concentrate contains VWF, it lacks the high-molecular-weight multimeric forms found in plasma, and the cryoprecipitate product. The preparation is poorly effective in hemophilia B. AHF has a distribution half-life of 4 to 8 hr and an elimination half-life of 12 to 15 hr.

In the past, viral transmission of hepatitis and human immunodeficiency viruses (HIV) was substantial, as concentrated preparations were prepared from large plasma pools. Specific viral transmission has been reduced significantly, as the concentrates now are sterilized by solvent-detergent or heat treatment. The monoclonal antibody–prepared products have shown hepatitis safety and very low risk for HIV, whereas the recombinant products are considered very low to no risk for both hepatitis and HIV. Traces of ABO isohemagglutinins are present in glycine precipitates, so that large doses may sometimes cause severe hemolysis. In contrast, monoclonal antibody–purified products have reduced blood-group-specific antibodies significantly. In addition, an antibody inhibitor to Factor VIII occurs in approximately 10% of patients, secondary to previous transfusions. Patients with high-titer Factor VIII inhibitor are treated with Anti-inhibitor Coagulant Complex or animal-derived Factor VIII. Mild allergic reactions are frequent. Occasionally there may be chills, fever, erythema, urticaria, bronchospasm, headache, lethargy, somnolence, and backache. The concentrate is more expensive than the cryoprecipitate.

See Table 67-3.

CRYOPRECIPITATED ANTIHEMOPHILIC FACTOR

A sterile, frozen concentrate of antihemophilic factor prepared from the Factor VIII–rich cryoprotein fraction of a single unit of human venous plasma obtained from whole blood or by plasmapheresis. It can be kept for 1 year at −18° or below and is thawed at a temperature not to exceed 37° just before use.

Comments—See *Antihemophilic Factor*. The cryoprecipitated form is used when an autologous replacement is necessary. Also, cryopreservation maintains the potency better than liquid preservation. The cryoprecipitate contains other factors, including one that improves the bleeding time in patients with VWD. This factor is not present in marketed preparations of antihemophilic factor, and the cryoprecipitated preparation or fresh frozen plasma should be used instead. Since the cryoprecipitate is type-specific, it may be cross-matched to the patient's blood to avoid hemolysis.

ANTITHROMBIN III (HUMAN)

Thrombate III; AT nativ

[52014-67-2]

Antithrombin III (AT III) is an α_2-globulin of molecular weight about 60,000, found in blood, and a major endogenous coagulation inhibitor that inactivates various clotting cascade serine proteases including thrombin.

Preparation—Produced from pooled units of human plasma from normal donors by modifications and refinements of the cold ethanol method of Cohn (Cohn EJ, et al. *J Am Chem Soc* 1946; 68(3): 459.).

Table 67-3. Factor VIII Products

PRODUCT	PURIFICATION METHOD	PURITY
Human plasma–derived Factor VIII		
Alphanate (*Alpha Therapeutics*)	Solvent and detergent	High purity with VWF under evaluation
Hemofil M (*Baxter Healthcare*)	Monoclonal antibody plus solvent and detergent	High purity with reduced VWF
Trace amounts of murine protein		
Humate-P (*Centeon*)	Glycine precipitation; pasteurized	Some VWF
Koate-HP (*Cutter*)	Gel chromatography and solvent and detergent	High purity
Monoclate-P (*Centeon*)	Monoclonal antibody and heat treatment	High purity with reduced VWF
Trace amounts of murine protein		
Porcine plasma-derived Factor VIII		
Hyate: C (*Speywood*)	Cryoprecipitate fractionation	High purity with significant VWF
Recombinate Factor VIII		
Bioclate (*Centeon*)	Recombinant DNA product	Highest purity
Trace amounts of murine, hamster, and bovine protein		
Helixate (*Centeon*)	Recombinant DNA product	Highest purity
Trace amounts of murine and hamster protein		
Kogenate (*Bayer Biological*)	Recombinant DNA product	Highest purity
Trace amounts of murine and hamster protein		
Recombinate (*Baxter-Hyland*)	Recombinant DNA product	Highest purity
Trace amounts of murine, hamster, and bovine protein		

Description—Lyophilized powder consisting of a glycoprotein of molecular weight 58,000 that has a pH of 6.0 to 7.5 upon reconstitution.

Uses—Administered to patients with hereditary AT III deficiency prior to surgical or obstetrical procedures or when they suffer from thromboembolism. AT III is the major plasma inhibitor of thrombin because of its covalent binding with the active residue of thrombin forming an inactive complex. AT III also inactivates other components of the coagulation cascade including Factors IXa, Xa, XIa, and XIIa. The neutralization rate of these serine proteases is relatively slow but is greatly accelerated in the presence of heparin. The hereditary deficiency of AT III may result in spontaneous episodes of thrombosis and pulmonary embolism, and these risks are increased with age, surgery, pregnancy, or delivery. To either treat or prevent acute thrombotic events, the AT III level should be raised to normal and maintained at this level for 2 to 8 days, depending on the treatment indication as well as the patient's medical condition. In some situations such as hemorrhage or acute thrombosis, following surgery, or concomitant heparin therapy, the half-life of AT III may be decreased, so plasma levels should be monitored more frequently, and dosage or frequency of drug administration adjusted as necessary.

Dose—*Intravenous* administration of 1 U/kg raises the level of AT III by 1% to 2%, depending on the patient's condition. The loading dose should be determined on an individual basis, based on the pretherapy AT III level, to achieve the level found in normal plasma, using the following formula:

$$\text{Dosage units} = \frac{[\text{Desired AT III level (\%)} - \text{baseline AT III level (\%)}] \times \text{weight (kg)}}{1.4}$$

This formula is based on an expected incremental increase of 1.4% per IU/kg administered. As the increase varies among patients, it is essential to measure AT III levels preceding and 20 min postinfusion so that subsequent doses can be adjusted if necessary on the basis of the initial dose effect. Plasma levels of AT III should be monitored initially at least twice daily until the patient is stabilized and thereafter once every 24 hr with the goal of keeping plasma AT III levels above 80%. Levels should always be obtained before the next infusion of Thrombate III. Plasma levels between 80% and 120% usually are maintained by dosing every 24 hr with 60% of the initial loading dose. These recommendations are a general guideline for therapy, and adjustments in the maintenance dose and dosing intervals should be based on the actual AT III levels achieved. The suggested rate of infusion is 50 IU/min and should not exceed 100 IU/min.

ANTI-INHIBITOR COAGULANT COMPLEX

Autoplex; Feiba

A cryodesiccated complex of activated and precursor clotting factors and factors of the kinin-generating system that is prepared from pooled human plasma. It is standardized by its ability to restore normal clotting time to Factor VIII–deficient plasma. One correctional unit will correct the clotting time to 35 sec in the ellagic acid-APTT test. The complex is reconstituted with Sterile Water for Injection. There should be no more than 2 U/mL of heparin and 0.02 *M* citrate after reconstitution.

Uses—As an alternative treatment for hemorrhagic diathesis in patients with titers of Factor VIII inhibitors above 5 Bethesda Units/mL only after the failure of conventional treatment. It is contraindicated when signs of fibrinolysis or disseminated intravascular coagulation exist. It may cause transient hypofibrogenemia in children, so fibrinogen levels should be monitored in young patients. Headache, flushing, tachycardia, and hypotension may result from too-rapid infusion. It is not free of the risk of serum hepatitis.

Dose—*Intravenous, initially* 25 to 100 U/kg, to be adjusted according to APTT 30 min after the end of infusion. The infusion rate should not exceed 10 mL/min.

FACTOR IX COMPLEX

Konyne

A preparation of pooled human plasma protein fraction containing clotting Factors II, VII, IX, and X and low levels of Factor VIII. The preparation is standardized in terms of Factor IX; the activity is one International unit (IU) of Factor IX, which is approximately equal to the level of Factor IX found in 1.0 mL of fresh normal plasma.

Preparation—See US Pat 3,717,708.

Description—White powder with a slight odor; fairly stable in light and air but unstable in heat. After reconstitution, solutions are stable up to 3 hr at room temperature; however, they should only be prepared immediately before use.

Solubility—Soluble in water.

Comments—Principally, as a source of Factor IX for the treatment of hemophilia B, a form of hemophilia separate and distinct from the more prevalent hemophilia A, or classic Factor VIII–deficient hemophilia. It can be used for the treatment of bleeding episodes in patients with hemophilia A (Factor VIII deficient) who have inhibitors to Factor VIII. Unlike earlier preparations, which were associated with a significant risk of posttransfusion hepatitis, the heat treatment employed in the preparation is thought to reduce the incidence of infectious transmission substantially. It also can be used in the treatment of congenital deficiencies of the other vitamin K–dependent coagulation factors, namely, Factors II, and X.

See Table 67-4.

Anticoagulants

Anticoagulants are substances or drugs that delay blood coagulation. They are of three general types.

Calcium Sequestering Agents—Calcium is essential to several steps in the clotting process; hence, its removal prevents clotting. The calcium-sequestering agents tie up calcium and other divalent cations; these agents are employed only in withdrawn blood. Thus, they find their most common use in anticoagulant solutions used by blood banks. These substances act rapidly, and their effect can be overcome rapidly by adding or

Table 67-4. Factor IX Products

PRODUCT	PURIFICATION METHOD	PURITY
Human Factor IX complexes		
Bebulin VH (*Immuno*)	2-step vapor heat treatment of 10 hr at 60° plus 1 hr at 80°	Hepatitis safety
Low Factor VII		
Konyne-80 Factor IX Complex (*Bayer Biologicals*)	Heat-treated for 72 hr at 80°	Low risk for HIV and hepatitis transmission
Low Factor VII		
Profilnine SD (*Alpha Therapeutics*)	Solvent and detergent (TNBP and polysorbate 80)	Reduced risk for HIV and hepatitis transmission
Low Factor VII		
Proplex T Factor IX Concentrate[a] (*Baxter-Biotech*)	Heat-treated for 144 hr at 60°	Risk for hepatitis and HIV seroconversion
Purified Factor IX products		
Alpha Nine SD (*Alpha Therapeutics*)	Affinity chromatography and solvent and detergent treatment	Hepatitis safety
Mononine (*Centeon*)	Monoclonal antibody and ultrafiltration	Hepatitis safety and low HIV risk
Trace amounts of murine protein		
Recombinant Factor IX		
BeneFIX (*Genetics Institute*)	Recombinant DNA product	Highest purity
Very low/no risk of viral transmission		

[a] Also indicated for Factor VII deficiency.

otherwise restoring calcium to normal. Thus, citrate-containing blood is, in effect, recalcified on transfusion back into the bloodstream.

Heparin and Heparin Substitutes—These agents combine with AT III. The complex then interacts with certain activated clotting factors, namely, Factors IX, X, XI, and XII, to prevent the conversion of prothrombin to thrombin. In high concentrations the complex interacts with thrombin and inhibits its effects to promote conversion of fibrinogen to fibrin. They inhibit the aggregation of platelets. They are fast-acting drugs. Heparin has the advantage of being a naturally occurring substance.

Prothrombopenic Anticoagulants (Oral Anticoagulants)—In this group dicumarol provides the prototype of action but not necessarily of structure. Prothrombopenic anticoagulants competitively inhibit vitamin K in the hepatic production of prothrombin (Factor II), the plasma content of prothrombin thus is reduced, and blood coagulation is impaired. These drugs also suppress formation of Factors VII, IX, and X, although the effect on prothrombin is the predominant one. Drugs in this category are slow acting because their effect is directed at inhibition of protein synthesis, and there is a latency determined by the long half-life (about 60 hr) of prothrombin. By the same token, their action is overcome only slowly by vitamin K.

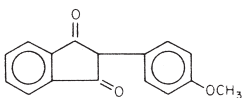
The heparin and prothrombopenic anticoagulants generally are not employed for the same purpose, since chronic medication with heparin is expensive and entails the nuisance of parenteral administration. Rather, they may be complementary, heparin being employed acutely or initially, and prothrombopenic anticoagulants being employed for longer-term therapy. Anticoagulants should be used with extreme caution in disease states in which there is an increased risk of hemorrhage. These include severe uncontrolled hypertension, acute bacterial endocarditis, congenital or acquired bleeding disorders, active ulcerative disease, and stroke, periods shortly after brain, spinal, or ophthalmological surgery, and postoperative indwelling epidural catheter use.

The enzymes urokinase and streptokinase are not true anticoagulants, although their effects to increase the fibrinolytic activity of blood have the effect of retarding red thrombus formation.

PROTHROMBOPENIC ANTICOAGULANTS

ANISINDIONE

Miradon



[117-37-3] $C_{16}H_{12}O_3$ (252.27).

Preparation—By rearrangement of 3-(*p*-methoxybenzylidene) phthalide. US Pat 2,899,359.

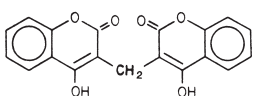
Description—White or off-white, crystalline powder.

Solubility—Practically insoluble in water.

Comments—A prothrombopenic anticoagulant with actions and uses similar to those of *Dicumarol*. It is reserved for patients who cannot tolerate coumarins. Its onset of action is 24 to 72 hr, and duration of action is ordinarily 3 to 5 days. The effective dose and duration of action are affected by factors including dietary intake, bacterial synthesis of vitamin K, and concurrently administered drugs that affect the hepatic microsomal drug-metabolizing system. Agranulocytosis, dermatitis, and hepatitis have occurred in patients on this drug, so blood studies and liver function tests need to be performed periodically. If fever or dermatitis appears, the drug should be discontinued because of the possible danger of blood dyscrasias. As with other oral anticoagulants, the bleeding risk is increased and dose-related. Patients should be advised to have periodic coagulation testing. Overdoses can be antagonized with phytonadione (vitamin K_1) but there is a long delay before prothrombin levels return to a safe range. It may cause some orange discoloration of urine that may obscure onset of hematuria, an important sign of impending hemorrhage; the color disappears on acidification. Hemorrhagic complications, including hemorrhagic necrosis, and drug interactions are as for *Dicumarol*. The drug is contraindicated in pregnancy because of its teratogenic effects.

DICUMAROL

2*H*-1-Benzopyran-2-one, 3,3′-methylenebis[4-hydroxy-, Biscumarol; Bishydroxycoumarin; Dicumarol



3,3′-Methylenebis[4-hydroxycoumarin] [66-76-2] $C_{19}H_{12}O_6$ (336.30).

Preparation—Methyl acetylsalicylate is stirred with sodium, thus effecting ring closure through demethanolation to form the sodium derivative of 4-hydroxycoumarin. Treatment with HCl liberates 4-hydroxycoumarin, which readily forms methylenebishydroxycoumarin on heating with formaldehyde and water.

Description—White or creamy white, crystalline powder, with a faint, pleasant odor and a slightly bitter taste; melts at about 290°.

Solubility—Practically insoluble in water, alcohol, or ether; slightly soluble in chloroform; readily soluble in solutions of fixed alkali hydroxides.

Comments—A *prothrombopenic anticoagulant*. It depresses hepatic production of prothrombin, probably by competing with vitamin K, both for transportation into liver cells and at the major site of vitamin K–dependent synthesis of clotting factors; the resultant lowering of the blood level of prothrombin renders the blood less coagulable. The plasma levels of VII, IX, and X also are depressed; indeed, in some persons the major effect of dicumarol is upon these factors. Plasma levels of Factor VII are the first to fall, since it has a half-life of about 6 hr; the half-lives of Factors IX, X, and II (prothrombin) are 20, 40, and 60 hr, respectively.

It has advantages over heparin for ambulatory and prolonged anticoagulant therapy in that it is *orally effective*, has a longer duration of action (2–7 days; plasma half-life, about 8.2 hr at low doses, but up to 30 hr at high doses), and is considerably less expensive. It is unsuitable for short-term or emergency therapy in that the maximal effect of a full initial dose does not occur for 48 to 96 hr after administration, which reflects both the long half-life of prothrombin and the slow onset of the steady state. During the period of onset of action, heparin may be given. This drug or one of its congeners is employed for long-term therapy to a much greater extent than heparin. Patients must have their therapy monitored by frequent prothrombin tests, preferably with the International Normalized Ratio (INR), to avoid thrombosis or hemorrhage due to under- or overcoagulation. It may be used in the treatment of the following: *pulmonary embolism,* to prevent further embolism; primary acute and postoperative *thrombophlebitis* and *traumatic injuries to blood vessels,* to forestall *venous thrombosis* and to prevent *thromboemboli;* sudden *arterial occlusion from thrombosis or embolism;* prophylaxis of *postoperative venous thrombosis or embolism or vascular surgery,* and prophylaxis after mechanical prosthetic valves or tissue heart valves.

In the absence of specific contraindications, it frequently is used routinely in acute *coronary thrombosis* with myocardial infarction. It also is advocated in the treatment of chronic diseases that predispose to thrombi or emboli, such as congestive heart failure, persistent phlebitis migrans, recurrent thrombophlebitis, recurrent coronary thrombosis, and atrial fibrillation. However, the exact status of such long-term therapy is undetermined.

The aim of treatment is to maintain the blood prothrombin activity at a level of 15% to 25% of normal. The onset of action is 1 to 5 days; the duration is 2 to 10 days.

With the recommended dosage, the incidence of hemorrhage is 2% to 4%, and strict laboratory control is mandatory to prevent hemorrhagic diatheses. Bleeding is most common from the mucous membranes, skin, gastrointestinal tract, urogenital tract, and uterus. Stools should be monitored for occult blood loss and urine for hematuria. Hemorrhage can be arrested by vitamin K (which has a latency), fresh frozen plasma, whole blood, or Factor IX concentrate (which contains prothrombin along with other vitamin K–dependent coagulation factors).

Other side effects include anorexia, nausea, vomiting, and diarrhea. Rarely, there may be hypersensitivity reactions, such as purpura; alopecia; urticaria; necrosis of the skin, breast, and genitals; and purple coloration of the toes. Tissue necrosis has been associated with protein C deficiency and may be minimized by concurrent heparin therapy for the first 5 to 7 days of treatment. Protein C, a plasma glycoprotein, is a vitamin K–dependent factor that upon activation functions as an endogenous anticoagulant.

It has perhaps the most drug interactions of any commonly prescribed agent, as well as being affected by the nutritional and health status of the patient, all of which may lead to unpredictable results. Therefore, whenever a patient on this drug is subjected to a new drug regimen or an old drug is withdrawn, it is essential that the patient's prothrombin time be monitored and the dosage of dicumarol be adjusted if necessary.

Drug interactions occur in various ways. Mechanisms of antagonism and offending drugs are as follows (*italics* indicate the most-important clinical interactions):

Interference with absorption: *griseofulvin, cholestyramine,* clofibrate.
Stimulation of synthesis of clotting factors: *vitamin K,* glucocorticoids, estrogens.
Induction of hepatic enzymes: *barbiturates, ethchlorvynol,*

glutethimide, carbamazepine, griseofulvin, meprobamate, phenytoin, rifampin.

Mechanisms of increasing the response to dicumarol, and the offending drugs are as follows:

Displacement from plasma protein: *aspirin, chloral hydrate* (as the trichloroacetate metabolite), *clofibrate,* diazoxide, ethacrynic acid, mefenamic acid, nalidixic acid, phenylbutazone and hydroxyphenylbutazone, long-acting sulfonamides.
Inhibition of hepatic metabolism: *chloramphenicol, clofibrate,* oral hypoglycemics, *cimetidine*, *disulfiram*, allopurinol, mercaptopurine, methylphenidate, nortriptyline.
Decrease in availability of vitamin K: *anabolic steroids, broad-spectrum antibiotics, clofibrate, cholestyramine, mineral oil,* D-thyroxine.
Inhibition of synthesis of clotting factors: acetaminophen, *anabolic steroids, glucagon,* mercaptopurine, *quinidine, salicylates*.
Increased catabolism of clotting factors: *anabolic steroids, D-thyroxine*.
Increased binding affinity to receptor enzyme: D-thyroxine.
Additivity of anticoagulant effects: *heparin, salicylates,* quinidine.

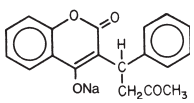
A complete table of interactions may be found in *USP DI*.

The drug is contraindicated if laboratory facilities are unavailable for determining prothrombin levels, and vitamin K, fresh blood, or plasma is not available. It also is contraindicated in any person with hemorrhagic tendencies, blood dyscrasias, peptic ulcer, ulcerative colitis, colitis, diverticulitis, subacute bacterial endocarditis, recent operations on the central nervous system (CNS), regional or lumbar block anesthesia, and severe renal or liver disease. Not only is it contraindicated in threatened abortion, but it should be withheld in pregnancy, since hemorrhage in the fetus can occur, and several teratogenic abnormalities including hydrocephaly, microcephaly, optic atrophy, other CNS defects, nasal hypoplasia, and chondrodysplasia punctata have been attributed to the drug. Patients with congestive heart failure are more sensitive to dicumarol than persons with normal cardiac function.

It is metabolized by the hepatic cytochrome P450 system. The half-life is 24 to 96 hr.

WARFARIN SODIUM

2*H*-1-Benzopyran-2-one, 4-hydroxy-3-(3-oxo-1-phenylbutyl)-, sodium salt; Coumadin; Panwarfin



3-(α-Acetonylbenzyl)-4-hydroxycoumarin sodium salt [129-06-6] $C_{19}H_{15}NaO_4$ (330.31); an amorphous solid or a crystalline clathrate. The clathrate consists principally of sodium warfarin, isopropyl alcohol, and water, the molecular proportions of which vary between 8:4:0 and 8:2:2.

Preparation—By addition of 4-hydroxycoumarin to benzalacetone under the catalytic influence of a mildly basic substance such as ammonia or piperidine. The reaction is a typical Michael *condensation.* Conversion to the sodium salt is effected by reacting purified warfarin with an equimolar portion of dilute NaOH solution at room temperature.

Description—White, odorless, amorphous or crystalline powder with a slightly bitter taste; discolored by light; pH (1 in 100 solution) 7.2 to 8.3.

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

Comments—The most widely used *prothrombopenic anticoagulant* (see *Dicumarol*). Although usually it is administered orally, its chief distinction from other prothrombopenic drugs is the fact that it is water-soluble and may be administered intravenously. By the intravenous route its onset of action is 12 to 18 hr, and its duration is 5 to 6 days. It is metabolized by the hepatic cytochrome P-450 system. The plasma half-life is 41 to 57 hr, except about 27 hr in alcoholics and probably even less in persons using phenobarbital or other hepatic microsomal enzyme inducers.

The hemorrhagic complications, precautions, and drug interactions are those of *Dicumarol*. Influenza vaccine increases the response; this interaction probably occurs also with dicumarol and anisindione.

Dose—*Oral, intramuscular,* or *intravenous,* adults, 10 to 15 mg for 2 to 4 days, followed by a daily *maintenance* dose of 2 to 10 mg, according to the prothrombin time. A prothrombin time 1.2 to 1.5 times the control time is effective for anticoagulation yet is associated with an incidence of hemorrhage of only 4.3%.

NONPROTHROMBOPENIC ANTICOAGULANTS

ANTICOAGULANT CITRATE DEXTROSE SOLUTION MODIFIED

ACD Solution Modified

Each sterile 10 mL contains 80 mg citric acid, 224 mg anhydrous sodium citrate, and 120 mg anhydrous dextrose.

Comments—It is used with *Sodium Chromatic Cr 51 Injection* for the labeling of erythrocytes in *in vitro* and *in vivo* diagnostic tests.

ANTICOAGULANT CITRATE DEXTROSE SOLUTION

ACD Solution

A sterile solution of citric acid ($C_6H_8O_7$), sodium citrate ($C_6H_5Na_3O_7.2H_2O$), and dextrose ($C_6H_{12}O_6.H_2O$) in water for injection. It contains no antimicrobial agents.

Preparation—See the USP.

Comments—The citrate chelates calcium ions and thus acts as an anticoagulant. The ratio of citric acid to sodium citrate is such that the pH is optimal for storage of whole blood. The dextrose provides a substrate for glycolysis during storage, thus extending the lifetime of the erythrocytes. The expiration time of whole blood anticoagulated with ACD solution is 21 days. The sterile solution is employed mainly for the anticoagulation and preservation of whole blood for transfusion.

ANTICOAGULANT CITRATE PHOSPHATE DEXTROSE SOLUTION

CPD Solution

A sterile solution of citric acid ($C_6H_8O_7$), sodium citrate ($C_6H_5Na_3O_7.2H_2O$), sodium biphosphate ($NaH_2PO_4.H_2O$), and dextrose ($C_6H_{12}O_6.H_2O$) in water for injection. It contains no antimicrobial agents.

Preparation—See the USP.

Description—Clear, colorless, odorless liquid; pH 5.0 to 6.0.

Comments—Citrate ion chelates calcium, thus making calcium unavailable to the coagulation system. Citric acid, sodium citrate, and sodium biphosphate are in the proper proportions to buffer the solution at the optimal pH for the storage of blood and its components. Dextrose provides a substrate for glycolysis and increases both storage and post-transfusion lives of blood cells. The expiration time of whole blood with CPD solution is 21 days. The 2,3-diphosphoglycerate (2,3-DPG) content of erythrocytes stored in CPD solution is 120% of the original content at 7 days and 40% at 21 days. The preservation helps keep the oxygen affinity of hemoglobin low so that it can yield its oxygen readily to the tissues. Consequently, CPD is the preferred anticoagulant for blood to be used for exchange transfusion.

The sodium concentration is 284 mEq/L, and 17.8 mEq is thus added to each unit of whole blood.

ANTICOAGULANT SODIUM CITRATE SOLUTION

A sterile 4% solution of sodium citrate $C_6H_5Na_3O_7H_2O$ (294.10) in water for injection. It contains no antimicrobial agents.

Preparation—Dissolve 40 g sodium citrate in sufficient water for injection to make 1000 mL, and filter until clear. Place the solution in suitable containers, and sterilize.

Note—Anhydrous sodium citrate (35.1 g) may be used instead of the dihydrate.

Description—Clear, colorless solution possessing a slightly saline taste; pH 6.4 to 7.5.

Comments—Prevents clotting of blood by forming an undissociated calcium citrate chelate. The solution also prevents either crenation or swelling of the cells. The sterile solution is employed for preparation of blood for fractionation, for banked blood for transfusion, and for preparation of citrated human plasma.

EDETATE DISODIUM—page 1343.

ANTICOAGULANT CITRATE PHOSPHATE DEXTROSE ADENINE SOLUTION

CPDA-1 Solution; CPD-Adenine Solution

Comments—The addition of adenine to CPD solution increases the storage life of blood by 40%, that is, blood can now be stored for 35 days. However, CPDA-1 solution does not preserve 2,3-diphosphoglycerate as well as does CPD solution; there is 97% of the initial content at 7 days but only 10% at 21 days. Therefore, CPDA-1 whole blood should not be used in exchange transfusion.

Application—14 mL per 100 mL of whole blood.

DANAPROID SODIUM

Orgaran

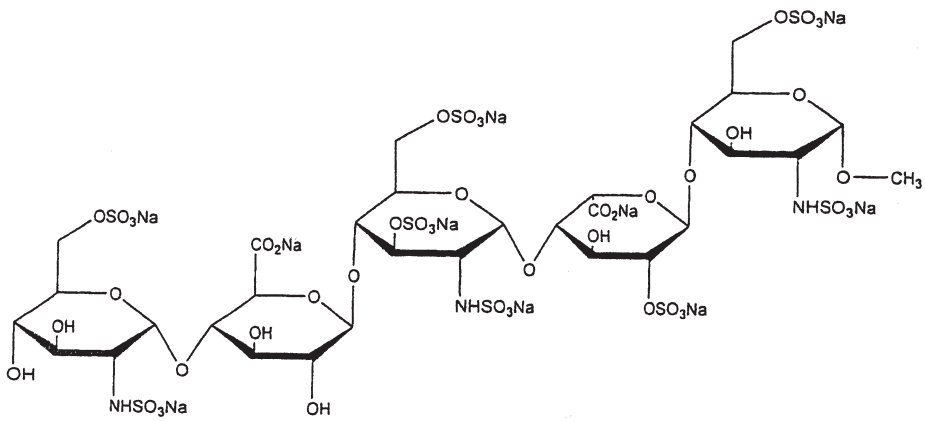
Preparation—It is extracted from porcine mucosa and has an average molecular weight of approximately 5500.

Description—Danaproid consists of heparan sulfate (84%), dermatan sulfate (12%), and a small amount of chondroitin 4- and 6-sulfates (4%) as the sodium salts.

Comments—It is an antithrombotic that acts via antithrombin III to inhibit both Factor Xa and thrombin, with additional inhibitory effect on thrombin through heparin cofactor II. Its predominant inhibitory effect is exerted on Factor Xa with the anti-Xa and antithrombin ratio of >22. It has little effect on clotting tests (ie, the partial thromboplastin time [PTT] or prothrombin time [PT]) so they are not useful for monitoring therapy with this drug. It has only minor effects on platelet function and aggregability. It is indicated for the prophylaxis of postoperative deep venous thrombosis, which may lead to pulmonary embolism in patients undergoing elective hip replacement therapy. The drug is administered by subcutaneous injection. As with other anticoagulant agents, bleeding and hemorrhage are the major adverse events, and patients must be monitored carefully while on the medication. There is no evidence that protamine sulfate is able to reduce severe nonsurgical bleeding due to danaproid. In the event of serious bleeding the drug should be discontinued and transfusion of blood or blood products administered. As the agent includes sodium sulfite as a preservative, allergic type reactions including mild-to-severe asthmatic symptoms or anaphylaxis can occur with this drug. The sulfite sensitivity is more common in asthmatic than nonasthmatic patients.

FONDAPARINUX SODIUM

α-D-Glucopyranoside, methyl *O*-2-deoxy-6-*O*-sulfo-2-(sulfoamino)-α-D-gluco-pyranosyl-(1→4)-*O*-β-D-glucopyranuronosyl-(1→4)-*O*-2-deoxy-3,6-di-*O*-sulfo-2-(sulfoamino)-α-D-glucopyranosyl-(1→4)-*O*-2-*O*-sulfo-α-L-idopyranuronosyl-(1→4)-2-deoxy-2-(sulfoamino)-, 6-(hydrogen sulfate), decasodium salt; Arixtra



[114870-03-0] $C_{31}H_{43}N_3Na_{10}O_{48}S_8$ (1728.08).

Preparation—US Pat 4,818,816 (1989) and *Mini Rev Med* 2004:4; 207–233.

Description—White, lyophilized powder; $[\alpha]^{23}/_D$ +48° (c = 0.61, water).

Comments—The antithrombotic activity of fondaparinux sodium is the result of antithrombin III (ATIII)-mediated selective inhibition of Factor Xa. By selectively binding to ATIII, fondaparinux sodium potentiates (about 300 times) the innate neutralization of Factor Xa by ATIII. Neutralization of Factor Xa interrunpts the blood coagulation cascade and thus inhibits thrombin formation and thrombus development.

Fondaparinux sodium does not inactivate thrombin (activated Factor II) and has no known effect on platelet function. At the recommended dose, fondaparinux sodium does not affect fibrinolytic activity or bleeding time.

LOW-MOLECULAR-WEIGHT HEPARINS

Ardeparin, Dalteparin, Enoxaparin, Fragmin, Lovenox, Normiflo

There are several products consisting of a mixture of low-molecular-weight fragments of heparin obtained by the depolymerization of unfractionated porcine heparin. Ardeparin contains fragments of 5650 to 6350 daltons, Dalteparin contains fragments of 2000 to 9000 daltons, and Enoxaparin contains fragments of 2000 to 8000 daltons.

Comments—Standard heparin forms a ternary complex with AT III and thrombin, whereas the low-molecular-weight heparins form primarily binary complexes with AT III. This results in enhanced inhibition of Factor Xa, with less inhibitory effect on thrombin. As with heparin, these agents also inhibit thrombin by binding to heparin cofactor II. As small heparin molecules bound to AT III react only slightly with platelets, deep vein thrombosis can be prevented or retarded without as much risk of hemorrhage as with standard heparin.

Ardeparin is indicated for the prevention of deep vein thrombosis that may lead to pulmonary embolism in patients following knee replacement therapy. Dalteparin is indicated for the prophylaxis of deep venous thrombosis in patients undergoing abdominal surgery who are at risk for thromboembolic complications, ie, those over age 40, obese, having general anesthesia lasting more than 30 min, or those with a malignancy or previous history of thrombosis.

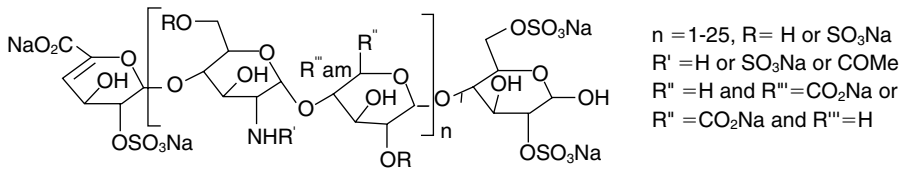
Enoxaparin is indicated for the prevention of deep venous thrombosis in patients undergoing hip or knee replacement therapy as well as for patients undergoing abdominal surgery who are at risk for thromboembolic complications. These agents have also been used (off-label) for systemic anticoagulation for both primary and secondary prophylaxis against thromboembolic events. These drugs are administered by subcutaneous injection only. The incidence of hemorrhagic complications is lower than with standard heparin; however, protamine sulfate is useful in treating patients who do experience hemorrhagic events. The concomitant use of antiplatelet agents or oral anticoagulants may increase the risk of hemorrhage.

These drugs should be administered with particular caution in patients who have a history of heparin-induced thrombocytopenia. In addition, there have been cases of epidural or spinal hematomas causing long-term or permanent paralysis with the use of low-molecular-weight heparins or heparinoids in patients undergoing spinal or dural anesthesia. The risk appears to be increased by repeated epidural or spinal puncture, by the use of indwelling epidural catheters, or by concomitant use of other drugs affecting hemostasis.

TINZAPARIN SODIUM

Tinzaparin sodium; Innohep, Logiparin

[9041-08-1].



Preparation—A low molecular weight heparin prepared by enzymatic depolymerization of porcine mucosal heparin with Flavobacterium heparinum. The reaction is followed using UV absorption (230-235 nm) and refractive index of a filtered portion of the medium to determine when the desired molecular weight is achieved.
US Pat 5,106,734 (1992).

Description—Average MW ranges from 5.5 to 7.5 kDa with 10% less than 2 kDa, 60% to 70% in the 2 to 8 kDa range and 22% to 36 % more than 8 kDa.

Comments-Tinzaparin sodium is a low molecular weight heparin with antithrombotic properties. Tinzaparin sodium inhibits reactions that lead to the clotting of blood including the formation of fibrin clots, both *in vivo* and *in vitro*. It acts as a potent co-inhibitor of several activated coagulation factors, especially Factors Xa and IIa (thrombin). The primary inhibitory activity is mediated through the plasma protease inhibitor, antithrombin.

Bleeding time is usually unaffected by tinzaparin sodium. Activated partial thromboplastin time (aPTT) is prolonged by therapeutic doses of tinzaparin sodium used in the treatment of deep vein thrombosis. Prothrombin time (PT) may be slightly prolonged with tinzaparin sodium treatment but usually remains within the normal range. Neither aPTT nor PT can be used for therapeutic monitoring of tinzaparin sodium.

Neither unfractionated heparin nor tinzaparin sodium have intrinsic fibrinolytic activity; therefore, they do not lyse existing clots. Tinzaparin sodium induces release of tissue factor pathway inhibitor, which may contribute to the antithrombotic effect. Heparin is also known to have a variety of actions that are independent of its anticoagulant effects. These include interactions with endothelial cell growth factors, inhibition of smooth muscle cell proliferation, activation of lipoprotein lipase, suppression of aldosterone secretion, and induction of platelet aggregation.

HEPARIN SODIUM

Heparin

A mixture of active glycosaminoglycans, having the property of prolonging the clotting time of blood. It usually is obtained from bovine or porcine lung tissue or intestinal mucosa. Potency: not less than 120 (when derived from lungs) and not less than 140 (when derived from other tissues) USP Heparin Units/mg.

Note—USP Heparin Units consistently are established on the basis of the USP assay, independently of International Units, and the respective units are not equivalent.

Preparation—Heparin is the body's natural anticoagulant, taking part in the physiological function of maintaining the fluidity of the blood. It is produced by the mast cells of Ehrlich, which are clustered in the perivascular connective tissue of the walls of major blood vessels and capillaries. Heparin is a polysulfuric ester of mucoitin. The molecular skeleton is constructed from acetylated glucosamine and glucuronic acid. The disaccharide unit is similar to that in *mucoitin sulfuric acid* and *hyaluronic acid*. Protein-free samples of heparin contain about 10% sulfur, present as ester sulfates. Original preparations of heparin contain mixtures consisting of mucoitin disulfuric and trisulfuric acids. The anticoagulant action is greater in preparations with the highest sulfuric content. Heparin in the final, therapeutic form is supplied in a solution made from the sodium salt, but in the steps of its purification the barium salts of heparin are prepared. Heparin, being a mixture of the several sulfuric esters, is not entirely homogeneous, and there is debate as to whether a truly crystalline or homogeneous preparation has been or ever can be prepared.

Description—White or pale-colored amorphous powder; odorless, or nearly so; hygroscopic. The molecular weight may vary from 6000 to 20,000, depending on the source and on the method used to determine the molecular weight. pH (1% solution) 5.0 to 7.5. It will not dialyze through a parchment membrane and only slightly through a collodion membrane. Heparin is resistant to all kinds of chemical agents, gives an insoluble precipitate with protamine and with toluidine blue, and interference with the sulfuric groups reduces its anticoagulant activity. It has a very low osmotic pressure in respect to its high degree of ionization. In contrast to the effect of oxalate, it has no osmotic influence on red blood cells. It may be stored for long periods without loss of activity.

Solubility—1 g in 20 mL of water; soluble in alcohol, acetone, or glacial acetic acid.

Comments—Its anticoagulant actions are described on page 1328. In addition, it releases lipoprotein lipase from the vascular endothelium, which has the effect of clearing chylomicrons and very-low-density lipoproteins from blood; only low doses are needed for this action. It has antiatherogenic activity, but only a few studies of its prophylactic efficacy have been made. It also has anti-inflammatory and antiallergy actions through its effects on the Hageman factor (XIIa), kallikreins, and other enzymes that have active groups containing or acting on substrates with lysine and/or arginine moieties.

It is employed clinically in conditions in which a rapid reduction in the coagulability of the blood is desired. It often is employed to initiate prolonged anticoagulant therapy to cover the latent period of onset of action of dicumarol-type anticoagulants. It also is used in lieu of dicumarol-type drugs in prolonged therapy when laboratory facilities are unavailable for determination of prothrombin time.

Some of the primary clinical applications are the treatment and prevention of *pulmonary embolism, prevention of mural thrombosis* after myocardial infarction, *initial treatment of deep-vein* and *proximal-vein thrombosis,* primary and postoperative *thrombophlebitis,* sudden *arterial occlusion* from thrombosis or embolism, prophylaxis of postoperative *venous thrombosis* or embolism, *prevention of cerebral thrombosis* during evolving stroke and after *vascular surgery*. For these purposes, low doses given subcutaneously are popular; however, recent reports indicate that blood levels are erratic, and monitoring is advisable. It is indicated for treatment of *diffuse intravascular coagulation* (DIC; consumptive coagulopathy) in patients with acute leukemia (only) and *immune thrombocytopenia* (in which vasculitis causes coagulopathy and consumption of platelets).

It sometimes is given during and after conversion of atrial fibrillation to prevent thrombosis from emboli and mural thrombi. It is recommended that myocardial infarction patients be treated with heparin for 24 to 72 hr following fibrinolytic therapy to reduce the risk of early reocclusion.

The indications for prolonged therapy are the same as with prothrombopenic anticoagulants (see *Dicumarol*), but usually this drug is used only during the early stages of treatment when the disorder is acute, to keep blood clotting suppressed until oral anticoagulants can be given and take effect. It also has special uses, such as prevention of clotting of blood samples or whole blood for transfusion; *prevention of clotting* during *blood transfusions*, *extracorporeal hemodialysis*, or *cardiopulmonary bypass*; and for the heparin tolerance test.

It is used in low concentrations in solutions for flushing intravenous catheters for intermittent injections; the residual heparin in the catheter keeps clots from occluding the catheter orifice. It also is used to prevent pleural and peritoneal *adhesions*. Sometimes it is used as an adjuvant to antineoplastic therapy to suppress formation of a fibrin network through which the neoplasm can spread.

Constant infusion appears to be more efficacious and safer than intermittent injection. Intramuscular injection often results in hematoma formation and should be avoided.

Hemorrhage is the principal toxic effect, usually the result of overdosage; protamine, with which it combines, may be employed for immediate control of hyperheparinemia. It must be administered cautiously when oral anticoagulants are in use or when there is thrombocytopenia, because of the enhanced risk of hemorrhage; it also interferes with laboratory tests for the effect of oral anticoagulants. The risk of hemorrhage also is increased by salicylates, dipyridamole, glyceryl guaiacolate, or other inhibitors of platelet adhesiveness.

Certain amine or ammonium compounds, especially bifunctional ones, interact with it directly and thus decrease the circulating levels in the blood; cimetidine, various antihistamines, quinine, and quinidine are examples. Even tetracyclines supposedly interact. Polymyxins and colistins are known to interact during simultaneous infusion but have not been reported to interact when administered separately.

Hypersensitivity and other adverse side effects may occur. Manifestations include bronchospasm (dyspnea, tightness in chest, wheezing), rash, urticaria, pruritus, chills, fever, vasospasm (chest pain, pain in extremities, priapism), neuropathy with paresthesias, and hair loss.

Thrombocytopenia occurs in up to 30% of patients, is often mild (platelet count remains $> 100{,}000/mm^3$), and may reverse or remain stable while heparin therapy continues. However, a more severe form of thrombocytopenia with platelet count $< 100{,}000/mm^3$ is accompanied by heparin resistance often leading to thromboembolism or DIC. Heparin therapy should be discontinued, and thromboembolic complications treated with lepirudin in such cases.

It is inactive orally and must be administered parenterally. Its plasma half-life is 1.3 to 1.6 hr.

POTASSIUM OXALATE

[583-52-8] $K_2C_2O_4.H_2O$ (183.23).

Description—Colorless crystals; effloresces in dry air.

Solubility—1 g in 3 mL water.

Comments—The oxalate anion of potassium oxalate combines with calcium ions to form the very insoluble calcium oxalate. Thus, when it is added to withdrawn (shed) blood it acts as an anticoagulant, for which purpose it may be employed in clinical laboratory procedures. Care must be exercised in its storage and use because it is highly toxic.

SODIUM CITRATE

1,2,3-Propanetricarboxylic acid, 2-hydroxy-, trisodium salt

$CH_2(COONa)C(OH)(COONa)CH_2COONa$

Trisodium citrate [68-04-2] $C_6H_5Na_3O_7$ (258.07) or trisodium citrate dihydrate [6132-04-3] (294.10).

Preparation—Usually, by adding sodium carbonate to a solution of citric acid until effervescence ceases, evaporating, and granulating the product.

Description—Colorless crystals or a white, crystalline powder; cooling, saline taste; stable in air; the aqueous solution is slightly alkaline to litmus but should not be reddened by phenolphthalein.

Solubility—1 g in 1.5 mL water at 25° or in 0.6 mL boiling water; insoluble in alcohol.

Comments—The most important use is as an *anticoagulant* for blood or plasma that is to be fractionated or for blood that is to be stored. The anticoagulant effect is due to conversion of ionized calcium in the blood to a citrato-calcium chelate. It is an ingredient of *Anticoagulant Citrate Dextrose Solution, Anticoagulant Citrate Phosphate Dextrose Solution,* and *Sodium Citrate and Citric Acid Solution*.

It also is used as an *expectorant* and a systemic and urine *alkalinizer*. Saline expectorants are useful especially when it is desired to liquefy thick, tenacious sputum. In the body sodium citrate is oxidized to bicarbonate and excreted in urine. Thus, when given orally it is useful in acidosis, to overcome excessive urinary acidity and to assist in the dissolution of uric acid nephroliths.

It is a chelating agent and thus increases *urinary excretion of calcium* and *lead*. It has been employed in hypercalcemia and urolithiasis and to facilitate elimination of lead in poisoning due to the latter. As a *pharmaceutic aid,* sodium citrate may be used to prevent darkening when iron is included in preparations containing tannin.

SODIUM OXALATE

[62-76-0] $Na_2C_2O_4$ (134.01). The actions and uses of sodium oxalate are virtually identical to those of *Potassium Oxalate*.

THROMBOLYTIC AGENTS

The fibrinolytic system comprises a group of proteins that complexly interact to cause the lysis of thrombi and also to keep the fibrinolytic factors in check. Plasminogen plays a key role in the activation of fibrinolysis. It is a proenzyme that is converted to the active enzyme, plasmin, by interactions among circulating intrinsic factors (prekallikrein; kininogens; Factors XII, XIIIa, and plasminogen proactivator and the extrinsic factor; endothelial tissue, which releases plasminogen activator (tissue plasminogen activator, tPA). Fibrinolytic activity is kept in check by the inhibitors, C1-*in*activator, α_2-macroglobulin and α_2-antiplasmin. Once formed, plasmin cleaves fibrin into its split-products. However, it also can degrade Factors V, VIII, and XII and other proteins. The rates of formation and inactivation of plasmin normally are balanced, such that there is always a small amount of fibrin being formed to maintain normal vascular integrity and the remainder is lysed before clots form. Vascular injury and inflammation increase both fibrin deposition and fibrinolytic activity.

In the early 1960s, a bacterial product called streptokinase-streptodornase was discovered to activate plasminogen. Subsequently, the active component, streptokinase (SK) has been purified sufficiently to permit clinical use in the dissolution of thrombi. Interest has been high, especially with respect to the ability to dissolve coronary thrombi and restore coronary perfusion. Timing is very critical, because once the fibrin has *aged* (more than 4 hr), very little dissolution occurs. Originally, administration was via the intracoronary route, requiring the placement of a coronary catheter. However, SK and other thrombolytic agents now are administered primarily IV with efficacy similar to that with intracoronary delivery and fewer bleeding complications due to the invasive procedure. SK presently still confers a considerably high risk of hypersensitivity reactions.

A natural plasminogen activator, urokinase (UK) was isolated and purified for the same uses as SK. It is free of allergic potential but has a slightly lower potential for generalized fibrinolyisis and hemorrhage than SK. It is several times more expensive. There are fewer clinical data concerning the long-term efficacy of UK in treating myocardial infarction, as intracoronary administration is no longer common. More recently, several other plasminogen activators have been isolated, characterized, and modified. They are anisoylated plasminogen-streptokinase activator complex (APSAC) and tissue plasminogen activator (tPA). APSAC is an inactive complex of human plasminogen and SK that is gradually deacylated and thus activated after injection. It has efficacy similar to that of intracoronary SK in achieving reperfusion and may be slightly superior in preventing reocclusion. APSAC's major advantage over SK is its ease of administration due to the prolonged half-life.

Both recombinant forms of tPA theoretically have considerably lesser tendencies to produce hemorrhage, because they bind selectively to fibrin and not to circulating clotting factors. Thus, they are selective for the intended target, a previously formed clot. They are not free of bleeding risk, however, because they attack the many microclots that constantly are forming at the sites of endothelial breaks, and clinical opinion is divided over whether there is a significant advantage over SK and UK in this respect. In fact, target selectivity creates a bleeding problem, in that clots tend to form around the intravenous catheters used for infusion, so that heparin also is infused to prevent this effect. Furthermore, their short half-lives favor rethrombosis unless heparin is coadministered. Anistreplase and the recombinant tPA products are considerably more expensive than SK or UK.

With respect to the treatment of coronary occlusion, there is very little difference in the percentage of reopened coronary arteries and reperfusion (65–70%) or in the reocclusion frequencies (about 20%) if treatment is begun earlier than 4 hr after occlusion. It is thought by some that the very short lifetime of infused tPA limits the concentration at the target, a situation that might be correctable by higher rates of infusion. There appears to be some advantage with recombinant tPA at later times, for reasons not altogether clear.

ABCIXIMAB

Immunoglobulin G, ReoPro, Centocor

[143653-53-6]

Description—It is the Fab fragment of the chimeric human-murine monoclonal antibody 7E3 produced in mammalian cell culture. The 47,615-dalton Fab fragment is purified in a series of steps from the cell culture supernatant.

Comments—It binds to the platelet glycoprotein IIb/IIIa receptor, resulting in inhibition of platelet aggregation by preventing the binding of fibrinogen, VWF, and other adhesive molecules to this receptor. In addition it binds to the vitronectin receptor that mediates the procoagulant properties of platelets as well as the proliferative response of smooth muscle and endothelial cells. It is indicated as an adjunct to percutaneous coronary intervention for the prevention of cardiac ischemic complications in patients undergoing percutaneous coronary intervention. In addition, it is recommended for use in patients with unstable angina not responding to conventional therapy when percutaneous coronary intervention is planned within 24 hr. The safety and efficacy of abciximab have only been evaluated with concomitant administration of conventional therapy with heparin and aspirin. It has the risk of bleeding complications, which can be significantly reduced by the use of low-dose, weight-adjusted heparin, by early femoral sheath removal, by careful patient and access-site management, and by weight adjustment of the abciximab infusion dose. It is contraindicated in patients with significant bleeding risk including those with active internal bleeding, recent GI or GU bleeding, bleeding diathesis, recent major surgery or trauma, or severe, uncontrolled hypertension. In addition to bleeding, thrombocytopenia is a common occurrence and most often occurs within the first 24 hr of therapy. Platelet counts should be monitored prior to dosing, at 2 to 4 hr following dosing, and at 24 hr after dosing or prior to discharge, whichever is first. If thrombocytopenia is verified, the drug should be discontinued immediately.

ALTEPLASE (RECOMBINANT)

Activase

[105857-23-6] $C_{2736}H_{4174}N_{914}O_{824}S_{45}$ (59,050.00).

Purified glycoprotein of a single, continuous chain containing 527 amino acids, with three carbohydrate side chains. The biological potency is determined by an *in vitro* clot lysis assay expressed in International Units as tested against a WHO standard. See Chapter 49.

Preparation—Using the complimentary DNA (cDNA) for natural human tissue-type plasminogen activator obtained from a human melanoma cell line. The enzyme alteplase is secreted into the culture medium by an established mammalian cell line (Chinese hamster ovary cells) into which the DNA for alteplase has been inserted genetically. It is harvested, purified by chromatography, and lyophilized.

Description—White to off-white powder.

Comments—Indicated for thrombolysis in patients with acute myocardial infarction (MI), to improve ventricular function, reduce the incidence of congestive heart failure, and reduce mortality. It should be ad-

ministered as soon as possible after the onset of symptoms. There is a standard and an accelerated dosing regimen, both of which also include concomitant administration of heparin and aspirin. The results of controlled studies comparing clinical outcomes with the two regiments are not currently available. The drug also is indicated for use in patients with acute massive pulmonary embolism when the diagnosis has been confirmed by objective means such as pulmonary angiography or lung scanning. Activase was approved in 1998 for the management of acute *ischemic* stroke in adults, for improving neurological recovery and reducing the incidence of disability. Treatment should only be initiated within 3 hr after the onset of stroke symptoms and after exclusion of intracranial hemorrhage by a cranial computerized tomography (CT) scan or other diagnostic imaging method sensitive to the presence of hemorrhage. Because of these stringent guidelines, there has been limited experience of therapeutic outcome in ischemic stroke patients treated with this drug. It is contraindicated if there is internal or external bleeding, arteriovenous malformation, aneurysm, severe hypertension, a history of cerebrovascular accident, recent (<2 months) trauma, or intracranial or spinal surgery. Adverse effects include nausea, vomiting, mild hypersensitivity reactions, fever, and bleeding. Part of the hemorrhage problem is the result of concomitant administration of heparin, which is given to prevent clots at the catheter tip and to decrease the reocclusion rate for MI patients. Alteplase is eliminated by the liver; the half-life is less than 5 min.

ANISTREPLASE

Eminase

[81669-57-0]

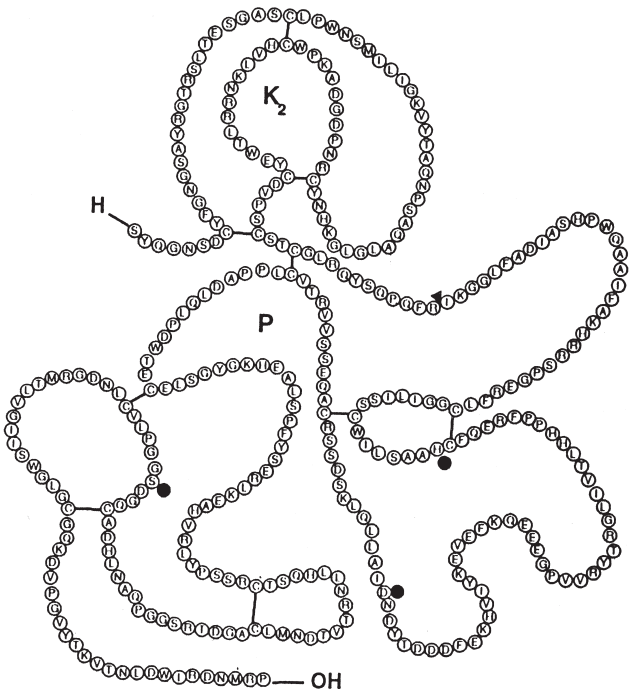
Preparation—By *p*-anisoylation of primary human lys-plasminogen SK complex (1:1) from Group C β-hemolytic streptococci.

Description—White to off-white powder.

Comments—Indicated for thrombolysis in patients exhibiting symptoms consistent with acute MI. Its comparison with SK is described above. Randomized, controlled studies comparing it with either placebo- or heparin-treated patients demonstrated that anistreplase significantly reduced mortality. As with other thrombolytics, it is contraindicated in patients with active internal bleeding, a history of cerebrovascular accident, recent intraspinal or intracranial surgery or trauma, severe hypertension, arteriovenous malformation, or aneurysm. Allergic type reactions including rash, bronchospasm, fever, angioedema, and anaphylaxis have been observed in patients receiving anistreplase and are similar in incidence to those with SK. Other reported adverse effects include facial flushing, nausea, vomiting, and muscle aches. The half-life of anistreplase is approximately 90 min, with a fibrinolytic activity duration of 4 to 6 hr after administration.

RETEPLASE

Retavase, 173-527-Plasminogen activator (human tissue type)



[133652-38-7]

Description—Nonglycosylated deletion mutant of tPA containing 355 of the 527 amino acids of native tPA; ie, amino acids 1–3 and 176–527. Occurs as a lyophilized powder.

Preparation—It is produced by recombinant DNA technology in *Escherichia coli,* and the protein is isolated as inactive inclusion bodies. It is converted into its active form by an *in vitro* folding process and purified by chromatography. Potency is expressed in units (U) using a reference standard that is specific for reteplase and is not comparable with units used for other thrombolytic agents.

Comments—It is indicated for use in the management of acute myocardial infarction in adults for the improvement of ventricular function, reduction of the incidence of congestive heart failure and reduction of mortality associated with myocardial infarction. The most common adverse reaction associated with reteplase administration is bleeding, and the drug is contraindicated in patients with significant bleeding risks. In addition, coronary thrombolysis may result in arrhythmias associated with reperfusion, and antiarrhythmic therapy should be readily available. Other adverse events include nausea and/or vomiting, hypotension, and fever. Reteplase is cleared primarily by the liver and kidney and has an effective half-life of 13 to 16 min.

STREPTOKINASE

Kabikinase; Streptase

[9002-01-1] Mol wt about 4700.

Preparation—A single-chain coenzyme obtained from cultures of the Group Cβ strain of *Streptococcus haemolyticus.* (*Methods Enzymol.* 1950; 19: 807.

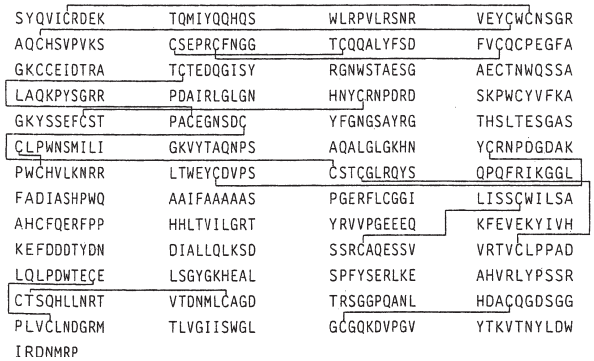
Description—Hygroscopic white powder of friable solid.

Solubility—Freely soluble in water; unstable in concentrations of less than 10,000 IU/mL.

Comments—Indicated for the management of acute myocardial infarction (AMI) in adults, for the lysis of intracoronary thrombi; the improvement of ventricular function; the reduction of mortality associated with AMI, when administered by either the IV or the intracoronary route; as well as for the reduction of infarct size and congestive heart failure associated with AMI when administered by the IV route. Earlier administration is correlated with greater clinical benefit. It also is indicated for the lysis of objectively diagnosed pulmonary emboli, involving obstruction of blood flow to a lobe or multiple segments, with or without unstable hemodynamics. In addition, this drug is indicated for the lysis of objectively diagnosed, acute, extensive thrombi of the deep veins as well as arterial thrombi and emboli. Individuals with recent streptococcal infections may have significant amounts of circulating antistreptokinase antibodies; thus a loading dose sufficient to neutralize these antibodies is required. It is contraindicted in patients with a predisposition for bleeding. Fever and shivering occur in 1% to 4% of patients with other allergic manifestations including urticaria, itching, flushing, nausea, headache, and musculoskeletal pain, which is also relatively common. Anaphylactic reactions ranging in severity from minor breathing difficulties to bronchospasm, periorbital swelling, or angioedma have been observed more rarely but can require drug discontinuation. SK acts with plasminogen to form an *activator complex,* and the half-life of this complex is approximately 23 min. The complex is inactivated, in part, by antistreptococcal antibodies.

TENECTEPLASE

103-L-Asparagine-117-L-glutamine-296-L-alanine-297-L-alanine-298-L-alanine-299-L-alanineplasminogen activator (human tissue type); Arixtra, TNKase, Metalyse



Recombinant (TNKase) thrombolytic [191588-94-0] $C_{2558}H_{3872}N_{738}O_{781}S_{40}$ (Mol wt about 65 kDa; polypeptide portion about 59kDa).

Preparation—(WO 93,24635) Tenecteplase is a tissue plasminogen activator (tPA) produced by a recombinant DNA procedure on a cell line from the ovaries of the Chinese hamster. It is a 527 amino acid glycoprotein formed by introducing the following modifications to the complementary DNA (cDNA) of natural human tPA:

In the kringle 1 domain; a. Substitution of threonine 103 with asparagine
b. Substitution of asparagine 117 with glutamine
In the protease domain; c. Substitution of amino acids 296 to 299 by tetra-alanine

The nutrient medium for the cell culture contains gentamycin (65 mg/L) but the antibiotic is not found in the final product at a limit of detection of 0.67 pg/vial.

Description—Sterile, white to off white, lyophilized powder.

Comments—Tenecteplase is a modified form of human tissue plasminogen activator (tPA) that binds to fibrin and converts plasminogen to plasmin. In the presence of fibrin, in vitro studies demonstrate that Tenecteplase conversion of plasminogen to plasmin is increased relative to its conversion in the absence of fibrin. This fibrin specificity decreases systemic activation of plasminogen and the resulting degradation of circulating fibrinogen as compared to a molecule lacking this property. Following administration of 30, 40, or 50 mg of TNKase, there are decreases in circulating fibrinogen (4-15%) and plasminogen (11-24%). The clinical significance of fibrin-specificity on safety (eg, bleeding) or efficacy has not been established. Biological potency is determined by an in vitro clot lysis assay and is expressed in Tenecteplase-specific units. The specific activity of Tenecteplase has been defined as 200 units/mg.

UROKINASE

Abbokinase

[9039-53-6]

Preparation—From human urine or tissue cultures of human kidney cells. (*Am J Physiol* 1952; 171: 768.

Description—A polypeptide chain of two active forms with molecular weights of 33,000 and 55,000; the principal component is the smaller of the two.

Solubility—Freely soluble in water.

Comments—Indicated for the lysis of acute massive pulmonary emboli and pulmonary emboli accompanied by unstable hemodynamics when the diagnosis has been confirmed by objective means such as pulmonary angiography or lung scanning. It has been reported to lyse acute thrombi obstructing coronary arteries associated with evolving transmural myocardial infarction (MI); however it has not been established that intracoronary administration during evolving MI results in salvage of myocardial tissue nor that it reduces mortality. The MI patients who might benefit from this therapy cannot be defined. As with other thrombolytics, it is contraindicated in conditions with a predisposition for bleeding. Relatively mild allergic reactions such as rash and bronchospasm have been reported. When administered intravenously it is cleared rapidly by the liver, with a plasma half-life of 20 min or less.

ANTIPLATELET DRUGS

Platelets play a key role in hemostasis and thrombus formation. Platelets adhere to thrombin, collagen, immunologically sensitized surfaces, and various other substances. At the site of vascular injury, collagen is exposed, thus causing platelet adhesion and the release of ADP, prostaglandins PGG_2 and PGH_2, TXA_2, and other substances. The growing platelet aggregate becomes a *white thrombus,* which may plug a small vascular break or grow sufficiently large to cause vascular occlusion. In a blood clot, adhesion to thrombin causes an aggregate known as the *white head* of a red thrombus, which by a self-regenerating process (since ADP and TXA_2 cause further aggregation) enlarges the thrombus. Serotonin, PGG_2, PGH_2, TXA_2, and platelet-derived growth factor (PDGF) cause local vasospasm, which helps arrest bleeding from ruptured capillaries.

Vascular endothelium generates prostacyclin (PGI_2), which suppresses platelet adherence and aggregation and thus is a protective substance that helps limit the progression of a white thrombus beyond the point of injury. PGI_2 is also a potent vasodilator.

Platelets adhering to the wall of a blood vessel promote atherogenesis. PDGF causes local smooth muscle cells to increase cholesterol synthesis, bind low-density lipoprotein (LDL), increase the rate of cell replication, and change into the foam cells characteristic of an atheroma. Platelets also are crucial to the process of thrombotic vascular occlusion once an atheroma has ruptured. Platelets also are involved in inflammation, bronchial asthma, eosinophilia, vascular tone, microcirculatory regulation, mitogenesis, and tissue growth and repair, but antiplatelet drugs have received little attention in these roles.

So-called antiplatelet drugs may suppress platelet adherence and aggregation and extend platelet viability by acting directly on mechanisms within the platelet (true antiplatelet activity) or indirectly, to decrease the availability of nonplatelet-derived agonists that promote aggregation. Much interest has been on inhibitors of prostaglandin and thromboxane synthesis, especially of *aspirin*.

Aspirin irreversibly inhibits (by acetylation) the cyclooxygenase system that generates prostaglandins, prostacyclin, and TXA_2. The effect of decreasing TXA_2 is inhibition of platelet aggregation, but at first this is counterbalanced by a decrease in PGI_2. However, vascular endothelial cells continue to synthesize cyclooxygenase, whereas anuclear platelets do not. Therefore, within a few hours after the administration of aspirin, PGI_2 synthesis returns to normal, but TXA_2 synthesis does not. Furthermore, oral aspirin interacts with circulating platelets during absorption but with most endothelial cells only after passing through the liver, where first-pass metabolism greatly decreases the plasma concentration, and after dilution with nonhepatic blood; consequently, platelets are the more affected, and it is possible to suppress platelet aggregation with doses that have little effect on the generation of PGI_2. In addition, aspirin probably inhibits platelet function by additional mechanism(s) unrelated to TXA_2 inhibition.

Other nonsteroidal anti-inflammatory drugs (NSAIDs), such as other salicylates, hydroxychloroquin, indomethacin, etc, are not irreversible inhibitors of cyclooxygenase and are not as effective as antiplatelet drugs. Sulfinpyrazone is a weak inhibitor of cyclooxygenase and possibly may have another mechanism of action. Aspirin also has an action to suppress secretion of ADP-containing dense granules from platelets, which also contributes to antiplatelet activity.

TICLOPIDINE HYDROCHLORIDE

Thieno[3,2-*e*]pyridine, 5-[(2-chlorophenyl)methyl]-4,5,6,7-tetrahydro-, hydrochloride; Ticlid Hydrochloride

[53885-35-1] $C_{14}H_{14}ClNS.HCl$ (300.25).

Preparation—From 2-thiophenecarboxaldehyde plus 2-aminoacetaldehyde diethyl acetal to form the Schiff base, which is cyclized with acid to form pyrido[3,4-*b*]thiophene. This latter compound with α,2-dichlorotoluene yields the tertiary iminium chloride, which with sodium borohydride affects reduction of the pyridine ring to yield the product. (*J Med Chem* 1974; 9: 483.)

Description—White, crystalline solid; melts at 189°.

Solubility—Freely soluble in methanol or water to pH 3.6; sparingly soluble in methylene chloride or alcohol; slightly soluble in acetone; insoluble in a buffered solution at pH 6.3.

Comments—An orally active *platelet inhibitor* that prevents both platelet aggregation and release of granule constituents. Its mechanism of action is not completely delineated but apparently results from interference with platelet membrane function by inhibition of. It inhibits ADP-induced platelet-fibrinogen binding and platelet-platelet interactions but has variable effects on aggregation due to other stimuli including thrombin, platelet-activating factor, epinephrine, or collagen. The inhibitory effect is irreversible and persists for the life of the platelet. After discontinuation of the drug, platelet function tests return to normal within 2 weeks in most patients. Ticlopidine is indicated to reduce the risk of thrombotic stroke (fatal or nonfatal) in patients who have experienced stroke precursors or who have had a completed thrombotic stroke. In a trial comparing ticlopidine with aspirin therapy in patients experiencing stroke precursors or a minor stroke, ticlopidine significantly reduced the risk of fatal and nonfatal stroke compared with aspirin. The risk reduction by ticlopidine was similar

in women and men. Side effects were more frequent with ticlopidine than with aspirin, and GI symptoms were the most common complaint. Neutropenia is the most serious adverse effect of ticlopidine and occurred in 2.4% of patients. Consequently, patients *must* have their blood tested every 2 weeks for the first 3 months of therapy. Patients also should be advised to contact their physician immediately if they experience symptoms of infection such as fever, chills, or sore throat. The drug is metabolized extensively by the liver and is contraindicated in patients with severe liver impairment. In addition, it should not be given to patients who have a hematopoietic or hemostatic disorder or active pathological bleeding such as a bleeding peptic ulcer or intracranial bleeding.

Dose—*Oral, adults,* 250 mg twice a day taken with food.

Dosage Form—Tablets: 250 mg.

Other Antiplatelet Drugs

Other drugs work in other ways.

Dipyridamole inhibits platelet phosphodiesterase, thus increasing cyclic AMP levels, which suppresses platelet aggregation and dense-granule secretion. It also blocks the reuptake and metabolism of adenosine and potentiates the antiaggregating action of PGI_2.

Calcium channel blockers (page 1290) decrease intraplatelet calcium concentration and, hence, also suppress dense-granule secretion.

β-*Adrenergic blockers* prevent β-receptor operation of calcium channels.

α-Blockers prevent α-agonist-induced dense-granule secretion.

Anagrelide suppresses platelet response to all stimuli; its mechanism may be that of inhibiting a distinct pool of cAMP phosphodiesterase.

Other inhibitors of platelet function are dextrans, glyceryl guaiacolate (very active), penicillin, tricyclic antidepressants, glucocorticoids, clofibrate, pyridinol carbamate, PGE_1, glucagon, antiserotonin drugs, certain antihistamines, caffeine, theophylline, pentoxifyllin, general anesthetics, and ethanol in high concentration.

Clopidogrel Bisulfate—A thienopyridine derivative chemically related to ticlopidine that inhibits platelet aggregation by irreversibly modifying the platelet-ADP receptor. It is indicated for the reduction of atherosclerotic events including MI, stroke, and vascular death in patients with documented atherosclerosis. The major adverse effects include chest pain, flulike symptoms, abdominal pain, arthralgia, and purpura.

Eptifibatide—A cyclic heptapeptide that binds to the platelet glycoprotein IIb/IIIa receptor and thus inhibits platelet aggregation, similar to *Abciximab.* It is indicated for the treatment of patients with acute coronary syndromes including those to be managed medically as well as those undergoing percutaneous coronary intervention. In the clinical trials with this drug, it was shown to decrease the rate of a combined endpoint of death, new MI, or need for urgent intervention. Most patients were also receiving aspirin and heparin in these clinical trials. Experience in 1998 was limited to the treatment of large numbers of patients with this drug.

Tirofiban Hydrochloride—A nonpeptide antagonist of the platelet glycoprotein IIb/IIIa receptor, which reversibly inhibits platelet aggregation. It is indicated for use along with heparin in the treatment of acute coronary syndromes including those to be managed medically as well as those undergoing percutaneous coronary intervention. In this setting it has been shown to decrease the rate of a combined endpoint of death, new MI, or refractory ischemia/repeat cardiac procedure. Experience in 1998 was limited to the treatment of large numbers of patients with this drug.

No clinical use of antiplatelet drugs is without some controversy. In general, except for dextrans 70 and 75, antiplatelet drugs have not been found effective alone in preventing or limiting venous thrombosis and pulmonary embolism, but they probably improve the response to oral anticoagulants. In such a combination, aspirin increases the incidence and severity of GI hemorrhage, whereas dipyridamole does not. This deleterious effect of combination therapy is reduced if the dose of aspirin is lowered, ie, 325 mg a day or less. In addition, it is essential that coagulation and platelet function tests are monitored routinely, with anticoagulant doses adjusted accordingly.

Antiplatelet-anticoagulant drug combinations appear to be superior to oral anticoagulants alone in preventing thrombosis from prosthetic heart valves and other foreign surfaces. After hip surgery, aspirin alone (in men), aspirin-dipyridamole, and hydroxychloroquin have been reported to be of value in preventing venous thrombosis and pulmonary embolism. Sulfinpyrazone decreases the incidence of systemic embolism in rheumatic mitral valve stenosis.

Aspirin is approved in the US to reduce the risk of death and/or nonfatal MI in patients with a previous infarction or unstable angina pectoris. One tablet is recommended immediately at the onset of symptoms of an MI. It also is approved to reduce the risk of stroke in persons experiencing transient ischemic attacks, although ticlopidine is perhaps superior. Completed strokes are not affected. Occlusive microvascular disorders in the fingers are resolved in 2 to 3 days and further prevented after treatment with aspirin. Microvascular occlusion after organ transplants also appears to be diminished by aspirin. In general, the combination of aspirin and dipyridamole is no more effective than aspirin alone.

There is much interest in the reputed ability of antiplatelet drugs to decrease the rate of MI. There have been two randomized trials examining whether aspirin has a protective effect in the primary prevention of vascular disease, with conflicting results. In a 5-year study, the US Physicians' Health Study, there was a 44% reduction (from approximately 0.4% to 0.2%/year) in the incidence of MI in men receiving aspirin (325 mg every other day) compared with placebo. This effect was only observed in men age 50 or over. Over the 5-year period the death rate from cardiovascular processes was similar in both placebo- and aspirin-treated groups. In contrast, in the British Doctors' Trial there was no difference in the rate of MI or cardiovascular death in the aspirin (500 mg/day) versus placebo group over a 6-year study period. In both of these studies there was a slight increase in the incidence of stroke and an increased risk of GI hemorrhage in the aspirin-treated cohort. The US Preventive Services Task Force recommends that "low-dose aspirin therapy may be considered for men aged 40 and over who are at a significantly increased risk of myocardial infarction and who lack contraindications to the drug." Aspirin therapy should be considered an adjunct approach in the management of cardiovascular disease. Reduction of significant risk factors including hypertension, high cholesterol levels, and smoking are the most effective treatment for patients at risk for MI and stroke. Of note, current epidemiological evidence suggests that aspirin is beneficial in women as well as men; however definitive recommendations must await the results of the ongoing Women's Health Study.

ANTICOAGULANT ANTAGONISTS

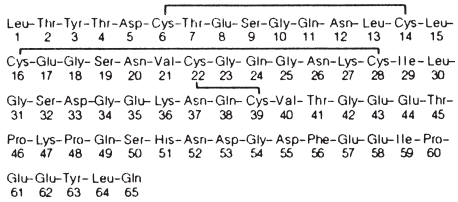
Anticoagulant therapy carries the risk of serious hemorrhage, so that there may be need to arrest the anticoagulant action. Prothrombopenic anticoagulants, as expected from their mode of action, are antagonized by vitamin K or its synthetic substitutes. Not all vitamin K preparations are equally effective, vitamin K_1 (phytonadione) being superior and menadione inferior. The efficacy of vitamin K preparations also varies according to the anticoagulant, but all agents of the dicumarol group may be antagonized by an appropriate dose of vitamin K_1. The antagonism is not manifested immediately, since normal coagulation is obtained only after the liver has had time to replenish the prothrombin and other vitamin K–dependent coagulation factors.

High doses of vitamin K_1 can antagonize oral anticoagulants, despite their being continually inhibited at their site of action, because high doses can activate a second latent enzyme not significantly productive with ordinary concentrations of vitamin K, which enzyme is not inhibited by the anticoagulants. Heparin is antagonized by various amines, ammonium compounds, and basic proteins that precipitate the polysulfate. Circulating heparinoid substances in the blood also can be assayed with such substances.

MENADIOL SODIUM DIPHOSPHATE—page 1700.
PHYTONADIONE—page 1700.

LEPIRUDIN

1-L-Leucine-2-L-threonine-63-desulfohirudin; *Hirudo medicinalis* isoform HVI



[138068-37-8] $C_{287}H_{440}N_{80}O_{111}S_6$ (6979.56).

Description—Lepirudin is a recombinant hirudin composed of 65 amino acids and is produced in yeast. It differs from natural hirudin by the absence of a sulfate group on tyrosine at position 63 and the substitution of leucine for isoleucine at the amino terminus.

Comments—A direct inhibitor of thrombin, with one molecule of lepirudin combining with one molecule of thrombin. It has no effect on antithrombin III. It is indicated for anticoagulation in patients with heparin-induced thrombocytopenia (HIT) and associated thromboembolic disorders, to prevent further thromboembolic complications. The major adverse effect is bleeding, and intracranial bleeding has occurred in acute MI patients following concomitant thrombolytic therapy with alteplase or streptokinase. Other adverse events include allergic reations involving the skin and airways. The systemic clearance of lepirudin depends on the glomerular filtration rate, and dosage adjustment based on creatinine clearance is recommended. There is no specific antidote for lepirudin, and life-threatening bleeding requires immediate discontinuation of the drug as well as possible blood transfusion. Therapy is monitored using the PTT ratio, with a target range of 1.5 to 2.5, and current data suggest that higher ratios increase the bleeding risk without a significant increase in clinical efficacy.

PROTAMINE SULFATE

A purified mixture of simple protein principles obtained from the sperm or testes of suitable species of fish, which has the property of neutralizing heparin. Each milligram neutralizes not less than 80 USP Units of heparin activity derived from lung tissue and not less than 100 USP Units of heparin activity derived from intestinal mucosa.

Preparation—Frozen, ripe, salmon testes are ground, water-washed, centrifuged, and dehydrated by means of solvents and vacuum drying. The dried material then is extracted with 10% H_2SO_4, and after filtering, a protamine sulfate–rich fraction is precipitated from the filtrate with cold alcohol. This fraction is dissolved in hot water, and the protamine sulfate separates as an oil upon cooling. This protamine-rich oil is dissolved in hot water and fractionated again with cold alcohol. The resulting fraction is dehydrated by means of solvents and vacuum dried.

Description—Fine, white or faintly colored, amorphous or crystalline, hygroscopic powder.

Solubility—Sparingly soluble in water.

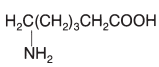
Comments—A *heparin antagonist*. Because it is a strongly basic macromolecule, it combines avidly with heparin, which is a polyanionic macromolecule. It combines with heparin in an approximately 1:1 ratio by weight regardless of the source of heparin; since the potency of heparin from different sources varies, the dose of protamine based on USP unitage also varies. It is injected slowly intravenously after suitable dilution with physiological salt solution, to counteract the effect of *overmedication with heparin*. The duration of the effect is about 2 hr.

Untoward effects are uncommon. They include abrupt hypotension, dyspnea, bradycardia, flushing, and a feeling of warmth. An overdose can itself exert an anticoagulant effect.

FIBRINOLYTIC INHIBITORS

AMINOCAPROIC ACID

***Epsilon* Aminocaproic Acid; Aminocaproic Acid; Amicar**



6-Aminohexanoic acid [60-32-2] $C_6H_{13}NO_2$ (131.17).

Preparation—The lactam group of the commercially available caprolactam (hexahydro-2*H*-azepin-2-one) is cleaved at the C-N linkage by heating an aqueous solution with calcium hydroxide. The calcium aminocaproate thus formed is reacted with sulfuric acid to free the official acid and precipitate the calcium. Various other methods of preparation are also available.

Description—Fine, white, crystalline powder; odorless, or nearly so; tasteless, stable in light and air; melts at about 205°.

Solubility—1 g in 3 mL water; slightly soluble in alcohol; practically insoluble in chloroform or ether.

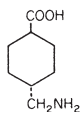
Comments—A competitive inhibitor of plasminogen activators, which also expresses antiplasmin activity. It is used in the treatment of *procedures or disorders in which fibrinolysis is enhanced,* such as cardiac bypass, postcaval shunt, major thoracic surgery, prostatic postoperative hematuria, and also nonsurgical hematuria, leukemia, metastatic prostatic carcinoma, cirrhosis and other hepatic diseases, eclampsia, intrauterine fetal death, amniotic fluid embolism, and abruptio placentae. It also is used to correct excessive, treatment-induced fibrinolysis. It has been reported to be of use in angioedema and subarachnoid hemorrhage. The drug is of no value in hemorrhage due to thrombocytopenia, hyperheparinemia, or other coagulation defects or to vascular disruption.

It may cause itching, erythema, rash, diuresis, heartburn, nausea, and diarrhea. It also has an antiadrenergic effect similar to that of guanethidine, so that nasal stuffiness, conjunctival suffusion, and hypotension may occur. The drug may enhance thrombotic processes by suppression of reactive fibrinolysis, which tends to limit clot formation and favor clot resolution. Therefore, it should not be given unless there is unequivocal evidence that disseminated intravascular clotting is not the cause of elevated fibrinolytic activity. It is not known whether this drug can cause fetal harm, and it is currently in pregnancy Category C.

It is excreted by the kidney; in the presence of renal disease the dose should be reduced.

TRANEXAMIC ACID

Cyklokapron



[1197-18-8] $C_8H_{15}NO_2$ (157.21).

Preparation—*J Org Chem* 1959; 24: 115, and US Pat 3,499,925.

Description—White crystals; melts over 300°.

Solubility—1 g in about 6 mL water; very slightly soluble in alcohol or ether; 5% aqueous solution, pH 6.5 to 7.5.

Comments—Resembles aminocaproic acid in decreasing the activity of the fibrinolysis system, in part by inhibiting plasminogen; it is approved for use in hemophiliac patients to prevent hemorrhage and reduce the need for replacement of blood factors. Its most interesting use has been in the treatment of malignant ovarian tumors, to promote formation of a fibrin capsule to wall off and inhibit growth of the tumor. It also causes regression of ascites secondary to carcinoma. In these uses heparin was given concomitantly to prevent intravascular coagulation. It causes nausea, vomiting, diarrhea, occasional vertigo, and hypotension from rapid injection. It passes through the placental barrier. It is excreted rapidly in urine.

HEMOSTATICS AND STYPTICS

Many substances not especially related to the clotting mechanism are capable of promoting clotting. Upon contact with most surfaces, platelets adhere, aggregate, and release mediators that promote fibrin deposition. Spongy and gauzy materials, which provide a large surface area, thus are used to arrest bleeding; absorbable sponges may be left permanently at the site of bleeding. Fibrin, fibrinogen, and thrombin are also potent hemostatics. Astringents also initiate clotting by precipitating proteins and by labilizing platelets; mostly ferric salts are employed as styptics.

ALUM—page 1282.

MICROFIBRILLAR COLLAGEN

Avitene

A preparation of animal origin of the polypeptide substance occurring as the main constituent of skin, connective tissue, and the organic substance of bones.

Comments—Platelets adhere naturally to collagen and are stimulated to release substances that promote further aggregation. Microfibrillar collagen is used to arrest bleeding, especially during surgery except neurological, urological, and ophthalmological procedures. It usually stops capillary bleeding in 1 min, *brisk* bleeding in 4 to 5 min, and oozing from bone in 5 to 10 min. The collagen is absorbed in less than 84 days. It may cause mild, chronic inflammation at the site of application, probably as the result of slight contamination by bovine albumin. It does not interfere with regeneration of bone. It may interfere mechanically with the closure of incisions. Plugging of pores in cancellous bone diminishes the strength of methacrylate adhesives. Spillage on nonbleeding surfaces should be avoided because it may cause adhesions.

DESMOPRESSIN—page 1441.

ABSORBABLE GELATIN POWDER

Gelfoam

A fine, dry, heat-sterilized light powder prepared by milling absorbable gelatin sponge.

Comments—Sterile powder, saturated with sterile sodium chloride solution; is indicated in surgical procedures to control capillary, venous, and arteriolar bleeding when conventional procedures such as pressure or ligature are ineffective.

ABSORBABLE GELATIN SPONGE

Gelfoam

Gelatin in the form of a sterile, absorbable, water-insoluble sponge.

Description—Light, nearly white, nonelastic, tough, porous, hydrophilic solid; 10-mm cube weighing approximately 9 mg will take up approximately 45 times its weight of well-agitated oxalated whole blood; it is stable in dry heat at 150 for 4 hr.

Solubility—Insoluble in water, but absorbable in body fluids; completely digested by a solution of pepsin.

Comments—A *hemostatic* and *coagulant* used to control bleeding. It is moistened with sterile sodium chloride or thrombin solution and may then be left in place following closure of a surgical incision. It should not be used in the closure of skin incisions because of interference with the rejoining of edges. It is absorbed in 4 to 6 week.

THROMBIN

Thrombinair; Thrombogen; Thrombostat

A sterile protein substance prepared from prothrombin of bovine origin through interaction with added thromboplastin in the presence of calcium. It is capable, without the addition of other substances, of causing the clotting of whole blood, plasma, or a solution of fibrinogen. It may contain a suitable antibacterial agent.

Note: Solutions of thrombin should be used within a few hours after preparation, and are not to be injected.

Description—White or grayish, amorphous substance dried from the frozen state.

Comments—When concentrated, it has an extraordinarily potent hemostatic or clotting effect on blood. Its powerful coagulant action is employed in coagulating fibrinogen solution. It also is useful for local application to *cuts* or *injuries*. In surgery and in emergency, it is useful for local application in the control of minor oozing. For more extensive or inaccessible *hemorrhage,* a matrix must be applied to hold the thrombin in place and provide a structure for clot formation. Such a matrix is provided by various products, including fibrin foam, gelatin sponge, etc. It is ineffective in arterial bleeding.

ELECTROLYTES AND SYSTEMIC BUFFERS

The concentration of several of the electrolytes in plasma is critical for proper functioning of cells, especially those of the excitable tissues. The proper balance of the several ions is complex, depending not only on the concentration in the extracellular fluid (of which plasma is one compartment) but also on the intracellular concentration, the ratio across the cell membrane being an essential factor as well as the ratio of one ion type to another. Thus, plasma electrolyte concentrations provide only a crude clue to the electrolyte status of the patient, and balance or other ancillary studies are often necessary to determine the true electrolyte needs. Certain electrolytes, for example calcium and phosphate, serve also as structural elements in hard tissues (bone, teeth, etc) and may be employed for that purpose.

Several of the phosphates described in this section often are used to remove calcium from blood in hypercalcemia and to prevent and even dissolve calcific kidney stones rather than to add an electrolyte.

AMMONIUM CHLORIDE—page 1423.
CALCIUM CARBONATE—page 1296.

CALCIUM CHLORIDE

Calcium chloride, dihydrate [10035-04-8] $CaCl_2.2H_2O$ (147.02); *anhydrous* [10043-52-4] (110.99).

Preparation—By saturating HCl with chalk or marble, then adding calcium hydroxide to alkalinity and boiling, which precipitates magnesium, iron, and other metals. After filtering, the filtrate is neutralized with HCl and evaporated until it contains about 24% water.

Description—White, hard, odorless fragments or granules; deliquescent.

Solubility—1 g in 0.7 mL of water or 4 mL of alcohol.

Comments—Provides calcium ions in the treatment of *hypocalcemic tetany*. It also relieves muscle spasms and pain from *black widow bites*. It is given during *exchange transfusions,* to repair the calcium deficit in citrated blood; however, calcium gluceptate is preferred for this use. It is *antispasmodic* to smooth muscle and effective in relieving the abdominal pain and diarrhea of *intestinal tuberculosis* and *lead colic;* for this purpose it is given orally, a neutral salt being preferred. It stimulates cardiac automaticity and contractility and is used in *cardiac resuscitation*. Calcium is used in the management of *hypersensitivity reactions,* especially urticaria and angioneurotic edema, and of *insect bites* and *stings*.

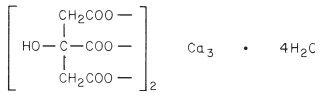
It is a specific antidote in cases of *magnesium poisoning*. It is used in the treatment of *hyperkalemia,* since it antagonizes the cardiac effects of potassium.

As an *electrolyte replenisher* it is a pharmaceutical necessity for *Ringer's Injection, Lactated Ringer's Injection,* and *Ringer's Solution*.

Side effects result from too-rapid injection; these include vasodilation and a burning sensation in the skin. Overdosage can cause hypercalcemia, characterized by persistent nausea and vomiting, lethargy, weakness, coma, and sudden death. Because of the danger of overdosage, it is contraindicated in renal insufficiency, even if hypocalcemia exists. It should be given cautiously to the digitalized patient, and the electrocardiogram should be monitored. In general, plasma electrolyte concentrations should be monitored before and during use. Extravasation and intramuscular or subcutaneous injection can cause tissue necrosis. For this reason, less-irritant salts are preferred, especially in pediatrics.

CALCIUM CITRATE

1,2,3-Propanetricarboxylic acid, 2-hydroxy-, calcium salt (2:3), tetrahydrate; Citracal



[5785-44-4]

$C_{12}H_{10}Ca_3O_{14}.4H_2O$ (570.50).

Preparation—By treating citric acid obtained from citrus fruits, with lime.

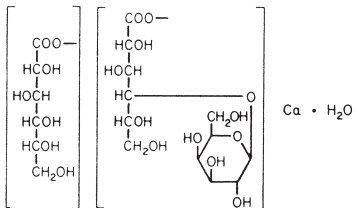
Description—White, odorless, crystalline powder losing all of its water of crystallization at 120°.

Solubility—1 g in 1050 mL cold water; more soluble in hot water; insoluble in alcohol.

Comments—Most calcium compounds given orally as a source of calcium are soluble in gastric acid but are converted mostly to insoluble calcium carbonate in the duodenum, so that only a fraction of the calcium is available for absorption. Calcium carbonate, especially, depends greatly upon gastric acid to make some of the calcium bioavailable. Persons with achlorhydria, pyloroplasty, or other conditions in which a calcium compound is not in an acidic environment long enough to liberate or maintain much soluble calcium usually do not obtain adequate calcium absorption from calcium carbonate and certain other calcium compounds. In this drug, the calcium ion is chelated sufficiently firmly that a large proportion remains in the soluble form in the alkaline environment of the small intestine. In individuals with normal gastric acid secretion, 20% to 66% more calcium is bioavailable from the citrate than from the carbonate, and in persons with achlorhydria it is 100% more available. It is used to treat *hypocalcemia* and as a *supplement* to dietary calcium, especially in persons in whom there is a probability of developing or exacerbating osteoporosis.

CALCIUM GLUBIONATE

Calcium, (4-*O*-β-D-galactopyranosyl-D-gluconato-*O*^{1})(D-gluconato-*O*1)-, monohydrate; Neo-Calglucon

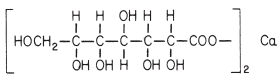


[12569-38-9] $C_{18}H_{32}CaO_{19}.H_2O$ (610.53).

Comments—As a source of calcium, more as a dietary supplement than for the treatment of hypocalcemia.

CALCIUM GLUCEPTATE

D-*glycero*-D-*gulo*-Heptonic acid, calcium salt (2:1); Calcium Gluceptate



Calcium D-*glycero*-D-*gulo*-heptonate (1:2) [17140-60-2] $C_{14}H_{26}CaO_{16}$ (490.43); *hydrate* [56348-83-5] (508.45).

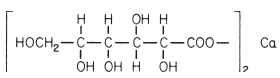
Preparation—From sodium glucoheptonate, US Pat 3,033,900.

Comments—To provide calcium ions when rapid availability is required. The clinical conditions in which calcium is required are stated under *Calcium Chloride*. This drug is even less irritating than *Calcium Gluconate,* so that it is preferred when intramuscular administration is required, as in neonatal tetany. Many authorities also prefer the gluceptate to the gluconate for intravenous injection, but once symptoms are controlled, maintenance usually is achieved with calcium gluconate given by intravenous infusion. The duration of action after intravenous administration is 2 to 3 hr and after intramuscular injection, 1 to 4 hr.

After rapid intravenous injection there may be tingling sensations and a chalky taste. The effects of overdoses, precautions, and drug interactions are those of *Calcium Chloride*. Mild local reactions may occur at the site of injection, but abscesses apparently do not occur.

CALCIUM GLUCONATE

D-Gluconic acid, calcium salt (2:1)



Calcium gluconate (1:2) [299-28-5] $C_{12}H_{22}CaO_{14}$ (430.38).

Preparation—D-Glucose is oxidized to gluconic acid in the presence of calcium carbonate. The oxidation may be effected by certain molds, eg, *Aspergillus niger,* or by bromine.

Description—White, crystalline granules or powder, without odor or taste; stable in air and does not lose its water on drying without undergoing decomposition; solutions are neutral to litmus paper; decomposed by dilute mineral acids into gluconic acid and the calcium salt of the mineral acid used.

Solubility—1 g slowly in about 30 mL water or about 5 mL boiling water; insoluble in alcohol or many other organic solvents.

Comments—Its uses are those of *Calcium Chloride*. It is less irritating than calcium chloride and may be given orally or by intramuscular or intravenous injection. However, intramuscular injection may cause abscesses. It usually is considered to be the calcium salt of choice for intravenous use.

CALCIUM GLYCEROPHOSPHATE

Calphosan; Neurosin; Phos-Cal

$(HOCH_2)_2CHOPO_3Ca$

[27214-00-2] $C_3H_7CaO_6P$ (210.15). A mixture of the β-calcium salt (center hydroxyl of glycerol is phosphorylated) and the α-salt (end hydroxyl is phosphorylated). Since the α-salt enjoys a chiral center, it exists as two stereoisomers; only the racemic form is present in this salt.

Preparation—*J Chem Soc* 1914; 105: 1238.

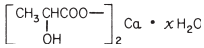
Description—Odorless, tasteless powder; decomposes at about 170°.

Solubility—1 g in about 50 mL water at 20°; less soluble at higher temperatures.

Comments—The actions, uses and adverse effects are much like those of *Calcium Gluconate*. The effects of overdoses, drug interactions and precautions are those of *Calcium Chloride*. The salt is marketed only in combination with calcium lactate or calcium levulinate.

CALCIUM LACTATE

Propanoic acid, 2-hydroxy-, calcium salt (2:1), hydrate



Calcium lactate (1:2) hydrate [41372-22-9] $C_6H_{10}CaO_6.xH_2O$; *anhydrous* 814-80-2 (218.22); *pentahydrate* (308.30).

Preparation—By fermenting hydrolyzed starch with a suitable mold in the presence of calcium carbonate, and purifying until the product meets USP purity requirements. It also is obtained, now in decreasing quantities, by fermentation of the mother liquors resulting from the production of milk sugar.

Description—White, almost odorless powder or granules, somewhat efflorescent; it becomes anhydrous at 120°; aqueous solutions are prone to become moldy.

Solubility—1 g in about 20 mL of water; practically insoluble in alcohol.

Comments—An excellent source of calcium ion in the oral treatment of *calcium deficiency*. It causes less GI irritation than does calcium chloride. It is used in the prevention and retardation of *osteoporosis*. The bioavailability of calcium is not as gastric acid–dependent as is that of $CaCO_3$; consequently, the lactate is superior in many elderly patients.

CALCIUM LEVULINATE

Pentanoic acid, 4-oxo-, calcium salt (2:1)

$[CH_3COCH_2CH_2OOO\text{-}]_2Ca \cdot 2H_2O$

[5743-49-7] $C_{10}H_{14}CaO_6.2H_2O$ (306.33).

Preparation—From levulinic acid and calcium carbonate. The acid may be obtained from crude cellulose and as a by-product in the manufacture of furfural. (*Ind Eng Chem* 1956; 48: 1331.)

Description—White, crystalline or amorphous powder; faint odor suggestive of burnt sugar; bitter, salty taste.

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

Comments—Much like *Calcium Gluceptate* in that it is less irritating than calcium gluconate. The side effects also are essentially the same. The effects of overdoses, precautions, and drug interactions are those of *Calcium Chloride*. The salt is marketed only in combination with calcium glycerophosphate.

DIBASIC CALCIUM PHOSPHATE

Phosphoric acid, calcium salt (1:1); Dicalcium Orthophosphate

Calcium phosphate (1:1) anhydrous [7757-93-9] $CaHPO_4$ (136.06); *dihydrate* [7789-77-7] (172.09).

Preparation—A phosphate mineral, eg, *apatite,* or preferably ignited animal bone, is decomposed with H_2SO_4, resulting in the production of phosphoric acid and calcium sulfate. After filtering off the calcium sulfate, the proper quantity of calcium hydroxide is added to form dibasic calcium phosphate.

It also may be prepared from animal bones as described under the preparation of *Tribasic Calcium Phosphate,* using only sufficient calcium hydroxide to form the dibasic salt.

Description—White, odorless, tasteless powder; stable in air; aqueous suspension is neutral to litmus.

Solubility—Practically insoluble in water; readily soluble in diluted hydrochloric or nitric acids; insoluble in alcohol.

Comments—An excellent *source of calcium* and *phosphorus* during pregnancy, lactation, or mild-to-moderate *hypocalcemia* characterized by a low degree of tetany. Because of the phosphate content, it is contraindicated in hypoparathyroidism. If the tetany is severe, intravenous calcium medication is administered. See *Calcium Chloride, Calcium Gluconate, Calcium Gluceptate, Calcium Glycerophosphate,* or *Calcium Levulinate*.

TRIBASIC CALCIUM PHOSPHATE

Calcium Hydroxide Phosphate

$Ca_5(OH)(PO_4)_3$

[12167-74-7] $Ca_5HP_3O_{13}$ (502.32).

Preparation—Commercially from phosphate rock; also occurs naturally.

Description—Amorphous, odorless, tasteless powder.

Solubility—Insoluble in water, alcohol, or acetic acid; soluble in mineral acids.

Comments—Mainly for the prophylaxis and treatment of *hypocalcemia,* although it also serves as a source of phosphate.

POTASSIUM ACETATE

[127-08-2] $C_2H_3KO_2$ (98.14).

Preparation—Potassium bicarbonate or carbonate is reacted with acetic acid previously diluted with water, and the solution is evaporated to dryness.

Description—Colorless, monoclinic crystals or a white, crystalline powder; rapidly deliquesces in moist air; saline and slightly alkaline taste; aqueous solutions are alkaline to litmus, but do not affect phenolphthalein TS.

Solubility—1 g in about 0.5 mL water or about 3 mL alcohol.

Comments—Therapeutically, as a systemic and urinary *alkalinizer,* and for the effects of the *potassium ion*. Its value in hypokalemia is limited, since the condition frequently is associated with a hypochloremic alkalosis. Consequently, potassium chloride usually is preferred in hypokalemia. Acetate anion is metabolized to bicarbonate. When used orally as an alkalinizer the salt should be diluted liberally with water or fruit juice to avoid gastric distress. Indiscriminate use of this or other potassium salts may produce toxic manifestations of hyperkalemia (see *Potassium Chloride*).

POTASSIUM CHLORIDE

Potassium chloride [7447-40-7] KCl (74.55).

Preparation—Occurs in sea water and in many mineral springs. Formerly it largely was imported from Germany where it is mined at Stassfurt, occurring there as *carnallite* [$KCl.MgCl_2.6H_2O$] and as *sylvite* [KCl]. It now is obtained from the Searles Lake deposit in the Mojave Desert of southern California and from deposits of carnallite and sylvite in New Mexico and Texas. Another source is the Dead Sea, where considerable quantities are found as dissolved carnallite. This double salt, in aqueous solution, is treated with live steam, the two separate salts form, and the less-soluble salt, potassium chloride, crystallizes out as the solution cools. In the laboratory it may be prepared from potassium carbonate or bicarbonate and HCl.

Description—Colorless, elongated, prismatic, or cubical crystals, or as a white granular powder; odorless, saline taste and stable in air; pH (aqueous solution) about 7.

Solubility—1 g in 2.8 mL water at 25° or about 2 mL boiling water; insoluble in alcohol.

Comments—The salt most frequently employed when the action of potassium cation is desired. It is used when *hypokalemia* or *hypochloremic alkalosis* exists, as after prolonged diarrhea or vomiting or consequent to adrenal steroid therapy or treatment with certain diuretics, especially the thiazides. It is used when it is desired to elevate normal plasma potassium levels, as in the treatment of digitalis intoxication. It may be used as a diuretic. Potassium chloride is of value for the relief of the symptoms of *hypokalemic periodic paralysis,* a rare disease characterized by recurrent attacks of muscular weakness. An increase in the daily intake of potassium decreases the risk of stroke-associated mortality; an increment of 10 mEq a day results in an average decrement in mortality of 40%. Potassium salts have been found to relieve the symptoms of Ménière's disease.

Potassium chloride is an ingredient of *Lactated Potassic Saline Injection, Ringer's Solution, Lactated Ringer's Injection, Ringer's Injection* and various other parenteral and oral electrolyte combinations.

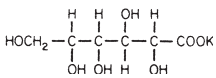
It is irritant to the GI tract, oral preparations may cause nausea, vomiting, epigastric distress, abdominal discomfort, and diarrhea. High, local concentrations in the GI tract can lead to ulceration. Esophageal ulceration may occur if there is dysphagia and gastric ulceration, especially if gastric emptying is delayed. Enteric coating lessens the incidence of such side effects but favors the development of small bowel lesions, especially when thiazides are used concurrently. In a wax matrix it has been promoted as a safe form, but esophageal, gastric, and small bowel ulcerations nevertheless occur occasionally. It is best to avoid solid forms; if they are used, they should be taken with one or more full glasses of water. Overdoses may cause paresthesias, generalized weakness, flaccid paralysis, listlessness, vertigo, mental confusion, hypotension, cardiac arrhythmias, and heart block. Death may ensue.

Signs of toxicity may occur even with apparently normal blood levels; consequently, the signs must be monitored frequently, and ambulatory patients must be apprised of premonitory symptoms. Most patients can be managed adequately and more safely with foods high in potassium and low in sodium (fruits, especially dried, and cereals).

It must be administered cautiously in the presence of heart or renal disease. It is contraindicated in untreated Addison's disease, heat cramps, adynamia episodica hereditaria, acute dehydration, and hyperkalemia from any cause.

POTASSIUM GLUCONATE

Kaon



[299-27-4] $C_6H_{11}KO_7$ (234.25).

Preparation—Glucose may be oxidized to gluconic acid by various processes, eg, electrolytic oxidation of an alkaline solution, reaction with hypobromites, or fermentation using *Aspergillus niger* or other microorganisms. Neutralization with potassium hydroxide provides the salt.

Description—White to yellowish white, crystalline powder or granules; odorless; slightly bitter taste; stable in air; solutions slightly alkaline to litmus.

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

Comments—A *source of potassium* for management of *hypokalemic states,* such as occur consequent to adrenocorticosteroid therapy or use of thiazide diuretics, or for deliberate production of hyperkalemia, as for treatment of digitalis intoxication. The gluconate anion supposedly makes the compound better tolerated in the GI tract than is potassium chloride. It also is claimed that the potassium of the gluconate is absorbed high in the GI tract, above the location where mucosal lesions sometimes occur in combined thiazide-potassium therapy, whereas other salts are not absorbed so quickly. Such faulty suppositions and claims ignore the unavoidable chemical fact that irrespective of the salt used, potassium ion is only dissociable completely and hence is unaffected in its irritant actions and absorption by the anion in the compound.

Its sugar-coated tablets dissolve at a higher level than do enteric-coated tablets of potassium chloride but, by this very fact, are free to cause the irritation for which the chloride tablet was coated. The fact that it may cause nausea, vomiting, diarrhea, and abdominal discomfort shows that the gluconate has no advantage over non-enteric-coated potassium chloride tablets. A full glass of water taken with either greatly reduces the irritant effects of either salt. Hypochloremia is a frequent accompaniment of hypokalemia; in such instances the chloride definitely is preferred. Furthermore, since gluconate metabolizes to bicarbonate, it contributes to alkalosis, which also may be present in hypokalemia. Only in a hypokalemic, hyperchloremic acidosis (as in renal failure, dehydration, and occasional diabetic acidosis) is the drug rational; however, clinical experience indicates no obvious superiority over KCl. The use and toxicity of, and contraindications to, it are the same as for *Potassium Chloride*.

POTASSIUM MIXTURES

A number of potassium-containing products are mixtures of KCl and $KHCO_3$; KCl, $KHCO_3$, and K_2CO_3; KCl, $KHCO_3$, and citric acid; KCl, $KHCO_3$, and potassium citrate; $KHCO_3$ and citric acid; KCl and potassium gluconate; $KHCO_3$, potassium citrate, and potassium acetate; and potassium citrate and potassium gluconate. Those that combine $KHCO_3$ with citric acid are effervescent; some effervescent preparations contain betaine.HCl or lysine.HCl in lieu of, or in addition to, citric acid. Those that are not reconstituted for effervescence are intended for their alkalinizing effects in addition to their effects to repair potassium deficits. $KHCO_3$ and K_2CO_3 are directly alkalotic; potassium acetate, citrate, and gluconate all metabolize to $KHCO_3$. Since hy-

pokalemia usually is accompanied by *alkalosis,* there are few situations in which an alkalinizing source of potassium is rational. Examples in which hypokalemia and acidosis coexist are renal failure, dehydration, and sometimes diabetic acidosis. Even in these, clinical experience is that KCl alone seems to be as useful as the combinations.

DIBASIC POTASSIUM PHOSPHATE

Potassium Phosphate Dibasic; Neutra-Phos

[7758-11-4] K_2HPO_4 (174.18).

Preparation—By partial neutralization of phosphoric acid with potassium hydroxide or carbonate.

Description—Granular powder; hygroscopic; pH (5% aqueous solution) about 8.5.

Solubility—Very soluble in water.

Comments—In the body, HPO_4^{2-} anion interacts with calcium ion in a way that favors the deposition of both calcium and phosphate in bone salts and in other tissues depots. Some of the phosphate also is converted to pyrophosphate, which is a chelator of calcium, the calcium-pyrophosphate complex being excreted in the urine. Furthermore, high plasma phosphate levels decrease calcitriol levels and thus decrease absorption of calcium. Thus, $KHPO_4$ causes redistribution from plasma to tissue, decorporation, and diminished incorporation of calcium. Its principal use is in the treatment of *hypercalcemia*. It is not used alone as a source of potassium or phosphate in potassium or phosphate deficiency. It is a component of *Potassium Phosphates, Potassium and Sodium Phosphates,* and *Dibasic Potassium and Sodium Phosphates*. It is also a reagent and pharmaceutical necessity for various buffers and parenteral fluids. It is no longer used as a laxative; it may cause diarrhea by the oral route. See *Monobasic Potassium Phosphate* for other adverse effects.

MONOBASIC POTASSIUM PHOSPHATE

Potassium Phosphate Monobasic; K-Phos; Neutra-Phos

[7778-77-0] K_2HPO_4 (136.09).

Preparation—As for *Dibasic Potassium Phosphate*.

Description—pH (5% aqueous solution) about 5.

Solubility—1 g in about 5 mL water.

Comments—See *Dibasic Potassium Phosphate* for actions to decrease calcium absorption, depress calcium levels in plasma, and enhance calcium excretion as pyrophosphate complex. The dibasic salt is likewise used to treat *hypercalcemia*. It is used to treat *nephrolithiasis* when the stones are calcific. In this, the decrease in free calcium excretion into the urine decreases stone formation, and acidification of the urine ($H_2PO_4^-$ causes acidosis) and free pyrophosphate ion favor dissolution of stones. It is a component of *Potassium Phosphates* and *Monobasic Potassium and Sodium Phosphates* and a pharmaceutical necessity for various parenteral fluids and buffers. Adverse effects are diarrhea by the oral route (it is poorly absorbed orally and acts as an osmotic cathartic), hypocalcemia (paresthesias, confusion, weakness, muscle cramps, dyspnea, irregular heartbeat) when employed vigorously in nonhypercalcemia patients, and the passing of loosened kidney stones.

POTASSIUM PHOSPHATES

A mixture of monobasic and dibasic potassium phosphate in the ratio described under each category below.

Comments—For actions, uses, and adverse effects, see *Dibasic Potassium Phosphate* and *Monobasic Potassium Phosphate*. Mainly used for hypercalcemia and hypophosphatemia.

POTASSIUM AND SODIUM PHOSPHATES

A mixture of mono- and dibasic potassium and sodium phosphates.

Comments—See *Dibasic Potassium Phosphate, Monobasic Sodium Phosphate, Dibasic Sodium Phosphate*. The mixture is advantageous in that it lessens the risk of sodium or potassium overload from a single-entity preparation. It is used mainly for *hypercalcemia* and *hypophosphatemia*.

MONOBASIC POTASSIUM AND SODIUM PHOSPHATES

A mixture of monobasic potassium and monobasic sodium phosphates.

Comments—See *Monobasic Potassium Phosphate* and *Monobasic Sodium Phosphate*. The combination is used to acidify the urine for the prevention and treatment of urolithiasis. The combination is advantageous in that it lessens the likelihood of excessive intake of either sodium or potassium from that of the single-entity components.

RINGER'S INJECTION—page 1323.
LACTATED RINGER'S INJECTION—page 1323.

SODIUM ACETATE

Sodium Acetate Trihydrate

[6131-90-4] $C_2H_3NaO_2.3H_2O$ (136.08); anhydrous [127-09-3] (82.03).

Preparation—By neutralizing acetic acid with sodium carbonate.

Description—Colorless, transparent crystals or granular, crystalline powder; slightly bitter, saline taste; effloresces in warm, dry air; the trihydrate liquefies at about 60°.

Solubility—1 g in 0.8 mL water or 19 mL alcohol.

Comments—The acetate ion is metabolized rapidly and completely in the body; consequently, administration eventually is equivalent to giving sodium bicarbonate. Solutions are stable and readily sterilized, and this salt has been used for parenteral therapy of metabolic acidosis and hyponatremia. It also may be used to alkalinize the urine. It is a pharmaceutical necessity used in solutions for hemodialysis and peritoneal dialysis.

SODIUM BICARBONATE

Carbonic acid, monosodium salt; Baking Soda; Sodium Acid Carbonate

Monosodium carbonate [144-55-8] $NaHCO_3$ (84.01).

Preparation—May be produced by the ammonia-soda, or *Solvay process*. In this process, CO_2 is passed into a solution of common salt in ammonia water, sodium bicarbonate is precipitated, and ammonium chloride, being much more soluble, remains in solution. The ammonium chloride solution is heated with lime, whereby the ammonia is regenerated and returned to the process.

Description—White, crystalline powder; odorless with a saline and slightly alkaline taste; solutions, when freshly prepared with cold water without shaking, are alkaline to litmus paper; alkalinity increases as the solutions stand, are agitated, or heated; stable in dry air, but slowly decomposes in moist air.

Solubility—1 g in 12 mL water; with hot water it is converted into carbonate; insoluble in alcohol.

Comments—All therapeutic uses accrue to the alkaline properties of $NaHCO_3$. Its most important uses are to *correct metabolic acidosis, alkalinize the urine,* and serve as a *buffer* in various parenteral, extracorporeal, and topical solutions. Examples of conditions that give rise to metabolic acidosis are uncontrolled diabetes mellitus, aspirin intoxication, ingestion of acidic or acid-forming drugs and other chemicals, hypoadrenalcorticism, renal tubular dysfunction, severe diarrhea, and circulatory shock. In metabolic acidosis, cardiac arrest may occur, and *cardiac resuscitation* may be accomplished with $NaCO_3$. Its systemic alkalinizing properties also are used in the management of *sickle-cell anemia,* an elevated plasma pH suppressing the sickling of erythrocytes. Urinary alkalinization is indicated in uricosuria (to favor the formation of the more soluble sodium urate and thus prevent uric acid nephroliths), *sulfonamide treatment* (to increase the solubility of sulfonamides and their metabolites and thus prevent crystalluria and nephrolithiasis), and *intoxication with weak acids,* in which the anionic form is excreted sufficiently fast that urinary alkalinization significantly hastens elimination (eg, aspirin or certain barbiturates).

It is used widely as a *gastric antacid* in lay medicine, but such use is discouraged by gastroenterologists. This is because $NaHCO_3$ is not retained in the stomach long, and the rapid evolution of CO_2 causes excessive belching, epigastric discomfort, and even sometimes dangerous gastric distention. Urinary alkalinization is considerable and favors calcific nephrolithiasis and nephrocalcinosis, and also the intake of sodium ion is held to be undesirable.

The effects of increased sodium intake are considered to be hypervolemia with consequent edema and hypertension. However, certain prominent medical opinion holds that it is the chloride and not the sodium ion in salt that favors hypervolemia and hypertension in persons with normal renal function. This may explain why few systemic adverse effects were found in clinical studies in which huge doses were administered chronically. This implies that systemic alkalosis, of itself, may be benign. Such studies notwithstanding, it is prudent to withhold $NaHCO_3$ from persons with congestive heart failure, edematous states, cirrhosis of the liver, hypertension, or the toxemia of pregnancy. It definitely is contraindicated in renal insufficiency, hypernatremia (can cause renal damage, especially in infants younger than 2 years), and calcific nephrolithiasis. It can promote an extracellular-to-intracellular shift of potassium, which can be especially adverse if hypokalemia and/or hypochloremia exists.

A paste or solution of $NaHCO_3$ is used topically on the skin as an antipruritic. It also is used in various effervescent mixtures as a source of carbon dioxide. Effervescence confers no therapeutic benefits except a placebo effect, but palatability is enhanced.

SODIUM CHLORIDE

Salt; Table Salt; Rock Salt; Sea Salt

Sodium chloride [7647-14-5] NaCl (58.44). It contains no added substance. (Table salt may contain added iodide and/or an anticaking agent).

Preparation—Common salt is distributed widely over the world, and may be obtained by mining, as rock salt, by evaporating a purified solution of saline deposits, or by evaporating sea water and purifying afterward. If free from contaminating salts it is not hygroscopic.

Description—Colorless, cubic crystals or a white crystalline powder; odorless with a saline taste; the solution is practically neutral; a 23% solution in water freezes at −20°.

Solubility—1 g in 2.8 mL water, 10 mL glycerin, or 2.7 mL boiling water; slightly soluble in alcohol.

Comments—Solutions of this salt more closely approximate the composition of the extracellular fluid of the body than solutions of any other single salt. For example, more than 90% of the cation of the extracellular fluid is sodium, more than 60% of the anion is chloride. Furthermore, a 0.9% solution has approximately the same osmotic pressure as body fluids, ie, is isotonic with body fluids. Thus, an isotonic solution can be injected without affecting the osmotic pressure of the body fluids and without causing any appreciable distortion in chemical composition. An isotonic solution, therefore, is the choice as a vehicle for many drugs that have to be administered parenterally. The 0.9% injection is used widely as a substitute for plasma in *volume expansion,* most practitioners preferring it to a dextran because not only is it free of allergenicity, but it also increases the flow of lymph. The solution has the added advantage of being nonirritating to tissue. Isotonic solutions may be used as an enema or applied topically to intact or exposed tissues for purposes of *irrigation,* to keep tissues moist or to keep a cavity flushed, as in irrigation of the urinary bladder; for this purpose 0.45 or 0.9% *Sodium Chloride Irrigation* is used. Although the *Irrigation* is sterile and meets the pyrogen requirements of the *Injection,* it should not be used parenterally. Hypertonic solutions (2% or 5%) may be applied to the cornea, to diminish corneal edema in inflammation or chemosis. Hypertonic solutions also are injected into the amniotic fluid in the 16th to 24th wk of gestation to *cause abortion*. Since accidental intravenous injection can cause shock, pneumonia, fever, and other adverse effects, this procedure should be performed only if an intensive care unit is available.

The injection is used as an *electrolyte replenisher* for maintenance or replacement of deficits of extracellular fluid. Since the solution potentially is capable of producing metabolic acidosis (by diluting bicarbonate ion) and does not supply all major cations of the extracellular fluid, other solutions, such as lactated Ringer's injection, may be preferred if large volumes of fluids are to be administered. Other solutions of appropriate composition also must be employed if the composition of the extracellular fluid is distorted markedly. Sterile, pyrogen-free solutions usually are administered intravenously.

In persons who are unable to take fluids by mouth, a hypotonic injection (0.45%) may be used as a source of water, but hypotonic balanced electrolyte solutions with dextrose usually are preferred. In patients in whom a salt deficit exists disproportionately to dehydration, a hypertonic injection (3% or 5%) may be used, preferably in conjunction with sodium bicarbonate.

It is administered orally for the prevention of *heat cramps* (miner's cramps, low-sodium syndrome) caused by the depletion of sodium salts through copious perspiration. It is common to use tablets, but a beverage containing only 0.5% will prevent development of the symptoms. This salt is given in *adrenal cortical insufficiency* (Addison's disease), in which it decreases the requirement for adrenal cortical extract. It is used in the treatment of hypercalcemia, to increase glomerular filtration and consequent excretion of calcium.

Common salt is used as a preservative; 6% or more prevents the growth of *Clostridium botulinum* and other pathogens.

Overdosage may cause pulmonary edema; generalized edema; headache; tinnitus; sensation of warmth in lips, tongue, and torso; hypernatremia (characterized by abdominal, back, and pelvic pain, diarrhea, muscle twitching, hyperreactivity, confusion, numbness, stupor, convulsions, or coma); and, occasionally, cellular dehydration. It must be used cautiously in patients with cardiac or renal impairment or hypoproteinemia.

SODIUM CITRATE AND CITRIC ACID SOLUTION

A solution of sodium citrate and citric acid in purified water. It contains, in each mL, 95 to 105 mg of sodium citrate dihydrate ($C_6H_5Na_3O_7.2H_2O$) and 57 to 63 mg of anhydrous citric acid ($C_6H_8O_7$). It may contain preservatives and flavoring agents.

Comments—A *systemic* and *urinary alkanizer*. In the body the citrate is metabolized to bicarbonate, so that the effect is that of a dose of bicarbonate. The citric acid is metabolized to carbon dioxide and water and thus has only a transient effect on the systemic acid-base status; its function is as a temporary buffer component. Citrate can mobilize calcium from the bones and increase its renal excretion; this, along with the elevated urine pH, may predispose to urolithiasis. Oral citrate also interferes with calcium absorption.

SODIUM LACTATE INJECTION

Propanoic acid, 2-hydroxy-, monosodium salt

$CH_3CH(OH)COONa$

Monosodium lactate [72-17-3] $C_3H_5NaO_3$ (112.06); a sterile solution of lactic acid ($C_3H_6O_3$) in water for injection prepared with the aid of NaOH.

Note—Sterilize sodium lactate injection, preferably by steam under pressure.

Preparation—A weighed quantity of lactic acid, sufficient to yield the desired amount of sodium lactate, is diluted with water for injection. A volume of assayed, concentrated NaOH solution equivalent to the quantity of lactic acid is added, and the mixture boiled gently until all the lactic anhydride also has been converted into sodium lactate. After quickly cooling, the solution is diluted with *Water for Injection* to the proper volume, promptly filtered if necessary, ampuled, and sterilized.

Description—pH, diluted if necessary to about 0.16 *M* (20 mg/mL), 6.0 to 7.3.

Comments—As a substitute for sodium bicarbonate in solutions for *parenteral fluid* and *electrolyte therapy*. Since lactate ion generally is metabolized rapidly in the body, this salt is a potential source of fixed cation for correction of *metabolic acidosis*. However, in shock, severe liver disease, and various other hyperlactic acidemic states, lactate oxidation is impaired, and the compound is contraindicated. In persons with normal cellular oxidative capacity, lactate will be converted to bicarbonate in 1 to 2 hr. An advantage over sodium bicarbonate is that its solutions may be sterilized by boiling. It is used to accelerate the heart in hypokalemia.

DIBASIC SODIUM PHOSPHATE—page 1307.
MONOBASIC POTASSIUM PHOSPHATE—pages 1088 and 1340.

MONOBASIC SODIUM PHOSPHATE

Phosphoric acid, monosodium salt, monohydrate; Sodium Acid Phosphate; Sodium Dihydrogen Phosphate; Monosodium Orthophosphate; Monobasic Sodium Phosphate

Monosodium phosphate monohydrate [10049-21-5] $NaH_2PO_4.H_2O$ (137.99); *anhydrous* [7558-80-7] (119.98).

Preparation—By adding phosphoric acid to a hot concentrated solution of disodium phosphate until the liquid ceases to give a precipitate with barium chloride. The solution is then concentrated to the crystallization point.

Description—Colorless crystals or a white, crystalline powder; odorless and slightly deliquescent; solutions are acid to litmus and effervesce with sodium carbonate.

Solubility—Freely soluble in water; practically insoluble in alcohol.

Incompatibilities—Since sodium biphosphate is an acid salt, it is incompatible with *carbonate* and *alkalies* in general. In solution with *methenamine* it causes a slow evolution of formaldehyde.

Comments—A source of phosphorus in *hypophosphatemia* and *total parenteral nutrition*. Excessive plasma phosphate not only interacts with plasma calcium to transfer it to bone but also indirectly brings about a decrease in calcium absorption in the gut. Consequently, it sometimes is used to treat *hypercalcemia*. It is a pharmaceutical necessity for *Sodium Phosphates Injection, Sodium Phosphates Oral Solution*, *Sodium Phosphate and Sodium Biphosphate Enema* and *Oral Solution*, and *Potassium and Sodium Phosphates*, and various parenteral and topical solutions and buffers. Adverse effects are diarrhea, hypertension, edema in heart failure, ascites in hepatic dysfunction, hypocalcemia, metastatic calcification, and renal damage in adrenal insufficiency.

SODIUM PHOSPHATES INJECTION

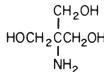
The usually available injection contains 276 mg (2 mmol) of monobasic sodium phosphate ($NaH_2PO_4.H_2O$) and 142 mg (1 mmol) of dibasic sodium phosphate (Na_2HPO_4) per mL, equivalent to a total of 93 mg (3 mmol) of phosphorus.

Comments—A source of phosphorus for *replacement* in phosphorus- depleted patients. It also can be used to treat *hypercalcemia,* since elevated plasma levels of phosphate promote deposition of calcium in bone salts and also loss in urine. The injection should be diluted before use and should be infused slowly to avoid phosphate intoxication. The patient should be monitored for serum levels of calcium, phosphorus,

and sodium and for renal function at frequent intervals. Concurrent administration with thiazides may cause renal damage. Each milliliter of the injection described above represents 92 mg (4 mEq) of sodium, which should be taken into consideration in using the injection in patients on sodium restriction.

TROMETHAMINE

1,3-Propanediol, 2-amino-2-(hydroxymethyl)-, THAM



2-Amino-2-(hydroxymethyl)-1,3-propanediol [77-86-1] $C_4H_{11}NO_3$ (121.14).

Preparation—Nitromethane is reacted additively with formaldehyde to yield tris(hydroxymethyl)nitromethane, and the nitro compound then is hydrogenated with the aid of Raney nickel. US Pat 2,174,242.

Description—White, crystalline powder with a slight, characteristic odor and a faint, sweet, soapy taste; stable in light and air; melts between 168 and 172°; pH (1 in 20 solution) 10.0 to 11.5.

Solubility—1 g in 1.8 mL water, 46 mL alcohol, or >10,000 mL chloroform.

Comments—For the prevention and correction of severe metabolic acidosis. It is a weak amine base with a pK_b of 7.8 at body temperature. This is close to plasma pH (7.4), so the compound is well-suited for the preparation of a buffer mixture for controlling extracellular pH.

Furthermore, at pH 7.4 it is 30% nonionized, and hence it gradually penetrates cells, where it also may buffer the intracellular contents. It can react with any proton donor, and the notion that it reacts primarily with carbonic acid or carbon dioxide is erroneous. By removing protons from hydronium ions, ionization of carbonic acid is shifted so as to decrease pCO_2 and to increase bicarbonate concentration. The excess bicarbonate then is excreted gradually in the kidney. This is an especially useful way to manage excessively high pCO_2 in *respiratory acidosis* (respiratory distress syndrome, asphyxia neonatorum, status asthmaticus, chronic respiratory insufficiency, drug intoxication, etc), in which pulmonary ventilation is inadequate. However, it equally is useful in the management of *metabolic acidosis* (drug intoxications, cardiac surgery, diabetic acidosis, etc), especially when the intracellular pH is low, since it readily penetrates cells.

It is used to prevent acidosis in cardiac bypass surgery, and it may be used in conjunction with other drugs in the treatment of cardiac arrest. The ionized drug is excreted by the kidney, so the effect is that of excretion of hydrogen ions. Elimination of the drug from the body is entirely by renal excretion. Excretion of tromethammonium ion is accompanied by osmotic diuresis, since clinical doses of the drug add considerably to the osmolarity of the glomerular filtrate. The drug should be used cautiously in renal disease. It also is used to buffer blood for transfusions, and it may be added to ACD blood as a buffer for storage purposes.

The principal untoward effects are related to its buffering action, namely that overdoses may cause alkalosis; respiration may be depressed because of the decrease in pCO_2 and increase in pH in plasma. Also, it is irritating locally because of its alkalinity; a slough may develop at a site of extravasation, and venospasm and thrombosis also may occur. The fact that about 70% remains in the extracellular space means that a sufficient amount of water must be given to prevent hyperosmolarity and hence to avoid tissue dehydration and the hemodynamic consequences of an increased blood volume.

Plasma hyperosmolarity, in general, causes hepatic and renal damage, and tromethamine is no exception. The hemorrhagic lines necrosis seen frequently in newborn infants treated with the drug may possibly have another origin, perhaps related to the route of administration (umbilical vein). The drug also causes hyperkalemia and hypoglycemia and may depress the respiratory center, especially in neonates and premature infants.

CATION-COMPLEXING AGENTS

The introduction of the arsenical war gas Lewisite and the proof by Carl Voegtlin that arsenicals combine with sulfhydryl groups led to the eventual development of dimercaprol (British antilewisite; BAL) in the 1940s. BAL has a high affinity constant because the two adjacent -SH groups enable the arsenic to attach to both sulfhydryl groups in a very stable five- membered ring structure. Such ring complexes were later called *chelates*. BAL also was shown to chelate a number of heavy metals, and it monopolized the role as a heavy metal antidote for nearly two decades.

In 1962, edetate disodium was introduced into medicine. It chelates calcium (and to a lesser extent, magnesium) in addition to various heavy metals. This led to an era in which edetate was used widely to lower plasma calcium levels and to attempt the decalcification of ateriosclerotic and calcinosed organs, and later it became an important decorporant for lead. Despite a spate of even newer chelating compounds, these early drugs are still in use.

Selectivity is a major problem in chelation therapy. Monovalent cations cannot be chelated sufficiently strongly so that chelating agents can be used to decrease plasma concentrations. Certain crown ethers can sequester monovalent cations selectively, but at present, only oral cation-exchange resins are used clinically in the decorporation of monovalent ions. With polyvalent cations, selectivity is achieved through the types of reactive groups, internal dimensions, and steric relations in the reagent. Still, selectivity presently is inadequate. For example, chelating agents for calcium also decorporate zinc and other alkaline earth metals. With radionuclides, this problem is circumvented, in part, by using the zinc chelate as a reagent for the radionuclide. Development in this area has been slow, not only because of chemical limitations but also because of a small market and consequent meager investment incentives.

CELLULOSE SODIUM PHOSPHATE

Calcibind

[68444-58-6] An insoluble, nonabsorbable ion-exchange resin with a great affinity for calcium ions.

Preparation—US Pat 2,759,924.

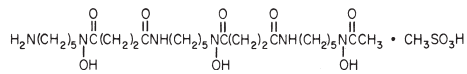
Description—White to cream-colored powder; must be stored in tightly closed containers to minimize hydrolysis during storage. It contains about 34% inorganic phosphate and 11% sodium. Each gram exchanges approx 1.8 mmol of Ca.

Solubility—Practically insoluble in water, dilute acids, and organic solvents.

Comments—Exchanges sodium for calcium and other polyvalent cations. By the oral route it decreases the amount of calcium absorbed from the diet, supposedly without altering calcium balance. It is used to treat a type of absorptive hypercalcuria that occurs even on low-calcium diets. The effectiveness in suppressing nephrolith formation ranges from nil to much according to various reports. During treatment, hyperoxaluria and hypermagnesemia occur, both of which favor certain kinds of kidney stones. The drug is unpalatable and may cause GI discomfort. Acute arthralgias from drug-induced hyperparathyroidism have been reported. Every 15 g contains 25 to 50 mEq of sodium.

DEFEROXAMINE MESYLATE

Butanediamide, *N′*-[5-[[4-[[5-(acetylhydroxyamino)pentyl]amino]-1,4-dioxobutylhydroxyamino]pentyl]-*N*-(5-aminopentyl)-*N*-hydroxy-, monomethanesulfonate; Desferal Mesylate



[138-14-7] $C_{25}H_{48}N_6O_8CH_4O_3S$ (656.79).

Preparation—Isolated from cultures of *Streptomyces pilosus* by the method of Bickel *et al* (*Helv Chim Acta* 1960; 43: 2118) or synthesized by the method of Prelog and Walser (*Helv Chim Acta* 1962; 45: 631).

Description—White crystals; reconstituted solutions are stable for 2 weeks at room temperature.

Solubility—1 g in 5 mL water or 20 mL alcohol; practically insoluble in organic solvents.

Comments—A chelating agent that is selective for iron, but it does complex with aluminum. It is used for the treatment of *severe iron intoxication,* iron overload resulting from hemolysis (from drugs, thalassemia, sickle-cell anemia, frequent blood transfusions, etc.), or *iron storage disease*. It is used to treat *hemodialysis-related porphyria*. Stoichiometrically, 100 mg of deferoxamine sequesters 8.5 mg of ferric iron. Although it does not bind ferrous ion appreciably, it has, nevertheless, proved useful in the treatment of intoxication by ferrous and ferric salts, probably partly because some of the toxicity of ferrous salts is due to ferric ion resulting from oxidation of the divalent iron. Also, partly because complexation of the ferric ion favors further oxidation of ferrous ion and

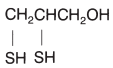
so promotes a diminution in the content of the divalent form. It can decorporate aluminum, and it has been used to manage aluminum accumulation in bone for patients on hemodialysis.

The drug is not absorbed orally and must be given parenterally. By intermittent or continuous subcutaneous infusion the drug is two to three times more effective than by intramuscular or intravenous injection. This can be achieved in ambulatory patients with an automatic syringe strapped to the waist. Ascorbic acid, 1 g twice a day, also greatly increases its efficacy.

Pain and induration may occur at the site of an intramuscular injection. Other untoward effects include erythema, flushing, diarrhea, blurring of vision, optic neuropathy, high-frequency hearing loss, abdominal discomfort, muscular spasms in the legs, itching, tachycardia, and fever. In long-term therapy, various allergic reactions, including anaphylaxis, have been reported. It is a growth factor for many bacteria and enhances virulence; *Yersinia* sepsis and mucormycosis have occurred in patients under treatment with the drug. Because of the side effects, it should not be used to treat mild iron intoxication. The drug is contraindicated in severe renal impairment. Long-term treatment has caused visual and hearing disturbances. The iron chelate (ferrioxamine) is excreted by the kidney and imparts a reddish color to the urine.

DIMERCAPROL

1-Propanol, 2,3-dimercapto-, British Anti-Lewisite; BAL in Oil



[59-52-9] $C_3H_8OS_2$ (124.22) and not more than 1.5% 1,2,3-trimercaptopropane ($C_3H_8S_3$).

Preparation—A methanol solution of NaOH is saturated with hydrogen sulfide, resulting in the formation of sodium hydrogen sulfide (NaSH). 2,3-Dibromopropanol is added and the mixture heated at 40° under pressure. 2,3-Dibromopropanol is prepared by bromination of allyl alcohol.

Description—Colorless or almost colorless liquid; offensive, mercaptan-like odor; specific gravity, 1.242 to 1.244; boiling range, 66 to 68° (0.2 torr).

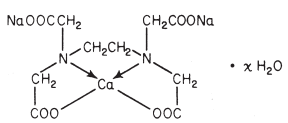
Solubility—1 g in about 20 mL water; soluble in alcohol, benzyl benzoate, or vegetable oils.

Comments—An *antidote,* in oil solution, in the treatment of *arsenic, gold,* or *mercury poisoning*. The drug may be of value in the treatment of antimony, thallium, or bismuth poisoning. It is used in the treatment of acute *lead encephalopathy* only in conjunction with *Edetate Calcium Disodium*. The thiol groups of dimercaprol compete with the physiologically essential-SH groups found in the tissues and thus remove the metal ions. The combination of heavy metal and dimercaprol is a stable compound that is excreted. It particularly is useful in hemorrhage encephalitis resulting from arsenotherapy, in arsenical or gold dermatitis, and, possibly, in postarsenical jaundice.

It usually causes hypertension and tachycardia, which lasts for about 2 hr. It often causes nausea, vomiting, headache, burning sensations in the mouth and throat, and a feeling of pressure in the throat, chest, and hands. It also may cause conjunctivitis, lacrimation, salivation and rhinorrhea, sweating, and abdominal pain. Sterile abscesses often occur at the site of injection. In children, fever frequently occurs; it appears after the third dose and remains throughout the course.

EDETATE CALCIUM DISODIUM

Calciate(2-), [[*N,N′*-1,2-ethanediylbis[*N*-(carboxymethyl)-glycinato-(4-)-*N,N′, O,O′,O*^{N}*O*$^{N′}$-, disodium, hydrate (*OC*-6-21)-, Calcium Disodium Versenate



Disodium (ethylenedinitrilo)tetraacetato] calciate(2-) hydrate; calcium disodium ethylenediaminetetraacetate hydrate [23411-34-9] $C_{10}H_{12}CaN_2Na_2O_8.xH_2O$; *anhydrous* [62-33-9] (374.27); a mixture of the dihyrate and trihydrate of calcium disodium ethylenediaminetetraacetate (predominantly the dihydrate).

Preparation—Among other ways, by boiling an aqueous solution of edetate disodium (below) with slightly more than an equimolar quantity of calcium carbonate until carbon dioxide no longer is evolved, filtering while hot, and crystallizing.

Description—White, crystalline granules or white, crystalline powder; odorless, slightly hygroscopic and a faint, saline taste; stable in air.

Solubility—Freely soluble in water.

Comments—Primarily in the diagnosis and treatment of *lead poisoning* but may be used for removing certain other heavy metals from the body. As a diagnostic agent, it causes a surge of lead into the urine, the magnitude of which reveals the extent of the body's burden of lead. Treatment is usually by intravenous infusion, but in lead encephalopathy the infusion fluid exacerbates the cerebral edema, so the drug is given, instead, by the intramuscular route in a hyperosmotic concentration. Since this agent already contains calcium it is useless as an anticoagulant or for treatment of hypercalcemia. Indeed, the purpose of calcium in the compound is to prevent the loss of calcium.

During infusion there may be transitory hypotension, inversion of the T-wave of the ECG, and prolongation of prothrombin time. Fever sometimes occurs 4 to 8 hr after an infusion. It is accompanied by malaise, fatigue, thirst, and chills. Myalgia, headache, vomiting, and increased urinary urgency often follow. Sneezing, nasal congestion, lacrimation, glycosuria, anemia, and dermatitis also occasionally occur. Edetate sometimes causes a usually reversible hydropic degeneration of the renal tubular epithelium, especially in the lower nephron. Some of the adverse effects are the result of decorporation of zinc.

It is eliminated entirely in the urine, with a half-life of 1 hr, except longer in renal insufficiency.

EDETATE DISODIUM

Glycine, *N,N′*-1,2-ethanediylbis[*N*-(carboxymethyl)-, disodium salt, dihydrate; Diso-Tate; Endrate; Edathamil; Disodium Versenate

$(HOOCCH_2)_2NCH_2CH_2N(CH_2COONa)_2 \cdot 2H_2O$

Disodium (ethylenedinitrilo)tetraacetate dihydrate [6381-92-6] $C_{10}H_{14}N_2Na_2O_8.2H_2O$ (372.24); *anhydrous* [139-33-3] (336.21).

Preparation—(Ethylenedinitrilo)tetraacetic acid is dissolved in a hot solution containing two equivalents of NaOH, and the disodium salt is allowed to crystallize.

Description—White, crystalline powder.

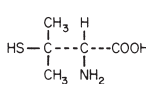
Solubility—Soluble in water; pH (1 in 20 solution) 4.0 to 6.0.

Comments—To remove free calcium ions from solution, since it readily chelates calcium; thus, it may be used as an *anticoagulant* in the same manner as sodium citrate. Intravenously, it *temporarily lowers plasma calcium* concentration, but the effect is too brief to be of value in the treatment of hypercalcemia; constant infusion can yield a more sustained effect. It is employed occasionally to *terminate* abruptly *the effects of injected calcium* and to *antagonize digitalis toxicity,* or *suppress tachyarrhythmias*. The drug is not effective in the treatment of arteriosclerosis, since calcium is mobilized more easily from bone. It can dissolve precipitated calcium salts.

It may cause nausea, vomiting, diarrhea, transient circumoral paresthesias, numbness, headache, and a transient hypotension. Too-rapid an injection can cause death. Fever, anemia, exfoliative dermatitis, and other toxic effects on skin and mucous membranes occasionally occur. When given intravenously, it sometimes has a nephrotoxic action. Overdosage can result in damage to the reticuloendothelial system. Prolonged infusion may cause zinc and magnesium deficiencies. It is contraindicated in patients with impaired renal function with severe azotemia and should be used cautiously in the presence of liver impairment and hypokalemia.

PENICILLAMINE

D-Valine, 3-mercapto-, Cuprimine; Depen



β,β-Dimethylcysteine; D-3-Mercaptovaline [52-67-5] $C_5H_{11}NO_2S$ (149.21).

Preparation—By acid hydrolysis of penicillin. It is precipitated from the hydrolysis mixture as the mercuric salt, which is then collected, suspended in water, and treated with hydrogen sulfide to liberate the free acid. Purification involves only recrystallization from water. Penicillamine also is obtained by synthesis.

Description—Fine, white or practically white, crystalline powder; slight, characteristic odor and a slightly bitter taste; relatively stable in both light and air; melts at about 200° with decomposition; pH (1 in 100 solution) 4.5 to 5.5.

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

Comments—A chelating agent useful in the treatment of *Wilson's disease* and *biliary cirrhosis* (in which the serum and liver copper concentrations, respectively, are excessively high), and *lead, gold,* or *mercury poisoning*. It especially is useful in the long-term treatment of lead poisoning because of its oral efficacy, which the edetates lack. It also is useful in the treatment of *cystinuria* and *rheumatoid arthritis;* plasma cystine levels fall in the former during treatment but rise in the latter. The mechanism in rheumatoid arthritis is uncertain but has been attributed to a marked reduction in concentrations of IgM rheumatoid factor or to the scavenging of oxygen free radicals. The drug is investigational in the treatment of biliary cirrhosis.

Side effects most often appear shortly after therapy has begun. It may cause ecchymosis, hematuria dermatitis, eruptions of the mucous membranes, leukopenia, thrombocytopenia, agranulocytosis, fever, polyarthralgia, glomerulopathy, nephrosis, lymphadenopathy, and optic neuritis. Anorexia, nausea, epigastric pain, diarrhea, vomiting, stomatitis, peptic ulcer, and disorders of taste are also common effects. Some of these effects are the result of decorporation of zinc. Tinnitus and optic neuritis occur as the result of drug-induced pyridoxine deficiency; pyridoxine supplements are advised. Cholestatic jaundice, toxic hepatitis, lupus erythematosus, bronchiolitis, alveolitis, pemphigoid, myasthenia, and pancreatitis occur rarely. Blood counts must be made every 2 weeks during the first 6 months of therapy. Once therapy has begun, treatment should be continued on a daily basis, as even short interruptions have been followed by sensitivity reactions.

SODIUM POLYSTYRENE SULFONATE

Benzene, ethenyl-, homopolymer, sulfonated, sodium salt; Kayexalate

Styrene polymer sulfonated, sodium salt; a cation-exchange resin prepared in the sodium form. Each gram exchanges 2.8 to 3.5 mEq of potassium.

Description—Golden brown, fine powder; odorless and tasteless.

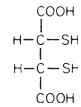
Solubility—Insoluble in water.

Comments—An ion-exchange resin used for the treatment of hyperkalemia resulting from acute renal failure. The resin is given orally by a stomach tube or as a high-retention enema. The sodium moiety of the resin is, in part, replaced by potassium, which subsequently is eliminated from the body when the resin is excreted in the feces or in the enema. The potassium-removing capacity of the resin is approximately 1/3 of that possible when measured under conditions in which potassium is the only cation present. The resin should be an adjunct to other therapeutic measures, such as restriction of electrolyte intake, control of acidosis, and high-caloric diet. Untoward effects include anorexia, nausea, vomiting, and constipation. Constipation and fecal impaction can be minimized by the administration of 70% sorbitol solution every 2 hr as needed to produce watery stools. Serum potassium levels should be determined daily to avoid hypokalemia.

The resin may cause gastric irritation, nausea, vomiting, and occasional diarrhea. Especially in elderly patients, large doses may cause fecal impaction. Since the resin can sequester calcium and magnesium, hypocalcemia, hypomagnesemia, or related effects may occur, and mineral metabolism should be monitored during prolonged treatment. The drug should be used with caution in patients with actual or impending cardiac failure; the absorption of the released (exchanged) sodium may be hazardous in such patients. It also may exaggerate the effects of digitalis.

SUCCIMER

Butanedioic acid, *(R,S)*-2,3-dimercapto-, Chemet



meso-2,3-Dimercaptosuccinic acid; DMSA; DIM-SA [304-55-2] $C_4H_6O_4S_2$ (182.21).

Preparation—*J Chem Soc* 1949; 71: 3109.

Description—White crystalline powder with an unpleasant mercaptan-like odor and taste; melts at about 193°.

Comments—Has a broader spectrum of chelating activity than does dimercaprol, owing to the presence of carboxyl groups in the molecule. However, it is selective for lead and is used in the treatment of lead intoxication. Its advantages are that it can be administered orally and that adverse effects are few and mild. Mild, transient elevation of plasma SGPT levels occurs. An increase in copper and zinc excretion has been noted, but no pathology attributed to loss of these metals has been observed. The drug probably will eventually replace dimercaprol in the treatment of lead and certain other heavy metal poisonings. Technetium-99 (^{99}Tc) DMSA is used for renal imaging. The compound is excreted in both the urine and bile.

TRIENTINE HYDROCHLORIDE

1,2-Ethanediamine, *N,N′*-bis(2-aminoethyl)-, dihydrochloride; Syprine (formerly Cuprid)

$H_2N(CH_2)_2NH(CH_2)_2NH(CH_2)_2NH_2 \cdot 2HCl$

Triethylenetetramine hydrochloride [38260-01-4] $C_6H_{18}N_4.2HCl$ (219.16).

Preparation—See *J Org Chem* 1944; 9: 125.

Description—White to pale-yellow hygroscopic crystals, melts about 117°.

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

Comments—A tetramine chelating agent that lacks sulfhydryl and oxygen-containing groups and hence has a low affinity for most of the transition and heavy metals, yet retains a high affinity for copper. The relative affinity for copper enables the drug to be used for the treatment of *Wilson's disease* without the side effects attributable to decorporation of zinc. It also presently does not appear to cause the hypersensitivity and immune disorders evoked by penicillamine. However, penicillamine-induced lupus erythematosus sometimes fails to remit or even recurs during treatment. It is approved only for the treatment of Wilson's disease in patients intolerant to penicillamine, but its low toxicity most certainly will result in the displacement of penicillamine in the treatment of this disease. The only significant adverse effect observed thus far is iron-deficiency anemia; that it is really the result of copper deficiency and not iron decorporation is demonstrated by the response of the anemia to copper.

HEMATOLOGICAL DRUGS AFFECTING BLOOD PRODUCTION

HEMATOPOIETICS

Hematopoietics are *antianemics* that aid in the production of red and white blood cells; *hematinics* are *antianemics* that increase the hemoglobin content of blood through erythropoiesis or through an increase in hemoglobin content of erythrocytes. The choice of a hematinic critically depends upon the nature of the anemia. The hypochromic anemias are nearly all iron-deficiency anemias in character and are treated with iron preparations. Occasionally, other accessory factors are indicated in the treatment of the hypochromic anemias. As long as 6 months of treatment may be required to replenish the body stores of iron and correct various anemias. For example, the anemia of nurslings may require copper to facilitate the mobilization of iron from the gut and tissues.

Ascorbic acid occasionally helps promote the antianemic action of iron. When given with iron salts, it promotes the absorption of iron, in part by reducing the less-well-absorbed ferric ion to the better-absorbed ferrous ion or maintaining the ferrous state of administered ferrous salts and in part by forming an absorbable complex with iron. However, ascorbic acid appears to have an additional but obscure role in hematopoiesis; it is included in a number of iron-containing products.

Cobalt and molybdenum probably also play a role in hematopoiesis, but deficiency syndromes in man are unknown, and the inclusion of these metals in hematinic preparations is irrational. The use of cobalt even may be dangerous. Although copper is known to have a hematopoietic function, a deficiency in man severe enough to impair erythropoiesis has never been

demonstrated, although trientine can cause a copper-responsive anemia.

The macrocytic anemias all respond to cyanocobalamin, but the route of administration and accessory factors depend critically upon the particular anemia. In tropical sprue, the absorption of folic acid is impaired to a greater extent than that of vitamin B_{12}, so that folic acid usually elicits the greater hematopoietic response. For reasons stated elsewhere, the promiscuous use of folic and folinic acids should be condemned. In pyridoxine deficiency, protoporphyrin synthesis and hence erythropoiesis is impaired, and pyridoxine restores normal erythropoiesis.

Iron and Iron Compounds

Iron is used in medicine in the form of inorganic and simple organic ferrous compounds (ferrous sulfate, etc) and complex ferrous compounds.

Complex (nonionic) iron compounds do not respond to the ordinary tests for ferrous or ferric ions because the iron in them is part of a complex radical. The stabilities of these complex radicals differ widely. Some are converted to simple ionic iron by the action of dilute acids, while others resist treatment with strong acids or with alkalies. The complex iron compounds occurring naturally in animal and vegetable tissues (termed *food irons*) belong generally to the more resistant class, while the complex iron compounds produced artificially are as a rule decomposed rather readily. There is, however, no sharp distinction between the natural complex iron compounds and those products artificially produced, nor is there any good evidence that they differ in therapeutic action.

Comments—The principal use of iron is in the treatment of *hypochromic, iron-deficiency anemias,* that is, in anemias characterized by a deficiency of hemoglobin. The two most common causes of such anemias are nutritional (deficient intake, especially in infancy, in childhood, at puberty, during pregnancy, and late in menstrual life or at the menopause) and chronic blood loss (especially bleeding peptic ulcer, carcinoma of the colon or stomach, bleeding from the urinary tract, or excessive loss of blood during menstruation). Iron therapy is of no particular value in other forms of anemia, such as pernicious anemia, unless patients have entered an iron-deficiency stage of the disease.

Complex iron compounds generally are less prone to produce gastric distress than the simple ferrous compounds; they also are used less efficiently physiologically. Indeed, in some complexes the iron may be chelated so effectively as to escape use altogether.

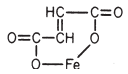
Differences exist among the different iron preparations in their local irritant and astringent actions, which are absent in most of the complex iron compounds; for this reason the less-astringent and less-irritant ferrous salts are used rather than ferric salts. The irritation occurs mostly in the stomach and upper duodenum, where the pH is low. It can exacerbate peptic ulcer, regional enteritis, ulcerative colitis, and other GI disorders. Enteric coatings allow the preparations to pass into the more alkaline portions of the gut before release occurs. However, the absorption of iron from enteric-coated preparations is less than in uncoated ones, especially in persons with bowel hypermotility. In steatorrhea or in persons with partial gastrectomy, iron preparations often are absorbed poorly. Antacids also diminish absorption. Constipation consequent to local actions of iron may be countered by cathartics, properly individualized. Suitable diet (especially liver, kidney, and meat) is sometimes more effective than the iron preparations, presumably by the cooperation of other factors.

All of the iron preparations are capable of causing severe intoxication in overdoses, especially in children. Iron preparations are a common cause of lethal intoxication in children.

ASCORBIC ACID—pages 912 and 913.

FERROUS FUMARATE

2-Butenedioic acid, *(E)*-, iron(2+) salt



Iron(2+) fumarate [141-01-5] $C_4H_2FeO_4$ (169.90).

Preparation—Ferrous sulfate and sodium fumarate are metathesized in hot aqueous solution, whereupon the sparingly soluble, anhydrous ferrous fumarate precipitates.

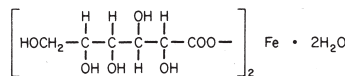
Description—Reddish orange to red-brown, odorless powder; may contain soft lumps that produce a yellow streak when crushed.

Solubility—Slightly soluble in water; very slightly soluble in alcohol; its solubility in dilute HCl is limited by the separation of insoluble free fumaric acid.

Comments—In the clinical management of *iron-deficiency anemias*. Its efficacy is about the same as that of ferrous sulfate, but the untoward effects are somewhat less severe. The drug may sometimes be employed without difficulty in patients who cannot tolerate other preparations of iron. When side effects occur, they include anorexia, nausea, vomiting, cramping, and constipation or diarrhea. Like other iron preparations, this drug may exacerbate GI diseases, especially ulcerative ones. The effects generally subside as therapy is continued. The untoward effects are minimized if the dose is taken shortly after eating.

FERROUS GLUCONATE

D-Gluconic acid, iron(2+) salt (2:1), dihydrate



Iron(2+) gluconate (1:2) dihydrate [12389-15-0] $C_{12}H_{22}FeO_{14}.2H_2O$ (482.17); *anhydrous* [299-29-6] (446.14).

Preparation—By metathesis between hot solutions of calcium gluconate and ferrous sulfate whereby ferrous gluconate and insoluble calcium sulfate are formed. The mixture is filtered while hot to minimize the solubility of calcium sulfate, and the filtrate is evaporated to crystallization.

It also may be produced by heating freshly prepared ferrous carbonate with the proper quantity of gluconic acid in aqueous solution.

Description—Fine, yellowish gray or pale greenish yellow powder or granules, with a slight burnt-sugar-like odor; affected by light; the ferrous iron slowly oxidizes to ferric on exposure to air; aqueous solution is acid to litmus (color of the solution depends on pH—they are light yellow at pH 2, brown at pH 4.5, and green at pH 7); the iron rapidly oxidizes at higher pH.

Solubility—1 g in about 5 mL water with slight heating; practically insoluble in alcohol; it forms supersaturated solutions that are stable for a period of time; its solubility is increased by addition of citric acid or the citrate iron.

Comments—A *hematinic,* similar to other ferrous salts. Its side effects and toxicity are those of all iron compounds; it is claimed that it causes fewer side effects than ferrous sulfate (see under *Iron and Iron Compounds*). The elixir can cause staining of the teeth if taken undiluted.

FERROUS SULFATE

Sulfuric acid, iron(2+) salt (1:1), heptahydrate; Ferri Sulfas; Feosol

Iron(2+) sulfate (1:1) heptahydrate [7782-63-0] $FeSO_4.7H_2O$ (278.01); *anhydrous* [7720-78-7] (151.90).

Note—Do not use Ferrous Sulfate that is coated with brownish yellow basic ferric sulfate.

Preparation—By dissolving iron in diluted H_2SO_4. The resulting solution is filtered and concentrated, if necessary, to the point of crystallization of ferrous sulfate. Commercially, scrap iron is used in the process.

Description—Pale, bluish green crystals or granules; odorless, has a saline, styptic taste, and effloresces in dry air, becoming white; oxidizes readily in moist air to form brownish yellow basic ferric sulfate; pH (1 in 10 solution) about 3.7.

Solubility—1 g in 1.5 mL of water or 0.5 mL of boiling water; insoluble in alcohol.

Comments—One of the most commonly employed *hematinic preparations* used in iron-deficiency anemias (see under *Iron and Iron Compounds*). The drug is dispensed most commonly as capsules or tablets coated for protection from air and moisture. The salt sometimes is mixed with glucose or lactose to protect it from oxidation.

Its adverse effects are those of iron compounds in general, but they are rarely severe when the salt is taken in therapeutic doses; however, relatively small overdoses can cause serious intoxication in infants and children. The oral solution can cause staining of teeth if used undiluted.

About 20% of this drug is absorbed when taken orally. Timed-release and enteric-coated preparations tend to be absorbed more erratically and are not recommended. Magnesium and aluminum hydrox-

ides, present in some preparations, make the iron unavailable for absorption.

IRON DEXTRAN INJECTION

InFeD

A sterile, colloidal solution of ferric hydroxide in complex with partially hydrolyzed dextran of low molecular weight, in water for injection. It may contain not more than 0.5% of phenol as a preservative.

Preparation—To an aqueous solution of partially depolymerized dextran (intrinsic viscosity 0.04–0.07) is added a solution of alkali and a solution of a ferric salt. The mixture is heated, then cooled to room temperature, clarified by centrifugation, and the solution dialyzed against running water. After concentrating to the required iron content, the solution is filtered, ampuled, and sterilized by autoclaving.

Description—Dark-brown, slightly viscous liquid; pH 5.2 to 6.

Comments—Because iron is strongly chelated by dextran, it is not locally irritating on intramuscular injection. Absorption is rapid from an intramuscular site. Thus the drug is used for intramuscular injection in patients with iron-deficiency anemias when oral therapy cannot be tolerated or does not evoke a therapeutic response. If the drug is administered to persons not in an iron-deficient state, hemosiderosis may occur. Absorption is very slow from a subcutaneous site, and a brown stain occurs that may remain for 1 to 2 years. Consequently, in injecting the drug, care must be taken to prevent leakage under the skin. Injections are given deeply into the upper-outer quadrant of the buttock by a special technique called a Z-track injection, which diminishes leakage to subcutaneous sites.

In the human the lymphatic system is well-developed, and the dose of the complex is relatively low, so that the danger of malignancy, as occurs in some animals, is very slight. However, it can cause fibrosis at the site of injection. Allergic reactions, even anaphylaxis, have occurred. Consequently, a test of 0.5 mL of the injection should be given prior to therapeutic administration. Headache, fever, nausea, vomiting, paresthesias, and regional lymphadenopathy are relatively common side effects. Hypotension, reactivation of quiescent arthritis, leukocytosis with fever, and sterile abscesses at an intramuscular injection site may occur. Phlebitis occasionally occurs after intravenous administration. The parenteral use of iron and carbohydrate has resulted in fatal anaphylactic-type reactions. Consequently, use of iron dextran should be reserved for patients with a clearly established iron deficiency not amenable to oral iron therapy.

POLYFEROSE

β-D-Fructofuranosyl α-D-glucopyranoside deriv, polymer, iron complex; Jefron

[9009-29-4] A chelate of iron with a polymerized derivative of sucrose, containing about 45% Fe.

Comments—For the treatment of iron-deficiency anemias. The complex is less astringent than ferrous salts and hence is more palatable in oral suspension.

Agents for Macrocytic Anemias

The macrocytic anemias are characterized by the presence of large, hypochromic erythrocytes. They include *pernicious anemia, the anemia of sprue, macrocytic tropical anemia, fish tapeworm anemia, achrestic anemia,* and anemias resulting from gastric carcinoma and resection or disease of the intestinal tract. In all of these, insufficient intake or absorption of *cyanocobalamin* (vitamin B_{12}) is the cause of the disorder, the vitamin being essential to normal hematopoiesis and to the integrity of the central nervous system. Early work on pernicious anemia established the need for a dietary factor, called the *extrinsic factor,* and a gastric and upper duodenal secretory factor, called the *intrinsic factor*.

It is now well-established that cyanocobalamin is the extrinsic factor; the vitamin is also the *antianemia component* of liver. The intrinsic factor is essential for the proper absorption of vitamins B_{12}. The intrinsic factor is absent in pernicious anemia; in this disease the secretion of hydrochloric acid and pepsin also is diminished or absent. Before the advent of cyanocobalamin (a vitamin B_{12}), various liver preparations were employed as sources of extrinsic factor, and stomach preparations as sources of the intrinsic factor. Since orally administered liver was not reliable, because it did not provide the intrinsic factor, it was necessary to administer a stomach preparation at the same time or to administer the liver parenterally. Today, the preparation of choice is cyanocobalamin, which is cheaper and causes less discomfort at the site of injection than liver. Oral cyanocobalamin, of course, like liver, optimally requires a source of intrinsic factor.

For the patient with uncomplicated pernicious anemia in relapse, the initial dose of cyanocobalamin is 30 μg a day, parenterally, or every other day for 5 to 10 doses, followed by 15 to 30 μg once or twice a week until the blood picture is normal. For maintenance, 40 to 60 μg every 2 weeks or 80 to 100 μg once a month is usually adequate. If there is demonstrable neurological damage, it may be necessary to administer 1000 μg a week for several months before switching to the maintenance schedule. Therapy must be maintained for life, since the basic deficiency in GI physiology remains. Nevertheless, the patient may be kept in good health and may lead a fairly normal life.

Despite the superiority of cyanocobalamin, liver and stomach preparations still are available. The ingestion of 200 to 400 g of whole liver may be effective irregularly in inducing a remission in pernicious anemia. Concentrates for oral administration are made from such amounts of liver, but concentration results in some loss of activity. Extracts suitable for parenteral administration may be prepared from 10 to 15 g of liver. Similar effects may be produced by the ingestion of 30 to 40 g of desiccated stomach; however, the combinations of stomach and liver are required for optimal oral therapy.

Liver preparations for injection may be assayed microbiologically, employing *Lactobacillus leichmannii* ATCC 7830, the assay being expressed in terms of cyanocobalamin. However, since oral preparations rarely are effective, owing to the absence of the intrinsic factor, the assay must be made in the human pernicious anemia patient in relapse, and the assay is expressed in terms of oral units. This reflects the ridiculousness of using archaic and irregularly effective preparations when the active ingredient, cyanocobalamin, or derivatives, readily is available and is administered more easily and safely.

Megaloblastic anemia of infancy, megaloblastic anemia of pregnancy, achrestic anemia, and nutritional macrocytic anemia generally respond better to liver preparations than they do to cyanocobalamin, and deficiencies in *folic* and *folinic acid* intake or metabolism are implicated; thus, either of these two acids may evoke a dramatic response in such anemias. Ascorbic acid also occasionally may confer additional benefits. The metabolic functions of folic or folinic acid and vitamin B_{12} converge in certain respects. Thus, folic or folinic acid may induce a remission in the blood pathology in pernicious anemia, but it will not revert or delay the progression of the epithelial and neurological pathology, which may develop insidiously and emerge explosively and irreversibly. Therefore, folic or folinic acid therapy of pernicious anemia is to be condemned. *Equally offensive and irresponsible is the inclusion of these acids in liver or multivitamin-hematinic preparations* because, in allaying the blood pathology of undiagnosed pernicious anemia, they prevent detection of the disease until the neurological pathology has advanced to a dangerous state. Unfortified liver preparations also may contain enough folic acid to constitute the same danger. *In general, a hematinic should be employed only upon accurate diagnosis of the anemia and upon specific indication*. Multiple preparations are to be avoided.

HEMATOPOIETIC GROWTH FACTORS

The hematopoietic growth factors regulate the proliferation and differentiation of progenitor stem cells found in the bone marrow. They are glycoproteins that bind to specific cell surface receptors, resulting in a sequence of events culminating in hematopoiesis. Recombinant DNA technology has allowed the manufacture of sufficient quantities of these factors to enable

clinical trials in patients. Erythropoietin, which stimulates red blood cell production was the first human hematopoietic growth factor to be isolated and studied. It improves the anemia associated with several clinical conditions. Several of the colony-stimulating factors also have been purified, molecularly cloned, and expressed as recombinant proteins. Clinical trials in progress are evaluating their effectiveness in treating patients for a variety of hematological disorders. Two of the colony-stimulating factors, granulocyte colony-stimulating factor (G-CSF) and granulocyte-macrophage colony-stimulating factor (GM-CSF) are efficacious in the management of bone marrow hypoplasia, particularly after myelosuppressive chemotherapy. They not only stimulate the progenitor cell target but also result in some functional activation of the mature cell. It is anticipated that future therapy will use additional hematopoietic growth factors in various conditions involving altered hematological status.

EPOETIN ALFA

1-165-Erythropoietin (human clone λHEPOFL 13 protein moiety), glycoform α; Epogen; Procrit

[113427-24-0] $C_{809}H_{1301}N_{229}O_{240}S_5$ (34,400 ± 400) A 165–amino acid glycoprotein produced by Chinese hamster ovary cells into which the human erythropoietin gene has been incorporated.

Comments—Erythropoietin, a naturally occurring glycoprotein, stimulates the division and differentiation of erythroid progenitors in the bone marrow, resulting in red blood cell production. The kidney is the major source of erythropoietin in adults. Epoietin alfa stimulates erythropoiesis in chronic renal failure (CRF) patients who are anemic because of impairment of their endogenous erythropoietin production. It is effective in both patients on dialysis and those not requiring regular dialysis. As it requires several days for erythroid progenitors to mature and be released into blood, a clinically significant increase in hematocrit generally is not observed before 2 weeks. The treatment goal is to increase hematocrit to 30% to 33% and eliminate the need for blood transfusions. The rate of hematocrit increase depends on several factors including availability of iron stores, baseline hematocrit, concurrent medical problems, and the dose administered. For reasons discussed below, a rapid increase in hematocrit (eg, >4 points in any 2-week period) is undesirable. Epoetin alfa also is indicated for treatment of anemias related to zidovudine (AZT) therapy in HIV-infected patients who have endogenous erythropoietin levels <500 mU/mL and are receiving <4200 mg a week of AZT. Patients with endogenous erythropoietin levels >500 mU/mL do not appear to have a clinically significant response with epoetin alfa.

Prior to and during therapy, the patient's iron stores should be evaluated; transferrin saturation should be at least 20%, and ferritin at least 100 ng/mL. Supplemental iron may be required to increase and maintain transferrin saturation to adequate levels. Epoetin alfa therapy has been associated with increased blood pressure in many CRF patients. Blood pressure should be controlled adequately prior to administration of the drug and must be monitored closely and controlled during therapy. During the time when hematocrit is increasing, approximately 25% of dialysis patients require initiation of, or increases in, antihypertensive medication. The dose of drug should be decreased in patients with an excessive rate of hematocrit rise (eg, >4 points in any 2-week period), as this rapid increase may exacerbate the hypertensive response. Epoetin alfa is contraindicated in patients with uncontrolled hypertension or known hypersensitivity to either mammalian cell–derived products or human albumin. During hemodialysis, patients on this drug may require increased anticoagulation with heparin to prevent clotting of the artificial kidney.

FILGRASTIM

Colony-stimulating factor (human clone 1034), *N*-L-methionyl-, Neupogen

[121181-53-1] $C_{845}H_{1339}N_{223}O_{243}S_9$ (18,000.00). A single chain of 175 amino acids, nonglycosylated, produced by recombinant DNA technology, expressed by *E coli*.

Comments—Granulocyte colony-stimulating factor (G-CSF) is an endogenous glycoprotein that acts primarily on hematopoietic cells regulating the production of neutrophils within the bone marrow. It is effective in accelerating the recovery of neutrophil counts following a variety of chemotherapy regimens. In addition to regulating the production of neutrophils, G-CSF also enhances neutrophil functional activity including enhanced phagocytic ability, priming of the cellular metabolism associated with respiratory burst, and antibody-dependent killing. It is indicated to decrease the incidence of infection in patients with nonmyeloid malignancies receiving myelosuppressive anticancer drugs. Such patients experience a significant incidence of severe neutropenia with fever. Because of the potential sensitivity of rapidly dividing myeloid cells to cytotoxic agents, it should not be used 24 hr prior to, or within 24 hr after, chemotherapy. It is essential to obtain complete blood counts and platelet counts prior to the chemotherapy and twice a week during treatment with filgrastim. A transient increase in the neutrophil count typically occurs within the first 1 or 2 days following administration of filgrastim; however, for a sustained therapeutic effect it should be continued until the postchemotherapy nadir count reaches 10,000/mm^3. Medullary bone pain of mild-to-moderate severity is the major adverse effect and occurs in approximately 24% of patients. It is most frequent in patients treated with higher doses (20–100 μg/kg/day) administered IV and is reported less in patients treated with lower SC doses (3 to 10 μg/kg/day). Although filgrastim is a growth factor that primarily stimulates neutrophils, it could potentially act as a growth factor for tumor cells, and caution should be used if this drug is administered in any malignancy with myeloid characteristics. It is contraindicated in patients with known hypersensitivity to *E coli*–derived proteins.

OPRELVEKIN

2-178-Interleukin 11 (human clone PXM/IL-11)

H– GPPPGPPRVS PDPRAELDST VLLTRSLLAD TRQLAAQLRD
KFPADGDHNL DSLPTLAMSA GALGALQLPG VLTRLRADLL
SYLRHVQWLR RAGGSSLKTL EPELGTLQAR LDRLLRRLQL
LMSRLALPQP PPDPPAPPLA PPSSAWGGIR AAHAILGGLH
LTLDWAVRGL LLLKTRL–OH

[145941-26-0] $C_{854}H_{1411}N_{253}O_{235}S_2$ (19,047.40).

Preparation—Oprelvekin is a nonglycosylated protein of approximately 19,000 daltons consisting of 177 amino acids which is produced by recombinant DNA technology in *E coli* bacteria. It differs from native IL-11, which is composed of 178 amino acids, only by lacking proline in the amino terminus.

Description—Interleukin eleven (IL-11) is a naturally occurring growth factor that stimulates the proliferation of hematopoietic stem cells and megakaryocyte progenitor cells as well as promoting megakaryocyte maturation resulting in increased platelet production.

Comments—It is indicated to increase platelet counts and decrease the need for platelet transfusion following chemotherapy in patients with nonmyeloid malignancies who are likely to develop thrombocytopenia. In clinical trials of patients undergoing chemotherapy for various malignancies who had previously required a platelet transfusion, oprelvekin was found to reduce platelet transfusions significantly compared with placebo administration. A trial in breast cancer patients who had not previously shown severe thrombocytopenia due to chemotherapy, demonstrated that 65% (26 of 40) of patients avoided platelet transfusion compared with 41% (15 of 37) in the placebo cohort following two dose–intensive chemotherapy with cyclophosphamide and doxorubicin. Oprelvekin has been administered safely using the recommended dosing schedule for up to 6 cycles following chemotherapy; however the efficacy and safety of more prolonged, chronic dosing is not established. Patients treated concurrently with G-CSF demonstrated no adverse effects on its activity by oprelvekin; little information is currently available regarding the combination of oprelvekin and GM-CSF. A complete blood count should be obtained prior to chemotherapy and at regular intervals during therapy with dosing continued until the postnadir platelet count is <50,000 cells/μL. Moderate decreases of 10 to 15% in hemoglobin, hematocrit, and red blood cell count commonly occur within a few days of drug initiation and are primarily due to an increase in plasma volume. Patients receiving this agent often experience mild-to-moderate fluid retention resulting in peripheral edema (~60%) and dyspnea with exertion (~50%). The fluid retention is reversible within several days following discontinuation of therapy. The drug should be used with caution in patients with congestive heart failure, and fluid balance should be monitored in these patients. Close monitoring of both fluid and electrolyte balance is also necessary in patients receiving chronic diuretic therapy. Transient atrial arrythymias occur in approximately 10% of patients treated with oprelvekin, and the drug should be used with caution in patients with a history of atrial arrthymias. No association of the agent with ventricular arrthymias has been found. Transient, mild visual blurring has been reported by patients taking oprelvekin, and the drug should be used with caution in patients with preexisting papilledema.

SARGRAMOSTIM

Colony-stimulating factor 2 (human clone pHG$_{25}$ protein moiety), 23-L-leucine-, rhu GM-CSF; Leukine; Prokine

[123774-72-1] $C_{639}H_{1002}N_{168}O_{196}S_8$ (15,500 to 19,500). A single chain of 127 amino acids, glycosylated, produced by recombinant DNA technology, expressed by *Saccharomyces cerevisiae*. There are three species having approx molecular weights of 19,500, 16,800, and 15,500, depending on the extent of glycosylation.

Description—White lyophilized powder.

Comments—Granulocyte-macrophage colony-stimulating factor (GM-CSF) is an endogenous multipotential hematopoietic growth factor that stimulates proliferation and differentiation of both early and late progenitor cells, resulting in increases in granulocytes and macrophages. It is indicated for accelerating myeloid engraftment in autologous bone marrow transplantation (BMT) in patients with non-Hodgkin's lymphoma, acute lymphoblastic leukemia, and Hodgkin's disease. It is effective in decreasing median duration of antibiotic therapy, reducing duration of infectious episodes, and shortening the median duration of hospitalization in these patients. It also is indicated for patients who have undergone allogeneic or autologous BMT in whom engraftment is delayed or has failed. In these patients, sargramostim is safe and effective in prolonging survival in both the presence or absence of infection. Hematological response to therapy should be assessed twice a week by CBC with differential. Sargramostim can induce WBC increases, and treatment should be interrupted or the dose reduced if excessive leukocytosis occurs (WBC > 50,000 cells/mm^3; absolute neutrophil count > 20,000 mm^3). It is contraindicated in patients with excessive (more than 10%) leukemic myeloid blasts in the bone marrow or peripheral blood or known hypersensitivity to yeast-derived products. Adverse effects include peripheral edema and a capillary leak syndrome, and it should be used with caution in patients with preexisting fluid retention, congestive heart failure, or pulmonary infiltrates. Because of the potential for promoting tumor growth, precaution is necessary when using this drug in any malignancy with myeloid characteristics.

ANTIHEMATOPOIETIC DRUGS

Polycythemia and erythrocytosis are conditions in which there is an increase in the number of circulating erythrocytes. The cause is usually the result of a deficient oxygenation of the arterial blood, and either condition may be corrected by management of the underlying primary disorder. However, in polycythemia rubra vera the condition is primary, and therapy thus is directed at the erythrocytes, either by their removal by venesection, their destruction by phenylhydrazines, or the suppression of their formation, by antihematopoietic drugs or by X-irradiation. Several of the antineoplastic drugs such as the nitrogen mustards, the antifolic acids, arsenicals, or radiophosphate may be employed. The *leukemias* result from excessive leukocytic hematopoietic activity of a neoplastic nature; either the bone marrow (myelogenous or granulocytic leukemia) or lymphatic tissue (lymphocytic leukemia) may be involved. In myelogenous leukemia there may be anemia because the erythropoietic cells are crowded out by leukopoietic cells.

MISCELLANEOUS DRUGS AFFECTING BLOOD

HEMIN

Ferrate(2−), chloro[7,12-diethenyl-3,8,13,17-tetramethyl-21*H*,23*H*-porphine-2,18-dipropanoato(4−)-*N*^{21},*N*^{22},*N*^{23},*N*^{24}]-, dihydrogen-, (*SP*-5-13).

Chlorohemin [16009-13-5] $C_{34}H_{32}ClFeN_4O_4$ (651.96).

Preparation—Usually from hemoglobin by treatment with a hot saline acetic acid solution. *Org Syn Coll,* vol III, 1955, p 442.

Description—Polychromatic crystals (usually brownish to blue) that do not melt under 300°.

Solubility—Freely soluble in dilute base through conversion to *hematin* by replacement of the chlorine atom by hydroxyl; sparingly soluble in alcohol; insoluble in water.

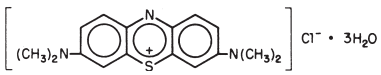
Comments—Inhibits the biosynthesis of porphyrin in juvenile erythrocytes and hence also indirectly decreases the rate of formation of porphyrins. It is used to ameliorate symptoms in *intermittent porphyria, porphyria variegata,* and hereditary *coproporphyria*. In some but not all patients pain, tachycardia, hypertension, mild-to-moderate neurological impairment, and abnormal mentation are abated. Neurological improvement is sometimes delayed weeks to months after treatment. Remissions are not permanent.

It is contraindicated in hypersensitivity to itself and in porphyria cutanea tarda. Excessive doses may cause renal failure. Phlebitis may occur in the injected vein. Coagulopathy and renal failure from an overdose have been reported. It may be antagonized by barbiturates, estrogens, and various steroid metabolites that induce aminolevulinate synthesis.

It is converted partially to bilirubin and partially excreted into the bile intact. Bilirubin metabolites and urobilinogen also appear in the urine.

METHYLENE BLUE

Phenothiazin-5-ium, 3,7-bis(dimethylamino)-, chloride, trihydrate; Methylthionine Chloride; Aniline Violet



C I Basic Blue 9 trihydrate [7220-79-3] $C_{16}H_{18}ClN_3S.3H_2O$ (373.90); *anhydrous* [61-73-4] (319.85).

Preparation—By treating a solution of *N,N*-dimethyl-*p*-phenylenediamine and *N,N*-dimethylaniline hydrochlorides with H_2S and $FeCl_3$ or another suitable oxidizing agent.

Description—Dark green crystals or a crystalline powder, with a bronze-like luster; odorless or with a slight odor; stable in air; solutions have a deep-blue color.

Solubility—1 g in 25 mL water or 65 mL alcohol; soluble in chloroform.

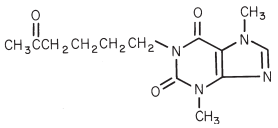
Comments—Readily reduced to leukomethylene blue, which, in turn, is readily reoxidized to methylene blue. Thus, it is useful as a reversible *oxidation-reduction* indicator. Its principal therapeutic use, in the *treatment of methemoglobinemia,* stems from this chemical property. It acts as an electron-acceptor in the transfer of electrons from reduced pyridine nucleotides (NADPH and NATPH) to methemoglobin, thus facilitating reduction of ferric to ferrous iron. Glucose 6-phosphate dehydrogenase is required; if this enzyme is absent, as it is in certain hemolysis-prone individuals, the drug is ineffective. If the dose is high, the oxidation potential favors the formation of methemoglobin from hemoglobin. This effect is used in the *treatment of cyanide poisoning*. The methemoglobin so formed complexes cyanide, which tends to spare the cytochrome system. However, other drugs are superior.

This drug formerly was employed as a urinary antibacterial agent, but this use is now obsolete. An outgrowth of this use is the belief that the drug is effective in the treatment of urolithiasis. Although a slight effect to retard crystal formation *in vitro* has been reported, no clinical benefits have been proven, and expert opinion holds the dye to be ineffective. Its use as an analgetic, antipyretic, and parasiticide has likewise been abandoned. The dye is used as a bacteriological stain.

It colors urine and feces green and the skin blue. It may cause bladder irritation, nausea, vomiting, and diarrhea. Large doses may cause vertigo, headache, confusion, sweating methemoglobinemia (paradoxical), and chest and abdominal pains. It can cause hemolysis in persons with glucose-6-phosphate dehydrogenase–deficient erythrocytes.

PENTOXIFYLLINE

1*H*-Purine-2,6-dione, 3,7-dihydro-3,7-dimethyl-1-(5-oxohexyl)-, Trental



1-(5-Oxohexyl)theobromine [6493-05-6] $C_{13}H_{18}N_4O_3$ (278.31).

Preparation—Ethyl acetoacetate and 1,3-dibromopropane are reacted to form the ethyl ester of 3*H*-dihydropyran-3-carboxylic acid, which is cleaved with HBr to form 6-bromo-2-hexanone. This latter compound, with theobromine, in the presence of base yields pentoxifylline.

Description—Bitter-tasting, colorless, odorless needles; melts about 105°.

Solubility—1 g in 13 mL water at 25° or in 5.5 mL at 37°; 1 g in 9 mL benzene.

Comments—Increases the ATP content of erythrocytes, which makes them both more deformable and less likely to aggregate. Consequently, they pass through precapillary sphincters and capillaries more easily, which improves blood flow through the microcirculation. It also stimulates the synthesis of prostacyclin by endothelial cells and inhibits phosphodiesterase activity (thus increasing cyclic AMP levels) in platelets; these two actions decrease the aggregation of platelets. It increases fibrinolytic activity and thus decreases fibrinogen concentration. These effects sum to decrease the viscosity of blood, which increases blood flow and decreases myocardial work. It is approved for the treatment of *intermittent claudication*. It is also investigational in the management of cerebrovascular insufficiency, transient ischemic attacks, stroke, diabetic angiopathy, sickle cell thalassemia and leg ulcers.

Adverse effects are dyspesia (2.8%), nausea (2.2%), vomiting (1.2%), bloating (0.6%), belching, flatus, anorexia, dry mouth, thirst, constipation, and cholecystitis; dizziness (1.9%), headache (1.2%), tremor (0.3%), anxiety and confusion; anginal pain (0.3%), hypotension and edema; blurred vision, conjunctivitis, and scotomata; dyspnea, flulike symptoms, laryngitis, nasal congestion and nose bleeds; brittle fingernails, pruritus, rash, and urticaria; earache, leukopenia, malaise, sialorrhea, bad taste, sore throat and swollen neck lymph glands, and change in weight; dysrhythmias, hepatitis and jaundice, hyperfibrinogenemia, pancytopenia, purpura, and thrombocytopenia are rare effects.

It is absorbed readily and first-pass metabolized by the oral route. Peak plasma levels occur in 2 to 4 hr. There are more than five metabolites, two of which probably have pharmacodynamic activity. The elimination half-life is only about 0.4 to 0.8 hr, but that of the major metabolites is 1 to 1.6 hr.

SODIUM NITRITE

Sodium nitrite [7632-00-0] $NaNO_2$ (69.00).

Preparation—By various methods, as by reduction of sodium nitrate with lead, a sulfite, or sulfur dioxide, or by absorption of NO obtained from catalytic oxidation of ammonia in sodium carbonate solution.

Description—White to slightly yellow, granular powder or white or nearly white, opaque, fused masses or sticks; deliquescent in air; solutions are alkaline to litmus.

Solubility—1 g in 1.5 mL water; sparingly soluble in alcohol.

Comments—Principally for treating *cyanide poisoning,* based on its causing methemoglobin, which complexes cyanide. In cyanide poisoning, it is injected intravenously in very large doses to produce methemoglobin, which combines with the highly lethal cyanide and renders it temporarily inactive as cyanmethemoglobin. Sodium thiosulfate then is injected intravenously to form the nontoxic thiocyanate. Nitrite ion relaxes smooth muscle, so sodium nitrite causes hypotension. Solutions are unstable and should be prepared directly before use.

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CHAPTER 68

Cardiovascular Drugs

Anna M Wodlinger, PharmD

The term *cardiovascular drug* refers to any medication that affects the heart, blood vessels, or the circulatory system. These drugs can be used alone or in combination with each other in the treatment of a variety of disease states such as hypertension, acute coronary syndromes, congestive heart failure (CHF), arrhythmias, and dyslipidemias. The majority of the drugs included in this category will be covered in this chapter, however some are discussed in more detail in other chapters and are referenced as such. The treatment of cardiovascular diseases is under constant study and recommendations may change. Several expert committees and associations publish guidelines periodically that provide specific treatment recommendations based on the most recent data available. I refer the reader to these publications for specific recommendations in the treatment of a particular cardiovascular disease state.

ANTIHYPERTENSIVE AND HYPOTENSIVE DRUGS

Hypertension is a disease characterized by an elevated blood pressure. The vast majority of patients with hypertension have primary (essential, idiopathic) hypertension in which the underlying cause is unknown. Secondary hypertension, in which there is an underlying cause such as renovascular disease or pheochromocytoma, affects a small percentage of patients. Malignant hypertension is a severe, progressive phase of primary hypertension. There are several drugs used in the treatment of hypertension, and no universal therapy for primary hypertension exists. Individual patients vary widely in response to antihypertensive drugs, and often more than one drug is necessary for effective treatment.

There are several factors that have been identified that contribute to the development of primary hypertension and several drugs target these processes. Some of these causes include abnormal central and autonomic nervous system response, abnormalities in renal or tissue autoregulatory processes, abnormality in the renin-angiotensin-aldosterone (RAS) system, vascular endothelium dysfunction, and dietary influences of sodium, calcium, and potassium.

Long-term studies have proven unequivocally that treatment of hypertension both decreases morbidity and prolongs life expectancy. Agents available for the treatment of hypertension include thiazide diuretics, β-adrenoreceptor-antagonists (β-antagonists), angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs) or calcium channel blockers (CCBs) as single agents. If a single drug is not effective alone, two from different classes are used in combination. The choice of initial antihypertensive regimen or combination therapy should be made dependent upon the latest clinical data. Therapy should be specific for each patient, and drugs that have compelling indications in certain disease states (eg, ACE inhibitors in diabetes and CHF) should be used preferentially.

Currently, diuretics, ACE inhibitors, β-antagonists, calcium channel blockers, and angiotensin receptor blockers dominate the field. Drugs such as hydralazine, clonidine, and minoxidil are used as a tertiary drug for resistant cases. There has been a marked decline in use of guanethidine, reserpine, and methyldopa.

Diuretics

It long has been suspected that certain hypertensive persons have abnormal salt metabolism, and epidemiological and endemiological studies have established a relationship between salt intake and blood pressure. In the essential and malignant hypertensive individual with an expanded blood volume and high sodium burden, the rationale for use of diuretic drugs is almost self-evident. However, certain diuretic drugs even have been found to lower blood pressure of persons with essential hypertension in the absence of expanded blood volumes.

It is held widely that the vascular smooth muscles in such persons have high intracellular sodium content. When thiazide diuretics are given, the fall in blood pressure in the first week or two correlates with diuresis and the decrement in extracellular fluid volume (hence, in venous return, stroke volume, and systolic blood pressure). In this phase, heart rate is accelerated, and peripheral resistance may increase. The antihypertensive action passes into a phase in which the extracellular volume and heart rate return toward normal and peripheral resistance falls. Not all diuretics are alike in this effect, which suggests that something more than diuresis is involved. For example, loop diuretics do not lower vascular resistance, and blood pressure is lowered only because cardiac output is decreased. Spironolactone is a useful antihypertensive agent when aldosterone or 18-hydroxycorticosterone levels are high.

Homeostatic mechanisms increase plasma renin activity in response to excessive diuresis, which counterproductively increases plasma levels of the potent endogenous vasoconstrictor angiotensin II. If they were available, drugs that inhibit renin secretion would be rational agents to combine with diuretics.

At present, thiazide-like diuretics often are the first drugs to be used in the treatment of essential hypertension, customarily being used alone in mild essential hypertension; other drugs are added in moderate and severe essential hypertension. Loop diuretics should be used in congestive heart failure or in patients with renal impairment.

For the pharmacology of specific diuretics, see Chapter 75.

Peripheral Antiadrenergic Drugs

Regardless of whether there is a sympathetic component of essential or malignant hypertension, a reduction of whatever sympathetic activity exists can cause a lowering of blood pressure in four ways:

- A decrease in sympathetically (α-receptor)-mediated arteriolar constriction will decrease systemic peripheral resistance.
- A decrease in sympathetically (α_1-receptor)-mediated venous tone will increase venous capacitance and decrease venous return and, hence, cardiac output; however, this effect tends not to be sustained in the long run because of compensation by fluid retention.
- A decrease in sympathetically (β_1-receptor)-mediated cardiac contractility and heart rate will decrease cardiac output.
- A decrease in sympathetically (β_1-receptor)-modulated secretion of renin by the juxtaglomerular apparatus of the kidney will decrease the plasma levels of angiotensin II, a potent vasoconstrictor and sensitizer to sympathetic nervous activity and stimulant of the secretion of aldosterone, an antidiuretic hormone.

The exact mechanism by which β-antagonists are effective in the treatment of hypertension is unknown. Explanations include their ability to decrease cardiac output, renin secretion, and the release of norepinephrine at the adrenergic nerve terminals. They are effective alone and can be considered first-line therapy for the treatment of essential hypertension. They are also important adjuncts to diuretics, which increase renin secretion, and vasodilator drugs, which cause reflex sympathetic cardiac stimulation. Some β-antagonists, such as metoprolol, are selective for the β_1 receptor, and others, such as carvedilol and labetalol, are non-selective and affect both β_1 and β_2 receptors as well as α-receptors. The agents with both α- and β-adrenoreceptor blocking activity are useful in the treatment of essential hypertension, since blockade of one type of receptor cannot result in counteractive reflex activation of the other. Nonselective α-adrenoreceptor-antagonists, such as phenoxybenzamine and phentolamine, have antihypertensive actions, but reflex cardiac stimulation and increased renin secretion limit their efficacy and their role as antihypertensive agents is limited to the treatment of pheochromocytoma. The selective α_1-antagonists, such as prazosin, cause less of such counterproductive homeostatic adjustments and hence are more efficacious and can be used in the treatment of essential hypertension at low doses. However, at higher doses fluid and sodium retention occurs and concurrent diuretic therapy is necessary to maintain hypotensive effects. Drugs such as reserpine and guanethidine, which act on adrenergic nerve terminals to deplete norepinephrine or prevent release of norepinephrine, have limited use due to their side effect profiles.

The important antihypertensive α- and β-adrenoreceptor-blocking drugs and drugs that act on the adrenergic nerve terminals are described in Chapter 72.

DOXAZOSIN MESYLATE—page 1400.
PRAZOSIN HYDROCHLORIDE—page 1400.
TERAZOSIN HYDROCHLORIDE—page 1400.

Centrally Acting Antihypertensive Drugs

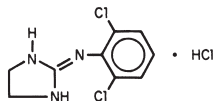
The drugs in this class stimulate α_2-receptors in the brain. The action of the α_2-receptor-agonists in the brain results in decreased sympathetic outflow to the blood vessels and heart and increased parasympathetic (vagal) outflow to the heart. This causes vasodilation, decreased heart rate, a decrease in renin release from the kidney, and blunted baroreceptor reflexes. It is also postulated that stimulation of presynaptic α_2-receptors peripherally contributes to the decrease in sympathetic tone. Only clonidine, guanabenz, guanfacine, methyldopa, and methyldopate are described in this section. There is no rationale for using more than one of these drugs at a time, and only clonidine is recommended for routine use.

Moderate doses of these drugs cause a high incidence of sedation, dry mouth, and mild-to-moderate orthostatic hypotension. Salt and water retention can occur with chronic use and concurrent diuretic therapy may be necessary to maintain antihypertensive efficacy.

If the drugs are discontinued abruptly a compensatory increase in norepinephrine release may occur and a rebound hypertension could result. The occurrence of this is increased if the patient is receiving concurrent therapy with a β-antagonist due to unopposed α-receptor simulation.

CLONIDINE HYDROCHLORIDE

2-Imidazoline, 2-(2,6-dichlorophenylamino)-, hydrochloride; Catapres



[4205-91-8] $C_9H_9Cl]_2N_3.HCl$ (266.56).

Preparation—Ammonium thiocyanate converts 2,6-dichloroaniline to the thiourea, which is treated with methyl iodide to yield the *S*-methylthiouronium salt. The latter compound, with ethylenediamine, closes the imidazoline ring to afford the product. See US Pat 3,202,660.

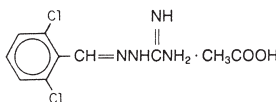
Description—White to off-white, odorless, bitter-tasting, crystalline powder; stable in light, air, and heat; does not exhibit polymorphism; melts about 300° with decomposition; pK_a 8.2.

Solubility—1 g in about 13 mL water (20°), about 25 mL alcohol, or about 5000 mL chloroform.

Comments—Available in a transdermal patch that delivers drug for 1 week.

GUANABENZ ACETATE

Hydrazine carboximidamide, 2-[(2,6-dichlorophenyl)methylene]-, monoacetate; Wytensin



[23256-50-0]$C_8H_8Cl_2N_4.C_2H_4O_2$ (291.14).

Preparation—Brit Pat 1,019,120.

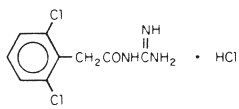
Description—White solid; melts about 193° (dec).

Solubility—1 g in 90 mL water, 20 mL alcohol or 10 mL propylene glycol.

Comments—Efficacy is enhanced by diuretics. The half-life is 7 to 10 hr. It causes a mild, usually insignificant, postural or exercise hypotension.

GUANFACINE HYDROCHLORIDE

Benzeneacetamide, *N*-aminoiminomethyl)-2,6-dichloro-, monohydrochloride; Tenex



[29110-48-3] $C_9H_2Cl_2N_3O.HCl$ (282.56).

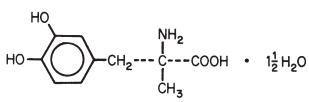
Preparation—US Pat 3,632,645.

Description—White needles; melts about 215°.

Comments—Its longer half-life permits once-a-day dosing. Tolerance is common in the absence of a diuretic. Withdrawal hypertension may occur 2 to 7 days after discontinuation of treatment. Elimination is by both hepatic metabolism (60–70%) and renal excretion (30–40%); dosage is said not to require adjustments in renal failure. The elimination half-life is 14 to 17 hr.

METHYLDOPA

L-Tyrosine, 3-hydroxy-α-methyl-, sesquihydrate; Alpha-methyldopa; Aldomet



[41372-08-1] $C_{10}H_{13}NO_4.1½H_2O$ (238.24); *anhydrous* [555-30-6] (211.22).

Preparation—The product of the reaction of 3,4-dimethoxyphenylacetonitrile with sodium ethoxide is hydrolyzed with acid to give 3,4-dimethoxyphenylacetone. This is reacted with ammonium carbonate and potassium cyanide to form a substituted hydantoin intermediate, which, on alkaline hydrolysis, yields racemic methyldopa. The acetylated form of this racemate is resolved using (−)-α-methylbenzylamine. The isolated acetylated (−)-methyldopate salt is deacetylated with base and treated with mineral acid to liberate (−)-methyldopa. US Pat 2,868,818.

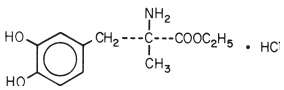
Description—White to yellowish white, odorless, fine powder, which may contain friable lumps; almost tasteless and relatively stable in both light and air; melts above 290° with decomposition; pK_a 2.2 (COOH), 10.6 (NH_2), 9.2 and 12 (ring OH).

Solubility—Sparingly soluble in water; very soluble in diluted hydrochloric acid; slightly soluble in alcohol; practically insoluble in ether.

Comments—Converted to methylnorepinephrine in the brain, which displaces norepinephrine from storage sites and is released as a *false transmitter* by nervous impulses in the adrenergic nerves. The metabolite α-methylnorepinephrine has potent α_2-agonist activity and probably acts to decrease blood pressure in the same way as clonidine. Its action begins in about 2 hr, becomes maximal in 6 to 8 hr, and lasts 18 to 24 hr. Used in hypertension in pregnancy.

METHYLDOPATE HYDROCHLORIDE

L-Tyrosine, 3-hydroxy-α-methyl-, ethyl ester, hydrochloride; Aldomet Ester Hydrochloride



[5208-79-4] $C_{12}H_{17}NO_4.HCl$ (275.73).

Preparation—By converting methyldopa to its ethyl ester and passing hydrogen chloride into a solution of the ester in a suitable organic solvent.

Description—White or practically white crystalline powder; odorless or practically odorless with a bitter taste; relatively stable both in light and air; melts about 160°; pH (1 in 100 solution) 3 to 5.

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

Comments—Parenteral form for IV injection.

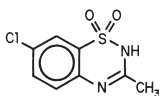
Antihypertensive Direct Vasodilators

Direct vasodilators act by several mechanisms, such as inhibition of cyclic nucleotide phosphodiesterase, adenosine mimicry, impairment of calcium and sodium influx in vascular smooth muscle, opening of potassium channels, release of nitric oxide (NO), stimulation of guanylate cyclase, and stimulation of dopamine receptors. Their usefulness in the treatment of hypertension depends a great deal on the selectivity of the drug for the resistance blood vessels, namely, the arterioles, which causes a lowering of blood pressure. If the capacitance veins also are dilated, venous return to the heart and hence cardiovascular adjustments to posture and exercise are impaired, and the patient may experience postural and exercise hypotensions, sometimes to the point of syncope. A slight degree of interference with venous return usually is considered to be desirable, especially in the treatment of severe hypertension, because it enables a greater lowering of blood pressure than arteriolar dilatation alone.

Some direct vasodilators can cause reflex palpitation and tachycardia and an increase in plasma renin activity that leads to fluid retention. Therefore, the long-term effectiveness of the drug is reduced unless combined with β-antagonists and/or diuretics to antagonize these effects.

DIAZOXIDE

2*H*-1,2,4-Benzothiadiazine, 7-chloro-3-methyl-, 1,1-dioxide; Hyperstat IV



[364-98-7] $C_8H_7ClN_2O_2S$ (230.67).

Preparation—One method reacts 2,4-dichloronitrobenzene with benzyl mercaptan and KOH and the 2-(benzylthiol) group thus introduced is converted to $—SO_2Cl$ with chlorine and aqueous acetic acid and thence to $—SO_2NH_2$ by reaction with NH_3. After reducing the NO_2 to NH_2 with Fe and NH_4Cl, cyclization is affected by condensation with ethyl orthoacetate. *Science* 133:2067, 1961. US Pats 2,986,573 and 3,345,365.

Description—White to cream-white crystals or crystalline powder; odorless; melts about 330°; pK_a 8.5.

Solubility—Practically insoluble to sparingly soluble in water.

Comments—A potent vasodilator, especially by the intravenous route. In therapeutic doses, vasodilation is primarily the result of arteriolar dilatation, so that orthostatic hypotension is usually minimal. The smooth muscle–relaxing effects result from hyperpolarization of vascular smooth muscle by activating ATPase-sensitive potassium channels. It can be used intravenously as a hypotensive drug in acute hypertensive crises. Increases in heart rate may occur following administration in response to blood pressure reduction.

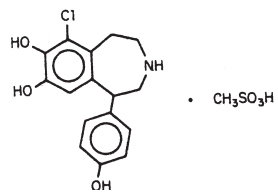
Although it is a benzothiazide, it is not a diuretic but instead actually causes salt and water retention and consequent gain in weight. This action sometimes precipitates congestive heart failure, especially if renal function is impaired.

It should be used cautiously in persons with coronary or cerebral insufficiency and patients with impaired renal function. The drug is contraindicated if hypersensitivity to thiazides exists. Thiazide diuretics and other antihypertensive drugs increase the response to diazoxide, even when they fail to lower blood pressure themselves.

It is about 90% protein-bound, but rapid intravenous injection permits distribution to smooth muscle before it is bound to protein. Thus, a greater and longer-lasting fall in blood pressure accrues to faster rates of injection. The drug persists in blood longer than the hypotensive effect. The plasma half-life is 20 to 60 hr in persons with normal renal function, but the hypotensive effect lasts only 2 to 15 hr. Different populations may eliminate the drug differently, some mostly by renal tubular secretion and others mostly by biotransformation.

FENOLDOPAM MESYLATE

1*H*-3-Benzazepine-7,8-diol, 6-chloro-2,3,4,5-tetrahy-dro-1-(4-hydroxyphenyl)-, methanesulfonate (salt); Corlopam



[67227-57-0](salt), [67227-56-9] (base) $C_{17}H_{20}ClNO_6S$ (401.87).

Preparation—Reduction of 2-chloro-3,4-dimethoxyphenylacetonitrile with B_2H_6 in THF gives 2-chlorohomoveratryl amine. This latter compound with styrene oxide yields α-[[2-(2-chloro-3.4-dimethoxyphenyl)ethyl]aminomethyl]benzyl alcohol which is cyclized with a refluxing trifluoroacetic acid/sulfuric acid mixture to give 9-chloro-7,8-dimeth-oxy-5-(*p*-methoxyphenyl)-1,3,4,5-tetrahydro-3(2*H*)-benzazepine. Cleavage of the three ether groups to the corresponding phenols affords the base which is converted to the salt with methanesulfonic acid. *J Med Chem* 1980: 23; 973. Also US Pat 4,197,297 (1980).

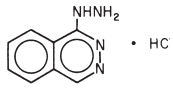
Description—White to off-white crystals melting about 274° (dec).

Solubility—Sparingly soluble in water, methanol or ethanol; soluble in propylene glycol.

Comments—A dopamine receptor agonist that binds to the D_1-like receptor and also has moderate affinity for a_2-adrenoceptors. Vasodilator effects occur in the coronary and peripheral arteries and in the renal efferent and afferent arterioles. Fenoldopam is indicated for short-term, continuous intravenous management of hypertensive emergencies. Significant side effects include hypotension and tachycardia.

HYDRALAZINE HYDROCHLORIDE

Phthalazine, 1-hydrazino-, monohydrochloride; Apresoline



[304-20-1] $C_8H_8N_4.HCl$ (196.64).

Preparation—Phthalazone is converted to 1-chlorophthalazine by treatment with phosphorus oxychloride, condensed with hydrazine hydrate to form hydralazine and neutralized with HCl to produce the hydrochloride.

Description—White to off-white, crystalline powder; melts between 270° and 280° with decomposition; pK_a 0.5, 7.3.

Solubility—1 g in 25 mL water, 500 mL alcohol; very slightly soluble in ether.

Comments—Causes vasodilation by stimulating guanylate cyclase in arteriolar smooth muscle; the stimulant appears to be nitric oxide (NO) from the local oxidation of the hydrazine moiety. NO is a natural, endothelium-derived relaxing factor.

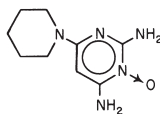
It is one of the few drugs that cause substantial vasodilatation in the kidney, and it increases renal plasma flow even when the blood pressure drops considerably. Vasodilatation also is pronounced in the splanchnic, cerebral, and coronary vascular beds; it exerts only slight vasodilator actions in skin and skeletal muscle. The veins participate very little in the effect, so that postural hypotension is negligible. As the result of the fall in blood pressure, reflex tachycardia, palpitations, and increases in plasma renin activity occur, although the renin activity sometimes decreases in long-term treatment. The side effects of tachycardia and palpitations may precipitate attacks of angina pectoris.

Its principal serious toxic effects are syndromes resembling rheumatoid arthritis or lupus erythematosus, appearance of which necessitates withdrawal of the drug. This toxicity is more frequent in slow than in fast acetylators and is associated with chronic daily doses greater than 200 mg.

It is absorbed by the oral route. With low doses, first-pass metabolism limits bioavailability to 16% to 35%; food enhances the bioavailability. Elimination is by both ring hydroxylation and *N*-acetylation, and only 10% of hydralazine is excreted unchanged. Elimination is dose-dependent, and plasma levels increase disproportionately with dose. The half-life is 1.5 to 6 hr; the difference between slow and fast acetylators is usually minor. It accumulates in fat in vascular smooth muscle, where it has a longer life than in plasma.

MINOXIDIL

2,4-Pyrimidinediamine, 6-(1-piperidinyl)-, 3-oxide; Loniten; Rogaine



[38304-91-5] $C_9H_{15}N_5O$ (209.25).

Preparation—US Pat 3,461,461.

Description—White to off-white, crystalline powder; pK_a 4.6.

Solubility—1 g in about 500 mL water; 25 mL alcohol; practically insoluble in chloroform.

Comments—Dilates arterioles by opening potassium channels, which causes hyperpolarization and relaxation of smooth muscle. This lowers the total peripheral vascular resistance and hence the blood pressure. Dilatation of capacitance veins is only slight to moderate and therefore postural and exercise hypotensions are usually minimal.

Reflex tachycardia and palpitations occur, but they are less than that expected from the fall in blood pressure, which suggests cardioaccelerator-suppressant actions not yet elucidated. Plasma renin activity may be elevated as the result of reflex sympathetic activity or diminished by an unknown mechanism. Irrespective of the plasma renin activity, salt and water retention occurs sufficiently to cause considerable tolerance to the antihypertensive effects, and diuretics, even occasionally loop diuretics, are necessary to restore the antihypertensive effects.

Minoxidil is used as a last line of therapy to treat moderate to severe essential hypertension. It often is effective in hypertension refractory to all other therapy.

A side effect is excessive hair growth. Consequently, the drug is used topically to restore hair growth in androgenic alopecia and alopecia areata.

The drug is absorbed well by the oral route. The volume of distribution is 9 to 15 L/kg. It is concentrated in vascular tissue. Metabolism in the liver accounts for about 90% of elimination, and no modification of dose is required in renal failure or hemodialysis. The apparent half-life of about 4 hr appears to be a distribution parameter; the β-half-life is about 24 hr. The duration of action is 1 to 3 days.

SODIUM NITROPRUSSIDE

Ferrate(2-), pentakis(cyano-*C*)nitrosyl-, disodium, (*OC*-6-22)-dihydrate; Sodium Nitroferricyanide; Nipride; Nitropress

[13755-38-9] $Na_2[Fe(CN)_5NO].2H_2O$ (297.95); *anhydrous* [14402-89-2] (261.92).

Preparation—Potassium ferrocyanide is dissolved in 50% HNO_3, and the solution is boiled for about 1 hr. After cooling and filtering to remove potassium nitrate, the solution is neutralized with Na_2CO_3 and evaporated to crystallization.

Description—Reddish brown, practically odorless, crystals or powder; freshly prepared solutions all have a faint brownish tint. Since nitroprusside ion forms colored compounds with many organic and inorganic substances, blue, green, red or any highly colored solutions should be discarded; aqueous solutions are photosensitive and should be protected from light.

Solubility—1 g in about 2.5 mL water; slightly soluble in alcohol.

Comments—A potent, directly acting peripheral vasodilator. It releases nitric oxide (NO), which is an endogenous, endothelium-derived relaxing factor. NO activates guanylyl cyclase in vascular smooth muscle to produce vasodilation. Its actions on arterioles decrease the total systemic vascular resistance, which is the main cause of the fall in blood pressure it evokes. Heart rate may be increased reflexly.

This drug has an immediate onset of effect and short duration of action so it is effective in treating hypertensive emergencies but must be given by continuous intravenous infusion. Side effects of this drug include significant hypotension and cyanide or thiocyanate toxicity.

Nitroprusside is broken down rapidly by reaction with hemoglobin to NO, cyanide ion, and cyanmethemoglobin, with a half-life of about 2 min. Cyanide is converted to thiocyanate by the enzyme rhodanese in the liver. Infants lack this enzyme, so the drug should not be used in neonates and probably also not in the treatment of toxemia of pregnancy. Conversion to thiocyanate requires endogenous thiosulfate, which can be depleted by high doses or prolonged administration, leading to toxic levels of cyanide. Thiocyanate is eliminated by the normal kidney, with a half-life of 3 days. Due to potential toxicities with accumulation of cyanide or thiocyanate high dosages and prolonged use, particularly in patients with renal or hepatic dysfunction, should be avoided.

Ganglionic Blocking Agents

The clinically available ganglionic blocking drugs compete with acetylcholine at postsynaptic nicotinic receptors. Since the ganglia of both the sympathetic and parasympathetic nervous systems are cholinergic, these drugs interrupt the outflow through both systems; thus, it is not possible to achieve a therapeutic block of autonomic outflow to a given locus without a number of undesirable side effects resulting from the blockade of other autonomic nerves. Blockade of sympathetic outflow to the blood vessels causes hypotension and increased blood flow.

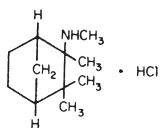
Blockade of sympathetics to the heart may cause slowing, but the parasympathetic outflow also is blocked, so that acceleration can result in persons with predominantly parasympathetic tone. Orthostatic hypotension results from blockade of reflex adjustments to posture. Blockade of parasympathetic outflow results in dry mouth, mydriasis, cycloplegia (loss of ocular accommodation), diminished GI motility, and urinary retention.

The ganglionic blocking agents should be used cautiously when other hypotensive, antihypertensive, or anesthetic drugs are used concomitantly, because the hypotension may be exaggerated to such an extent that blood flow through the brain, heart, or kidney may be jeopardized. Overdose of the ganglionic blocking drug alone can have this effect. Because compensatory cardiovascular reflexes are suppressed by the ganglionic blocking drugs, pressor drugs given during ganglionic blockade may elicit dangerously enhanced responses.

Ganglionic blocking drugs are contraindicated when there is pyloric stenosis, cerebral arteriosclerosis, coronary insufficiency, recent myocardial infarction, or glaucoma. They should be used cautiously in elderly patients, patients with renal insufficiency, and those receiving neuromuscular blocking antibiotics. These drugs were used in the past to treat essential hypertension, but have been replaced by newer drugs

MECAMYLAMINE HYDROCHLORIDE

Bicyclo[2.2.1]heptan-2-amine, *N*,2,3,3-tetramethyl-, monohydrochloride; Inversine



[826-39-1] $C_{11}H_{21}H.HCl$ (203.75).

Preparation—From camphene *J Am Chem Soc* 1946; 78:1514.

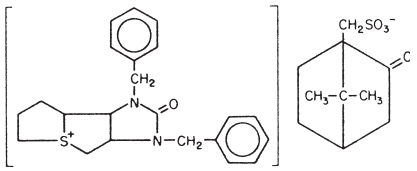
Description—White, crystalline powder; melts about 245° (dec); can be sterilized by autoclaving.

Solubility—1 g in 5 mL water, 12 mL alcohol, or 10 mL glycerol.

Comments—Differs from most other ganglionic blocking agents in that it is not a quaternary ammonium compound, so it is ionized poorly in the small intestine and thus is readily and completely absorbed. It is the only orally effective ganglionic blocker available. Its nonionic form permits it to pass into the CNS, so occasional bizarre central disturbances may occur. It has a low renal clearance and hence a long duration of action. It will produce a variety of unpleasant, unavoidable side effects that result from the interruption of both sympathetic and parasympathetic outflow. Orthostatic hypotension, blurring of vision, dry mouth, diarrhea followed by constipation, occasional paralytic ileus, nausea and vomiting, urinary retention, fatigue, sedation, and impotence are among these general side effects. Tremor and delusions or hallucinations may occur. It is absorbed readily from the gut. It penetrates the blood-brain barrier into the CNS and also into the fetus (hence, it should be avoided in pregnancy). Elimination is by renal tubular secretion. The duration of action is 6 to 12 hr.

TRIMETHAPHAN CAMSYLATE

Thieno[1′,2′:1,2]thienol[3,4-*d*]imidazol-5-ium, decahydro-2-oxo-1, 3-bis(phenylmethyl)-, salt with (+)-7,7-dimethyl-2-oxobicyclo[2.2.1]heptane-1-methanesulfonic acid (1:1); Arfonad



[68-91-7] $C_{32}H_{40}N_2O_5S_2$ (596.80).

Preparation—The bromide, prepared from an intermediate produced in the synthesis of biotin, is metathesized with silver *d*-camphor-10-sulfonate; the silver bromide is removed by filtration, and the camsylate is obtained by evaporating the filtrate.

Description—White crystals or crystalline powder; melts between 230° and 235° with decomposition.

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

Comments—Usually classified as a ganglionic blocking agent, but it only moderately blocks ganglia in the therapeutic dose range. Some of its hypotensive effects result from a direct peripheral vasodilator action. It has an extremely brief duration of action and must be administered via intravenous infusion. It can be used in the treatment of hypertensive emergencies, but other drugs are preferred. Adverse effects that are mostly the result of ganglionic blockade and necessitate a reduction in dosage include anorexia, nausea, vomiting, constipation, and possibility of paralytic ileus, mydriasis, cycloplegia, glaucomatous attack, dry mouth, anginal pain, tachycardia, postural hypotension, and urinary retention.

Drugs Affecting the Renin-Angiotensin System

Renin is a protease released by the kidney in response to reduced renal perfusion, hyponatremia, or sympathetic activity. It acts on the plasma α_2-globulin substrate, angiotensinogen, to yield the decapeptide, angiotensin I. Angiotensin I is hydrolyzed by a converting enzyme to yield the octapeptide angiotensin II. Angiotensin II may lose one amino acid residue to yield angiotensin III. Angiotensins II and III are destroyed by carboxypeptidases.

Angiotensin I is inactive in the cardiovascular system, although it may have some effect to contract the renal glomerular mesangium. Angiotensin II has several cardiovascular-renal actions.

It stimulates the zona glomerulosa of the adrenal cortex to secrete aldosterone. Aldosterone causes the renal retention of sodium (and hence of water) and the loss of potassium. The extracellular fluid volume and body burden of sodium are thus increased, which promotes an increase in blood pressure in many persons and edema in congestive heart failure. Angiotensin III also stimulates the adrenal secretion of aldosterone.

It is a very potent vasoconstrictor, which contributes to an elevation of blood pressure in most persons and to reduced cardiac output (from increased afterload), particularly in congestive heart failure.

It facilitates transmission in sympathetic ganglia, increases the release of norepinephrine at adrenergic nerve terminals, and increases the response of blood vessels and the heart to norepinephrine, thus amplifying sympathetic factors in the maintenance of elevated blood pressure.

It stimulates the release of ADH (vasopressin) from the neurohypophysis and thirst receptors, thus adding to volume and vasopressor factors in some conditions of hypertension and in congestive heart failure. Angiotensin II is also a putative neurotransmitter in the CNS.

The principal site of the angiotensin converting enzyme (ACE) is in the endothelial cells, but ACE also is found in many tissues including the kidney and lungs. ACE is the same enzyme as kininase II and therefore, inhibition of ACE not only decreases the amount of the vasoconstrictor, angiotensin II, but also increases the amount of bradykinin and other potent vasodilator peptides. The increased kinins may contribute to the hypotensive effects and side effects of ACE inhibitors.

ANGIOTENSIN CONVERTING ENZYME INHIBITORS

ACE inhibitors are used to treat mild-to-moderate essential and renovascular hypertension. These agents should be used as first line therapy in patients with compelling indications such as left ventricular dysfunction and/or diabetes mellitus. Alone or in combination, ACE inhibitors are becoming the drugs of choice in the first-line treatment of essential hypertension. Many drugs that lower blood pressure homeostatically increase renin release, hence increasing angiotensin II concentrations.

Centrally acting and β-antagonist antihypertensive drugs decrease sympathetically mediated, but not hemodynamically or intrarenally mediated, increases in angiotensin levels; ACE inhibitors suppress the production of angiotensin II that results from increased angiotensin levels from any cause. In combination with diuretics, they suppress the renin-angiotensin-aldosterone factor in diuretic-induced hypokalemia, thus attenuating the risk of hypokalemia. In fact, they may produce hyperkalemia, if there is concurrent renal failure or if potassium-sparing diuretics or potassium supplements are being taken. By preventing homeostatic rises in aldosterone levels and even by themselves causing a decrease in extracellular fluid volume, ACE inhibitors have a synergism with diuretics.

Except for captopril and lisinopril, all of the other ACE inhibitors listed below are esterified prodrugs, which are well absorbed from the GI tract and then deesterified to the much more active metabolite with a long duration of action. The suffix *-at* is added to the respective general name to denote the active metabolite (eg, enalaprilat, for IV administration). All of them except captopril are effective with single daily doses, although several are recommended to be administered twice daily when being used for the treatment of congestive heart failure.

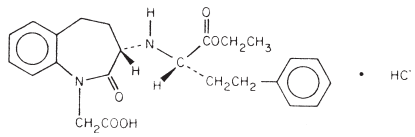
Although ACE inhibitors, as a group, are relatively free of side effects or toxicities in most patients, they do occur and some can be life-threatening. Initial doses can produce first-dose hypotension, especially in patients currently taking diuretics or otherwise volume depleted. Reports of dizziness may be due to the expected but less severe reduction of blood pressure. Angioedema or angioneurotic edema occurs early in therapy in 0.1% to 0.2% of patients and is characterized by rapid swelling of tissues in the oral cavity, throat, and larynx, a life-threatening condition, which should be treated with epinephrine and/or a corticosteroid. This condition as well as the occurrence of a dry cough is thought to be due to inhibition of bradykinin metabolism by ACE.

Captopril contains a sulfhydryl group and has been reported to cause a rash in some patients. Neutropenia and hepatotoxicity are rare, but potentially serious side effects of ACE

inhibitors; both are reversible if detected early. ACE inhibitors are definitely contraindicated in pregnancy, especially during the second and third trimesters when they are teratogenic; they should be discontinued as soon as pregnancy is detected.

BENAZEPRIL HYDROCHLORIDE

1*H*-1-Benzazepine-1-acetic acid, [*S*-(*R,*R**)]-, 3-[[1-(ethoxycarbonyl)-3-phenylpropyl]-amino]-2,3,4,5-tetrahydro-2-oxo-, monohydrochloride, Lotensin**



[86541-74-4] $C_{24}H_{28}N_2O_5.HCl$ (490.96).

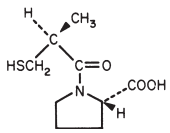
Description—White to off-white crystalline powder.

Solubility—Greater than 1 g in 10 mL of water, ethanol, or methanol.

Comments—A prodrug rapidly absorbed and converted to the active ACE inhibitor benazeprilat, which has a half-life of 10 to 11 hr. It is approved for treating essential hypertension and may be effective for treating congestive heart failure.

CAPTOPRIL

L-Proline, 1-[(2*S*)-3-mercapto-2-methyl-1-oxopropyl]-, Capoten



[62571-86-2] $C_9H_{15}NO_3S$ (217.28).

Preparation—See *Science* 1977; 196:441.

Description—White crystals melting about 88° which resolidify and melt again about 105°; $pK_1 = 3.7$, $pK_2 = 9.8$.

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

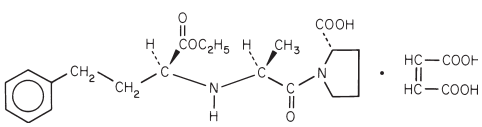
Comments—The first orally effective ACE inhibitor to have been marketed. It is approved for use in the treatment of hypertension, heart failure, and left ventricular dysfunction post-myocardial infarction.

Rashes (erythematous, morbilliform, macropapular, edematous, urticarial) occur during the first 4 weeks of treatment in 4% to 10% of recipients. Approximately 7% to 10% of these manifest eosinophilia and antinuclear antibody, so that the rashes may have an immune origin. Eruptions do not occur until the dose exceeds 600 mg a day and may disappear even with continued treatment.

About 50% is eliminated in the urine, the remainder is metabolized. The half-life is less than 2 hr.

ENALAPRIL MALEATE

L-Proline, (*S*)-1-[*N*-[1-(ethoxycarbonyl)-3-phenylpropyl]-L-alanyl]-, (*Z*)-2-butenedioate (1:1); Vasotec



[76095-16-4] $C_{20}H_{28}N_2O_5.C_4H_4O_4$ (492.52).

Preparation—See *Nature* 1980; 288:280.

Description—White to off-white crystalline powder melting about 143°; pH (1% aqueous solution) about 2.5; pK_a 3.0, 5.4.

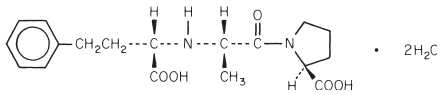
Solubility—Very soluble in water; soluble in ethanol; freely soluble in methanol.

Comments—A prodrug converted to the active ACE inhibitor enalaprilat. It is indicated for use in the treatment of hypertension, heart failure and asymptomatic left ventricular dysfunction.

About 60% is absorbed by the oral route. Peak plasma levels occur in 0.5 to 1 hr. In the body, about 40% is deesterified to enalaprilat, the active form of the drug (below). Enalaprilat and the remaining enalapril are eliminated in the urine. The half-life of enalapril is 1.3 hr, but that of enalaprilat is about 11 hr, thus providing a duration of action of over a day.

ENALAPRILAT

L-Proline, (*S*)-1-[*N*-[1-(carboxy)-3-phenylpropyl]-L-alanyl]-, dihydrate; Vasotec IV



[84680-54-6] $C_{18}H_{24}N_2O_5.2H_2O$ (384.43).

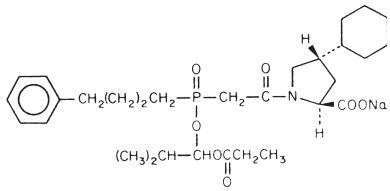
Preparation—See *Enalapril Maleate.*

Description—White crystals melting about 150°.

Comments—The active form of enalapril (see above). It is water-soluble and hence is the parenteral form of enalapril. It is absorbed too slowly and erratically to be given orally.

FOSINOPRIL SODIUM

L-Proline, *trans*-4-cyclohexyl-1-[[[2-methyl-1-(1-oxopropoxy)propoxy](4-phenylbutyl)phosphinyl]acetyl]-, sodium salt; Monopril



[88889-14-9] $C_{30}H_{45}NNaO_7P$ (585.65).

Preparation—See *J Med Chem* 1988; 31:1148.

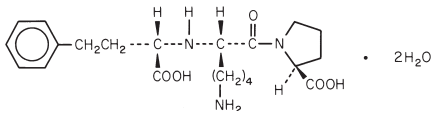
Description—White to off-white crystalline powder.

Solubility—1 g in 10 mL water; soluble in methanol or ethanol.

Comments—A prodrug rapidly absorbed and hydrolyzed by esterases in the intestine and liver to the active ACE inhibitor fosinoprilat, which has a half-life of about 12 hr. It is approved for treating hypertension and heart failure. Total-body clearance is not reduced by renal impairment because it is conjugated to inactive glucuronide in the liver and excreted in the bile and urine.

LISINOPRIL

L-Proline, (*S*)-1-[N^2-[1-(carboxy)-3-phenylpropyl]-L-lysyl]-, dihydrate; Prinivil



[83915-83-7] $C_{21}H_{31}N_3O_5 \cdot 2H_2O$ (441.52).

Preparation—US Pat 4,555,502.

Description—White crystals; pK_a 2.5, 4.0, 6.7, and 10.1.

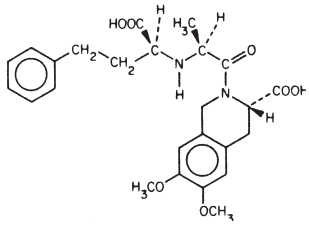
Solubility—1 g in 10 mL water or 70 mL of methanol.

Comments—An ACE inhibitor approved for use in the treatment of hypertension, heart failure and acute myocardial infarction.

Only about 30% is absorbed by the oral route. Peak plasma levels occur in about 7 hr. Elimination is almost entirely by renal excretion; the dose must be adjusted in renal failure. The normal half-life is about 12 hr but is longer in elderly patients.

MOEXIPRIL HYDROCHLORIDE

3-Isoquinolinecarboxylic acid, (3*S*)-2-[(2*S*)-*N*-[(1*S*)-1-carboxy-3-phenylpropyl]alanyl]-1,2,3,4-tetrahydro-6,7-dimethoxy-, hydrochloride; Univasc



[103775-14-0] $C_{25}H_{30}N_2O_7$ (470.53).

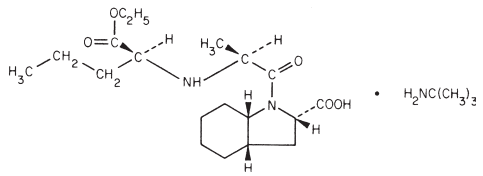
Description—Fine white to off-white powder.

Solubility—Soluble in water about 1 in 10 at 20°.

Comments–A prodrug converted to the active moexiprilat. Approved for the treatment of hypertension. Bioavailability is about 13% and is decreased by food.

PERINDOPRIL ERBUMINE

1*H*-Indole-2-carboxylic acid, [2*S*-[1[*R(*R**)],2α,3a,7aβ]]-1-[2-[[1-(ethoxycarbonyl)butyl]amino]-1-oxopropyl]octahydro-, compd with 2-methyl-2-propaneamine; Aceon; Procaptan**



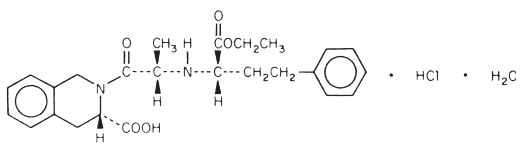
[82834-16-0] $C_{19}H_{32}N_2O_5.C_4H_{11}N$ (441.61).

Preparation—See US Pat 4,508,729 (1985).

Comments—Following absorption in the gut it releases perindoprilat in the liver. It is approved for the treatment of essential hypertension.

QUINAPRIL HYDROCHLORIDE

3-Isoquinolinecarboxylic acid, [3*S*-[2[*R(*R**)]],3*R**]-2-[2-[[1-(ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]-1,2,3,4-tetrahydro-, monohydrochloride, monohydrate; Accupril**



[90243-99-5] $C_{25}H_{30}N_2O_5.HCl.H_2O$ (493.00).

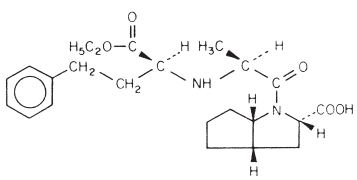
Preparation—*J Med Chem* 1986; 29:1953.

Description—White crystals melting between 120 to 130° (dehydrated salt).

Comments—A prodrug rapidly absorbed and rapidly hydrolyzed to quinaprilat, which is active for 24 hr despite a plasma half-life of about 2 hr. It is approved for treating hypertension heart failure.

RAMIPRIL

Cyclopenta[*b*]pyrrole-2-carboxylic acid, [2*S*-[1[*R(*R**)],2α,3aβ,6aβ]]-1-[2-[[1-(ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]octahydro-, Altace**



[87333-19-5] $C_{23}H_{32}N_2O_5$ (416.52).

Preparation—See *Arzneimittel-Forsch* 1984; 34:1399.

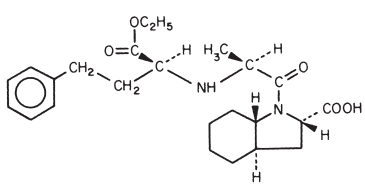
Description—Fine needles melting about 109°; pK_a (ramiprilat) 3.1, 5.6.

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

Comments—A prodrug rapidly absorbed and converted to ramiprilat, which has a half-life of 13 to 17 hr. It is approved for treating essential hypertension, heart failure post-myocardial infarction and for reducing the risk of myocardial infarction, stroke and death from cardiovascular causes in high risk patients. Dosage should be reduced in renal failure because 60% is excreted in the urine.

TRANDOLAPRIL

2-Indolinecarboxylic acid, (2*S*,3a*R*,7a*S*)-1-[(*S*)-*N*-[(*S*)-1-carboxy-3-phenylpropyl]alanyl]hexahydro-, Mavik; Odrik



[87679-37-6] $C_{24}H_{34}N_2O_5$ (430.54).

Preparation—See US Pat 4,933,361 (1990).

Description—Colorless crystals melting about 125°.

Solubility—Soluble in chloroform, methylene chloride, or methanol at greater than 100 mg/mL.

Comments—A prodrug of the nonsulfhydryl ACE, trandoliprat, which is formed by the hydrolysis of the ethyl ester. Approved for the treatment of hypertension and heart failure post-myocardial infarction.

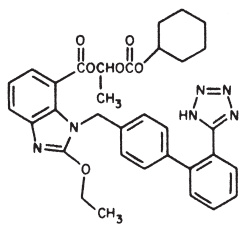
ANGIOTENSIN II RECEPTOR ANTAGONISTS

The angiotensin II receptor blockers (ARBs) are a newer class of antihypertensive agents. They inhibit the effects of angiotensin II by directly blocking the angiotensin AT_1 receptor. The generation of angiotensin II can occur through mechanisms other than ACE activity and the AT_1 receptor is the site of action for angiotensin II that results in vasoconstriction, aldosterone, and ADH release, constriction of the efferent arteriole of the glomerulus and sympathetic activation. The ARBs inhibit the action of angiotensin II regardless of the pathway of generation; however, unlike the ACE inhibitors they do not block the breakdown of bradykinin. They are indicated for use in the treatment of hypertension and have also been studied in the treatment of heart failure and myocardial infarction. Their exact role in the treatment of heart failure and myocardial infarction has yet to be determined.

The side effects of the angiotensin II receptor antagonists are similar to those of the ACE inhibitors. However, the incidences of cough and angioedema are significantly lower, probably because of their lack of effect on bradykinin metabolism. They are contraindicated in pregnancy. Frank neutropenia or hepatotoxicity has not been reported, but caution should dictate until their use becomes more widespread.

CANDESARTAN CILEXETIL

(±)-1-*H*-Benzimidazole-7-carboxylic acid, 2-ethoxy-1-[[2′-(1*H*-tetrazol-5-yl)[1,1-biphenyl]-4-yl]methyl]-, 1-[[cyclohexyloxy)carbonyl]oxy]ethyl ester; Atacand



[145040-37-5] $C_{33}H_{34}N_6O_6$ (610.67)

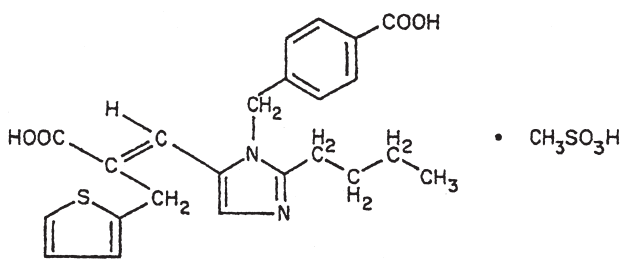
Preparation—See *J Med Chem* 1993; 36:2343; US Pat 5,196,444 (1993).

Description—Colorless crystals melting about 163° with decomposition.

Comments—Prodrug for the free acid which is formed by hydrolysis of the ethyl ester.

EPROSARTAN MESYLATE

2-Thiophenepropionic acid, (*E*)-α-[[2-butyl-1-[(4-carboxyphenyl)-methyl]-1H-imidazol-5-yl]methylene]-, monomethanesulfonate; Teveten



[44143-96-4] $C_{23}H_{24}N_2O_4S.CH_4O_3S$ (520.62).

Preparation—US Pat 5,185,351 (1993); *J Med Chem* 1991; 1514:34.

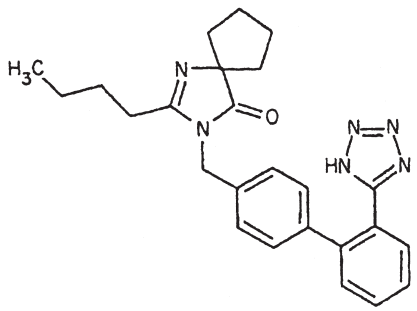
Methyl 4-(bromomethyl)benzoate and 5-chloro-2-propylimidazole are condensed using potassium carbonate in DMF to give the 1-(4-methoxycarbonyl)benzyl derivative of the imidazole (I). I, with the monomethyl ester of 2-thenylmalonate, in a solution of piperidine and pyridine in toluene forms the dimethyl ester of eprosartan, which is saponified to the diacid. The mesylate salt is obtained by reaction with methanesulfonic acid.

Description—Crystals from methanol. Free base melts about 260o.

Solubility—Insoluble in water; freely soluble in ethanol.

IRBESARTAN

Diazaspiro[4.4]non-1-en-4- one, 2-butyl-3-[[2′-(1*H*-tetrazol-5-yl)- [1,1-biphenyl]-4-yl]methyl]-, Avapro



[138402-11-6] $C_{25}H_{28}N_6O$ (428.53).

Preparation—US Pat 5,270,317 (1993); *J Med Chem* 1993; 36:3371.

A multi-step synthesis starting with butyl 2-[(4-methylamino)-phenyl] benzoate and 1-aminocyclopentane carboxylic acid.

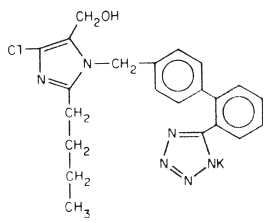
Description—White to off-white crystals from ethanol; melts about 180°.

Log P (pH 10.1) 7.4.

Solubility—Slightly soluble in ethanol or methylene chloride; practically insoluble in water.

LOSARTAN POTASSIUM

1*H*-Imidazole-5-methanol, 2-butyl-4-chloro-1-[[2′(1*H*-tetrazol-5-yl)-[1,1′-biphenyl]-4-yl]methyl]-, potassium salt; Cozaar



[124750-26-4] $C_{22}H_{22}ClKN_6O$ (461.01).

Preparation—See *J Med Chem* 1991; 34:2525; US Pat 5,138,069 (1992).

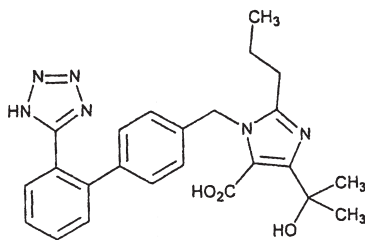
Description—White to off-white free-flowing crystalline powder melting at about 184°; pK_a approx 5.5 (free acid).

Solubility—Freely soluble in water; soluble in alcohol; slightly soluble in acetonitrile or 2-butanone.

Comments—Oxidation of the hydroxymethyl group on the 5- position of the imidazole ring yields the active metabolite.

OLMESARTAN

1*H*-Imidazole-5-carboxylic acid, 4-(1-hydroxy-1-methyl-ethyl)-2-propyl-1-[[(2′-(1*H*-tetrazol-5-yl) [1,1′-biphenyl]-4-yl]methyl]-, Benicar



[144689-24-7] $C_{24}H_{26}N_6O_3$ (446.50).

Preparation—US Pat 5,616,599 (1997); *J Med Chem* 1996; 39:323.

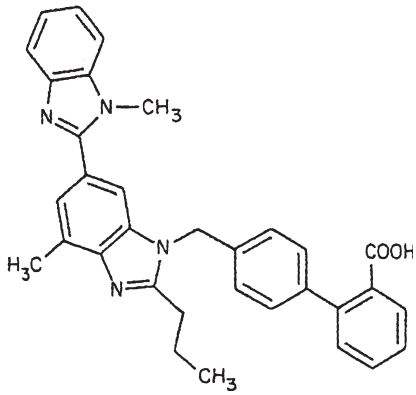
Description—White to light yellow crystals from ethanol melting about 180o (dec).

Solubility—Practically insoluble in water; sparingly soluble in methanol.

Comments—A Prodrug hydrolyzed to olmesartan during absorption from the gastrointestinal tract.

TELMISARTAN

[1,1′-Biphenyl]-2-carboxylic acid, 4′-[(1,4′-dimethyl-2′-propyl[2,6′-bi-1H-benzimidazol]-1′-yl)methyl]-, Micardis



[144701-48-4] $C_{33}H_{30}N_4O_2$ (514.62).

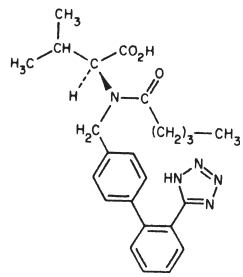
Preparation—EP 502,314 (1992); *Chem Abstr*; 1993;117: 251,352; also *J Med Chem* 1993;36: 4040.

Description—White solid melting about 262°.

Solubility—Practically insoluble in water or in aqueous solutions ranging from pH 3 - 9. Soluble in basic solutions above pH 10.

VALSARTAN

L-Valine, *N*-(1-oxopentyl)-*N*-[[2′-(1*H*-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-, Diovan



[137862-53-4] $C_{24}H_{29}N_5O_3$ (435.53).

Preparation—See US Pat 5,399,578 (1991).

Description—White crystals melting at about 117°.

PERIPHERAL VASODILATORS

Peripheral vasodilators are substances that dilate the arterioles and increase blood flow in the numerous systemic vascular beds, especially in the extremities. To the pharmacologist, the word peripheral may indicate that the action is directly on the arterioles, but to the clinician the word merely indicates the site of the final effect. Thus, centrally acting, reflexly acting, or ganglionic blocking drugs that reduce sympathetic tone to the periphery are peripheral vasodilators, clinically speaking. Consequently, all of the hypotensives listed in the previous section may be considered to be peripheral dilators. Some sympathomimetics with prominent β_2-receptor stimulant actions are employed for their peripheral vasodilator effects. The adrenergic blocking drugs also are used to improve flow through specific peripheral vascular beds (Table 68-1).

Table 68-1. Other Peripheral Vasodilators

DRUG	DESCRIPTION
Cyclandelate (Cyclospasmol)	Synthetic
Ethaverine HCl (Ethaquin, Ethatab)	Semisynthetic homolog of papaverine
Papaverine HCl	Nonopioid alkaloid in crude opium

Peripheral vasodilators are employed in the treatment of vasospastic disorders such as Raynaud's disease, causalgias and reflex dystrophy, vasospasm associated with arterial embolism and thrombophlebitis, immersion foot, trench foot, herpes zoster, decubitus ulcers, and degenerative arterial diseases such as thromboangiitis obliterans, arteriosclerosis obliterans, acrocyanosis, and diabetic gangrene. However, there is a great deal of justifiable skepticism about the value of peripheral vasodilators in most uses, since vasospastic ischemia usually is self-limiting because of autoregulatory factors that counteract the spasms. An organic obstruction cannot be corrected for by vasodilatation, since the obstruction is the principal resistance in the line. However, vasodilatation may (or may not) improve circulation in the ischemic area through collateral vessels. Papaverine, alone or in combination with phentolamine, has been used as an intracavernous injection for impotence.

DIPYRIDAMOLE—see RPS-18, page 844.
ISOXSUPRINE HYDROCHLORIDE—page 1384.
NYLIDRIN HYDROCHLORIDE—page 1384.
PHENTOLAMINE—page 1400.

ANTIANGINAL DRUGS

Drugs considered in this section are used primarily for the treatment of angina pectoris of several types: *classical* (exercise-induced or stable), *variant* (vasospastic or Prinzmetal's), and *unstable anginas*.

Three classes of drugs are the mainstays of angina therapy: the organonitrates, the calcium channel blockers, and the β-antagonists. Nitrates and calcium channel blockers dilate coronary arteries, which may contribute to their antianginal effects, particularly in vasospastic angina.

Organic nitrates dilate the capacitance veins (which decreases ventricular filling pressures) and the conducting arteries (which decreases arterial impedance). Both effects lead to a reduction in wall stress, the major determinant of myocardial oxygen demand, as a result of decreased ventricular volume and pressure and, hence, provide relief from anginal pain. There is also a decrease in cardiac output and total peripheral resistance, which may lower the blood pressure, eliciting reflex arteriolar constriction (which opposes the direct arteriolar dilating actions of the drug) and tachycardia, both of which are counterproductive.

The organonitrates also decrease pulmonary pressures. The result is a decrease in pulmonary congestion and edema in left heart failure, and hence, organonitrates can be used to relieve orthopnea and paroxysmal nocturnal dyspnea.

Organonitrates all have a common mechanism of action briefly summarized as follows. The nitrates are converted *in vivo* to nitric oxide (NO), which is an endothelium-derived relaxing factor (EDRF) endogenously generated by the oxidation of L-arginine. In turn, NO stimulates guanylate cyclase, thus causing smooth muscle relaxation. Sustained use of organic nitrates can produce tolerance to the nitrates. Therefore, many experts now recommend pulse or intermittent dosing (a 6- to 8-hour nitrate-free interval) rather than continuous nitrate administration, to reduce the likelihood of tolerance during chronic therapy. Sustained exposure to high doses of nitrates can result in a physical dependence that, upon abrupt discontinuation of drug, can be manifested as anginal attacks. They should be withdrawn gradually after continuous or chronic use.

Calcium entry blocking drugs act somewhat differently from the organonitrates in relieving angina. They are both coronary and peripheral arteriolar dilators, however their antianginal effect in exercise-induced and unstable anginas derives from the reduction in wall tension from a decrease in cardiac afterload. Coronary artery dilatation has some contribution, particularly in vasospastic angina. Effects on cardiac preload are negligible. Some calcium entry antagonists directly slow the heart; this effect decreases myocardial oxygen demand and blunts reflex responses to arteriolar dilatation. Prevention of calcium influx into ischemic myocardial cells also may have a direct effect to decrease myocardial oxygen demand by preserving myocardial ATP.

Other pharmacological approaches to the treatment of angina include the use of β-antagonists and various drugs that decrease the incidence and consequences of coronary artery disease.

Beta-antagonists increase exercise tolerance in angina because they improve blood flow to the vulnerable subendocardium, mostly by slowing the heart rate and increasing diastolic time, during which subendocardial perfusion mainly occurs. Also, a decrease in heart rate and contractility decreases myocardial oxygen demand. These drugs are discussed in Chapter 72.

The use of drugs to lower blood cholesterol and, hence, prevent coronary atherosclerosis are effective and are discussed later in this chapter.

Antiplatelet drugs prevent the formation of white thrombus that occurs following rupture of an atheromatous plaque. Aspirin and clopidogrel are effective as primary and secondary prevention of acute coronary syndromes that occurs from formation of thrombus in the coronary arteries.

ORGANONITRATES

Organonitrates are available in a variety of dosage forms listed below. For aborting an acute attack of angina, sublingual nitrates or lingual spray have a rapid onset of action and are effective for short periods. For chronic prophylaxis, sustained-release tablets or topical ointment provide antianginal effects for up to 8 hours and can be administered on a scheduled basis. Transdermal systems of nitroglycerin can provide sustained blood levels for up to 24 hr. Since tolerance can develop when used on a continuous basis, a 10- to 12-hour nitrate-free interval should occur in order to prevent tolerance.

AMYL NITRITE

Mixture of nitrous acid, 2-methylbutyl ester, and nitrous acid, 3-methylbutyl ester; Vaporole; Aspiroles

[8017-89-8] $C_5H_{11}NO_2$ (117.15).

Preparation—A good grade of commercial amyl alcohol (isoamyl alcohol) boiling above 125° is esterified with nitrous acid. The acid is generated in contact with the alcohol from sodium nitrite and dilute H_2SO_4.

Description—Clear, yellowish liquid with an ethereal, fruity odor and pungent, aromatic taste; boils about 96° but is volatile even at low temperatures and is flammable; slowly decomposes on exposure to air and light; moisture accelerates decomposition; specific gravity 0.870 and 0.876.

Solubility—Practically insoluble in water; miscible with alcohol, chloroform, or ether.

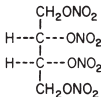
Comments—Although a nitrite, its actions are those of organonitrates (see the general statement). It causes more reflex arteriolar constriction than the nitrates. It is quite volatile and is inhaled to obtain a rapid effect (onset 0.5 min). In practice, however, amyl nitrite is employed rarely in the treatment of attacks of angina pectoris. An unusual, but at times life-saving, use for amyl nitrite is in the emer-

gency treatment of cyanide poisoning, when nitrites are given to produce methemoglobin, which temporarily inactivates the toxic cyanide ion by combining with it to form cyanmethemoglobin. For this purpose, sodium nitrite is employed intravenously, but this drug may be inhaled while the solution of sodium nitrite is being prepared. It is administered by crushing a glass perle of this drug in a handkerchief and inhaling the liquid that volatilizes, or by dropping a small quantity on a handkerchief and inhaling the vapor. It has become a drug of abuse because of a rush (an acute vasodilatory episode) felt after inhalation. Abuse may cause methemoglobinemia, hemolytic anemia, and immunological disorders.

Caution—Amyl nitrite is very flammable. Do not use where it may be ignited.

ERYTHRITYL TETRANITRATE

(*R*,S)-1,2,3,4-Butanetetrol, tetranitrate; Tetranitrol; Cardilate**



[7297-25-8] $C_4H_6N_4O_{12}$ (302.11); a dry mixture with lactose or other suitable inert excipients, to permit safe handling and compliance with federal ICC regulations pertaining to interstate shipment.

Caution: Undiluted erythrityl tetranitrate is a powerful explosive, and proper precautions must be taken in handling. It can be exploded by percussion or by excessive heat. Only extremely small quantities should be isolated.

Preparation—Erythritol is reacted with nitric acid in the presence of sulfuric acid under controlled temperature.

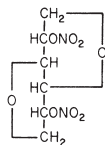
Description—White powder with a slight odor of nitric oxides and a bitter taste; unstable in light or heat.

Solubility—Soluble (undiluted) in acetone or alcohol; practically insoluble in water.

Comments—By the sublingual route, it has a relatively long duration of action (about 2 hr). By the oral route, the duration is longer, but quite variable. This agent should not be used as a chronic prophylactic therapy.

ISOSORBIDE DINITRATE

D-Glucitol, 1,4:3,6-dianhydro-, dinitrate; Isordil; Sorbitrate; Dilatrate-SR



[87-33-2] $C_6H_8N_2O_8$ (236.14).

Preparation—An aqueous syrup of 1,4:3,6-dianhydro-D-glucitol is added slowly to a cooled mixture of HNO_3 and H_2SO_4. After standing a few minutes, the mixture is poured into cold water, and the precipitated product is collected and recrystallized from ethanol.

Description—*Diluted* (with mannitol, lactose, or other inert ingredients): ivory-white, odorless powder. *Undiluted:* white, crystalline rosettes.

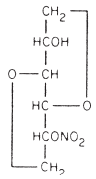
Solubility—*Undiluted:* very slightly soluble in water; very soluble in acetone; freely soluble in chloroform; sparingly soluble in alcohol.

Comments—The long-acting organonitrate of choice when chronic prophylaxis of angina is necessary. With sublingual and chewable tablet forms, the onset of effect is 2 to 5 min (absorption from the chewable tablet is also mainly from the mouth); with oral forms, the onset is about 30 min and duration is 4 to 6 hr; with sustained-release forms, the duration is 8 to 12 hr.

The most frequent complaint by users is headache. Oral bioavailability is approximately 22% because of high first-pass metabolism. Sublingual administration is said to increase bioavailability, but there is some disagreement on this point. However, sublingual and chewable tablet dosages are predicated on bioavailabilities at least twice the bioavailability with oral administration. The metabolites of isosorbide dinitrate are the 2- and 5-mononitrates, both of which have antianginal effects. The 5-mononitrate is the more active (see below). The half-life varies with the route of administration and ranges from 20 min (IV) to 4 hr (oral), probably because there is more mononitrate formed after oral administration; mononitrate inhibits the metabolism of the parent drug.

ISOSORBIDE MONONITRATE

D-Glucitol, 1:4,3:6-dianhydro-, 5-nitrate; ISMO



[16051-77-7] $C_6H_9NO_6$ (191.14).

Preparation—See *Acta Physiol Scand* 1948; 15:173.

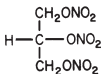
Description—White powder melting about 90°.

Solubility—About 1 g in 20 mL alcohol or water.

Comments—A metabolite of isosorbide dinitrate (above). Its bioavailability is about 100%. The half-life is 4 to 6 hr. Advantages over isosorbide dinitrate include no first-pass metabolism, no active metabolites, and a significantly longer half-life.

NITROGLYCERIN

1,2,3-Propanetriol, trinitrate; Glyceryl Trinitrate, Glonoin, Trinitrin



Nitroglycerin [55-63-0] $C_3H_5N_3O_9$ (227.09).

Preparation—By nitrating glycerin with a mixture of nitric and sulfuric acids, called *nitration acid.* This acid usually consists of 3 parts of concentrated nitric acid and 5 parts of sulfuric acid.

Description—Practically colorless, odorless liquid with a sweet taste.

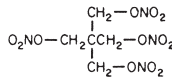
Packaging—Sufficiently volatile to require packaging of tablets in glass containers with tightly fitting metal screw caps and holding no more than 100 tablets in each container; only original unopened containers may be dispensed. Patients should keep the tablets in the original container, close it tightly after each use and avoid exposure to heat. Some manufacturers have added a *fixing* agent (polyethylene glycols) to the tablet preparation to minimize volatilization. Regardless, the unopened container *only* should be dispensed and under no circumstance should a label, absorbent cotton, or a desiccant be placed in the container.

Comments—The classical organonitrate once was the drug of choice for the treatment of angina pectoris. After oral administration, it is metabolized rapidly in the intestinal wall and liver, so systemic bioavailability is rather low. Consequently, oral doses are quite high, and plasma levels are erratic. The sustained-release forms are not recommended since oral bioavailability is so poor and tolerance is favored. Bioavailability is much greater by the buccal and sublingual routes. By the sublingual route, the vasodilator effects of the drug appear in 2 to 3 min and last about 20 min, but exercise tolerance may be increased for as long as an hour in some patients. Buccal tablets, if retained in the mouth, release nitroglycerin for 3 to 5 hr. Sustained-release oral capsules and tablets maintain plasma levels for 8 to 12 hr. A nitroglycerin ointment can provide therapeutic blood levels for 2 to 12 hr per application. Transdermal preparations may sustain plasma levels for 24 hr or longer. An intravenous formulation is available but has a short half-life of 1 to 5 minutes and, therefore, must be administered via continuous infusion.

Cerebral vasodilation may cause transient headaches. Paradoxical angina occurs when the dose is too large and blood pressure falls too low to sustain coronary flow. Dizziness, nausea, and other symptoms of hypotension also occur. High, repetitive doses can cause methemoglobinemia.

PENTAERYTHRITOL TETRANITRATE

1,3-Propanediol, 2,2-bis-[(nitrooxy)methyl]-, dinitrate, ester; Peritrate



[78-11-15] $C_5H_8N_4O_{12}$ (316.14).

Description—A dry mixture of pentaerythritol tetranitrate (prepared by nitration of pentaerythritol) with lactose or other suitable inert excipient to permit safe handling of the explosive undiluted substance; melts about 140°.

Solubility—Practically insoluble in water; sparingly soluble in polar organic solvents.

Comments—A so-called long-acting organonitrate, the long duration of which is mainly the result of prolonged release and absorption from oral dosage forms. Medical authorities state that the sustained-release forms are poorly effective. It is not absorbed sublingually. Since absorption by the oral route is erratic, efficacy is unpredictable.

VASOPRESSOR DRUGS

A number of drugs in several classes have vasoconstrictor or cardiostimulator activity and are necessary to elevate the blood pressure in certain conditions. These drugs are used in patients who require vasoconstrictive or inotropic support, primarily those with critically low blood pressure due to decreased cardiac output or systemic vasodilation, or both. Before initiating vasopressors treatment of underlying conditions, such as hypovolemic shock or sepsis, should be initiated. The most important of these drugs, the sympathomimetics, are alpha- and beta-receptors agonists and are discussed in detail in Chapter 70.

In the treatment of patients with cardiogenic shock, it is necessary to increase the cardiac output in order to maintain perfusion to vital organs. Dobutamine is an option in these patients because of its beta-agonist activities that result in positive inotropic activity. However, it may cause some afterload reduction resulting in hypotension and may cause arrhythmias. Dopamine has both alpha- and beta-agonist activity, depending on the dosage used, and will increase the cardiac output while not lowering afterload. For this reason, it is a better option in patients who require inotropic support but have low blood pressures.

DOBUTAMINE—page 1269.
DOPAMINE—page 1387.

CARDIAC GLYCOSIDES (DIGITALIS)

The primary action of digitalis on the heart is a direct cardiotonic action on the myocardium to increase the force of contraction. The increased contractility results from inhibition of the membrane sodium/potassium-activated ATPase, which inhibition ultimately increases the intracellular stores of calcium. In congestive heart failure, stroke volume may be increased, which more effectively empties the ventricles and lowers diastolic ventricular pressures and ultimately pulmonary and central venous pressures. Congestion thus is diminished.

Increased cardiac output improves renal blood flow and glomerular filtration and decreases juxtaglomerular renin secretion, so that the renal resorption of sodium and water is diminished. Hepatic blood flow also is increased, which increases the clearance of aldosterone. The result of this is a decrease in edema and an improvement in symptoms.

Slowing of the cardiac rate occurs only when the rate was originally rapid, as the result of compensatory sympathetic reflexes, consequent to failure. When the failure is abolished, there is no longer any need for the compensatory tachycardia, and consequently, the heart rate slows to normal. This slowing also has been attributed to a vagal action of digitalis. Digitalis does sensitize the sinoatrial node, atrium, and atrioventricular node to vagal impulses and increases vagal tone by actions in the CNS and on the baroreceptors. High doses also may slow the ventricle by a direct action on atrioventricular conduction.

The chief therapeutic use for digitalis is in the treatment of low-output congestive heart failure. When the failure is due to an acute toxic or infectious process, such as viral myocarditis, rather than to a chronic degenerative process such as arteriosclerosis or failure secondary to hypertensive heart disease, digitalis may give poor results. High-output failure in patients with anemia, hyperthyroidism, and thiamine deficiency is likewise not much benefited.

The action of digitalis to impair atrioventricular conduction is employed in the management of atrial flutter, atrial fibrillation, and paroxysmal supraventricular tachycardia (PSVT). The action sought is to decrease the ventricular rate toward a more optimal value, that is, a partial heart block to decrease the number of atrial impulses that pass through to the ventricles. In an occasional case of atrial flutter, the proper use of fairly large doses of digitalis may abolish the arrhythmia. In PSVT a properly selected dose can interrupt one segment of the reentrant pathway within the AV node, thus terminating the circus movement yet allowing orthograde conduction of normal impulses.

There are two glycoside products available. When absorbed in adequate amounts, the active digitalis principles produce identical effects on the myocardium, and their toxic effects are essentially the same, although there is some evidence that digitoxin gains better access to the CNS and causes more neurological side effects and CNS-initiated arrhythmias. They differ from each other largely in speed of onset of action, duration of cardiac effects, and the degree of absorption by the oral route. With some glycosides (eg, digoxin), bioavailability varies widely from product to product, which may require clinical or plasma-level monitoring.

Initial digitalization may be accomplished rapidly or slowly, depending on the urgency of the case. The vast majority of patients with congestive heart failure can be digitalized without a loading dose, so that about 5 half-lives are required to achieve a maintenance steady state.

In acute heart failure or symptomatic atrial tachyarrhythmias, loading may be desirable. The process of loading is known as rapid digitalization. It is not unusual to digitalize a patient in 12 or 24 hr by giving one-half of the calculated dose at once and the remainder in two or three divided doses at intervals of 6 hr. This principle is applied to other cardiac glycosides, and only the timing differs. Dosing should be individualized to the patients weight and renal function, and patients should be monitored closely to observe the developing effects of the drug and to prevent unpleasant or serious toxic effects from overdosage.

Intravenous administration can be utilized in patients who have severely symptomatic congestive heart failure or atrial tachyarrhythmias or who are unable to tolerate oral digitalis or who have GI disorders that preclude oral dosage.

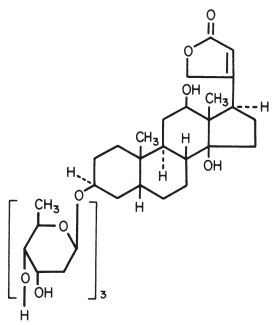
Cardiac glycosides have a low margin of safety. They may cause nausea, vomiting, diarrhea, abdominal pain, headache, drowsiness, fatigue, malaise, backache, decreased libido, impotence, trigeminal neuralgia, white vision and other visual disturbances, convulsions, mental disturbances, eosinophilia, rashes, gynecomastia, and, rarely, thrombocytopenia.

Cardiac arrhythmias of all types are a sign of excessive plasma levels. Heart block and premature ventricular contractions (PVC) are the most frequent, ventricular tachycardia the most ominous. Toxic doses also can result in serious ventricular arrhythmias. Toxicity is more likely in the presence of hypokalemia, a common result of concomitant diuretic therapy for the cardiac edema.

Toxicity can be antagonized by digoxin immune Fab (see below), edetate disodium, potassium (especially if hypokalemia exists), lidocaine, phenytoin, or to a lesser extent, propranolol, quinidine, or procainamide.

DIGITOXIN

Card-20(22)-enolide, (3β,5β)-3-(*O*-2,6-dideoxy-β-D-*ribo*-hexopyranosyl-(1 → 4)-*O*-2,6-dideoxy-β-D-*ribo*-hexopyranosyl-(1 → 4)-2, 6-dideoxy-D-*ribo*-hexopyranosyl)oxy-14-hydroxy-,



[71-63-6] $C_{41}H_{64}H_{13}$ (764.95); a cardiotonic glycoside obtained from *Digitalis purpurea* Linné, *Digitalis lanata* Ehrh, and other suitable species of *Digitalis*.

The side chain consists of 3 molecules of digitoxose in glycosidic linkage. Removal of the side chain by hydrolysis yields the aglycone, digitoxigenin ($C_{23}H_{34}O_4$).

Description—White or pale buff, odorless, microcrystalline powder.

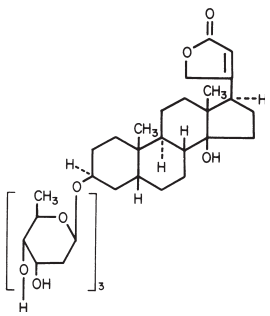
Solubility—Practically insoluble in water; 1 g in about 150 mL alcohol or 40 mL chloroform; very slightly soluble in ether.

Comments—This drug is currently not available in the United States. It is absorbed almost completely after oral administration. Action is maximal in 4 to 12 hr. After full digitalization, the duration of action is about 14 days. In plasma, about 97% is protein-bound. The volume of distribution is about 0.6 mL/g. Plasma concentrations of 15 to 25 ng/mL are considered to be therapeutic, and 35 to 40 ng/mL or more to be toxic. Hepatic metabolism accounts for 52% to 70% of elimination. The β-half-life ranges from 2.4 to 9.6 (av 7.6) days.

Caution—Handle digitoxin with exceptional care, since it is highly potent.

DIGOXIN

Card-20(22)-enolide, (3β,5β,12β)-3-[(*O*-2,6-dideoxy-β-D-*ribo*-hexopyranosyl-(1 → 4)-*O*-2,6-dideoxy-β-D-*ribo*-hexopyranosyl-(1 → 4)-2,6-dideoxy-β-D-*ribo*-hexopyranosyl)oxy]-12,14-dihydroxy-, Lanoxin, Digitek



[20830-75-5] $C_{41}H_{64}O_{14}$ (780.95); a cardiotonic glycoside obtained from the leaves of *Digitalis lanata Ehrh* (Fam *Scrophulariaceae*).

The side chain of digoxin consists of three molecules of digitoxose in glycosidic linkage. Hydrolytic cleavage yields the aglycone, digoxigenin ($C_{23}H_{34}O_5$)

Description—Clear to white crystals or a white crystalline powder; odorless; melts with decomposition above 235°.

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

Comments—In plasma 20% to 30% is protein-bound. It has a high volume of distribution, with a volume of distribution of about 7 L/kg in normal adults and neonates and even larger in infants; in renal failure the volume of distribution is approximately 4-6 L/kg.

The therapeutic concentration in plasma is 0.5 to 2.0 ng/mL, although efficacy in heart failure has been observed with plasma concentrations ranging from 0.8 to 1.2 ng/mL. Concentrations above 2.0 ng/mL are considered toxic, although symptoms of toxicity may occur at lower concentrations when other conditions, such as hypokalemia and hypercalcemia, exist. In adults, renal excretion accounts for 60% to 90% of elimination. Biliary secretion and enterohepatic recirculation account for about 7% to 30%. The elimination half-life is 29 to 135 (usually 36–41) hours in normal adults. In renal failure, the β-half-life may be as long as 89 to 177 hours. By the oral route, about 50% to 85% is absorbed from solid dosage forms, but it is 90% to 100% absorbed from hydroalcoholic solutions in capsules.

DIGOXIN IMMUNE FAB (OVINE)

F(ab); Digibind

Comments—The toxicity and long half-life of digitalis glycosides led to the development of specific antidigoxin antibody fragments obtained from immunized sheep. The antibodies bind and inactivate molecules of digoxin or digitoxin, and the resulting complex is excreted in the urine. It takes 40 mg of Fab to bind about 0.6 mg of digoxin or digitoxin. Allergic reactions are rare (0.8%), but hypokalemic reactions can develop rapidly. It is administered intravenously, on the basis of the amount of drug ingested or serum digoxin concentration (see package insert for specific instructions).

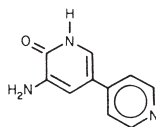
PHOSPHODIESTERASE INHIBITORS

Cardiac glycosides had been the drugs of choice in the treatment of congestive heart failure for two centuries. Later, dopamine and dobutamine were introduced for their positive inotropic actions in the management of decompensated congestive heart failure. Dobutamine, initially, was the focus of attention because its vasodilator actions decrease the cardiac impedance (unload the left ventricle), which increases stroke output beyond that achieved by the positive inotropic action. The discovery of amrinone in 1977 has led to interest in drugs that combine positive inotropic with vasodilator actions. Such drugs are selective or nonselective phosphodiesterase inhibitors and have become known as inodilator drugs.

These drugs inhibit phosphodiesterase III and thus increase intracellular cAMP and calcium. In heart muscle the result is an increase in contractility, and in vascular smooth muscle the result is relaxation. Both effects contribute to improvement in cardiac output in congestive heart failure. Amrinone and milrinone are presently the only available inodilators, and their use is limited to decompensated heart failure that is refractory to other treatments.

AMRINONE

[3,4′-Bipyridin]-6(1*H*)-one, 5-amino-, amrinone, Inocor



[60719-84-8] $C_{10}H_9N_3O$ (187.20).

Preparation—US Pat 4,004,012.

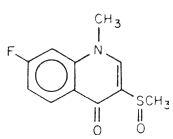
Description—Pale-yellow crystals; melts about 295° with decomposition.

Solubility—At pH 4, 6, and 8 is 25, 0.9, and 0.7 mg/mL, respectively.

Comments—To avoid confusion with similarly sounding drugs, the name was changed from amrinone to inamrinone in 2000. Metabisulfite preservative in the preparation can cause hypersensitivity in certain individuals. Amrinone is not effective by the oral route even though it is absorbed. It has a volume of distribution of 1.2 L/kg. Over 70% is conjugated in the liver, the remainder is excreted in the urine. The half-life is about 3.6 hr in normal persons but 5 to 8 hr in subjects with heart failure. The duration of action is 30 to 120 min.

FLOSEQUINAN

4(1*H*)-Quinolone, 7-fluoro-1-methyl-3-(methylsulfinyl)-, Manoplax



[76568-02-0] $C_{11}H_{10}FNO_2S$ (239.26).

Preparation—US Pat 4,302,460.

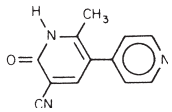
Description—White crystals melting about 227°.

Comments—Not currently available in the United States. A fluoroquinolone derivative that produces both venous and arterial vasodilatation and increases heart rate and contractility. Although its precise mechanism of action remains unknown, it appears to influence intracellular release of calcium by attenuating levels of inositol triphosphate or inhibiting protein kinase C. It is also a nonselective inhibitor of phosphodiesterases.

It is absorbed rapidly after oral administration and undergoes slow conversion to an equally active sulfone metabolite. Although the half-life of flosequinan is only about 1.7 hr, that of its active metabolite is 30 to 40 hr. Half-lives may be prolonged markedly in patients with congestive heart failure or with renal or hepatic impairment. The active and several inactive metabolites are excreted in the urine.

MILRINONE LACTATE

[3,4′-Bipyridine]-5-carbonitrile, 1,6-dihydro-2-methyl-6-oxo-, Primacor



[78415-72-2] $C_{12}H_9N_3O$ (211.22).

Preparation—US Pat 4,313,951.

Description—White crystals melting over 300°.

Comments—It is 20 to 30 times more potent than inamrinone as a positive inotropic agent and somewhat more potent as an arteriolar and venous dilator. It does not affect renal function significantly. In patients with congestive heart failure it improves cardiac index and decreases systemic vascular resistance. An oral form is not available. It has a volume of distribution of 0.4 L/kg and a mean half-life of 2.3 hr. It is excreted rapidly in the urine by active secretion.

ANTIARRHYTHMIC DRUGS

Cardiac arrhythmias may result from disturbances in the pacemaker function of the sinoatrial node, from alterations in conduction pathways and velocity, or from activation of pacemakers outside the sinus node and are often classified as tachyarrhythmias or bradyarrhythmias.

Autonomic drugs are often utilized to manage arrhythmias. Sinus tachycardia may be slowed by β_1-antagonists, and anticholinergics. β_1-agonists are used to revive an arrested heart and treat certain types of heart block.

Antiarrhythmic drugs have specific actions that alter cardiac conduction and are classified by their electrophysiological properties *in vitro*. The classification that follows is based on the classification of Vaughn-Williams. For simplicity, the most prominent effects at normal doses are used to determine placement in groups, but drugs may have properties that place them in more than one group. They may act differently in different parts of the heart, and in normal and diseased hearts the effects may be modified. Some drugs, such as digoxin or adenosine, are used in the treatment of arrhythmias; however, they are not included in the Vaughn-Williams classification.

Type I drugs are classified as sodium channel blockers. They inhibit the influx of sodium into the cardiac cell, thereby slowing conduction velocity. The action of the individual subclasses depends on the receptor binding and unbinding characteristics and the rate dependence properties.

Subtype IA drugs slow conduction velocity, prolong refractoriness, and decrease automaticity. They are typically effective for both supraventricular and ventricular arrhythmias.

Subtype IB drugs have minimal effects on conduction velocity but does shorten refractoriness and decreases automaticity. They are more effective in treating ventricular than supraventricular arrhythmias, particularly in ischemic tissue.

Subtype IC drugs decrease conduction velocity but have little effect on the refractory period. They are effective in the treatment of both supraventricular and ventricular arrhythmias; however, their use in patients with ischemic heart disease is limited secondary to the increased risk of proarrhythmias.

Type II drugs are the β-antagonists. These drugs are utilized in the treatment of arrhythmias, particularly tachyarrhythmias associated with high sympathetic tone. Their antiadrenergic properties make them particularly effective in the treatment of arrhythmias of the sinoatrial and atrioventricular node and in slowing the ventricular response in atrial tachyarrhythmias. These agents are discussed in detail in Chapter 72.

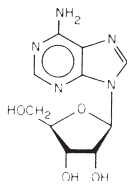
Type III drugs block the potassium channels thereby prolonging repolarization and increasing refractoriness. The individual properties of the drugs in this category are very different and several of them have multiple electrophysiologic actions.

Type IV drugs are the classical calcium entry blockers. These agents are similar to the Type II drugs in that they are particularly effective in the treatment of arrhythmias of the sinoatrial and atrioventricular node and in slowing the ventricular response in atrial tachyarrhythmias. They are discussed in more detail later in this chapter.

All antiarrhythmic drugs may cause new or worsened arrhythmias, a characteristic termed proarrhythmia. Although the incidence of proarrhythmias is higher with Type I and Type III drugs, both β-antagonists drugs (Type II) and calcium channel blocking drugs (Type IV) can be proarrhythmic, usually causing sinus bradycardia or AV block. These new arrhythmias are often difficult to distinguish from worsening of the original arrhythmia, which can lead to further or more aggressive treatment with the offending drug. A large clinical trial using several Type IC drugs in post–myocardial infarction patients found that there was a significant increase in mortality or nonfatal cardiac arrest in patients taking the drugs over those taking placebo.

ADENOSINE

9*H*-Purine, 6-amino-9-β-D-ribofuranosyl-, Adenocard



[58-61-7] $C_{10}H_{13}N_5O_4$ (267.24).

Preparation—Derived from yeast nucleic acids.

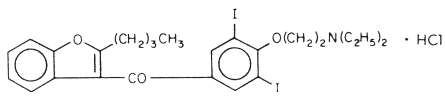
Description—White crystals melting at about 235°.

Solubility—Very soluble in water; solution may be sterilized by filtration or short-term autoclaving.

Comments—An antiarrhythmic drug approved for supraventricular tachycardia. It is given IV only and has a half-life less than 10 seconds. Major side effects are flushing and dyspnea.

AMIODARONE HYDROCHLORIDE

Methanone, (2-butyl-3-benzofuranyl)[4-[2-(diethylamino)ethoxy]-3,5-diiodophenyl]-, Cordarone



[1951-25-3] $C_{25}H_{29}I_2NO_3$ (645.32).

Preparation—US Pat 3,248,301.

Description—White to cream-colored, crystalline powder; melts about 156°; pK_a 6.56.

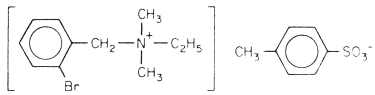
Solubility—Slightly soluble in water; soluble in alcohol; freely soluble in chloroform.

Comments—Type III antiarrhythmic drug used in atrial fibrillation and life- threatening recurrent ventricular arrhythmias that do not respond to other antiarrhythmic drugs. Its half-life is 25 to 100 days. Major side effects are serious pulmonary toxicity (about 10% fatal), complex CNS effects, proarrhythmia, hyper- and hypothyroidism, photosensitivity, drug deposits in the eye and skin, nausea, vomiting, and hepatic toxicity.

β-ANTAGONIST DRUGS—page 1400.

BRETYLIUM TOSYLATE

Benzenemethanaminium, 2-bromo-*N*-ethyl-*N,N*-dimethyl-, salt with 4-methylbenzenesulfonic acid (1:1); Darenthin; Bretylol



[61-75-6] $C_{18}H_{24}BrNO_3S$ (414.36).

Preparation—By interaction of *o*-bromobenzyl bromide and dimethylethylamine, the product being quaternized with *p*-toluenesulfonic acid.

Description—White, crystalline powder; melts about 98°.

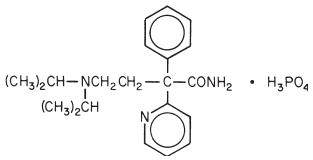
Solubility—Freely soluble in water or alcohol.

Comments—Type III antiarrhythmic drug approved for life-threatening, ventricular arrhythmias that do not respond to first-line antiarrhythmic drugs and ventricular fibrillation. Intravenous use is limited to intensive-care units. A major side effect is hypotension (adrenergic neuron blocking mechanism).

DIGITALIS AND CARDIAC GLYCOSIDES—page 1360.

DISOPYRAMIDE PHOSPHATE

2-Pyridineacetamide, α-[2-[bis(1-methylethyl)amino]ethyl]-α-phenyl-, phosphate (1:1); Norpace



[22059-60-5] $C_{21}H_{29}N_3O.H_3PO_4$ (437.47).

Preparation—One process for one synthesis of disopyramide converts 4-diisopropylamino-2-phenyl-2-(2-pyridyl)butyronitrile to the corresponding amide (disopyramide) by heating with concentrated H_2SO_4, followed by isolation and purification of the product (*CA 58:*12522c, 1963).

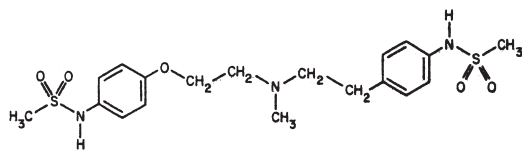
Description—White, crystalline powder; pK_a 8:36.

Solubility—Freely soluble in water.

Comments—Subtype IA antiarrhythmic drug approved for life-threatening ventricular arrhythmias and may also be used in the treatment of paroxysmal supraventricular tachycardia. It has prominent antimuscarinic activity. Major side effects are proarrhythmia and typical antimuscarinic effects.

DOFETILIDE

Methanesulfonamide, *N*-[4-[2-[(methyl[2-[4-[(methylsulfonyl)amino]phenoxy]ethyl]amino]ethyl]phenyl]-, Dogmatyl, Dolasetron, Tikosyn



[115256-11-6] $C_{19}H_{27}N_3O_2S_2$ (441.58).

Preparation—By nucleophilic displacement of the halogen in 4-(2-bromoethoxy)methanesulfonanilide by *N*-methyl-*p*-nitrophenethylamine and potassium carbonate in acetonitrile, the tertiary amine precursor of the product is formed. The *p*-nitro group is catalytically reduced to the amine, which is then sulfonated with dimethyl sulfate in methylene chloride to afford the product. *J Med Chem* 1990: 33;1151. Also US Pat 4,959,366 (1990).

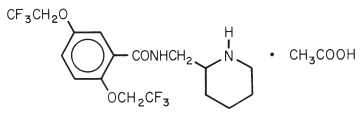
Description—White to off-white crystals from ethyl acetate/methanol melting about 149°. pK_a 7.0, 9.0, 9.6. Log P (pH 7.4) 0.96.

Solubility: Very slightly soluble in water; soluble in acetone or 0.1 M HCl or NaOH.

Comments—A Type III antiarrhythmic agent approved for the treatment of atrial fibrillation/flutter. It is metabolized by CYP3A4 and also excreted unchanged in urine via both glomerular filtration and active tubular secretion and, therefore, has several drug interactions. Major side effects include proarrhythmias and QT prolongation.

FLECAINIDE ACETATE

Benzamide, *N*-(2-piperidinylmethyl)-2,5-bis(2,2,2-trifluorethoxy-, monoacetate; Tambocor



[54143-56-5] $C_{17}H_{20}F_6N_2O_3 \cdot C_2H_4O_2$ (474.40).

Preparation—See *J Med Chem* 1977; 20:821.

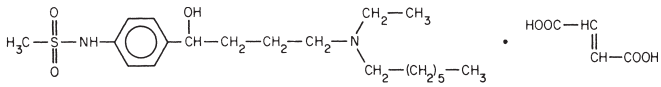
Description—White crystalline solid melting about 146°; pK_a 9.3.

Solubility—1 g in about 21 mL water at 37° or 3.5 mL alcohol.

Comments—Subtype IC antiarrhythmic drug approved for atrial fibrillation/flutter, paroxysmal supraventricular tachycardia, and life-threatening ventricular arrhythmias. Major side effects include proarrhythmias, complex CNS effects, dizziness, dyspnea, headache, nausea, fatigue, and visual disturbances. Should be avoided in patients with structural heart disease.

IBUTILIDE FUMARATE

Methanesulfonamide, (±)-*N*-[4-[4-(ethylheptylamino)-1-hydroxybutyl]phenyl]-, (*E*)-2-butenedioate (2:1) salt; Corvert



[122647-31-8] $(C_{20}H_{36}N_2O_3S)_2.C_4H_4O_4$ (885.23).

Preparation—See *J Med Chem* 1991; 34:308; US Pat 5,155,268.

Description—White to off-white powder melting about 118°.

Solubility—soluble (1 in 10) in water at pH 7 or below.

Comments—A Type III antiarrhythmic drug approved for atrial fibrillation/flutter. It is only available IV. A major side effect is proarrhythmia.

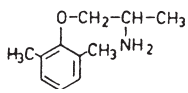
LIDOCAINE HYDROCHLORIDE

For the full monograph, see page 1481.

Comments—A Subtype IB antiarrhythmic drug approved for life-threatening ventricular arrhythmias. Most effective in arrhythmias associated with myocardial ischemia. Major side effects include seizures, dizziness, vertigo, nausea, parasthesia, rash, blood dyscrasias, and proarrhythmias.

MEXILETINE HYDROCHLORIDE

Ethylamine, 1-methyl-2-(2,6-xylyloxy)-, Mexitil



[31828-71-4] $C_{11}H_{17}NO$ (179.26).

Preparation—US Pat 3,659,019.

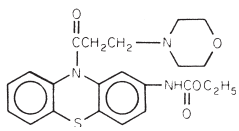
Description—White crystals; melts about 205°; pK_a 8.4.

Solubility—1 g in 2 mL water or 3 mL alcohol.

Comments—A Subtype IB antiarrhythmic drug approved for used in the treatment of refractory life-threatening ventricular arrhythmias. Major side effects are proarrhythmias, complex CNS effects (including convulsions), nausea, vomiting, hepatoxicity, leukopenia, agranulocytosis, and rash.

MORICIZINE HYDROCHLORIDE

Carbamic acid, [10-[3-(4-morpholinyl)-1-oxopropyl]-10*H*-phenothiazin-2-yl]-, ethyl ester; Ethmozine



Ethyl 10-(3-morpholinopropionyl)phenothiazine-2-carbamate [31883-05-3] $C_{22}H_{25}N_3O_4S$ (427.52).

Preparation—US Pat 3,864,487.

Description—White crystals melting at about 190° (dec).

Solubility—Soluble in water or alcohol.

Comments—A Subtype IA antiarrhythmic drug approved for life-threatening ventricular arrhythmias. Major side effects are serious proarrhythmias, dizziness, and nausea.

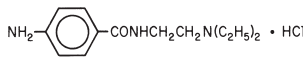
PHENYTOIN SODIUM

For the full monograph, see page 1506.

Comments—A Subtype IB antiarrhythmic drug approved for ventricular arrhythmias and digitalis intoxication, but more often used as an antiepileptic agent. Major side effects are complex CNS effects, gingival hyperplasia, hirsutism, rash, blood dyscrasias, and proarrhythmias.

PROCAINAMIDE HYDROCHLORIDE

Benzamide, 4-amino-*N*-[2-(dimethylamino)ethyl]-, monohydrochloride; Procan; Pronestyl



[614-39-1] $C_{13}H_{21}N_3O.HCl$ (271.79).

Preparation—Among other ways, by condensing *p*-nitrobenzoyl chloride with β-diethylaminoethylamine and then reducing the nitro group to amino by any of the usual methods. The hydrochloride forms readily when a stream of hydrogen chloride is passed into a solution of the base in an appropriate organic solvent.

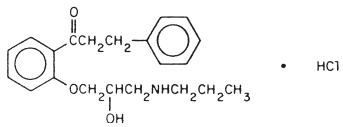
Description—White to tan, crystalline powder, odorless; pH (1 in 10 solution) 5 to 6.5; melts between 165° and 169°; pK_a 9.2.

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

Comments—A Subtype IA antiarrhythmic drug approved for life-threatening ventricular arrhythmias and also used for atrial fibrillation/flutter. It has less muscarinic effect than quinidine. Major side effects are proarrhythmias, lupus erythematosus syndrome, agranulocytosis, nausea, and diarrhea.

PROPAFENONE HYDROCHLORIDE

Propiophenone, 2′-[2-hydroxy-3-(propylamino)propoxy]-3-phenyl-, hydrochloride; Rythmol



[34183-22-7] $C_{21}H_{27}NO_3.HCl$ (377.91).

Preparation—Ger Pat 2,001,431.

Description—White crystals; pK_a 8.8.

Solubility—Soluble in hot water or alcohol; slightly soluble in cold water.

Comments—A Subtype IC antiarrhythmic drug approved for life-threatening ventricular arrhythmias and also used in the treatment of supraventricular arrhythmias. About 10% of patients are slow metabolizers with 3-fold increase in half-life. Major side effects are nausea, vomiting, unusual taste, dizziness, constipation, and blood dyscrasias.

QUINIDINE GLUCONATE

Cinchonan-9-ol, (9*S*)-6′-methoxy-, mono-D-gluconate (salt); Quinidine Monogluconate (salt); Quinaglute

[7054-25-3] $C_{20}H_{24}N_2O_2.C_6H_{12}O_7$ (520.58); the gluconate of an alkaloid that may be obtained from various species of *Cinchona* and their hybrids or from *Remijia pedunculata* Flückiger (Fam *Rubiaceae*) or prepared from quinine.

Description—White powder; odorless; very bitter taste.

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

Comments—A Subtype IA antiarrhythmic drug approved for atrial fibrillation/flutter and ventricular tachycardia. It exerts antimuscarinic action on the heart and alpha-blockade on blood vessels. Major side effects are proarrhythmias, cinchonism, nausea, vomiting, diarrhea, quinidine syncope, and blood dyscrasias.

QUINIDINE POLYGALACTURONATE

Cardiaquin

A compound described as a polymer of quinidine and polygalacturonic acid and assigned the molecular formula $(C_{20}H_{24}N_2O_2.C_6H_{10}O_7.H_2O)_x$ [7681-28-9].

Preparation—From quinidine and polygalacturonic acid (from pectin); described in *Am J Pharm* 1958; 130:190; and US Pat 2,878,252.

Description—Creamy white, amorphous powder; melts about 180° with decomposition.

Solubility—Sparingly soluble in water.

Comments—See Quinidine Gluconate.

QUINIDINE SULFATE

Cinchonan-9-ol, (9*S*)-6′-methoxy-, sulfate (2:1) (salt), dihydrate

[6591-63-5] $(C_{20}H_{24}N_2O_2)_2.H_2SO_4.2H_2O$ (782.95); anhydrous [50-54-4] (746.92); the sulfate of an alkaloid obtained from various species of *Cinchona* and their hybrids and from *Remijia pedunculata* Flückiger (Fam *Rubiaceae*) or prepared from quinine.

Quinidine is a stereoisomer of quinine and occurs in cinchona bark in amounts ranging from 0.3 to over 1%, although in some barks it may be practically absent. Quinidine of commerce usually is accompanied by up to 20% of *hydroquinidine* (which is quinidine with an ethyl group replacing the vinyl), which, however, is therapeutically as potent as quinidine and no more toxic.

Preparation—By treating quinine with a metallic alkoxide (Doering WE et al. *J Am Chem Soc* 1947; 69:1700; or by oxidizing quinine to quininone and then reducing the latter with sodium isopropoxide (Woodward RB et al. *J Am Chem Soc* 1945; 67:1428. It also may be obtained directly from the mother liquors remaining after removal of quinine from extracts of *Cinchona;* separation from cinchonine and other alkaloids is effected by special processes.

Description—Fine, needle-like, white crystals, frequently cohering in masses; very bitter taste; darkens on exposure to light; solutions neutral or alkaline to litmus; pK_{a1} 5.4; pK_{a2} 10.0.

Solubility—1 g in about 100 mL water, 10 mL alcohol, or 15 mL chloroform; insoluble in ether.

Comments—See Quinidine Gluconate.

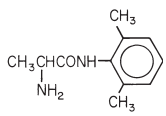
SOTALOL HYDROCHLORIDE

For the full monograph, see page 1403.

Comments—A Type III antiarrhythmic drug approved for life-threatening ventricular arrhythmias and used in the treatment of atrial fibrillation/flutter. It is a β-antagonist with Type III actions. Major side effects include proarrhythmias, bradycardia and hypotension.

TOCAINIDE HYDROCHLORIDE

Propanamide, 2-amino-*N*-[2,6-dimethylphenyl)-, Tonocard



[35892-53-1] $C_{11}H_{16}N_2O.HCl$ (228.72).

Preparation—*J Med Chem* 1979; 22:1171.

Description—White, crystalline powder; bitter taste; melts about 247°; pK_a 7.7.

Solubility—Freely soluble in water or alcohol.

Comments—A Subtype IB antiarrhythmic drug approved for life-threatening ventricular arrhythmias. Major side effects are proarrhythmias, dizziness, vertigo, paresthesia, rash, and blood dyscrasias.

CALCIUM CHANNEL BLOCKING DRUGS

Calcium channel blockers (CCBs) are a heterogeneous group of drugs consisting of four classes: the phenylalkylamines (verapamil), benzothiazepines (diltiazem), diarylaminopropylamine ethers (bepridil), and dihydropyridines (amlodipine, felodipine, nicardipine, nifedipine, nimodipine, and isradipine). Their main pharmacological effect is to block the voltage dependent, L-type calcium channels in the vascular smooth muscle and heart. The entry of calcium into cells is of fundamental importance for the normal functioning of the cardiovascular system, and the CCBs can affect this system in several ways. In vascular smooth muscle, calcium influx into cells is the excitation-contraction link that is necessary for smooth muscle contraction whenever smooth muscle is stimulated. The CCBs, by blocking the calcium channels in the arterial smooth muscle, result in peripheral vasodilation. The depolarization of the sinoatrial (SA) node and atrioventricular (AV) node in the heart is dependent on the inward movement of calcium ions through the slow channel. All CCBs reduce the inward current of calcium ions in the SA and AV node which has no effect on overall function, however diltiazem and verapamil delay the recovery of the channel which results in slowing of the SA node pacemaker rate and AV nodal conduction. In cardiac muscle the plateau phase of the action potential (Phase 2) is the result of inward calcium movement, which, in turn, couples the electrical excitation of these cells with muscle contraction. By blocking this process, the CCBs re-

sult in a negative inotropic effect. The reflex tachycardia that results from the significant peripheral vasodilation associated with the dihydropyridines is enough to overcome this negative inotropic effect. However, because of their effect on AV nodal conduction, verapamil and diltiazem prevent the tachycardic response and therefore the heart cannot overcome the negative inotropic effects of these drugs.

CCBs are utilized for the treatment of variant (vasospastic) and chronic stable angina pectoris. They are useful in the therapy of these diseases for three reasons: they directly dilate coronary arteries and increase myocardial blood flow, they decrease myocardial oxygen demand by peripheral arteriolar dilatation that decreases afterload, and they exert negative chronotopic (verapamil and diltiazem) and inotropic actions that also decrease oxygen demand.

Verapamil and diltiazem are utilized for the intravenous therapy of supraventricular tachyarrhythmias because of their significant depressant effects on SA nodal automaticity and AV nodal conduction. Oral verapamil and diltiazem can also be used for rate control in the treatment of chronic atrial flutter/fibrillation.

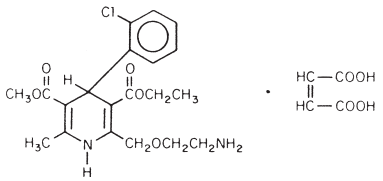
CCBs are utilized in the treatment of systemic hypertension because they are potent arteriolar vasodilators. They can be used as monotherapy or can be combined with other antihypertensive drugs. Newer formulations allow for once-daily or twice-daily dosing, and they are associated with minimal side effects. The CCBs, particularly diltiazem and verapamil because of their negative chronotropic and inotropic effects, should be used cautiously in patients with congestive heart failure. In those patients with CHF who are on appropriate therapy (ACE Inhibitors) that require additional afterload reduction, the dihydropyridine CCBs should be used preferentially to the non-dihydropyridines (verapamil and diltiazem).

Untoward effects of the CCBs are consequences of calcium entry blockade and are limited primarily to the cardiovascular system. Drug-induced vasodilatation leads to hypotension and to dizziness, lightheadedness, flushing, and headache. The non-dihydropyridines effects on decreased SA automaticity AV conduction can result in bradycardia and heart block. The use of these agents with β-antagonists, particularly, can induce heart block. Decreased myocardial contractility can result in congestive heart failure, particularly when these drugs are used with β-antagonists drugs. Peripheral edema caused by these drugs may be due to a combination of heart failure and peripheral vasodilatation, but direct effects to decrease sodium excretion have been noted with some CCBs.

Constipation sometimes is reported, particularly with verapamil and may be caused by mild excitation-contraction uncoupling in GI smooth muscle. Excitation-secretion coupling in exocrine and endocrine glands is another important role of calcium, but the effects of CCBs on glandular function have not proved to be important clinically, although nifedipine has been reported to decrease insulin secretion. In usual doses, CCBs do not appear to affect norepinephrine release from sympathetic nerve endings, although calcium is necessary for norepinephrine release. In contrast to the β-antagonists, CCBs do not increase airway resistance.

AMLODIPINE MALEATE

3,5-Pyridinedicarboxylic acid, 2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-, 3-ethyl 5-methyl ester, (±)-, (*Z*)-2-butenedioate (1:1); Norvasc



[88150-47-4] $C_{20}H_{25}ClN_2O_5.C_4H_4O_4$ (524.96).

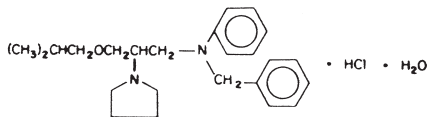
Preparation—*J Med Chem* 1986; 29:1696.

Description—White crystals melting about 180°; pK_a (base- NH_2) 9.0.

Comments—Approved for hypertension and angina (chronic stable or vasospastic). Its half-life is 34 hr.

BEPRIDIL HYDROCHLORIDE

β-[(2-methylpropoxy)methyl]-*N*-phenyl-*N*-(phenylmethyl)-, monohydrochloride, monohydrate; Vascor



[74764-40-2] $C_{24}H_{34}N_2O.HCl.H_2O$ (421.02).

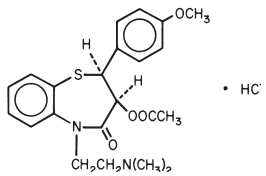
Preparation—US Pat 3,962,238.

Description—White crystals melting about 91°.

Comments—Approved for chronic stable angina. Associated with proarrhythmias because of its Type I properties. Torsades de pointes has been reported rarely, and there have been some reports of agranulocytosis associated with its use.

DILTIAZEM HYDROCHLORIDE

Benzothiazepin-4(5*H*)-one, (+)-*cis*-3-(acetyloxy)-5-[2-(dimethylamino)ethyl]-2,3-dihydro-2-(4-methoxyphenyl)-, monohydrochloride; Cardizem; Dilacor XR, CartiaXT, Tiazac



[33286-22-5] $C_{22}H_{26}N_2O_4S.HCl$ (450.98).

Preparation—*Chem Pharm Bull* 1971; 19:595.

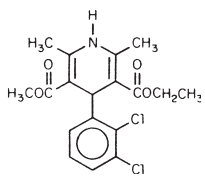
Description—White crystals melting about 188°; pK_a 7.7.

Solubility—Freely soluble in water, alcohol, or chloroform; slightly soluble in dehydrated alcohol.

Comments—Indicated orally for the treatment of angina (chronic stable or due to coronary artery spasm) and hypertension or intravenously for atrial fibrillation/flutter or paroxysmal supraventricular tachycardia.

FELODIPINE

3,5-Pyridine dicarboxylic acid; (±)-4-(2,3-dichlorophenyl)-1,4-dihydro-2,6-dimethyl-, ethyl methyl ester; Plendil



[72509-76-3] $C_{18}H_{19}Cl_2NO_4$ (384.26).

Preparation—US Pat 4,264,611.

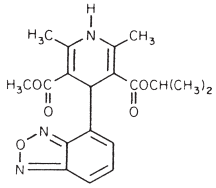
Description—White crystals melting about 145°.

Solubility—Practically insoluble in water, very soluble in alcohol.

Comments—Indicated for the treatment of hypertension.

ISRADIPINE

3,5-Pyridinedicarboxylic acid, (±)-4-(4-benzofurazanyl)-1,4-dihydro-2,6-dimethyl-, methyl 1-methylethyl ester; DynaCirc

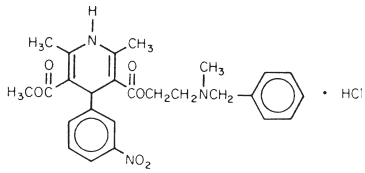


[75695-93-1] $C_{19}H_{21}N_3O_5$ (371.39)

Preparation—US Pat 4,466,972.
Description—White crystals melting about 142°.
Solubility—Practically insoluble in water; very soluble in alcohol.
Comments—Indicated for the treatment of hypertension.

NICARDIPINE HYDROCHLORIDE

3,5-Pyridinedicarboxylic acid, 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)-, methyl 2-[methyl(phenylmethyl)aminoethyl ester, monohydrochloride; Cardene

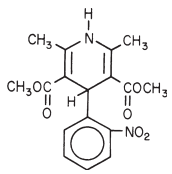


[54527-84-3] $C_{26}H_{29}N_3O_6.HCl$ (515.99).

Preparation—*Chem Pharm Bull* 1979; 27:1426.
Description—White crystals melting about 180° (α-form) or about 169° (β-form); pK_a 7.2.
Comments—Indicated for oral use in the treatment of chronic angina or hypertension. Also available parenterally for short-term treatment of hypertension.

NIFEDIPINE

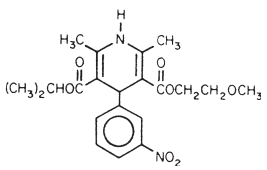
3,5-Pyridinecarboxylic acid, 1,4-dihydro-2,6-dimethyl-4-(2-nitrophenyl)-, dimethyl ester; Adalat CC; Procardia



[21829-25-4] $C_{17}H_{18}N_2O_6$ (346.34).
Preparation—See US Pat 3,485,847.
Description—Yellow crystals melting about 174°.
Solubility—Practically insoluble in water; slightly soluble in alcohol; very soluble in chloroform or acetone; solutions are extremely light-sensitive.
Comments—Indicated for angina (vasospastic and chronic stable) and hypertension.

NIMODIPINE

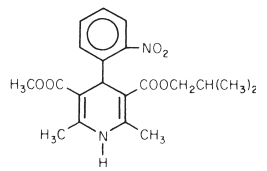
3,5-Pyridinedicarboxylic acid, 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)-, 2-methoxyethyl 1-methylethyl ester; Nimotop



[66085-59-4] $C_{21}H_{26}N_2O_7$ (418.45).
Preparation—US Pat 3,799,934.
Description—Yellow crystals melting at about 125°.
Solubility—Insoluble in water; soluble in alcohol.
Comments—Approved for *subarachnoid hemmorrhage* (the only CCB approved for this purpose). It causes high brain levels because of its high lipid solubility despite a short plasma half-life.

NISOLDIPINE

3,5-Pyridinecarboxylic acid, (±)-1,4-dihydro-2,6-dimethyl-4-(2-nitrophenyl)-, methyl 2-methylpropyl ester; Sular

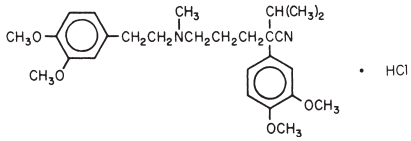


[63675-72-9] $C_{20}H_{24}N_2O_6$ (388.42).

Preparation—By the reaction of isobutyl 2-(*o*-nitrobenzylidene)-3-oxobutyrate and methyl 3-aminobutyrate in a Knoevenagel-type reaction. See US Pat 4,154,839 (1979).
Description—Yellow crystalline powder melting about 152°.
Solubility—Practically insoluble in water; soluble in ethanol.
Comments—Approved for hypertension.

VERAPAMIL HYDROCHLORIDE

Benzeneacetonitrile, α-[3-[[2-(3,4-dimethoxyphenyl)ethyl]-methylamino]propyl]-3,4-dimethoxy-α-(1-methylethyl)-, hydrochloride; Calan; Isoptin; Veralan



[52-53-9] $C_{27}H_{38}N_2O$ (454.61).
Preparation—See *Arzneimittel-Forsch* 1962; 12:563; and *Helv Chim Acta* 1975; 58:2050.
Description—White to off-white crystals melting about 140°; pH (7% w/w solution) about 4.2.
Solubility—1 g dissolves in about 15 mL water, 25 mL alcohol, or 2 mL chloroform; soluble in most polar organic solvents.
Comments—Approved orally for angina (vasospastic, chronic stable and unstable), atrial fibrillation/flutter and paroxysmal supraventricular tachycardia and hypertension. Also available parenterally for the management of supraventricular tachycardias and atrial fibrillation/flutter.

DRUGS AFFECTING BLOOD LIPIDS

Drugs that affect blood lipids are often classified as cardiovascular drugs because of the relation of blood lipids to atherosclerosis. Several studies, including the large epidemiological Framingham study, have found a positive correlation between elevated cholesterol levels and risk of coronary heart disease (CHD), and recent studies have shown inconclusively that lowering low-density lipoprotein (LDL) cholesterol is associated with a reduction in the risk of CHD. In addition to elevated total cholesterol (TC) and LDL levels, elevated triglycerides (TG) and/or low high-density lipoprotein (HDL) levels are independently associated with an increased risk of CHD. Studies have also demonstrated that raising HDL levels results in decreased risk of CHD.

Several drugs are available that lower TC, LDL, and TG levels and increase HDL levels. One source of cholesterol is from a diet with high cholesterol content. Consequently there are drugs, such as the recently approved ezetimibe, and plant derivatives that affect the absorption of cholesterol from the intestine in an attempt to decrease dietary absorption of cholesterol. These agents are used mainly for their LDL lowering effect. The bile acid sequestrants are utilized because of their ability to increase the catabolism of LDL cholesterol. In addition, the 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins), which work by inhibiting the synthesis of cholesterol, are used primarily for their LDL lowering effect and also have some effect on lowering TG and raising HDL. Niacin inhibits the mobilization of free fatty acids from peripheral adipose tissue to the liver resulting in decreased TG synthesis and very-low density lipoprotein (VLDL) secretion that results in decreased TG and LDL levels. It also blocks the hepatic uptake of apolipoprotein A-I, a major component of HDL, resulting in increased HDL levels. Finally, the fibric acid derivatives (fibrates) increase lipoprotein lipase activity, inhibit the synthesis of triglyceride-containing very low density lipoprotein (VLDL), and increase synthesis of the major HDL apolipoproteins A-I and A-II. Their greatest effect is on lowering TG levels and increasing HDL. They also convert small, dense LDL particles to larger, more buoyant particles that are less atherogenic.

The statins, bile acid sequestrants, and fibrates have demonstrated a reduction in CHD risk and a reduction in over-

all mortality in dyslipidemic patients. Please refer to the latest report published by the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel) for specific recommendations on the use of lipid lowering drugs.

CHOLESTYRAMINE RESIN

Cholybar; Questran

Cholestyramine [11041-12-6]; a strongly basic anion-exchange resin in the chloride form, consisting of styrene-divinylbenzene copolymer with quaternary ammonium functional groups. Each gram exchanges 1.8 to 2.2 g of sodium glycocholate, calculated on the dried basis.

Preparation—Polystyrene trimethylbenzylammonium chloride is copolymerized through cross-linkage with divinylbenzene.

Description—White to buff-colored, hygroscopic, fine powder; odorless or has not more than a slight amine-like odor; pH between 4 and 6 in a slurry (1 in 100).

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

Comments—Binds weak acid anions with partial hydrophobic character. It binds bile acids in the intestine and, hence, prevents their absorption. The depletion of bile acids in the intestines not only decreases the absorption of dietary and enterohepatic cholesterol but also increases the synthesis of bile acids from cholesterol, which decreases the size of the systemic cholesterol pool. In familial hypercholesterolemia, the plasma concentration of LDL is decreased by 20% to 30%, which upregulates LDL-receptor populations in hepatocytes and vascular myocytes and thus accelerates LDL catabolism. The effect is even more pronounced in the presence of statins and niacin.

Side effects, attributable to depletion of intraintestinal bile acids, include constipation (20–50%), heartburn and dyspepsia, colic, belching, bloating, biliary stasis and lodged gallstones, steatorrhea and malabsorption syndrome (with doses > 24 g/day), and consequent hypovitaminoses A, D, and K. The bulkiness of the dose along with the decrease in bowel motility exacerbates constipation and favors impaction and may be the cause of nausea, vomiting, and GI bleeding from ulcers. Hypochloremic alkalosis sometimes occurs. In hypertriglyceridemias, the drug may elevate VLDLs and intermediate-density lipoproteins.

It binds numerous weakly acidic drugs and interferes with their absorption during concurrent oral administration.

COLESTIPOL HYDROCHLFORIDE

Tetraethylenepentamine polymer with 1-chloro-2,3-epoxypropane hydrochloride; Colestid

Copolymer of diethylenetriamine and 1-chloro-2,3-epoxypropane, hydrochloride [37296-80-3].

Preparation—Colestipol hydrochloride is a high-molecular-weight, highly cross-linked, basic anion-exchange copolymer of diethylenetriamine and 1-chloro-2,3-epoxypropane, with approximately one of five amine nitrogens protonated (chloride form). US Pat 3,692,895 and 3,803,237.

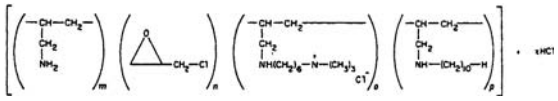
Description—White to pale-yellow beads; odorless; tasteless; hygroscopic.

Solubility—Insoluble in water, the beads swelling when placed in water or aqueous fluids.

Comments—An anion-exchange resin similar to Cholestyramine Resin (above) in its actions and uses, but there are differences in the anions for which it will exchange.

COLESEVELAM HYDROCHLORIDE

2-Propen-1-amine polymer with (choromethyl)oxirane, *N,N,N*-trimethyl-6-(2-propenylamino)1-hexanaminium chloride and *N*-2-propenyl-1-decanamine hydrochloride; WelChol



[182815-44-7] (HCl), [182815-43-6] (base).

$(C_3H_7N)_m(C_3H_5ClO)_n(C_{12}H_{27}N)_p.x$HCl.

Preparation—US Pat 5,693,675 (1997).

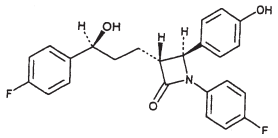
Description—An alkylated cross-linked polymer.

Solubility—It is hydrophilic but insoluble in water.

Comments—Similar in action to the bile acid sequestrants it is a non-absorbed polymer that binds bile acids in the intestine, preventing their reabsorption. Unlike cholestyramine and colestipol, it is administered in tablet formulation and therefore is associated with less gastrointestinal discomfort and increased compliance.

EZETIMIBE

2-Azetidinone, [3*R*-[3α(*S),4β]]-1-(4-fluorophenyl)-3-hydroxypropyl]-4-(4-hydroxyphenyl)-, Zetia**



[163222-33-1] $C_{24}H_{21}F_2NO_2$ (409.43).

Preparation—An imine formed from 4-fluoroaniline and 4-(benzyloxy)benzaldehyde is treated with 4-(methoxycarbonyl)butanoyl chloride in heptane/tributyl amine which cyclizes to produce 1-(4-fluorophenyl)-3-(2-methoxycarbonyl)-4-(4-benzyloxyphenyl)-2-azetidinone. The racemic ester is resolved, hydrolyzed to the free acid, converted to the acyl chloride and reacted with 4-fluorphenylzinc bromide. The resulting ketone is reduced to the secondary alcohol, debenzylated and resolved on a chiral column to afford the product. US 5,767,115(1998); *J Med Chem* 1998; 41:973.

Description—White, crystalline solid melting about 165°.

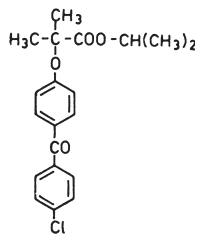
$[\alpha]^{22}_D$ − 33.9 (c = 3, MeOH).

Solubility—Freely soluble in methanol, ethanol, or acetone: practically insoluble in water.

Comments—This is a new class of lipid-lowering agents that inhibit the absorption of cholesterol from the intestine. Ezetimibe localizes and acts at the brush borders of the small intestine to inhibit the absorption of cholesterol, which leads to a decreased delivery of cholesterol to the liver. This reduction in hepatic cholesterol stores leads to an increase in cholesterol clearance from the blood. Ezetimibe has no effect on bile acid excretion or cholesterol synthesis. Side effects reported in clinical studies were minimal and similar to placebo.

FENOFIBRATE

Propionic acid, 2-[4-(4-chlorobenzoyl)phenoxy-, 1-methylethyl ester; Antara; Lofibra; Procetofene; TriCor



[49562-28-9] $C_{20}H_{21}ClO_4$ (360.84).

Preparation—One method involves the formation of the sodium salt of 4-chloro-4'-hydroxybenzophenone with sodium hydroxide in anhydrous acetone followed by nucleophilic reaction with α-chloroisobutyric acid to form the ether (Williamson method) and subsequent esterification with isopropyl alcohol to yield the product. See *Arzneimittel-Forsch* 1976; 26:885; US Pat 4,059,552 (1977).

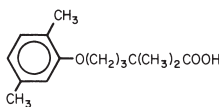
Description—White crystals melting about 78°.

Solubility—Practically insoluble in water; slightly soluble in ethanol or methanol; soluble in ether, acetone, chloroform, or benzene.

Comments—A fibric acid derivative structurally similar to gemfibrozil. Mechanism of action is similar to gemfibrozil. Once-a-day dosing is an advantage.

GEMFIBROZIL

Pentanoic acid, 5-(2,5-dimethylphenoxy)-2,2-dimethyl-, Lopid



[25812-30-0] $C_{15}H_{22}O_3$ (250.34).

Preparation—See US Pat 3,674,836.

Description—White crystals melting about 61°.

Solubility—Practically insoluble in water or alcohol; slightly soluble in dilute alkali; pK_a 4.7.

Comments—It increases lipoprotein lipase activity and catabolism of very-low-density lipoprotein (VLDL) which leads to reduced TG level. It also inhibits the synthesis of triglyceride-containing very low density lipoprotein (VLDL) which may lower LDL levels and increases synthesis of the major HDL apolipoproteins A-I and A-II which reduces HDL catabolism. Also converts small, dense LDL to larger, more buoyant and less atherogenic particles. When used in combination with statins the risk of hepatotoxicity is increased.

NIACIN

Nicotinic Acid, Niacor, Niaspan,

Comments—Niacin is available in several forms, two FDA-approved (immediate-release and extended-release) formulations and numerous long-acting formulations available over-the-counter from different manufacturers. Some of the differences among these products include their pharmacodynamic profiles and, more significantly, the toxicities associated with them. Niacin is associated with several dose-dependent adverse effects including flushing, rashes, hyperglycemia, and hyperuricemia. Flushing is most common with the immediate-release formulation and can be avoided by administering niacin with food or by pre-medicating with aspirin. Flushing is not as common with the extended-release or long-acting formulations; however, they are associated with significant hepatotoxicity. The over-the-counter long-acting formulations appear to be associated with more hepatotoxicity than the FDA approved extended-release formulations. It should also be noted that the FDA-approved formulations have undergone rigorous study to evaluate the efficacy and safety of these products in the treatment of hyperlipidemia and must comply with strict manufacturing standards. Niacin should be administered cautiously with other vasodilators because it may increase the risk of hypotension.

The Statins—HMG-CoA Reductase Inhibitors

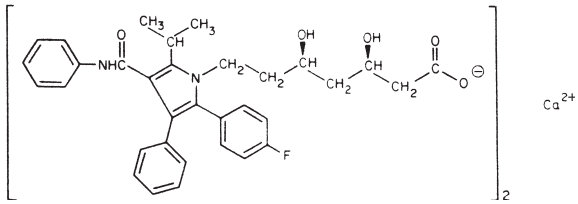
The 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) revolutionized the treatment of hyperlipidemia. They are more effective than the bile-acid sequestrants, fibrates, and niacin in reducing LDL and have been proven effective in both primary and secondary prevention of CHD in patients with hyperlipidemia. They are high-affinity inhibitors of HMG-CoA reductase, which is the rate-limiting step in the biosynthesis of cholesterol. Cholesterol synthesis is suppressed by therapeutic doses, but sufficient cholesterol is synthesized for body needs. Decreased intracellular concentrations of cholesterol cause upregulation of LDL receptors, so that LDL catabolism is increased, and plasma LDL concentrations fall by 25% to 40%; when combined with cholestyramine, or ezetimibe LDL levels could decrease by up to an additional 25%. Statins can also increase HDL levels by up to 12% and can reduce TG by 10% to 30%.

Most of the statins are metabolized by the liver and are substrates for and inhibitors of the cytochrome P450 enzyme system (CYP450). Side effects are rare and include headache, flatus, abdominal pain or cramps, diarrhea, rash, pruritus, constipation, nausea, myalgia, dizziness, blurred vision, muscle cramps, and dysgeusia. Some patients have reported sleep disturbances. Photosensitivity may occur in some patients.

Myopathy, occasionally leading to frank rhabdomyolysis, has also been associated with therapy and the recent voluntary removal of one product, cerivastatin, from the market. Its incidence appears to be associated with use in the elderly or as a result of coadministration with therapies that are known to inhibit the CYP450. A baseline creatinine phosphokinase (CPK) level should be checked; however, follow-up monitoring is only necessary if the patient develops symptoms of myalgias or muscle tenderness and weakness. The statins are concentrated in the liver, where they inhibit HMG-CoA and may cause elevated serum transaminases, which should be monitored during therapy; they should be used cautiously in patients with active liver disease or in combination with other hepatotoxic medications. Some of these agents that should be used cautiously with statins include gemfibrozil, niacin, cyclosporine, erythromycin, azole antifungals, and amiodarone. Since cholesterol is an essential nutrient in fetal and infant development, the statins are contraindicated during pregnancy or lactation.

ATORVASTATIN CALCIUM

1*H*-Pyrrole-1-heptanoic acid, [*R*-(*R,*R**)]-2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-, calcium salt (2:1), Lipitor**



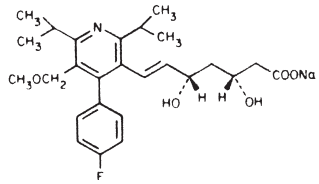
[134523-03-8] $C_{66}H_{68}CaF_2N_4O_{10}$ (1155.37).

Preparation—See US Pat 5,273,995 (1993).

Comments—An HMG-CoA reductase inhibitor that appears to lower LDL and triglycerides more than other drugs in its class at recommended doses. It has a long effective half-life of 20 hr.

CERIVASTATIN SODIUM

6-Heptenoic acid, [*S*-[*R,*S**-(*E*)]]-7-[4-(4-fluorophenyl)-5-methoxymethyl-2,6-bis(1-methylethyl)-3-pyridinyl]-3,5-dihydroxy-, sodium salt; Baycol**

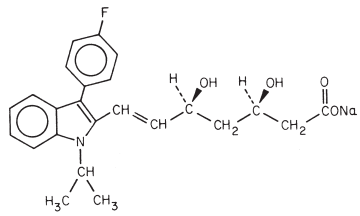


[143201-11-0] $C_{26}H_{33}FNNaO_5$.

Comments—An HMG-CoA reductase inhibitor that is about 100 times as potent as the other drugs in its class and costs less than most of the others. This agent was voluntarily removed from the US Market in August 2001 by the manufacturer.

FLUVASTATIN SODIUM

6-Heptenoic acid, [*R,*S**-(*E*)](±)-7-[3-(4-fluorophenyl)-1-(1-methyl)-1*H*-indol-2-yl]-3,5-dihydroxy-, monosodium salt; Lescol; Fluindostatin**



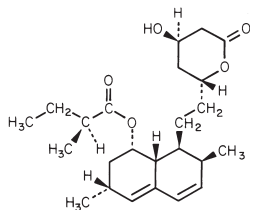
Preparation—See US Pat 4,739,073 (1988).

Description—White to pale yellow hygroscopic powder melting at about 195° with decomposition.

Solubility—Soluble in water, ethanol, or methanol.

LOVASTATIN

Butanoic acid, (*S*)-2-methyl-, [1α(*R),3α,7β,8β(2*S**,4*S**),8αβ]-1,2,3,7,8,8α-hexahydro-3,7-dimethyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2*H*-pyran-2-yl) ethyl]-1-naphthalenyl ester; Mevacor**



[75330-75-5] $C_{24}H_{36}O_5$ (404.55).

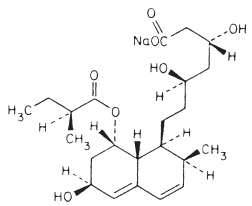
Description—White, nonhygroscopic, crystalline powder that is isolated from a strain of *Asperigillus terreus*. The drug is an inactive lactone, which, after ingestion, is hydrolyzed to the corresponding β-hydroxy acid, the active principle.

Solubility—Insoluble in water; sparingly soluble in alcohol, methanol, or acetonitrile.

Comments—Absorption is enhanced when given with food.

PRAVASTATIN SODIUM

1-Naphthaleneheptanoic acid, [1*S*-[1α(β*S,δ*S**),2α,6α,8β(*R**),8aα]]-1,2,6,7,8,8a-hexahydro-β,δ,6-trihydroxy-2-methyl-8-(2-methyl-1-oxobutoxy)-, monosodium salt; Pravachol**



[81131-70-6] $C_{23}H_{35}NaO_7$ (446.52).

Preparation—US Pat 4,346,227; by microbial action on mevastatin.

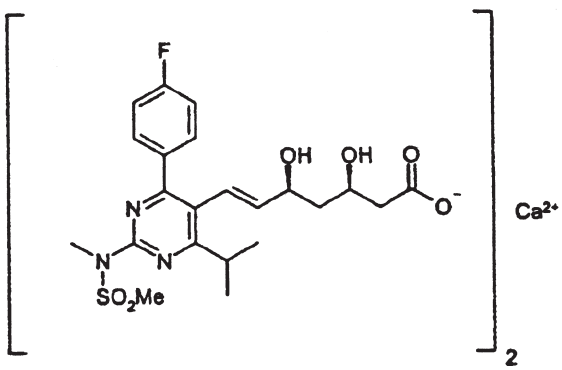
Description—White, crystalline powder.

Solubility—Very soluble in water or alcohol.

Comments—Is not metabolized by, nor does it induce the CYP450 system.

ROSUVASTATIN CALCIUM

6-Heptenoic acid, (3*R*,5*S*,5*E*)-7-[4-(4-fluorophenyl)-6-(1-methyl-ethyl)-2-[methyl(methylsulfonyl)amino]-5-pyrimidinyl]-3,5-dihydroxy-, calcium salt (2:1); Crestor



[147098-20-2] $(C_{22}H_{27}FN_3O_6S)_2Ca$ (1001.14).

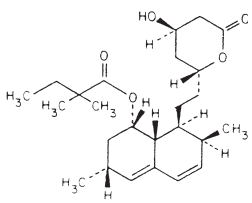
Preparation—A ten-step synthesis starting with *p*-fluorobenzaldehyde and ethyl β-ketocaproate. *Biorg Med Chem* 1997; 5:1997.

Description—Hydrophilic white, amorphous powder. Log P 0.13 at pH 7.

Solubility—Sparingly soluble in water or methanol; slightly soluble in ethanol.

SIMVASTATIN

Butanoic acid, 2,2-dimethyl-, [1*S*-[1α,3α,7β,8β-(2*S,4*S**)8αβ]]-1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2*H*-pyran-2-yl)ethyl]-1-naphthalenyl ester, Zocor**



[79902-63-9] $C_{25}H_{38}O_5$ (418.57).

Preparation—*J Med Chem* 1986; 29:849.

Description—White crystals melting about 137°; it is a derivative of lovastatin.

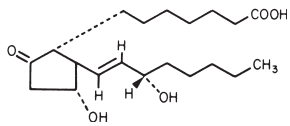
Solubility—Practically insoluble in water, freely soluble in alcohol.

Comments—Metabolized by CYP4S0 34A, therefore the potential for drug interactions exists.

Special-Use Cardiovascular Drug

ALPROSTADIL

Prost-13-en-1-oic acid, (11α,13*E*,15*S*)-11,15-dihydroxy-9-oxo-, Edex; MUSE; Prostaglandin E_1; PGE_1; Prostin VR



[745-65-3] $C_{20}H_{34}O_5$ (354.49). Isolated from the seminal vesicle tissue of sheep. See *J Biol Chem* 1963; 238:3555.

Preparation—For the synthesis see *J Org Chem* 1974; 37:2921.

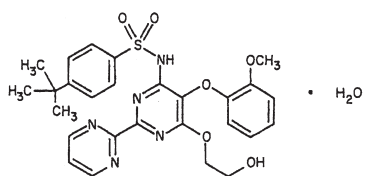
Description—White crystals melting about 115°; $[\alpha]_{578}$ = 61.6° (c = 0.56, THF). Unstable (dehydrates) in solution at low (<4) or high (>8) pH.

Comments—Endogenous prostaglandin E_1 helps maintain the patency of the ductus arteriosus of the fetus. After birth, prostaglandin production falls and the ductus closes. However, when there are congenital heart defects, such as the tetralogy of Fallot, transposition of the great vessels, pulmonary atresia, pulmonary stenosis, coarctation of the aorta, tricuspid atresia, or imperfect aortic arch, it is necessary that the ductus remain patent until corrective surgery can be accomplished. In such instances, infusion of alprostadil (PGE) helps maintain patency pending surgery.

Alprostadil is also available for treating erectile dysfunction by injection into the corpora cavernosa of the penis (Edex) or by insertion of a suppository into the urethra (MUSE). A transdermal cream is also under development. It acts by relaxation of trabecular smooth muscle and by dilatation of cavernous arteries. Prolonged priapism is an infrequent but potentially serious side effect.

BOSENTAN

Benzenesulfonamide, 4-(1,1-dimethyl)-*N*-[6-(2-hydroxy-ethoxy)-5-(2-methoxyphenoxy)[2,2′-bipyrimidin]-4-yl]-, monohydrate; Tracleer



[157212-55-0, hydrate] [147536-97-0, anhydrous]
$C_{27}H_{29}N_5O_6S.H_2O$ (569.63).

Preparation—US Pat 5,292,740(1994).

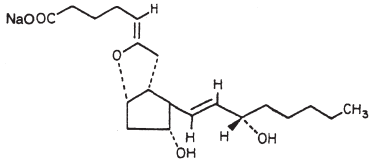
Description—White to yellowish white powder; not hygroscopic or light-sensitive. Melts about 198°.

Solubility—Poorly soluble in water (ca 1 mg/100 mL at pH 1.1). At pH 5, 0.2 mg/100 mL and at pH 7, 43 mg/100mL).

Comments–Bosentan is an endothelin-1 (ET-1) antagonist. Endothelin-1 (ET-1) is a neurohormone that binds to ET_A and ET_B receptors in the endothelium and vascular smooth muscle. Bosentan is a competitive antagonist at endothelin receptor types ET_A and ET_B, with a slightly higher affinity for ET_A receptors than for ET_B receptors. Bosentan is used in the treatment of pulmonary arterial hypertension, a disease that is associated with elevated ET-1 concentrations in the plasma and lung tissue. Specifically, it is indicated for the treatment of pulmonary arterial hypertension in patients with WHO Class III or IV symptoms, to improve exercise ability and decrease the rate of clinical worsening. Bosentan is available only as an oral formulation and is administered twice daily. Bosentan has been associated with clinically significant hepatotoxicity and dosage reduction or cessation of therapy is necessary if elevated aminotransferase levels occur during therapy.

EPOPROSTENOL SODIUM

(5*Z*,9α,11α,13*E*,15*S*)-Prosta-5,13-dien-1-oic acid, 6,9-ep-oxy-11,15-dihydroxy-, sodium salt; Flolan



Prostacyclin, PGI_2, Prostaglandin I_2, Prostaglandin X.

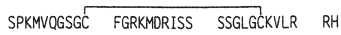
Preparation—One method involves the conversion of arachidonic acid into prostenoids by prostaglandin G/H synthetase (PGHS).

Description—White to off-white powder. The injection has a pH of 10.2 - 10.8 and is unstable at lower pH.

Comments—Epoprostenol is a naturally occurring prostaglandin. Its actions include vasodilation of pulmonary and systemic arterial vasculature and inhibition of platelet aggregation. It is indicated for the treatment of primary pulmonary hypertension and pulmonary hypertension associated with the scleroderma spectrum of disease in NYHA Class III and Class IV patients failing to respond to conventional therapy. Epoprostenol has a short half-life (2.7 minutes) and must, therefore, be administered via continuous intravenous infusion. Dose-limiting adverse effects include flushing, jaw pain, nausea, headache, hypotension, and also include chest pain, anxiety, dizziness, bradycardia, dyspnea, abdominal pain, musculoskeletal pain, and tachycardia.

NESIRITIDE

Natriuretic factor-32; Natrecor



(Human brain clone λhBNP57) [124584-08-3] base;

[189032-40-4] citrate salt; $C_{143}H_{244}N_{50}O_{42}S_4$ (3464 daltons).

Preparation—From *E Coli* strain rhBNP.

Description—White to off-white lyophilized powder.

Comments—Nesiritide is a purified preparation of human B-type natriuretic peptide (hBNP). Human BNP has several actions including reducing systemic arterial pressures and the pulmonary capillary wedge pressure (PCWP). Nesiritide is indicated for the treatment of patients with acutely decompensated congestive heart failure who have dyspnea at rest or with minimal activity. Its use should be avoided in patients with systolic blood pressures less than 90 mm Hg. It is generally well tolerated with the most significant adverse effect being hypotension. It is currently only available intravenously and should be administered via continuous infusion.

CHAPTER 69

Respiratory Drugs

John E Hoover, BSc Pharm, RPh

The drugs used to treat asthma are the main group of respiratory drugs emphasized in this chapter because it is an extremely common respiratory disorder that afflicts 14 to 15 million people in the US. Asthma is now recognized to be an inflammatory illness that has bronchial hyperreactivity and bronchospasm that accounts for more than 100 million days of restricted activity and 470,000 hospital admissions annually. Clinical trials have shown the benefits of anti-inflammatory therapy for treatment of the underlying inflammatory component of this respiratory disorder and reserving bronchodilators primarily for symptomatic use. The drugs for asthma therapy include bronchodilators, corticosteroids, inhibitors of mediator release, leukotriene pathway inhibitors, and anticholinergic agents. Other important categories of respiratory drugs that are mentioned include antitussives, expectorants, and surfactant preparations.

Bronchodilators are used to open air passages and facilitate breathing as well as diminish bronchospasms by relaxing the smooth muscles of the bronchioles. They provide respiratory relief from conditions such as asthma, bronchitis, emphysema, or bronchiectasis. A number of pharmacologically different groups of drugs possess bronchodilator properties. *Sympathomimetic drugs,* such as metaproterenol, albuterol, terbutaline, isoetharine, pirbuterol, and salmetrol, exert a preferential effect on β_2-adrenergic receptors and mediate relaxation of the smooth muscle of the respiratory tract. The bronchial muscles are controlled by the autonomic nervous system with parasympathetic fibers predominating in number and effect. Stimulation of parasympathetic nerves causes calcium-dependent contraction of the bronchi and enhances the release of chemical mediators that induce bronchospasm. Consequently, *anticholinergic drugs* (eg, atropine) are useful for reducing bronchospasm (Table 69-1).

Corticosteroids (eg, beclomethasone dipropionate, dexamethasone, triamcinolone acetonide, flunisolide, and fluticasone) not only are effective anti-inflammatory agents, but also potentiate the bronchodilator effects of adrenergic drugs. These corticosteroids are not direct bronchodilators and are not effective for rapid relief of bronchospasm. Use of corticosteroid inhalers provides effective and localized anti-inflammatory activity within the bronchial airways, while having minimal systemic effects (Table 69-2).

Cromolyn sodium and nedocromil inhibit the release of mediators of inflammation from mast cells. These mediators include histamine, leukotrienes, platelet activating factor (PAF), prostaglandins, proteases, interleukins, and numerous cytokines. These diverse mediators are induced by specific antigens as well as nonspecific mechanisms (such as exercise) resulting in vasodilation, microvascular leakage, leukocyte chemotaxis, mucus secretion, and bronchoconstriction. The cells recruited during inflammation include eosinophils, T lymphocytes, basophils, and macrophages. Their mediators can cause epithelial disruption, bronchoconstriction, altered ciliary function, smooth muscle hypertrophy, mucus secretion, airway edema, and tissue damage. Early asthmatic reactions to allergen exposure are dominated by mediators released from mast cells, while delayed (2–8 hr) or late asthmatic reactions are related to mediators released from eosinophils.

Nedocromil and cromolyn block both early and late asthmatic responses induced by either episodic or continuous allergen inhalation or exercise. They control the symptoms of mild-to-moderate chronic asthma in 60% to 70% of patients in doses that induce few, if any, adverse effects. They are not recommended for acute asthma or status asthmaticus since they have no intrinsic bronchodilator activity. Cromolyn has local effects on the lungs and consequently is administered often in aerosol forms. It frequently is used in combination with corticosteroid and/or bronchodilator treatment.

Leukotriene pathway inhibitors include receptor antagonists and leukotriene synthesis inhibitors. Leukotrienes are endogenous mediators clearly involved in the inflammatory process associated with asthma and are recognized to have three main effects: increased vascular permeability, recruitment of inflammatory leukocytes (PMNs), and induction of bronchoconstriction. The first leukotriene synthesis inhibitor to be approved by the Food and Drug Administration (FDA) was zileuton, which inhibits 5-lipoxygenase and improves airway function and reduces asthma symptoms in mild-to-moderate asthma patients. Zafirlukast is the first leukotriene D4 receptor antagonist approved, but others are now under investigation that produce similar benefits without the increases in liver enzymes or drug interactions reported with zileuton and zafirlukast.

The *xanthine drugs,* especially theophylline, its soluble salts, and derivatives, are thought to be the most useful bronchodilators for moderate or severe reversible bronchospasm. Moreover, they also improve respiratory exchange by increasing diaphragmatic contractility. The mechanism for the therapeutic effect of theophylline on respiratory systems is not clear. However, the bronchodilator action may be due in part to increased cyclic adenosine monophosphate (cAMP) following competitive inhibition of phosphodiesterase, the enzyme that degrades cAMP. Other proposed mechanisms include mobilization of intracellular calcium in smooth muscle, inhibition of prostaglandin action, blockade of adenosine receptors, and inhibition of the release of histamine and leukotrienes from mast cells. This drug has several notable actions that influence other target organs such as cardiac muscle and the central nervous system (CNS) including

1. It competitively inhibits phosphodiesterase, which increases cAMP and the release of endogenous epinephrine.
2. It inhibits neural transmission at certain synapses, especially in the CNS, where adenosine, a structural analog, may be a neurotransmitter.
3. It antagonizes the action of PGE_2 and $PGF_{2\alpha}$.
4. It affects the mobilization of intracellular calcium.

Table 69-1. Inhaled β_2-Adrenergic Agonists

DRUG	COMMENTS
Albuterol	Rapid onset (<5 min), duration of 3 to 8 hr
Metaproterenol	Similar to albuterol
Pirbuterol	Similar to albuterol
Terbutaline	Similar to albuterol
Salmeterol	Slower onset (20 min), long duration (12 hr)
Fenoterol	Similar to salmeterol

It is important to note that theophylline induces learning and behavioral problems in about 5% of school children receiving the drug.

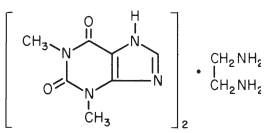
The effectiveness of the theophylline salts and derivatives in the treatment of bronchial asthma depends on their hepatic conversion to theophylline, which is the active constituent. Consequently, the dosage of theophylline, its salts, and dyphylline usually is expressed in terms of anhydrous theophylline base, despite the marked pharmacokinetic interpatient variability among these preparations. The approximate anhydrous theophylline content of some theophylline derivatives is theophylline monohydrate (91%), anhydrous aminophylline (86%), aminophylline dihydrate (79%), dyphylline (70%), and oxytriphylline (64%). Numerous sustained-action preparations of theophylline are also used to control nocturnal symptoms in asthma patients. A major variable with all of these products is the variability in pharmacokinetics, especially the hepatic metabolism of theophylline, which can be altered by an extensive list of other drugs. The adverse effects and potential toxicities of theophylline are dose-related, so it is often necessary to monitor serum levels in patients who receive chronic therapy. A summary of theophylline pharmacokinetics and associated adverse reactions is included in a monograph.

The anticholinergic drugs are discussed in Chapter ??, β_2 and other adrenergic drugs in Chapter ??, and corticosteroids in Chapter ??. The currently available inhaled β_2-adrenergic agonists used for treatment of asthma are shown in the cross references below.

ALBUTEROL—page 1382.

AMINOPHYLLINE

1*H*-Purine-2,6-dione, 3,7-dihydro-1,3-dimethyl-, compd with 1,2-ethanediamine (2:1)



Theophylline compound with ethylenediamine [317-34-0] $C_{16}H_{24}N_{10}O_4$ (420.43); *dihydrate* [49746-06-7] (456.46).

Preparation—By adding, with vigorous stirring, a weighted quantity of theophylline to a volume of solution containing the required equivalent quantity of the diamine in anhydrous alcohol. After a few hours, the precipitate of aminophylline is filtered off, washed with cold alcohol, and dried at a low temperature.

Description—White or slightly yellowish granules or powder, with a slight ammoniacal odor and a bitter taste; on exposure to air it gradually loses ethylenediamine and absorbs CO_2 with liberation of free theophylline; its solution is alkaline to litmus.

Solubility—1 g in about 5 mL water, but, owing to hydrolysis, separation of crystals of less-aminated theophylline begins in a few minutes, these crystals dissolving on the addition of a small amount of ethylenediamine. When, however, 1 g is dissolved in 25 mL water, the solution remains clear; insoluble in alcohol or ether.

Incompatibilities—Aqueous solutions are alkaline and display the incompatibilities of the alkalies. *Acids* cause a precipitation of theophylline; even *carbon dioxide* of the air behaves thus.

Comments—Indicated for *bronchial asthma,* and for reversible bronchospasm associated with chronic bronchitis and emphysema. Aminophylline (injection, oral solution, enema) also is used as a respiratory stimulant in neonatal apnea and in Cheyne-Stokes respiration. It also is useful as a diuretic agent. Absorption from the GI tract after oral or rectal administration is incomplete, slow, and variable. Approximately 79% is converted to theophylline. Optimal serum therapeutic levels range from 10 to 20 μg/mL. It is most effective when given intravenously; if given slowly in dilute solution, the drug is relatively nontoxic, although nausea, vomiting, and anorexia may appear in some patients. The simultaneous administration of aluminum hydroxide decreases the incidence of this side effect. See *Theophylline.*

Table 69-2. Inhaled Corticosteroids

DRUG	COMMENTS
Beclomethasone dipropionate	High topical activity, active metabolite formed in lung fluids, low systemic bioavailability due to high lipophilicity
Budesonide	High topical activity, used as powder, rapid hepatic metabolism, limited systemic bioavailability
Flunisolide	Good topical activity, higher systemic bioavailability, short plasma half-life
Fluticasone propionate	Very high topical activity, very low systemic bioavailability
Triamcinolone acetonide	Good topical activity, short plasma half-life, limited systemic bioavailability

AROMATIC AMMONIA SPIRIT

Aromatic ammonia spirit contains, in each 100 mL, 1.7–2.1 g of total NH_3 (17.03), and ammonium carbonate corresponding to3.5–4.5 g of $(NH_4)_2CO_3$ (96.09).

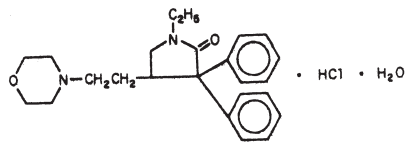
Description—A nearly colorless liquid when recently prepared, but gradually acquires a yellow color on standing. It has the taste of ammonia, has an aromatic and pungent odor, and is affected by light. Its specific gravity is about 0.90.

Comments—This preparation is given orally as a reflex respiratory stimulant. It should be well diluted with water.

ATROPINE—page 1408.
BITOLTEROL—page 1383.
CROMOLYN SODIUM—page 1547.

DOXAPRAM HYDROCHLORIDE

2-Pyrrolidinone, 1-ethyl-4-[2-(4-morpholinyl)ethyl]-3,3-diphenyl-, monohydrochloride, monohydrate; Dopram



1-Ethyl-4-(2-morpholinoethyl) -3,3-diphenyl -2- pyrrolidinone monohydrate [7081-53-0]$C_{24}H_{30}N_2O_2.HCl.H_2O$ (432.99); anhydrous [113-07-5](414.97).

Preparation—1-Ethyl-3-pyrrolidinol is reacted with thionyl chloride to form the 3-chloro compound which is condensed with diphenylacetonitrile in toluene solution with the aid of sodamide. The resulting α-(1-ethyl-3-pyrrolidinyl)diphenylacetonitrile is hydrolyzed with 70% H_2SO_4 to the corresponding acid. On treatment with thionyl chloride, the acid is converted into the acid chloride which immediately isomerizes to 4-(2-chloroethyl)-3,3-diphenyl-1-ethyl-2-pyrrolidinone. Condensation of this with morpholine in a dehydrohalogenating environment yields doxapram (base) which, on reaction with HCl, gives the official salt.

Description—White to off-white, odorless, crystalline powder; stable in light and air; melts at about 220°.

Solubility—1 g in 50 mL of water; soluble in chloroform; sparingly soluble in alcohol; practically insoluble in ether.

Comments—Doxapram hydrochloride has respiratory stimulant, pressor, and general CNS arousing properties. Respiratory stimulation is mediated principally through the central respiratory centers in the medulla. There may be some contribution through stimulation of peripheral carotid chemoreceptors.

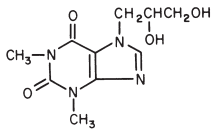
Following a single intravenous injection of doxapram hydrochloride the onset of respiratory stimulation usually occurs in 20–40 seconds with peak effect at 1–2 minutes. The duration of effect may vary from 5–12 minutes. Continuous infusion is a means of controlling the effect and extending its duration.

The respiratory stimulant action is manifested by an increase in tidal volume associated with an increase in respiratory rate.

A pressor response with tachycardia is common following doxapram administration. The pressor response is due more to an increased cardiac output than to peripheral vasoconstriction. Following doxapram administration an increased release of catecholamines has been noted.

DYPHYLLINE

1-*H*-Purine-2,6-dione, 7-(2,3-dihydroxypropyl)-3,7-dihydro-1,3-dimethyl-, Dilor; Lufyllin



7-(2,3-Dihydroxypropyl)theophylline $C_{10}H_{14}N_4O_4$ (254.25).

Preparation—By interaction of 1-chloro-2,3-dihydroxypropane with theophylline dissolved in a sodium hydroxide or potassium hydroxide solution. US Pat 2,575,344 (see *CA* 1952; 46:1722i).

Description—White, crystalline powder; bitter taste; melts about 158°; pH (1 in 100 solution) 6.6 to 7.3; protect aqueous solutions from light.

Solubility—1 g in 3 mL water, 50 mL alcohol or 100 mL chloroform.

Comments—Indicated for relief of *bronchial asthma* and for reversible *bronchospasm* associated with *chronic bronchitis* and *emphysema*. It exhibits peripheral vasodilator and bronchodilator actions characteristic of theophylline. It also has some diuretic and myocardial stimulant effects, and is effective orally. Dyphylline is a derivative of theophylline and is not metabolized to theophylline *in vivo*. Following oral administration, dyphylline is 68% to 82% bioavailable. Peak plasma concentrations are reached in 1 hr; its half-life is 2 hr. The minimal therapeutic concentration is 12 μg/mL; 88% is excreted unchanged in the urine. Because of its somewhat shorter half-life, other theophylline derivatives usually are preferred for chronic bronchodilator therapy. Otherwise, its pharmacological profile, effective and toxic serum levels, contraindications, precautions, adverse reactions, and drug interactions are similar to those for theophylline.

EPHEDRINE—page 1385.
EPINEPHRINE—page 1386.
ETHYLNOREPINEPHRINE—page 1386.
ISOETHARINE—page 1383.
ISOPROTERENOL—page 1383.
METAPROTERENOL—page 1384.
NEDOCROMIL—page 1375.
OXTRIPHYLLINE—see RPS-20, page 1298.
PIRBUTEROL—page 1384.
SALMETROL—page 1385.
TERBUTALINE SULFATE—page 1385.

THEOPHYLLINE

1*H*-Purine-2,6-dione, 3,7-dihydro-1,3-dimethyl-, monohydrate or anhydrous; 1,3-Dimethylxanthine; Elixophyllin; Quibron

Theophylline monohydrate [5967-84-0] $C_7H_8N_4O_2.H_2O$ (198.18); *anhydrous* [58-55-9] (180.17).

Preparation—Present in tea but in too small an amount to make it an economical source. It has been made from caffeine but is produced more successfully by total synthesis.

Description—White, odorless, crystalline powder with a bitter taste; stable in air; melts between 270° and 274°; saturated aqueous solution is neutral or slightly acid to litmus; weaker as a base than caffeine or theobromine and scarcely forms salts even with the strong acids, but is more "acidic" than those and readily dissolves in ammonia water.

Solubility—1 g in about 120 mL water or 80 mL alcohol; more soluble in hot water; sparingly soluble in ether or chloroform; freely soluble in solutions of alkali hydroxides or ammonia.

Comments—Theophylline and its salts and derivatives are used as *bronchodilators* in the symptomatic treatment of *mild bronchial asthma* and *reversible bronchospasm,* which may occur in association with *chronic bronchitis, emphysema,* and *other obstructive pulmonary diseases*. The drug also suppresses exercise-induced asthma and, in doses that maintain therapeutic serum levels, prevents symptoms of chronic asthma. Theophylline is well absorbed after administration. Food has little effect on its availability, although absorption may be slower in the presence of food. Rectal suppositories are absorbed slowly and erratically. The time required to reach peak plasma levels varies with the route and formulation used; following oral administration of liquids or uncoated tablets, peak plasma levels are reached in 2 hr. Average volume of distribution is 0.5 L/kg. Plasma or serum levels of about 10 to 20 μg/mL usually are needed to produce optimum bronchodilator response.

Theophylline is excreted by the kidneys. Less than 15% of the drug is excreted unchanged in the urine. Elimination kinetics vary greatly among individuals. The elimination half-life of theophylline averages about *7 to 9 hr in the adult nonsmoker, 4 to 5 hr in the adult smoker* (one or two packs per day), *3 to 5 hr in children,* and *20 to 30 hr in premature neonates.* The premature neonate excretes about 50% unchanged theophylline and may accumulate the caffeine metabolite. Theophylline, its salts, and dyphylline exert identical pharmacological actions.

Theophylline has less stimulatory effect on the CNS and skeletal muscles than caffeine but has a greater effect on coronary dilatation, smooth muscle relaxation, diuresis, and cardiac stimulation than caffeine. In general, it has relatively more pharmacological activity in all categories than theobromine.

Theophylline produces CNS stimulation and GI irritation following administration by any route. It and its salts and analogs are all somewhat irritating to gastric mucosa. The most common GI side effects (both locally and centrally mediated) include nausea, vomiting, epigastric pain, abdominal cramps, anorexia, and, rarely, diarrhea. Cardiovascular side effects include palpitation, sinus tachycardia, and increased pulse rate. These side effects are usually mild and transient. It also may produce transiently increased urinary frequency, dehydration, twitching of fingers and hands, and elevated SGOT levels. Hypersensitivity reactions characterized by urticaria, generalized pruritus, and angioneurotic edema have been reported with theophylline administration.

Drug interactions are common in patients on theophylline. Agents that *decrease* the effects of theophylline include cigarette and marijuana smoking, phenobarbital, and charcoal-broiled foods. Agents that *increase* the effects of theophylline include cimetidine, erythromycin, influenza virus vaccine, troleandomycin, allopurinol, and thiabendazole. Theophylline *increases* the effects of sympathomimetic drugs, digitalis, and oral anticoagulants. Theophylline *decreases* the effects of phenytoin and lithium carbonate. Concomitant administration of theophylline with β-adrenergic blocking agents may result in antagonistic effects; theophylline with reserpine or halothane may induce tachycardia or cardiac arrhythmias, respectively.

Theophylline toxicity is most likely to occur when plasma levels exceed 20 μg/mL and becomes progressively more severe at higher serum concentrations. Tachycardia, in the absence of hypoxia, fever, or administration of sympathomimetic drugs, may be an indication of theophylline toxicity. Anorexia, nausea and occasional vomiting, diarrhea, insomnia, irritability, restlessness, and headache commonly occur. Fatalities in adults have occurred during or following IV administration of large doses of theophylline in patients with renal, hepatic, or cardiovascular complications. In other patients, the rapidity of the injection, rather than the dose used, appears to be the more important factor precipitating acute hypotension, convulsions, coma, cardiac standstill, ventricular fibrillation, and death. There is no specific antidote for theophylline toxicity; therapy is usually supportive. Treatment includes stopping the drug, gastric lavage and/or emesis, and administration of antacids or demulcents and oxygen. Prompt restoration of fluid and electrolyte balance is essential. Other symptomatic procedures are instituted as necessary.

CORTICOSTEROIDS

In general, inhaled corticosteroids are used to treat persistent asthma and control the inflammatory component of this disease. However, oral corticosteroids may be used intensively for limited time periods to treat more severe, acute exacerbations when other measures, such as β_2-selective agonists do not provide adequate relief. The long-term use of systemic corticosteroids may be necessary in some patients, which can cause adrenal insufficiency. Corticosteroid therapy for asthma is done often in combination with concurrent use of other asthma medication, such as inhaled β_2-adrenergic agonists and/or sustained-action theophylline-related oral medication. Such combinations help to reduce the number of doses of corticosteroids required to provide adequate asthmatic control and decrease the chance of serious side effects. If done conservatively, inhaled glucocorticoids often are effective in relieving bronchial hyperreactivity associated with moderately severe asthma without significant suppression of adrenal function. However,

oral inhalation of corticosteroids such as dexamethasone should not be used for the treatment of occasional mild attacks of asthma that are controlled adequately by treatments with β_2-selective sympathomimetics.

It should be remembered that corticosteroids are not bronchodilators and will not provide rapid relief from bronchospasm and thus should not be the primary treatment for status epilepticus or other acute episodes of asthma. The relative topical potency of inhaled corticosteroid agents is flunisolide = triamcinolone acetonide < beclomethasone dipropionate < budesonide < fluticasone propionate. The delivery systems used can affect the topical and systemic activity of inhaled corticosteroids. The factors that influence clinical efficacy and systemic toxicity of inhaled corticosteroids include topical activity, retention in bronchial fluids, and rapid inactivation when absorbed from the lungs. Increased lipophilicity can slow dissolution and prolong the residence in the lung, but complete pharmacokinetic studies have not compared all these parameters. Also, there is no clear evidence of greater efficacy of any inhaled corticosteroid when administered in equipotent dosages. The most common adverse effects associated with inhaled corticosteroids include a huskiness in the voice (dysphonia) and candidiasis. Rinsing the mouth after inhalation usually controls the potential for oral candidiasis. The higher doses of all inhaled corticosteroids can produce systemic effects that include hypothalamic-pituitary-adrenal axis suppression, bone resorption, carbohydrate and lipid metabolism changes, cataracts, skin thinning, and growth retardation. Some of the inhaled corticosteroids have less potential for such systemic effects because of their rapid hepatic metabolism upon systemic absorption, such as budesonide and beclomethasone dipropionate. These drugs are discussed in greater detail in Chapter ??. A summary of the currently available inhaled corticosteroids is shown below. The inhaled corticosteroids and some potent topical corticosteroids including dexamethasone are also available as either an aqueous spray or aerosol for intranasal administration and are used extensively for allergic rhinitis, without significant adverse effects in most patients. Some patients may experience mild nasopharyngeal irritation, dryness, and headache. Effects are not immediate, but regular use usually results in benefits within a few days.

OMALIZUMAB

Immunoglobulin G, anti-(human immunoglobulin E Fc region) (human-mouse monoclonal E25 clone pSVIE26 γ-chain), disulfide with human-mouse monoclonal E25 clone pSVIE26 -chain, dimmer; Xolair

[242138-07-4]

Preparation—From Chinese hamster ovary cell culture in a nutrient medium containing gentamycin (which is not detectable in the finished product).

Description—Sterile, white, lyophilized powder in a single dose vial. MW about 150 kDa.

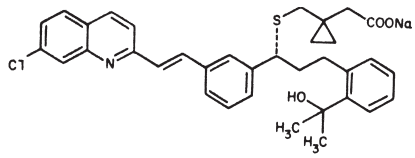
Comments—Used to treat moderate-to-severe persistent allergic asthma not adequately controlled by inhalation corticosteroids. It inhibits the binding of IgE to the high-affinity IgE receptor (FcεRI) on the surface of mast cells and basophils. Reduction in surface-bound IgE on FcεRI-bearing cells limits the degree of release of mediators of the allergic response. Treatment with Xolair also reduces the number of FcεRI receptors on basophils in atopic patients.

LEUKOTRIENE PATHWAY ANTAGONISTS

The major differences in the new drugs designed to interfere with the formation or action of the bronchoconstrictor leukotrienes (LTC_4, LTD_4, and LTE_4) are their duration of action, frequency of side effects, and potential drug interactions. Zileuton inhibits the enzyme 5-lipoxygenase, which converts arachidonic acid to a leukotriene A that is a precursor to the proinflammatory leukotriene (LTB_4) that augments the migration of neutrophils and eosinophils as well as the potent bronchoconstrictor leukotrienes. Zafirlukast and montelukast are LTC_4 receptor antagonists that attenuate bronchoconstriction resulting from the immediate and delayed release of this leukotriene in asthmatic patients exposed to allergens as well as other types of inhalation challenges. However, these drugs are not indicated for acute asthmatic attacks.

MONTELUKAST SODIUM

Cyclopropaneacetic acid, [*R*-(*E*)-1-[[[1-[3-[2-(7-chloro-2-quinolinyl)ethenyl]-phenyl]-3-[2-(1-hydroxy-1-methylethyl)phenyl]propyl]thio]methyl]-, sodium salt; Singulair



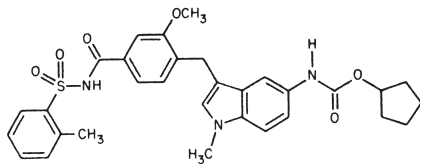
[151767-02-1] $C_{35}H_{35}ClNNaO_3S$ (608.18)

Preparation—See *Drugs of the Future* 1997; 22:1103.

Comments—Approved for *oral prophylaxis* and *chronic treatment* of asthma in patients ≥ 6 yr of age. It is a selective leukotriene receptor antagonist of LTD_4 receptors. It is absorbed rapidly following oral administration, with mean bioavailability of 64% that is not influenced by food. It is extensively metabolized by CYP3A4 and CYP2C9 but does not inhibit these enzymes at therapeutic doses. The mean half-life is 2.7 to 5.5 hr. Adverse effects include some dyspepsia in a few patients. Phenobarbital can induce its metabolism.

ZAFIRLUKAST

Carbamic acid, [3-[[2-methoxy-4-[[[2-methylphenyl)sulfonyl]amino]-carbonyl]phenyl]methyl]-1-methyl-1*H*-indol-5-yl]-, cyclopentyl ester; Accolate



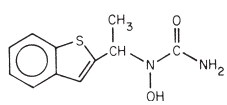
Preparation—See US Pat 4,859,692; *J Med Chem* 1990; 33:1781.

Description—White solid melting about 139°.

Comments—Approved for *oral prophylaxis* and *chronic treatment* of asthma in patients ≥ 12 yr of age. It is a selective and competitive leukotriene receptor antagonist of LTD_4 receptors, which induce bronchoconstriction. It can attenuate the increase in bronchial hyperresponsiveness to inhaled histamine that follows inhaled allergan challenge. Pretreatment also attenuates early and late-phase reaction to inhaled allergens. It is absorbed rapidly following oral administration and is metabolized extensively, with a mean half-life of 10 hr. It inhibits the cytochrome P-450 isoenzymes 3A4 and 2C9. Food reduces bioavailability by 40%, so it should be taken 1 hr before or 2 hr after meals. Adverse effects include headache, dizziness, nausea, diarrhea, elevation of serum liver enzymes, and dyspepsia. Drug interactions due to inhibition of CYP2C9 and CYP3A4 include aspirin, erythromycin, terfenadine, theophylline, and warfarin.

ZILEUTON

Urea, (±)-*N*-(1-benzo[*b*]thien-2-ylethyl)-*N*-hydroxy-, Zyflo



[406-87-2] $C_{11}H_{12}N_2O_2S$ (236.29).

Preparation—In one procedure, 2-acetylbenzothiophene is converted to the oxime and reduced with BH_3/pyridine to form the corresponding hydroxylamine derivative. The latter is acylated and esterified with acetyl chloride in triethylamine; the ester cleaved with LiOH, then treated with HCl and phosgene to yield the *N*-hydroxyacyl chloride, which with ammonia is converted to the urea product. See US Pat 4,873,259 (1989).

Description—Crystals melting about 158°.

Comments—Approved for *oral prophylaxis* and *chronic treatment* of asthma in patients ≤12 yr of age. It is a specific inhibitor of 5-lipoxygenase, which results in the inhibition of leukotriene (LTB_4, LTC_4,LTD_4, LTE_4) formation. LTB_4 augments neutrophil and eosinophil migration as well as adhesion and activation of neutrophils. Increased inflammation, capillary permeability, edema, mucus secretion, and bronchoconstriction are produced by these leukotrienes. Zileuton is absorbed rapidly upon oral administration and can be taken with or without food. It is metabolized extensively by hepatic cytochrome P-450 enzymes (1A2, 2C9, and 3A4), with a mean half-life of 2.5 hr. Adverse reactions include hepatotoxicity, which requires monitoring of serum hepatic transaminases. Drug interactions are observed with several drugs undergoing hepatic metabolism such as propranolol, terfenadine, theophylline, and warfarin. Other adverse effects include dyspepsia and nausea in some patients.

OTHER INHALED DRUGS USED FOR ASTHMATIC PATIENTS (ANTICHOLINERGICS AND INHIBITORS OF MEDIATOR RELEASE)

The synthetic anticholinergic drug ipratropium bromide is a quaternary ammonium compound that acts like atropine to block muscarinic receptors. It is administered by inhalation to limit its systemic anticholinergic actions and to reduce bronchoconstriction due to parasympathetic tone that is present in some patients with chronic obstructive pulmonary disease (eg, chronic bronchitis and emphysema). The inhibitors of mediator release, cromolyn and nedocromil, are not used to treat acute bronchospasm but require several days to weeks before a decrease in the bronchospasm and congestive symptoms associated with the release of inflammatory mediators from mast cells, eosinophils, neutrophils, basophils, and alveolar macrophages that are involved in the inflammatory component of this disease. Combination therapy with these agents may help decrease the dose of inhaled or systemic corticosteroid therapy as well as decrease the frequency of use of inhaled β_2-selective agonists.

CROMOLYN SODIUM

Disodium salt of 1,3-bis(2-carboxychromon-5-yloxy)-2-hydroxy propane; $C_{23}H_{14}Na_2O_{11}$ (512.34)

For the full monograph see page 1547.

Comments—Prophylactic management of severe bronchial asthma by inhalation of nebulized solution, aerosol, or dry powder contained in capsules. Patients must have substantial bronchodilator-reversible component to their airway obstruction. Response to treatment generally occurs within the first 2 to 4 weeks. Therapy also may include prevention of exercise-induced bronchospasm or exposure to other known precipitating factors (eg, cold dry air, environmental pollutants, allergens). Nasal solution may be used to treat seasonal or perennial allergic rhinitis. Cromolyn inhibits the release of histamine and bronchoconstrictor leukotrienes from mast cells, which may involve effects on calcium channels, but its exact mechanism has not been defined. Only 7% to 8% of drug is absorbed from the lung after inhalation, and it is rapidly excreted unchanged in the urine and bile. When drug from the respiratory tract is swallowed, it is absorbed poorly from the GI tract. Adverse reactions with inhalation include dizziness, headache, cough, wheezing, nasal congestion, bad taste, and rash.

IPRATROPIUM BROMIDE

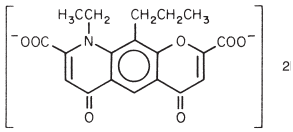
3-(3-hydroxy-1-oxo-2-phenylpropoxy)-8-methyl-(1-methylethyl)-bromide monohydrate; $C_{20}H_{30}BrNO_3.H_2O$ (430.38)

For the full monograph, see page 1408.

Comments—As a *bronchodilator* by inhalation for maintenance of treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema. It also is used as a nasal spray for symptomatic relief of rhinorrhea associated with allergic and nonallergic rhinitis in patients ≥12 yr of age. Ipratropium bromide is a synthetic quaternary anticholinergic ammonium compound that is chemically related to atropine. It has local effects when inhaled, and it is absorbed poorly into the systemic circulation from the nasal mucosa when used as an intranasal spray. About half the dose is swallowed and eliminated in the feces. The half-life is 3 to 4 hr. Adverse effects from inhalation are cough, mouth dryness, headache, dizziness, and nausea. Few systemic effects are observed in most patients. Use as a nasal spray induces epistaxis, nasal dryness, dry throat, and nasal congestion in some patients.

NEDOCROMIL SODIUM

4*H*-Pyrano[3,2-*g*]quinolone-2,8-dicarboxylic acid, 9-ethyl-6,9-dihydro-4,6-dioxo-10-propyl-, disodium salt; Tilade



[69049-74-7] $C_{19}H_{15}NNa_2O_7$ (415.31)

Preparation—See US Pat 4,474,787; *J Med Chem* 1985; 28:1832.

Description—Yellow powder.

Comments—Used as an inhaled aerosol in maintenance therapy for patients with mild-to-moderate bronchial asthma. It inhibits the activation and mediator release from a variety of inflammatory cell types associated with asthma including eosinophils, neutrophils, macrophages, mast cells, monocytes, and platelets. It inhibits release of mediators including histamine, leukotriene C_4, and prostaglandin D_2. These actions provide the basis for inhibition of the development of early and late bronchoconstrictor responses to inhaled antigen and other causes of bronchoconstriction such as exercise, cold air, and pollutants (eg, sulfur dioxide). Systemic bioavailability is low, and absorbed drug is excreted unchanged, with a mean half-life of 3.3 hr. The drug is well tolerated with few adverse reactions. Some patients experience unpleasant taste, upper respiratory tract infections, nausea, dyspepsia, and headache.

ANTITUSSIVES

Antitussives are substances that specifically inhibit or suppress the act of coughing. Such inhibition may be due to

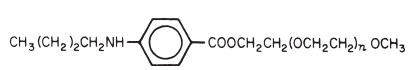
1. Depression of the medullary center or associated higher centers.
2. Increased threshold of the peripheral reflexogenous zones.
3. Interruption of tussal impulses in the afferent limb of the cough reflex.
4. Inhibition of conduction along the motor pathways.
5. Removal of irritants by facilitating bronchial drainage and mucociliary activity.

The first four ways of inhibiting cough are believed to characterize the *antitussive* agents, whereas the last one is theoretically associated with *expectorant* agents.

Antitussives may be classified in various ways. For example, centrally acting antitussives either depress the CNS and inhibit the *cough center* in the medulla or raise the threshold for central noxious stimuli and diminish the cough reflex, whereas peripherally acting antitussives act principally within the respiratory tract. Another possible classification considers these drugs as *narcotic antitussives* or *nonnarcotic antitussives*. Agents that have addiction potential are identified, however, since the addiction liability of these substances is the same regardless of therapeutic use.

BENZONATATE

Benzoic acid, 4-(butylamino)-, 2,5,8,11,14,17,20,23,26-nonaoxaoctacosan-28-yl ester; Tessalon



Average: n = 8; [104-31-4] $C_{30}H_{43}NO_{11}$ (average, 603).

Benzonatate is a mixture of the *p*-butylaminobenzoate esters of the monomethyl ethers derived from a mixture of polyethylene glycols having the average composition of a nonaethylene glycol. The chemical name above is for the average compound.

Preparation—Ethyl *p*-(butylamino)benzoate is transesterified with a polyethylene glycol monomethyl ether fraction in a methanol solution of sodium methoxide. The crude ester is purified by extracting its benzene solution with sodium carbonate solution, the ester being retained in the benzene. US Pat 2,714,606.

Description—Pale yellow, clear, viscous liquid with a faint characteristic odor and a bitter taste followed by a sense of numbness.

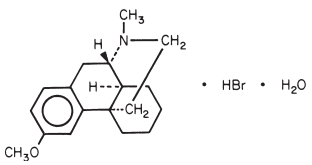
Solubility—Freely soluble in chloroform, alcohol, or benzene; miscible with water in all proportions.

Comments—An *antitussive*. It is related to tetracaine and reduces the cough reflex at its source by anesthetizing the stretch receptors in the respiratory passages, lungs, and pleura. It begins to act within 15 to 20 min and its effect lasts for 3 to 8 hr. Although its antitussive potency essentially is the same as that of codeine when evaluated against experimentally induced cough in animals and man, it is somewhat less effective than codeine against cough associated with clinical illness. Benzonatate is tolerated well in therapeutic doses. Untoward effects reported to date include headache, mild dizziness, pruritus and skin eruptions, nasal congestion, constipation, nausea, GI upset, a sensation of burning of the eyes, and numbness or tightness in the chest. Hypersensitivity reactions have been reported. If the capsules are allowed to dissolve in the mouth, they exert a local anesthetic effect that is disagreeable to a few patients. Dependence, euphoria, respiratory depression, or constipation have not been reported. Overdosage can lead to CNS stimulation, resulting in restlessness, tremors, and, ultimately, seizures.

CODEINE—page 1527.
CODEINE PHOSPHATE—page 1527.
CODEINE SULFATE—page 1528.

DEXTROMETHORPHAN HYDROBROMIDE

(9α,13α,14α)-Morphinan, 3-methoxy-17-methyl-, hydrobromide, monohydrate



[6700-34-1] $C_{18}H_{25}NO.HBr.H_2O$ (370.33); *anhydrous* [125-69-9] (352.32).

Preparation—Dextromethorphan base (*d*-3-methoxy-*N*-methylmorphinan) is prepared from the corresponding *d*-3-hydroxy compound by methylation with phenyltrimethylammonium hydroxide. The procedure is analogous to that employed for the methylation of morphine to produce codeine. Treatment of the base with HBr yields the hydrobromide.

Description—Practically white crystals, or crystalline powder, with a faint odor; melts about 126° with decomposition, pH (1 in 100 solution) 5.2 to 6.5.

Solubility—1 g in about 65 mL water; freely soluble in alcohol or chloroform; insoluble in ether.

Comments—Dextromethorphan, the *d*-isomer of the codeine analog of levorphanol, is employed as an *antitussive agent*. It controls cough spasms by depressing the cough center in the medulla. Controlled studies in man indicate it has a cough suppression potency approximately one-half that of codeine. The oral administration of 30 mg to an adult provides effective antitussive activity over an 8- to 12-hr period. Unlike codeine, it is devoid of analgesic properties and produces little or no depression of the CNS. Addiction does not usually occur even after the administration of rather large doses for prolonged periods. However, there have been reports of abuse of OTC dextromethorphan-containing cold and cough medicines, especially by teenagers. Animal studies suggest that this drug has some effects similar to those of phencyclidine (PCP), which may account for its abuse. Additional data are needed for better assessment of the potential for dextromethorphan dependence. High doses of this drug can cause ataxia, respiratory depression, and convulsions in children, while in adults high doses can alter sensory perception and cause ataxia, slurred speech, and dysphoria. The side effects include slight drowsiness and GI upset; these are less severe and less frequent than with codeine. Accidental poisoning in children is characterized by stupor and ataxia with rapid recovery after emesis. Dextromethorphan hydrobromide should not be given to patients on monoamine oxidase inhibitors.

DIPHENHYDRAMINE HYDROCHLORIDE—pages 1545 and 1548.
HYDROCODONE BITARTRATE—page 1528.
METHADONE HYDROCHLORIDE—page 1532.
MORPHINE SULFATE—page 1527.

EXPECTORANTS

Expectorants are drugs that have been proposed to be useful in loosening and liquefying mucous, in soothing irritated bronchial mucosa, and in making coughs more productive. Such agents are thought to affect the respiratory tract in two ways:

1. By decreasing the viscosity of the bronchial secretions and facilitating their elimination so that local irritants are removed and ineffectual coughing is alleviated or made more productive.
2. By increasing the amounts of respiratory tract fluid so that demulcent action is exerted on the dry mucosal lining, thus relieving the unproductive cough.

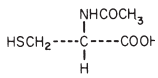
The FDA has proposed that orally administered expectorants available OTC be divided into three categories:

Category I—those generally recognized as safe and effective.
Category II—those not generally recognized as safe and effective.
Category III—those with insufficient data to classify as safe and effective.

The FDA has approved only guaifenesin for classification as a Category I expectorant. Thus, it is not surprising that many of the orally administered cough and cold combinations include guaifenesin as the expectorant. Even so, there is a lack of scientific evidence to demonstrate that guaifenesin is of value in the treatment of coughing. It should be remembered, however, that humidification of room air and adequate fluid intake (6–8 glasses of water a day) can effectively liquefy respiratory mucus and are useful therapeutic procedures.

ACETYLCYSTEINE

L-Cysteine, *N*-acetyl-, Mucomyst



N-Acetyl-L-cysteine [616-91-1] $C_5H_9NO_3S$ (163.19).

Preparation—By direct acetylation of L-cysteine.

Description—White, crystalline powder with a very slight acetic odor and a characteristic sour taste; stable in ordinary light; nonhygroscopic (oxidizes in moist air); stable at temperatures up to 120°; melts between 104° and 110°; pK_a 3.24; pH (1 in 100 solution) 2 to 2.75.

Solubility—1 g in 5 mL water or 4 mL alcohol; practically insoluble in chloroform or ether.

Comments—To *reduce the viscosity of pulmonary secretions* and *facilitate their removal*. Hence, it is used as adjuvant therapy in bronchopulmonary disorders when mucolysis is desirable. It is thought the sulfhydryl group in the molecule *opens* the disulfide bonds in mucus and lowers the viscosity. The mucolytic activity of acetylcysteine is related to pH; significant mucolysis occurs between pH 6 and 9. Clinical studies indicate that after inhalation, onset of action is within 1 min, and time to peak effect is 5 to 10 min. Side effects are rare. However, bronchospasm, hemoptysis, and nausea and vomiting have been observed. Antimicrobial drugs, including ampicillin, tetracyclines, amphotericin B, and erythromycin lactobionate, should not be administered in acetylcysteine solution, since it inactivates antibiotics. Effectiveness of acetylcysteine as a mucolytic is difficult to assess and has been based on subjective observations; it may not be any greater than adequate humidification.

Acetylcysteine is used orally and parenterally as an antidote to prevent or minimize hepatotoxicity in acute acetaminophen overdosage. It also has been used with some success as an ophthalmic solution for the treatment of keratoconjunctivitis sicca (dry eye) and as an enema for the management of bowel obstruction due to meconium ileus.

AMMONIUM CHLORIDE—page 1423.
ANTIMONY POTASSIUM TARTRATE—page 1596.

CARBETAPENTANE TANNATE

ing of Tussizone-12, Rynatuss, Xiratuss, etc.

Preparation—Carbetapentane is dissolved in 2-propanol (water also has been used), heated to 65–70° to effect solution and a solution of

tannic acid in the same solvent is added over a 60 min period while stirring. After cooling, the suspension is filtered, washed with solvent and vacuum dried. US Pat 5,663,415 (1997), US Pat 6,455,727 (2002).

Description—Light tan-colored powder; softens about 80 - 85°; purity is reported as approximately 95%.

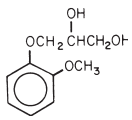
Solubility—Slightly soluble in water or alcohol; insoluble in CH_2Cl_2.

Comments—For the symptomatic relief of cough associated with respiratory tract conditions such as the common cold, bronchial asthma, and acute and chronic bronchitis.

GLYCERIN—pages 758, 1081, and 1423.

GUAIFENESIN

1,2-Propanediol, 3-(2-methoxyphenoxy)-, Glyceryl Guaiacolate



3-(*o*-Methoxyphenoxy)-1,2-propanediol [93-14-1] $C_{10}H_{14}O_4$ (198.22).

Preparation—Guaiacol and 3-chloro-1,2-propanediol are condensed via dehydrochlorination by warming a mixture of the reactants with a base.

Description—White to slightly gray crystalline powder with a bitter taste; may have a slight characteristic odor; stable in light and heat and is nonhygroscopic; melts with a range of 3° between 78° and 82°; pH (1 in 100 solution) between 5 and 7.

Solubility—1 g in 60 to 70 mL water; soluble in alcohol, chloroform, glycerin, or propylene glycol; insoluble in petroleum ether.

Comments—Used for the *symptomatic relief of respiratory conditions* characterized by a dry, nonproductive cough and the presence of mucus in the respiratory tract. Subjective clinical studies suggest that the action of guaifenesin ameliorates dry unproductive cough by decreasing sputum viscosity and difficulty in expectoration and increasing sputum volume. However, experimentally, it only increases respiratory tract secretions, but only when given in doses larger than those used clinically. Adverse effects are infrequent and usually consist of nausea, gastric disturbance, and drowsiness. Guaifenesin may produce a false-positive test result for 5-hydroxyindoleacetic acid. It is an ingredient of many OTC proprietary expectorant formulations.

POTASSIUM IODIDE

Potassium iodide [7681-11-0] KI (166.00).

Preparation—Potassium iodide may be prepared by reacting iodine with a hot solution of potassium hydroxide, the iodate simultaneously formed being subsequently reduced to iodide by heating the dry reaction mixture with carbon.

Description—Hexahedral crystals, either transparent and colorless or somewhat opaque and white, or a white granular powder; slight hygroscopic in moist air; aqueous solution is neutral or slightly alkaline to litmus.

Solubility—1 g in 0.7 mL water, 22 mL alcohol, 2 mL glycerin, 75 mL acetone at 25°, or 0.5 mL boiling water; when dissolved in water heat is absorbed; 100 mL of a saturated aqueous solution at 25° contains 100 g of KI.

Comments—Used as an *expectorant* and when the action of iodide is desired. It is used as an expectorant to liquefy thick and tenacious sputum in chronic bronchitis, bronchiectasis, bronchial asthma, and pulmonary emphysema. It also is used as adjunctive treatment in cystic fibrosis, in chronic sinusitis, and after surgery to prevent atelectasis. However, the therapeutic value of potassium iodide as an expectorant has not been demonstrated convincingly. Although a substantial number of patients tolerate potassium iodide well, iodide-induced goiter and hypothyroidism have been observed. Consequently, alternative drugs that are safer and more effective should be considered when an expectorant action is desired.

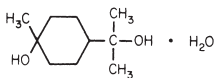
Mild untoward reactions occur frequently with iodide medication. The syndrome is known as iodism. The symptoms include salivation, lacrimation, coryza, soreness of the teeth and gums, eruption of the skin, headaches, swollen salivary glands, and gastric irritation. The symptoms disappear when the drug is discontinued. Serious reactions occur very rarely. Concurrent use of potassium iodide with lithium and other antithyroid drugs may potentiate the hypothyroid and goitrogenic effects of these medications. Likewise, use with other potassium-containing medications and potassium-sparing diuretics may induce hyperkalemia and cardiac arrhythmias or cardiac arrest.

Potassium Iodide Solution—[Saturated Potassium Iodide Solution; Lugol's Solution] contains, in each 100 mL, 97 to 103 g of KI. *Preparation:* Dissolve potassium iodide (1000 g) in hot purified water (680 mL), cool to about 25°, and add sufficient purified water to make 1000 mL; filter, if necessary. *Note:* If the solution is not to be used within a short time, 500 mg of sodium thiosulfate should be added to each 1 L. *Description:* Clear, colorless, and odorless solution with a characteristic, strongly salty taste; neutral or slightly alkaline to litmus paper; specific gravity about 1.700. *Comment:* Iodide supplement and expectorant; see *Potassium Iodide.*

SODIUM CITRATE—page 1331.

TERPIN HYDRATE

Cyclohexanemethanol, 4-hydroxy-α,α-4-trimethyl-, monohydrate; Terpinum; Terpinol



p-Menthane-1,8-diol monohydrate [2451-01-6] $C_{10}H_{20}O_2.H_2O$ (190.28); *anhydrous* [80-53-5] (172.27).

Preparation—By hydration of the pinenes in turpentine oil (or pine oil) in the presence of a strong acid.

Description—Colorless, lustrous crystals, or as a white powder; slight odor, and efflorescent in dry air; a hot 1:100 aqueous solution is neutral to litmus; when dried over H_2SO_4 in a vacuum, it melts about 103°.

Solubility—1 g in about 200 mL water, 13 mL alcohol, 140 mL chloroform, or about 140 mL ether at 25°; 1 g in about 35 mL boiling water or about 3 mL boiling alcohol.

Comments—In *bronchitis* as an *expectorant.* Terpin hydrate elixir contains too little of the compound to be effective alone and is employed mainly as a vehicle for cough mixtures such as *Terpin Hydrate and Codeine Elixir* and *Terpin Hydrate and Dextromethorphan Elixir.*

Terpin Hydrate Elixir contains, in each 100 mL, 1.53 to 1.87 g of $C_{10}H_{20}O_2.H_2O$. *Preparation:* Dissolve terpin hydrate (17 g) in the alcohol (430 mL); add successively sweet orange peel tincture (20 mL), benzaldehyde (0.05 mL), glycerin (400 mL), syrup (100 mL), and purified water (qs) to make the product measure 1000 mL; mix well and filter, if necessary, until the product is clear. *Note*—The sweet orange peel tincture may be replaced by 1 mL orange oil dissolved in 15 mL alchol. *Alcohol Content:* 39 to 44%. The high alcoholic content in this elixir is required for the solution of the terpin hydrate. *Incompatibilities:* Dilution of this elixir with water or liquids of low alcohol content causes precipitation of the terpin hydrate.

Terpin Hydrate and Codeine Elixir contains, in each 100 mL, 1.53 to 1.87 g of $C_{10}H_{20}O_2.H_2O$ (terpin hydrate), and 180 to 220 mg of $C_{18}H_{21}NO_3.H_2O$ (codeine). *Preparation:* Dissolve codeine (2 g) in terpin hydrate elixir (qs) to make the product measure 1000 mL. *Alcohol Content:* 39 to 44%. *Comments:* This elixir is an *expectorant* and *sedative* used to allay excessive coughing. Its value resides primarily in its content of codeine. *Caution*—This elixir is sometimes used by addicts, by whom it is known as *GI Gin,* for its alcohol and codeine content. In some states pharmacists are required to register and limit its sale. Its repeated sale to an individual should be noted and stopped.

Terpin Hydrate and Dextromethorphan Hydrobromide Elixir contains, in each 100 mL, 1.53 to 1.87 g of $C_{10}H_{20}O_2.H_2O$ (terpin hydrate), and 180 to 220 mg of $C_{18}H_{25}NO.HBr.H_2O$ (dextromethorphan hydrobromide). *Preparation:* Dissolve dextromethorphan hydrobromide (2 g) in terpin hydrate elixir (qs) to make the product measure 1000 mL. *Comments:* The same indications as *Terpin Hydrate and Codeine Elixir.* It is used in the control of coughs associated with the common cold, laryngitis, tracheitis and bronchitis. Dextromethorphan acts to elevate the threshold for coughing. Unlike codeine, it rarely produces drowsiness or GI disturbances.

TOLU BALSAM—page 1068.

Expectorant Combinations

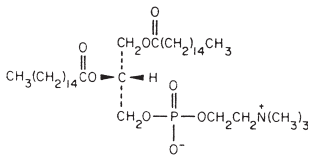
The most frequent expectorant combinations include an antitussive with guaifenesin. However, expectorants also are found in combination with sympathomimetics, antihistamines, and analgesics in OTC cold and cough medicines. The benefit of such combinations in the treatment of coughing or other respiratory ailments is controversial.

SURFACTANT PREPARATIONS

Surfactant preparations are used as replacement therapy for the treatment of premature infants suffering from neonatal respiratory distress syndrome (also known as hyaline membrane disease). This pulmonary condition occurs in approximately 20% of the 250,000 premature babies born in the US each year and accounts for 5000 deaths annually. A substantial deficiency in the endogenous lung surfactant (of which beractant is the primary phospholipid) is the principal factor contributing to the pathology of respiratory distress syndrome. The lung surfactant preparations are used in combination with supplemental oxygen and mechanical ventilation to facilitate gas exchange for either prophylactic or rescue treatment of neonatal respiratory distress syndrome. The exogenous surfactants are either derived from animals or synthesized. The efficacy of lung surfactants has been demonstrated in double-blind, randomized studies in comparison to air placebo in premature infants with respiratory distress syndrome, particularly in infants with a birth weight exceeding 700 g. Studies suggest the exogenous lung surfactants are tolerated well, with few direct adverse effects.

BERACTANT

3,5,9-Trioxa-4-phosphapentacosan-1-aminium, *(R)*-4-hydroxy-*N,N,N*-trimethyl-10-oxo-7-[(1-oxohexadecyl)oxy]-, hydroxide, inner salt, 4-oxide; Survanta



1,2-Dipalmitoyl-*sn*-glycero-3-phosphocholine [63-89-8] $C_{40}H_{80}NO_8P$ (734.05).

Comments—*Beractant* is a modified bovine extract consisting of phospholipids, neutral lipids, fatty acids, and surfactant-associated proteins beractant, palmitic acid, and tipalmitin are added to improve the surface-active properties. Exosurf is a synthetic lung surfactant composed of beractant, cetyl alcohol, and tyloxapol. The cetyl alcohol facilitates spreading and adsorption of beractant at the air-alveolar interface.

CALFACTANT

Calfactant; Infasurf

[183325-78-2]

Preparation—A natural surfactant extracted from the lungs of calves using a chloroform/methanol lavage.

Description—A sterile, non-pyrogenic lung surfactant; off-white suspension in 0.9% aqueous sodium chloride solution and contains 35 mg total phospholipids (including 26 mg phosphatidylcholine of which 16 mg is disaturated phosphatidylcholine) and 0.65 mg proteins including 0.26 mg of SP-B. It has a **pH** of 5.0-6.0.

Comments—Calfactant is indicated for the prevention of Respiratory Distress Syndrome (RDS) in premature infants at high risk for RDS and for the treatment ("rescue") of premature infants who develop RDS. It decreases the incidence of RDS, mortality due to RDS, and air leaks associated with RDS.

PORACTANT ALFA

Poractant Alfa; Curosurf

[129060-19-8]

Description—An extract of porcine lung containing not less than 90% of phospholipids, about 1% hydrophobic proteins (SP-B and SP-C) and about 90% of other lipids. The phospholipid component is composed of phosphatidyl choline and derivatives.

Comments—Poractant Alfa is used to treat or "rescue" premature babies with Respiratory Distress Syndrome (RDS). It reduces air trapped in the lining of the lungs (pneumothoraces) associated with RDS.

MISCELLANEOUS RESPIRATORY DRUGS

ALPHA-1 PROTEINASE INHIBITOR

Aralast, Prolastin, Zemaira

$Alpha_1$-PI, $Alpha_1$-antitrypsin

Preparation—From pooled human blood plasma by a cold ethanol fractionation. *Vox Sang* 1985; 48:333.

Description—White lyophilized powder. A single polypeptide chain of 394 amino acid molecules plus 3 carbohydrate molecules linked to asparagine residues. It is the major serine protease inhibitor in mammalian plasma.

Comments—Alpha-1 proteinase inhibitor is indicated for chronic augmentation therapy in patients having congenital deficiency of α1-PI with clinically evident emphysema. Clinical and biochemical studies have demonstrated that with such therapy, it is effective in maintaining target serum α1-PI trough levels and increasing α1-PI levels in epithelial lining fluid. Clinical data demonstrating the long-term effects of chronic augmentation or replacement therapy are not available. It is not indicated as therapy for lung disease patients in whom congenital α1-PI has not been established.

CHAPTER 70

Sympathomimetic Drugs

It is helpful to review briefly the autonomic nervous system (ANS) and the classification of drugs that act on or simulate components of that system. The ANS generally is defined as that aspect of the nervous system involved in the regulation of involuntary, visceral function. As such, the ANS is responsible for regulating the activity of cardiac muscle; the activity of smooth muscle of the viscera, blood vessels, and the eye; and the secretory activity of cells in the viscera, as well as sweat, salivary, and lacrimal glands. The ANS functions to maintain or restore homeostasis of vital physiological functions, such as cerebral blood flow, body temperature, visual accommodation, blood sugar, and body fluid composition.

There are two main efferent divisions to the ANS—the sympathetic (thoracolumbar) and the parasympathetic (craniosacral). Most organs or systems (effectors) receive innervation from both of these divisions. Generally, but not invariably, the two divisions exert opposite influences on a given effector.

The opposite effects exerted by the two divisions of the ANS arise largely because the chemical substances (neurotransmitter/neuromodulator) liberated by the postganglionic nerve terminals in the effector organs are not the same for the two divisions. Parasympathetic *post*ganglionic nerves liberate acetylcholine and, hence, are called *cholinergic*. This acetylcholine acts on muscarinic receptors in the effectors. Most sympathetic *post*ganglionic nerves liberate norepinephrine (noradrenaline), and thus are considered to be *noradrenergic*. The adrenal medulla, however, which is innervated by sympathetic preganglionic nerves, liberates both epinephrine (adrenaline/*adrenergic*) and norepinephrine, with epinephrine release predominating under many, but not all, conditions. These two catecholamines activate α- and β-adrenergic receptors. Although most *post*ganglionic sympathetic neurons are noradrenergic, it should be noted that sympathetic *post*ganglionic fibers to the sweat glands and a few fibers to the vascular beds of the mouth, face, and skeletal muscles are cholinergic.

In the sympathetic ganglia, *pre*ganglionic nerves of either division liberate acetylcholine (ie, are cholinergic). However, the acetylcholine released by the preganglionic neurons acts on nicotinic cholinergic receptors, rather than muscarinic receptors. Thus, the effects of acetylcholine release at these two sites (sympathetic ganglia versus effector organ) are not blocked by the same drugs. Somatic motor neurons also are cholinergic and are similar to autonomic preganglionic nerves in this regard. However, the nicotinic receptors at the neuromuscular junction also are pharmacologically distinguishable from those in the sympathetic ganglia.

Autonomic drugs are classified on the basis of their effects relative to activation of the ANS. Thus, *sympathomimetic drugs* are those whose effects mimic (hence *-mimetic*) the effects seen with activation of the sympathetic nervous system. Likewise, *parasympathomimetics* are drugs that mimic the effects of parasympathetic nervous system activation. Since the sympathetic nervous system liberates norepinephrine (noradrenaline) and epinephrine (adrenaline), sympathomimetics sometimes are referred to as adrenomimetics. Parasympathomimetics are referred to as cholinomimetics, since the parasympathetic system releases acetylcholine at the effector organ.

The effects of sympathetic nervous system activation and, therefore, the effects of sympathomimetic drugs are determined largely by the type and localization of the postsynaptic receptor to which the released neurotransmitter or exogenous sympathomimetic binds. Norepinephrine and epinephrine bind to two general families of receptors, the α- and β-adrenergic receptors. α-Adrenergic receptors have been further divided into α_1 and α_2 receptors on the basis of their pharmacology, and each of these subclasses can be divided further on the basis of their pharmacology and molecular biology. Thus, at least three distinct α_1 receptors have been identified, designated α_{1A}, α_{1B}, and α_{1D}. Similarly, molecular biological techniques have identified at least three distinct α_2 receptors, termed $\alpha_{2A\text{-}2C}$. The β receptors have been subdivided into β_1, β_2, and β_3 receptors on the basis of their pharmacological properties and molecular cloning as well. It should be noted, however, that despite the cloning of a number of α and β receptors, clinically available pharmacological agents at present only distinguish between the broad classes of α_1, α_2, β_1, and β_2 receptors. Therefore, in this chapter reference is not made to the subtypes of receptor within each broad classification.

α_1 Receptors increase phosphatidyl inositol hydrolysis, leading to the production of inositol trisphosphate (IP_3) and diacylglycerol (DAG). These second messengers lead to an increase in intracellular calcium concentrations. α_2 Receptors, on the other hand, are coupled negatively to adenylate cyclase through the $G_{i/o}$ signaling system, leading to a decrease in intracellular cyclic AMP (cAMP) levels. In addition, stimulation of α_2 receptors decreases the opening of voltage-sensitive calcium channels and increases the activity of voltage-sensitive potassium channels, both effects contributing to decreased cell excitability. All three types of β receptors are positively coupled to adenylate cyclase, leading to increased levels of cAMP and increased activity of protein kinase A in the cell.

Knowledge of the localization of the different adrenergic and dopaminergic receptors is critical for understanding the physiological effects of sympathomimetic drugs. The localization of the adrenergic and dopaminergic receptors in a number of effector organs important for the therapeutic usefulness of sympathomimetics and the effects of stimulation of those receptors are given in Table 70-1. The bold-face type indicates, where relevant, which receptor subtype dominates in determining function under normal conditions. It should be noted,

Table 70-1. Localization and Function of Adrenergic and Dopaminergic Receptors in the Periphery

EFFECTOR ORGAN	RECEPTOR SUBTYPE	EFFECT
Arterial vascular smooth muscle	α_1	Vasoconstriction
	α_2	Vasoconstriction
	β_2	Vasodilation (especially in skeletal muscle beds)
Venous vascular smooth muscle	α_1	Vasoconstriction
	α_2	Vasoconstriction
	β_2	Vasodilation (especially in skeletal muscle beds)
Heart	β_1	Positive inotropy, positive chronotropy
	α_1	Positive inotropy
Lungs	β_2	Relaxation of smooth muscle
Eye		
Radial muscle	α_1	Contraction (mydriasis)
Aqueous humor outflow	α_2	Decreased
Kidney	α_1	Decreased sodium and water excretion
		Decreased renin release
	β_1	Increased renin release
Gastrointestinal tract		
Motility	α_2	Decreased ACh release so decreased motility
Ion absorption	α_2	Increased Na^+ and Cl^- absorption
Pancreas	α_2	Decreased insulin release
Urinary bladder		
Detrusor muscle	β_2	Relaxation
Trigone muscle and sphincter	α_1	Contraction
Urethra	α_1	Contraction
Prostate gland	α_1	Contraction of smooth muscle
Uterus	α_1	Contraction
	β_2	Relaxation
Skeletal muscle	β_2	Increased K^+ uptake; increased glycogenolysis
Liver	β_2	Increased glycogenolysis; increased gluconeogenesis
	α_1	
Fat cells	β_3	Lipolysis; thermogenesis

however, that under pathological conditions, the relative contributions of the receptors may be altered. For example, whereas β_1 receptors predominate in regulating cardiac function under normal conditions, α_1-mediated effects become more prominent after chronic treatment with β-blockers, after myocardial ischemia, and in congestive heart failure. Knowledge of the localization of the different receptor subtypes and the effect of their stimulation on the effector organ allows prediction of many of the therapeutic indications and likely side effects of the sympathomimetic drugs. Because of this, the sympathomimetic drugs are classified largely relative to the receptor subtypes that they affect and are presented in this chapter in such a manner.

The role of dopamine in the sympathetic nervous system remains controversial. There is little evidence for dopamine nerves *per se* in the sympathetic nervous system. Although dopamine is the immediate biosynthetic precursor of norepinephrine and therefore is present in postganglionic sympathetic nerves, there is little support for the idea that dopamine is released as a neurotransmitter from those nerve terminals in response to sympathetic nervous system activation. Dopamine is thought to be synthesized, however, by cells in the proximal tubules of the kidney and might exert a paracrine function in that region. Despite the lack of dopamine innervation, a number of effector organs express dopamine receptors of both the D1 and D2 dopamine-receptor families. For example, D1 dopamine receptors are located on the splanchnic, renal, cardiac, and cerebral vascular beds. Stimulation of these D1 dopamine receptors produces vasodilation. In addition, D1 receptors are expressed throughout the nephron of the human kidney. Stimulation of these receptors decreases tubular sodium reabsorption, thereby promoting natriuresis and diuresis. Although dopamine does not appear to mediate the effects of sympathetic nervous system activation, dopamine receptor stimulation produces effects analogous to those seen with other sympathomimetics and are therefore are covered in this section.

α_1 AGONISTS

Given the distribution of α_1 receptors outlined above and the effects of their stimulation, it follows that pure α_1 agonists often are used for their ability to produce vasoconstriction. Increases in total peripheral resistance achieved with systemic α_1 stimulation are useful in the management of hypotension associated with spinal shock or spinal anesthesia, situations in which there is a loss of sympathetic outflow to the vasculature. Although they can be used in the treatment of other types of shock once blood volume has been restored, their use in these situations is not recommended, as further vasoconstriction in vital organs that already are insufficiently perfused is undesirable.

Local administration of α_1 agonists is beneficial for the production of local vasoconstriction. Thus, local administration is often used in surgery to control local hemorrhage. This vasoconstriction is also of benefit when combined with a local anesthetic, as the vasoconstriction decreases absorption of the anesthetic, thereby prolonging its duration of action. When applied topically to the nasal mucosa or the eye, the local vasoconstriction produced promotes decongestion.

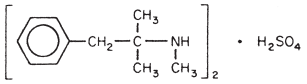
Stimulation of α_1 receptors in the eye produces mydriasis (pupillary dilation) due to contraction of the radial muscle of the iris. The α_1 agonists therefore are useful in producing mydriasis for ophthalmologic examinations.

As is the case for their clinical utility, most of the contraindications and side effects of the α_1 agonists arise from their marked ability to produce vasoconstriction. The resulting increase in blood pressure can precipitate cerebrovascular accidents (ie, stroke), coronary artery occlusion resulting in myocardial infarction, or aneurysm. Because the heart must work harder against the increased pressure, angina may result or heart failure may be exacerbated. For these reasons, the use of α_1 agonists in patients with *hypertension, coronary artery disease, arteriosclerosis, atherosclerosis, cardiac arrhythmias,* or a history of *myocardial infarction* is contraindicated except under strict medical supervision. They also are contraindicated in patients with *venous thrombosis* and *diabetes* because the vascular pathology that is or may be present in these patients can be exacerbated by the vasoconstriction produced. It should be noted that sufficient absorption of α_1 agonists can occur with topical administration to the conjunctiva or nasal mucosa to produce systemic hypertension.

Other peripheral side effects of the α_1 agonists arise from stimulation of α_1 receptors in other sites. Thus, stimulation of α_1 receptors in the urethra and sphincter of the bladder can lead to urinary retention. For this reason, α_1 agonists should be used cautiously in patients with *prostatic hypertrophy*. The mydriasis produced by stimulation of α_1 receptors in the radial muscle of the iris can lead to *photophobia*. Because rebound miosis can occur after the adrenergic effects wear off, α_1 agonists should be used cautiously when there is *retinal detachment*. In addition, the mydriasis produced by α_1 agonists may significantly increase intraocular pressure in patients with *angle-closure (narrow angle) glaucoma*.

MEPHENTERMINE SULFATE

Benzeneethanamine, *N*,α,α-trimethyl-, sulfate; Wyamine Sulfate



[1212-72-2] $(C_{11}H_{17}N)_2 \cdot H_2SO_4$ (424.60); *dihydrate* [6190-60-9] (460.63).

Preparation—By a seven-step synthesis starting with phenyl isopropyl ketone and conversion of the free base to the salt with sulfuric acid. US Pat 2,590,079.

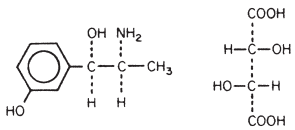
Description—White, odorless crystals or a crystalline powder; solutions are acid to litmus, having a pH of about 6.

Solubility—1 g in 18 mL water, 220 mL alcohol, >1000 mL chloroform, or >10,000 mL ether.

Comments—Has indirect and direct actions.

METARAMINOL BITARTRATE

Benzenemethanol, [*R*-(*R*,S)]-α-(1-aminoethyl)-3-hydroxy-, [*R*-(*RI,R**)]-2-3-dihydroxybutanedioate (1:1) (salt) Aramine; Pressonex**



(−)-α-(1-Aminoethyl)-*m*-hydroxybenzyl alcohol, tartrate (1:1) (salt) [33402-03-8] $C_9H_{13}NO_2 \cdot C_4H_6O_6$ (317.29).

Preparation—Among other methods, by reactions using *m*- hydroxybenzaldehyde and benzylamine as the principal reactants. The base is converted to the bitartrate with an equimolar quantity of tartaric acid.

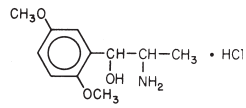
Description—White, practically odorless, crystalline powder; melts between 171° and 175°; pH (1 in 20 solution) between 3.2 and 3.5.

Solubility—Freely soluble in water; 1 g in about 100 mL alcohol; practically insoluble in chloroform or ether.

Comments—A direct-acting α and β_1 agonist with little β_2 activity. It releases norepinephrine and is used mainly for maintaining blood pressure during spinal shock or spinal anesthesia.

METHOXAMINE HYDROCHLORIDE

Benzenemethanol, α-(1-Aminoethyl)-2,5-dimethoxy-, hydrochloride; Vasoxyl Hydrochloride



(±)-α-(1-Aminoethyl)-2,5-dimethoxybenzyl alcohol hydrochloride [61-16-5] $C_{11}H_{17}NO_3 \cdot HCl$ (247.72).

Preparation—Among other ways, from 2′ ,5′-dimethoxypropiophenone through reaction with nitrous acid to form the 2-isonitroso derivative followed by catalytic hydrogenation which reduces both the carbonyl function to carbinol and the isonitroso function to amino. The methoxamine, dissolved in a suitable organic solvent, is readily converted to the hydrochloride by a stream of hydrogen chloride.

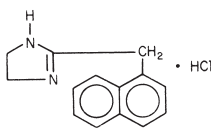
Description—Colorless or white, plate-like crystals, or a white, crystalline powder; odorless or has only a slight odor; solutions are acid to litmus, having a pH of about 5; melts between 214° and 219°.

Solubility—1 g in about 2.5 mL water or 12 mL alcohol; almost insoluble in chloroform or ether.

Comments—A direct-acting α_1 agonist with a rapid and prolonged pressor action. It also has some β receptor–blocking properties. It is used mainly to support blood pressure during anesthesia.

NAPHAZOLINE HYDROCHLORIDE

1*H*-Imidazole, 4,5-dihydro-2-(1-naphthalenylmethyl)-, monohydrochloride; Privine Hydrochloride



2-(1-Naphthylmethyl)-2-imidazoline monohydrochloride [550-99-2] $C_{14}H_{14}N_2 \cdot HCl$ (246.74).

Preparation—In almost quantitative yields by heating 1- naphthalene-acetonitrile with ethylenediamine monohydrochloride at 175° to 200° for 1 hr. The 1-naphthaleneacetonitrile is made from naphthalene by chloromethylation with formaldehyde and HCl followed by treatment of the resulting 1-naphthylmethyl chloride with potassium cyanide.

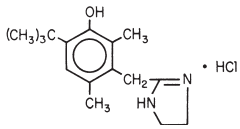
Description—White, crystalline, odorless, bitter powder; melting range 253° to 258°, with decomposition; pH (1 in 100 solution) between 5 and 6.6.

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

Comments—An OTC and Rx nasal and ocular decongestant used topically.

OXYMETAZOLINE HYDROCHLORIDE

Phenol, 3-[(4,5-dihydro-1*H*-imidazol-2-yl)methyl]-6-(1,1-dimethylethyl)-2,4-dimethyl-, monohydrochloride; Afrin; Neo-Synephrine; Visine



6-*tert*-Butyl-3-(2-imidazolin-2-ylmethyl)-2,4-dimethylphenol monohydrochloride [2315-02-8] $C_{16}H_{24}N_2O \cdot HCl$ (296.84).

Preparation—2,4-Dimethyl-6-*tert*-butylphenol is converted into the benzyl cyanide intermediate, which is reacted with ethylenediamine *p*-toluenenesulfonate whereby, through addition and deammoniation, the imidazoline ring is formed. The resulting oxymetazoline is converted to the salt through interaction with an equimolar quantity of hydrogen chloride. US Pat 3,147,275.

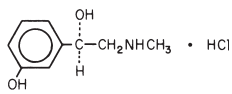
Description—White to nearly white, fine, crystalline powder; odorless; stable in light and heat, nonhygroscopic; melts about 300° with decomposition; pH (1 in 20 solution) between 4 and 6.5.

Solubility—1 g in 6.7 mL water, 3.6 mL alcohol or 860 mL chloroform; practically insoluble in ether.

Comments—An OTC drug used topically as a nasal and ocular decongestant. It causes less rebound congestion than *Naphazoline*.

PHENYLEPHRINE HYDROCHLORIDE

Benzenemethanol, 3-hydroxy-α-[(methylamino)methyl]-, hydrochloride



(−)-*m*-Hydroxy-α-[(methylamino)methyl]benzyl alcohol hydrochloride [61-76-7] $C_9H_{12}NO_2 \cdot HCl$ (203.67).

Preparation—*m*-Hydroxyphenacyl bromide is condensed with methylamine, and the carbonyl group then is reduced to a carbinol via catalytic hydrogenation. The phenylephrine so formed is dissolved in a suitable solvent and neutralized with HCl.

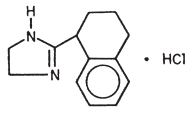
Description—White or nearly white crystals; odorless; bitter taste; melts between 140° and 145°.

Solubility—Freely soluble in water or alcohol.

Comments—Used to maintain blood pressure and as a nasal, scleroconjunctival, and uveal decongestant. It also is used as a mydriatic agent and to promote aqueous humor outflow in the treatment of open-angle glaucoma. Its vasoconstricting properties are used in conjunction with local or spinal anesthetics to prolong their duration of action. It is orally active.

TETRAHYDROZOLINE HYDROCHLORIDE

Imidazole, 4,5-dihydro-2-(1,2,3,4-tetrahydro-1-naphthalenyl)-, monohydrochloride; Collyrium Fresh; Murine; Soothe; Tyzine



[522-48-5] $C_{13}H_{16}N_2 \cdot HCl$ (236.74).

Preparation—Ethyl phenylacetate and methyl acrylate undergo a Michael condensation and cyclization using sodium ethoxide as

catalyst, followed by acidification to form 4-keto-1,2,3,4-tetrahydro-1-naphthoic acid. The keto group is reduced by catalytic hydrogenation to methylene, and the resulting 1,2,3,4-tetrahydro-1-naphthoic acid is condensed with ethylenediamine in the presence of HCl.

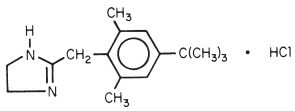
Description—White crystals; odorless; melts with decomposition about 256°.

Solubility—1 g in 3.5 mL water or 7.5 mL alcohol; very slightly soluble in chloroform or ether.

Comments—An OTC drug used topically as a nasal and ocular decongestant. It causes systemic constriction.

XYLOMETAZOLINE HYDROCHLORIDE

1*H*-Imidazole, 2-[[4-(1,1-dimethylethyl)-2,6-dimethylphenyl]-methyl]-4,5-dihydro-, monohydrochloride; Otrivin Hydrochloride



2-(4-*tert*-Butyl-2,6-dimethylbenzyl)-2-imidazoline monohydrochloride [1218-35-5] $C_{16}H_{24}N_2 \cdot HCl$ (280.84).

Preparation—Using (4-*tert*-butyl-2,6-dimethylphenyl)acetonitrile as the participating nitrile, by the method described for *Naphazoline Hydrochloride,* page 1307.

Description—White, odorless, crystalline powder, melts above 300° with decomposition; pH (1 in 20 solution) between 5 and 6.6.

Solubility—1 g in about 30 mL water; freely soluble in alcohol; sparingly soluble in chloroform; practically insoluble in benzene or ether.

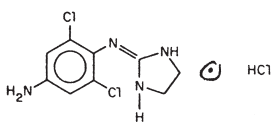
Comments—A nasal decongestant with possibly less reactive hyperemia.

α_2 AGONISTS

The α_2 agonists presented in this section are those used for their actions at peripheral α_2 receptors, thus mimicking the effects of sympathetic nervous system activation. These α_2 agonists are used peripherally in the treatment of open-angle glaucoma, as stimulation of α_2 receptors increases uveoscleral outflow and decreases the production of aqueous humor. Other α_2 agonists, such as clonidine and guanfacine, act on α_2 receptors in the central nervous system (CNS) to decrease sympathetic nervous system activity. Such drugs are reviewed in Chapter 68.

APRACLONIDINE HYDROCHLORIDE

1,4-benzenediamine,2,6-dichloro-*N*$_1$-2-imidazolidinylidene-, monohydrochloride; Iopidine



[73218-79-8] $C_9H_{10}Cl_2N_4 \cdot HCl$ (281.57)

Preparation—US Pat 4,517,199.

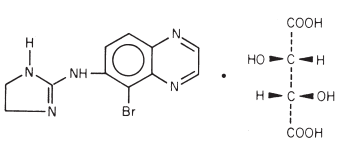
Description—White to off-white powder.

Solubility—1 g in 34 mL water, 74 mL ethanol, 13 mL methanol; practically insoluble in chloroform or nonpolar organic solvents, pH of a 1% soln is about 5.5.

Comments—Used to prevent increases in intraocular pressure following eye surgery including argon laser trabeculoplasty, iridotomy, capsulotomy, and cataract surgery. Its usefulness in the long-term management of glaucoma is limited by the development of tachyphylaxis and ocular allergy.

BRIMONIDINE TARTRATE

Quinoxalinamine, 5-bromo-*N*-(4,5-dihydro-1*H*-imidazol-2-yl)-, [*S*-(*R,*R**)-2,3-dihydroxybutanedioate salt (1:1); Alphagan**



[79570-19-7]) $C_{11}H_{10}BrN_5 \cdot C_4H_6O_6$ (442.23)

Preparation—See Ger 2,538,620 (1976).

Description—Yellow crystals melting about 207°.

Comments—The first selective α_2 agonist approved for long-term use in the treatment of open-angle glaucoma or ocular hypertension. It also is indicated for use in the prevention of increased intraocular pressure in patients undergoing argon laser trabeculoplasty. It is applied topically to the eye and has a peak effect 2 hr after instillation and a duration of action up to 12 hr. It is effective in the long-term management of patients with glaucoma who cannot tolerate a β-blocker or as add-on therapy. Although it has 1000-fold greater selectivity for α_2 over α_1 receptors, mydriasis, vasoconstriction, and eyelid retraction can occur because of α_1 stimulation. Adverse side effects are minimal and include dry mouth, eye redness or stinging (25%), and allergic reactions (10%). The effectiveness of brimonidine in decreasing intraocular pressure may decrease over time in some patients. Brimonidine is contraindicated in patients taking *monoamine oxidase inhibitors* (MAOIs).

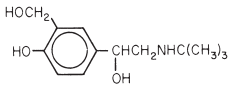
β AGONISTS

The localization of β-receptors to the smooth muscle of the trachea and bronchi, as well as to uterine smooth muscle, underlies most of the clinical utility of the β agonists. Since the β receptors located on the smooth muscle in those effector organs are of the β_2 subtype, efforts have been focused on developing β_2-selective agonists. β agonists are used in the treatment of reversible obstructive pulmonary diseases such as asthma, emphysema, and bronchitis because they produce bronchodilation, inhibit the release of inflammatory mediators from mast cells, and increase ciliary motility. Their ability to cause relaxation of the uterine smooth muscle underlies their usefulness in the prevention of preterm labor and delivery. β_2 agonists also have been used to treat peripheral vascular disease, particularly intermittent claudication and thrombophlebitis, which has a predominate vasospastic component and occurs in vascular beds that contain β_2 receptors (eg, skeletal muscle). β agonists also are of some use in the emergency management of heart block, bradycardia, and torsades de pointes.

Selective β_2 receptor agonists have less tendency to produce cardiac stimulation than do nonselective β agonists that stimulate β_1 receptors in cardiac muscle. Thus, the incidence of adverse cardiac side effects such as tachycardia and more serious arrhythmias is lower, but not absent, in selective β_2 agonists. Patients with underlying cardiovascular disease and those on MAO inhibitors or tricyclic antidepressants are at greater risk for such cardiovascular side effects. β_1 agonists are therefore contraindicated in patients with *heart disease* or *cardiac arrhythmias*. They also are contraindicated in patients with *thyrotoxicosis,* as the heart in such patients is sensitized to the stimulatory effects of β receptor activation. β_2 receptor agonists also can precipitate tachycardia and arrhythmias because they can decrease blood pressure (by vasodilation), leading to reflex tachycardia. Consequently, they should be used with caution in patients with underlying cardiovascular disease as well. Other potential side effects of β agonists include skeletal muscle tremor (β_2), although tolerance to this effect usually develops; decreased arterial O_2 tension (β_1 and β_2); feelings of restlessness, anxiety, or apprehension; decreased plasma K^+ concentrations (β_2); and increased plasma glucose (β_2) and free fatty acid ($\beta_{1/3}$) concentrations. The decreased plasma K^+ concentration may be problematic for cardiac patients, especially those taking cardiac glycosides and diuretics, and the hyperglycemia may necessitate dietary or insulin changes in diabetic patients. All side effects are less likely when β agonists are administered by inhalation.

ALBUTEROL

1,3-Benzenedimethanol, α^1-[[(dimethylethyl)amino]methyl]-4-hydroxy-, Proventil; Ventolin



α[1]-[(*tert*-Butylamino)methyl]-4-hydroxy-*m*-xylene-α,α-diol, [18559-94-9] $C_{13}H_{21}NO_3$ (239.31).

Preparation—*J Med Chem* 1970; 13:674.

Description—Off-white to white, crystalline powder; odorless; slightly bitter taste.

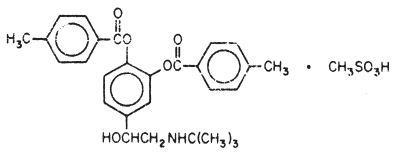
Solubility—1 g dissolves in 4 mL of water; slightly soluble in alcohol, chloroform or ether.

Comments—The prototypic β_2 selective agonist and the most widely used in the treatment of asthma and other forms of reversible obstructive pulmonary disease. It has weak β_1 agonist activity. It is administered via oral inhalation through a metered-dose inhaler or nebulizer (albuterol sulfate) or orally as a syrup or tablet (albuterol sulfate). Albuterol is the only metered-dose inhaler currently FDA approved for use in children age 4 yr and above. It often is administered nebulized in the emergency room for the treatment of acute exacerbations of asthma.

Although the oral administration of albuterol and other β_2 agonists has been used in the past to provide a more prolonged duration of action, this approach is being supplanted by the use of β_2 agonists that have long durations of action when administered by inhalation, as administration via inhalation decreases the incidence of systemic side effects.

BITOLTEROL MESYLATE

Benzoic acid, 4-methyl-, 4-[2-[(1,1-dimethylethyl)amino]-1-hydroxyethyl]-1,2-phenylene ester, methanesulfonate (salt); Tornalate



[30392-41]-7] $C_{28}H_{31}NO_5 \cdot CH_4O_3S$ (557.66)

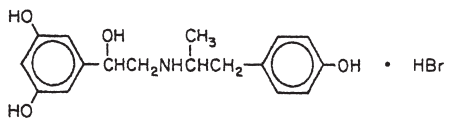
Preparation—*J Med Chem* 1976; 19:834.

Description—Crystalline solid melting about 171°.

Comments.—A prodrug converted to colterol; a β_2-selective agonist. It is used as a bronchodilator with a long duration of action (5 to 8 hr).

FENOTEROL HYDROBROMIDE

1,3-benzenediol, 5-[1-hydroxy-2-[[2-(4-hydroxyphenyl)-1-methylethyl]amino]ethyl]-, hydrobromide salt; Berotec



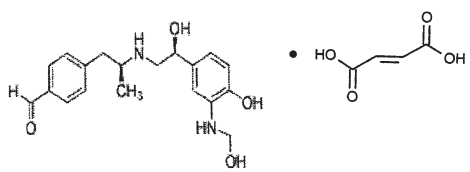
[13392-18-2] (base) [1944-12-3] (HBr) $C_{17}H_{21}NO_4$.HBr (397.26).

Preparation—3,5-Diacetoxyphenacyl bromide and 1-(*p*-methoxybenzyl)-2-propanamine react to form the fenoterol nucleus, wherein the three phenolic groups remain protected. Hydrolysis with acid removes the acetyl groups and demethylation of the methoxy group is accomplished with refluxing HBr to yield the product. US Pat 3,341,593 (1962).

Description—Crystals from methanol/ether melting about 222°.

FORMOTEROL FUMARATE

Formanilide, (±)-2'-hydroxy-5'-[(R*)-1-hydroxy-2-[[(R*)-p-meth-oxy-α-methylphenethyl]amino]ethyl]-, fumarate (2:1) salt; Foradil



[43229-80-7] $(C_{19}H_{24}N_2O_4)_2.C_4H_4O_4$ (804.88).

Preparation—*Pharm Chem Bull* 1977; 25: 1368 and US Pat 3,994,974.

Description—Crystals from 95% isopropyl alcohol melting about 139o; pK_{a1} 7.9, pK_{a2} 9.2; log P (octanol/water) 0.4 (pH 7.4).

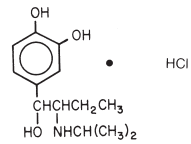
Solubility—Readily soluble in water at physiological pH.

Comments—Formoterol fumarate is a long-acting selective beta$_2$-adrenergic receptor agonist (beta$_2$-agonist). Inhaled formoterol fumarate acts locally in the lung as a bronchodilator. In vitro studies have shown that formoteral has more than 200-fold greater agonist activity at beta$_2$-receptors than at beta$_1$-receptors. Although beta$_2$-receptors are the predominant adrenergic receptors in bronchial smooth muscle and beta$_1$-receptors are the predominant receptors in the heart, there are also beta$_2$-receptors in the human heart comprising 10% to 50% of the total beta-adrenergic receptors. The precise function of these receptors has not been established, but they raise the possibility that even highly selective beta$_2$-receptors may have cardiac effects.

The pharmacologic effects of beta$_2$-adrenoceptor agonist drugs, including formoterol, are at least in part attributable to stimulation of intracellular adenyl cyclase, the enzyme that catalyzes the conversion of adenosine triphosphate (ATP) to cyclic 3', 5'-adenosine monophosphate (cyclic AMP). Increased cyclic AMP levels cause relaxation of bronchial smooth muscle and inhibition of release of mediators of immediate hypersensitivity from cells, especially from mast cells.

ISOETHARINE HYDROCHLORIDE

1,2-Benzenediol, 4-[1-hydroxy-2-[(1-methylethyl)amino]butyl]-, hydrochloride; *N*-isopropylethylnorepinephrine hydrochloride; Bronkosol; Arm-a-Med



3,4-Dihydroxy-α-[1-(isopropylamino)propyl]benzyl alcohol hydrochloride $C_{13}H_{21}NO_3 \cdot HCl$ [2576-92-3] (275.77).

Preparation—Synthesis of isoetharine and other 1-(3,4-dihydroxyphenyl)-2-monoalkyl-1-butanols, starting with 3,4-dihydroxybutyrophenone, is described in German Pat 638,650 (*CA* 1937; 31:3209[4]). The base is converted to the hydrochloride or the mesylate (below).

Description—White to off-white, crystalline solid; odorless; melts between 196° and 208° with decomposition.

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

Comments—A moderate α and β agonist used as a bronchodilator. It has a duration of action of 1 to 3 hr.

ISOETHARINE MESYLATE

1,2-Benzenediol, 4-[1-hydroxy-2-[(1-methylethyl)amino[butyl]-, methanesulfonate (salt); *N*-isopropylethylnorepinephrine methanesulfonate; Bronkometer

For the formula of isoetharine base, see *Isoetharine Hydrochloride.* 3,4-Dihydroxy-α-[1-(isopropylamino)propyl]benzyl alcohol methanesulfonate [7279-75-6] $C_{13}H_{21}NO_3 \cdot CH_4O_3S$ (335.41).

Preparation—See *Isoetharine Hydrochloride.*

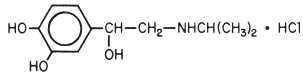
Description—White to off-white, crystalline solid; odorless; slightly bitter, salty taste; melts about 165°.

Solubility—Freely soluble in water; soluble in alcohol; very slightly soluble in ether.

Comments—See *Isoetharine Hydrochloride*.

ISOPROTERENOL HYDROCHLORIDE

1,2-Benzenediol, 4-[1-hydroxy-2-[(1-methylethyl)amino]ethyl]-, hydrochloride; Isopropylarterenol Hydrochloride



3,4-Dihydroxy-α-[(isopropylamino)methyl]benzyl alcohol hydrochloride [51-30-9] $C_{11}H_{17}NO_3 \cdot HCl$ (247.72).

Preparation—By the synthetic procedure given for *Epinephrine* (page 1311), using isopropylamine in place of methylamine; the base is then converted to the hydrochloride without resolution.

Description—White to nearly white, odorless, crystalline powder, with a slightly bitter taste; gradually darkens on exposure to air and light; solutions become pink to brownish pink on standing exposed to air, and almost immediately so when rendered alkaline; pH (1% aqueous solution) about 5; melting range between 165° and 170°.

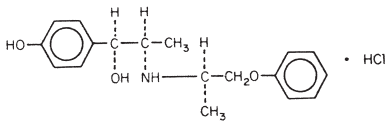
Solubility—1 g in 3 mL water or 50 mL alcohol; less soluble in dehydrated alcohol; insoluble in chloroform or ether.

Comments—A prototypic, nonselective β agonist used to stimulate heat rate in bradycardia, heart block, or *torsades de pointes*. Its use in

the treatment of asthma largely has been replaced by more-selective agents.

ISOXSUPRINE HYDROCHLORIDE

Benzenemethanol, 4-hydroxy-α-[1-[(1-methyl-2-phenoxyethyl)-amino]ethyl]-, hydrochloride; Vasodilan



[579-56-6] $C_{18}H_{23}NO_3 \cdot HCl$ (337.85).

Preparation—Phenoxyacetone (from sodium phenoxide and chloroacetone), on reductive amination, yields 1-phenoxy-2-aminopropane (**I**). Sodium *p*-propionylphenoxide is converted to the ether with benzyl bromide, to protect the phenolic group; brominated α to the carbonyl and then condensed with **I**. The resulting secondary aminoketone is catalytically hydrogenated to remove the protective benzyl group, the carbonyl reduced to the secondary alcohol with $NaBH_4$ and the base converted to the salt. *Rec Trav Chim* 1956; 75:1215.

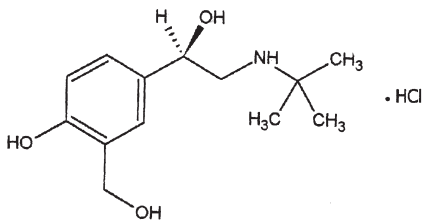
Description—White, crystalline powder; odorless; bitter taste; melts with decomposition about 200°; pH (1 in 100 solution) between 4.5 and 6.

Solubility—1 g in 500 mL water, 100 mL alcohol, >10,000 mL chloroform or >10,000 mL ether.

Comments—An α antagonist with slight β_2 activity and nonselective vasodilatory action.

LEVALBUTEROL

1,3-Benzenedimethanol, (R)-α^1-[[(1,1-dimethylethyl)amino]methyl]-4-hydroxy-, hydrochloride salt; Xopenex



[50293-90-8] $C_{13}H_{21}NO_3$.HCl (275.78).

Preparation—*J Med Chem*, 1970; 13:674.

Description—The *R*- isomer of racemic albuterol which is the effective moiety as a bronchodilator. White to off-white crystalline powder melting about 187°.

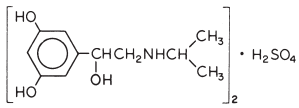
Solubility—Approx 180 mg/mL in water.

Comments—Activation of beta2-receptors on airway smooth muscle leads to the activation of adenylcyclase and to an increase in the intracellular concentration of cyclic 3', 5'-adenosine monophosphate (cyclic AMP). This increase in cyclic AMP leads to the activation of protein kinase A, which inhibits the phosphorylation of myosin and lowers intracellular ionic calcium concentrations, resulting in relaxation. Levalbuterol relaxes the smooth muscles of all airways, from the trachea to the terminal bronchioles. Levalbuterol acts as a functional antagonist to relax the airway irrespective of the spasmogen involved, thus protecting against all bronchoconstrictor challenges. Increased cyclic AMP concentrations are also associated with the inhibition of release of mediators from mast cells in the airway.

While it is recognized that beta2-adrenergic receptors are the predominant receptors on bronchial smooth muscle, data indicate that there is a population of beta2-receptors in the human heart that comprise between 10% and 50% of cardiac beta-adrenergic receptors. The precise function of these receptors has not been established. All beta-adrenergic agonist drugs can produce a significant cardiovascular effect in some patients, as measured by pulse rate, blood pressure, and/or electrocardiographic changes.

METAPROTERENOL SULFATE

1,3-Benzenediol, 5-[1-hydroxy-2-[(1-methylethyl)amino]ethyl]-, sulfate (2:1) salt; Orciprenaline Sulfate; Alupent; Metaprel



3,5-Dihydroxy-α-[(isopropylamino)methyl]benzyl alcohol sulfate (2:1) [5874-97-5] $(C_{11}H_{17}NO_3)_2 \cdot H_2SO_4$ (520.59).

Preparation—One method involves condensing 2-chloro-3',5'- dihydroxyacetophenone with isopropylamine, reducing the CO group to CHOH, and reacting the resulting metaproterenol base with H_2SO_4. US Pat 3,341,594.

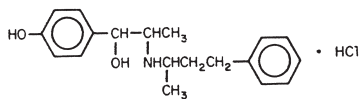
Description—White to off-white, odorless, bitter, crystalline powder; photosensitive and oxidizes in air; melts about 202°.

Solubility—Freely soluble in water or alcohol.

Comments—An orally effective β_2 agonist frequently used to treat acute exacerbations of asthma.

NYLIDRIN HYDROCHLORIDE

Benzeneethanol, 4-hydroxy-α-[1-[(1-methyl-3-phenylpropyl)amino]-ethyl]-, hydrochloride



[900-01-6; 849-55-8] $C_{19}H_{25}NO_2 \cdot HCl$ (335.87).

Preparation—By reacting *p*-hydroxynorephedrine and benzylacetone in alcohol and catalytically hydrogenating the product.

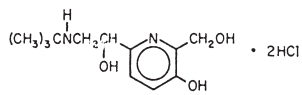
Description—White, crystalline powder; odorless; practically tasteless.

Solubility—1 g in about 65 mL water or 40 mL alcohol; very slightly soluble in chloroform or ether.

Comments—Has β_2 activity more selective for skeletal muscle. It is used to treat vascular disease of skeletal muscle with a vasospastic component.

PIRBUTEROL HYDROCHLORIDE

2,6-Pyridinedimethanol, α^6-[[(1,1-dimethylethyl)amino]methyl]-3-hydroxy-, hydrochloride; Maxair



[38029-10-6] $C_{12}H_{20}N_2O_3 \cdot 2HCl$ (313.22); [65652-44-0 (acetate)]. $C_{12}H_{20}N_2O_3 \cdot C_2H_4O_2$ (300.35); [38677-82-5(pirbuterol)].

Preparation—In a 7-step synthesis from 3-hydroxypyridine; see Ger Pat 2,105,464 (CA 77:151974h, 1972).

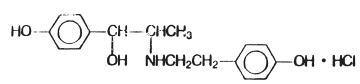
Description—(Hydrochloride) White, crystalline powder; melts with decomposition about 182°; maximum stability of aqueous solutions occurs at pH 1 to 2 (*J Pharm Sci* 1977; 66:819.)

Solubility—Soluble in water.

Comments— A β_2-selective bronchodilator.

RITODRINE HYDROCHLORIDE

Benzenemethanol, (*R*,S)-4-Hydroxy-α-[1-[[2-4-hydroxyphenyl)-ethyl]amino]ethyl]-, hydrochloride; Yutopar**



[23239-51-2] $C_{17}H_{21}NO_3 \cdot HCl$ (323.82).

Preparation—*p*-Methoxyphenethyl amine and *p*-(benzyloxy)-2-bromopropiophenone are condensed to form the corresponding secondary amine, which then successively is reduced with hydrogen in the presence of palladium, to remove the benzyl group, and HBr, to cleave the methoxyl group. Reduction of the carbonyl group, using a palladium catalyst, yields the secondary alcohol ritodrine. The base is converted to the hydrochloride in the usual fashion. US Pat 3,410,944.

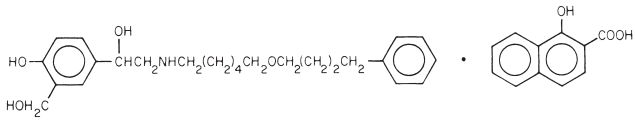
Description—White, odorless crystals melting with decomposition between 196° and 205°

Solubility—Freely soluble in water.

Comments—A beta-2 selective drug used only to suppress labor.

SALMETEROL XINAFOATE

1,3-Benzenedimethanol, (±)-4-hydroxy-α[1]-[[[6-(4-phenylbutoxy) hexyl]amino]-methyl]-, 1-hydroxy-2-naphthalenecarboxylate (salt); Serevent



[94749-08-3] $C_{25}H_{37}NO_4 \cdot C_{11}H_8O_3$ (603.76)

Preparation—See US 4,992,474 (1991). This is a longer-acting analog of albuterol (page 1309) with almost 10 times the potency, achieved by extending the nonpolar side secondary amine side-chain from 3 carbon atoms (albuterol) to 16, which includes an aromatic ring.

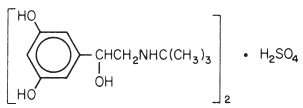
Description—White to off-white powder melting about 138°.

Solubility—Freely soluble in methanol; slightly soluble in ethanol, 2-propanol, or chloroform; sparingly soluble in water.

Comments—A more lipophilic β_2 agonist indicated for long-term *bid* maintenance treatment of asthma, it has a duration of action after inhalation of 12 hr.

TERBUTALINE SULFATE

1,3-Benzenediol, 5-[2-[(1,1-dimethylethyl)amino]-1-hydroxyethyl]-, sulfate (2:1) (salt); Brethaire, Brethine; Bricanyl



α-[(*tert*-Butylamino)methyl]-3,5-dihydroxybenzyl alcohol, sulfate (2:1) (salt) [23031-32-5] $(C_{12}H_{19}NO_3)_2 \cdot H_2SO_4$ (548.65).

Preparation—One method involves reduction of 2-(*tert*-butylamino)-3',5'-dihydroxyacetophenone (I) to the carbinol by catalytic hydrogenation, followed by neutralization of the base with H_2SO_4 (Brit Pat 1,199,630). Substance I may be prepared by various routes starting with 3,5-dihydroxybenzoic acid.

Description—White to gray-white, crystalline powder; odorless or a faint odor of acetic acid; slightly bitter; unstable in light; melts about 247°; pK_{a1} 8.8; pK_{a2} 10.1; pK_{a3} 11.2.

Solubility—1 g in 1.5 mL water or 250 mL alcohol.

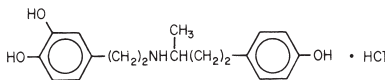
Comments—Recommended, but not labeled, for treating premature labor. It is used parenterally for the emergency treatment of status asthmaticus.

MIXED α-β AGONISTS

A number of sympathomimetics exert effects on both α and β receptors. Therefore, the effects of such agents depend on their relative affinities for the different receptors and will, to a great extent, be a weighted summation of their actions through the different receptors.

DOBUTAMINE HYDROCHLORIDE

1,2-Benzenediol, (±)-4-[2-[[3-(4-hydroxyphenyl)-1-methylpropyl]amino]ethyl]-, hydrochloride, Dobutrex



(±)-4-[2-[[3-(*p*-Hydroxyphenyl)-1-methylpropyl]amino]ethyl]pyrocatechol hydrochloride [49745-95-1] $C_{18}H_{23}NO_3 \cdot HCl$ (337.85).

Preparation—For a summary of a patented process see *CA* 80: 14721z, 1974.

Description—White to off-white powder; melts about 185°; pK_a (dobutamine) 9.4.

Solubility—Sparingly soluble in water or methanol; soluble in ethanol.

Comments—A cardioselective sympathomimetic with strong β_1 agonist properties and weaker β_2 and α agonist properties. It is unique in that its effects on the heart are to increase the force of contraction (positive inotropy) and increase atrioventricular and intraventricular conduction without significantly increasing heart rate at therapeutic doses. Higher rates of infusion, however, can elicit tachycardia. Blood pressure usually is only minimally affected, because of the combined β_2-mediated vasodilation and α-mediated vasoconstriction. It is the preferred treatment in patients with cardiac decompensation after surgery or with congestive heart failure or acute MI who have only mild-to-moderate hypotension. It increases cardiac output, decreases pulmonary artery wedge pressure, and increases urine output in such patients. It also is sometimes used to treat hypovolemic or septic shock after volume replacement, although dopamine or norepinephrine are preferred for the treatment of shock. Its half-life is 2 min, so it is given by continuous IV infusion.

INDIRECT AGONISTS

A number of sympathomimetics derive activity from their ability to promote the release of norepinephrine from the terminals of sympathetic postganglionic neurons or to block the reuptake of norepinephrine and epinephrine into the sympathetic nerve terminals. Since reuptake is the primary means of terminating the action of the catecholamines, blockade of reuptake will result in an increase in the intensity and/or duration of the response to catecholamines released by sympathetic nerves or the adrenal medulla. Although these compounds predominately increase the release/concentration of norepinephrine, the levels achieved often exceed those seen with normal activation of postganglionic neuron stimulation. Therefore, the effects of these drugs, although mediated by norepinephrine, may include more β_2 receptor activation than is normally observed. In addition, the effects of some indirect-acting agonists may be greater in particular effector organs, thereby restricting the types of effects that may be observed.

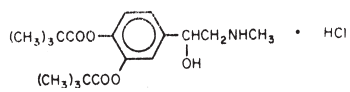
COCAINE HYDROCHLORIDE

For the full monograph see Chapter 79.

Comments—Cocaine blocks the reuptake of released norepinephrine into the nerve terminal, thereby increasing its concentration and duration of action. It is recognized most widely for its abuse potential, its abuse being related to its ability to increase extraneuronal levels of catecholamines in the CNS. However, as a sympathomimetic it often is used to produce local hemeostasis and anesthesia during surgery, especially of the eye, nose, ear, rectum, and vagina. Whereas the vasoconstriction produced by cocaine is related to the activity of the norepinephrine at α_1 receptors, the anesthetic properties are unrelated to its ability to block the reuptake of norepinephrine. Many of the adverse effects of cocaine administration, such as tachycardia and hypertension, are secondary to enhanced sympathetic nervous system activity.

DIPIVEFRIN HYDROCHLORIDE

Propanoic Acid, (±)-2,2-dimethyl-, 4-[1-hydroxy-2-(methylamino)-ethyl]-1,2-phenylene ester, hydrochloride; Propine



[64019-93-8] $C_{19}H_{29}NO_5 \cdot HCl$ (387.90).

Preparation—By esterification of epinephrine under mildly basic conditions, with pivaloyl chloride (trimethylacetyl chloride); US Pat 4,085,270.

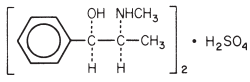
Description—White crystals melting about 158°.

Solubility—Soluble in water or alcohol.

Comments—A prodrug converted to epinephrine, used topically for open-angle glaucoma.

EPHEDRINE SULFATE

Benzenemethanol, [*R*-(*R,*S**)]-α-[1-(methylamino)ethyl]-, sulfate (2:1) (salt)**



(−)-Ephedrine sulfate (2:1) (salt) [134-72-5] $(C_{10}H_{15}NO)_2 \cdot H_2SO_4$ (428.54).

Preparation—First obtained by Nagai in 1887 from a Chinese herb, *ma huang,* ephedrine is related structurally to epinephrine. Ephedrine may be obtained by alkalinizing powdered *ma huang* with milk of lime or sodium carbonate solution, and extracting the base with alcohol or benzene. It is now, however, almost exclusively produced by synthetic methods. The most economic process (Neuberg) for synthetic production commences with fermentation of a mixture of benzaldehyde and molasses to form the ketoalcohol, $C_6H_5CH(OH)COCH_3$, which is hydrogenated in a methylamine solution. The keto group is thereby reduced to—CHOH—, which condenses with the methylamine.

Description—Fine, white, odorless crystals or a powder; affected by light; aqueous solution practically neutral to litmus; rotation −30.5° to −32.5°.

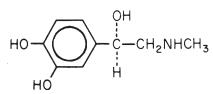
Solubility—1 g in about 1.3 mL water or about 90 mL alcohol; insoluble in ether.

Incompatibilities—See *Ephedrine Hydrochloride.*

Comments—Acts as a direct and indirect agonist (ie, releases norepinephrine). It has CNS stimulatory actions and is used mainly in OTC cold, allergy, and asthma remedies.

EPINEPHRINE

1,2-Benzenediol, (*R*)-4-[1-hydroxy-2-(methylamino)ethyl], Adrenaline; Suprarenalin; Nephridine; Adrenalin



(−)-3,4-Dihydroxy-α-[(methylamino)methyl]benzyl alcohol [51-43-4] $C_9H_{13}NO_3$ (183.21).

Preparation—By several processes; one of these starts with catechol (1,2-dihydroxybenzene), which is converted successively to (chloroacetyl)catechol with chloroacetyl chloride, then to (methylaminoacetyl)-catechol with methylamine, and to racemic epinephrine by hydrogenation. The racemic form is resolved with D-tartaric acid.

Description—White to nearly white, microcrystalline, odorless powder, gradually darkening on exposure to light and air; conbines with acids, forming salts that are readily soluble in water, and from these solutions the base may be precipitated by ammonia water or by alkali carbonates; solutions are alkaline to litmus; pK_a (apparent) 5.5.

Solubility—Very slightly soluble in water or alcohol; insoluble in ether, chloroform, or fixed or volatile oils.

Incompatibilities—Solutions usually are prepared with the aid of HCl, and an acid reaction is essential to the stability of such solutions not only because of possible precipitation but also because of the possibility of rapid oxidation to inert products. Oxidation generally is evidenced by development of a pink to brown color. Air, light, heat, and alkalies promote deterioration. Solutions buffered to a pH of 4.2 and containing a suitable antioxidant such as 0.1% sodium metabisulfite are stable for prolonged periods of time if protected from light, heat, and undue exposure to air. *Metals,* notable *copper, iron* and *zinc,* destroy its activity.

Comments—The major endogenous catecholamine released from the adrenal medulla in response to sympathetic nervous system activation. It acts on all α and β receptors, although the affinity of β receptors for epinephrine is higher than the affinity of α receptors for epinephrine. Consequently, with low doses and slow rates of infusion, epinephrine can decrease diastolic blood pressure because of β_2 receptor–mediated vasodilation and increase heart rate through activation of β_1 receptors. Systolic blood pressure may be increased because of increased cardiac output. With increasing doses, α_1-mediated vasoconstriction rapidly appears, with a resultant net increase in vascular resistance and blood pressure. It is the treatment of choice for severe allergic reactions such as anaphylactic shock and angioneurotic edema. It also is the treatment of choice for the parenteral management of severe acute asthma attacks. In advanced life-support settings, it is used in the restoration of cardiac function in patients with cardiac arrest, as it is of benefit in restoring electrical activity in patients with asystole and in enhancing the effects of defibrillation. It often is combined with a local anesthetic to reduce blood flow to the region, thereby retarding absorption of the anesthetic and prolonging its duration of action. In the past it also has been used for the treatment of open-angle glaucoma, for preventing preterm labor, as a mydriatic, and as a decongestant. However, its use for these conditions has been largely supplanted by other, more selective compounds.

It may cause severe cardiovascular side effects due to excessive α and β receptor stimulation. Its use is contraindicated in patients taking β-*blockers,* as the unopposed stimulation of α receptors can precipitate a hypertensive crisis. It should be used with caution (as should all catecholamines) in patients receiving *halogenated hydrocarbon anesthetics* that sensitize the heart to the stimulatory effects of catecholamines, as well as in patients with *cardiovascular disease, hypertension, diabetes,* or *hyperthyroidism*. It should be administered cautiously to patients on *tricyclic antidepressants,* as it is cleared from the bloodstream by the high-affinity transporter that is blocked by tricyclic antidepressants.

EPINEPHRINE BITARTRATE

1,2-Benzenediol, (*R*)-4-[1-hydroxy-2-(methylamino)ethyl]-, [*R*-(*R*,R*)]-2,3-dihydroxybutanedioate (1:1) (salt); Adrenaline Bitartrate BP

(−) 3,4-Dihydroxy-α-[(methylamino)methyl]benzyl alcohol (+)-tartrate (1:1) salt [51-42-3] $C_9H_{13}NO_3 \cdot C_4H_6O_6$ (333.29). For the structure of the base, see *Epinephrine.*

Preparation—By reacting epinephrine with an equimolar portion of tartaric acid and precipitating by the addition of alcohol.

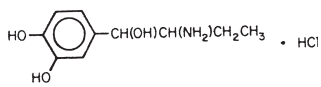
Description—White, grayish white, or light brownish gray crystalline powder; odorless; slowly darkens on exposure to air and light; melting range 147° to 152° with decomposition; pH (1% solution) 3.5.

Solubility—1 g in about 3 mL water or about 500 mL alcohol; practically insoluble in chloroform or ether.

Comments—see *Epinephrine*.

ETHYLNOREPINEPHRINE HYDROCHLORIDE

1,2-Benzenediol, 4-(2-amino-1-hydroxybutyl)-, hydrochloride; Bronkephrine



[3198-07-0] $C_{10}H_{15}NO_3 \cdot HCl$ (233.70).

Preparation—By the procedure for *norepinephrine* (this page), using ethyl amine in place of methyl amine.

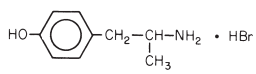
Description—Crystalline substance; decomposes about 200°. Darkens on exposure to light.

Solubility—Soluble in water.

Comments—An α, β_1, and β_2 agonist used as a bronchodilator.

HYDROXYAMPHETAMINE HYDROBROMIDE

Phenol, 4-(2-aminopropyl)-, hydrobromide; Paredrine



(±)-*p*-(2-Aminopropyl)phenol hydrobromide [306-21-8] C_9H_{13}-NO · HBr (232.12).

Preparation—Among other methods, by reducing *p*-methoxybenzyl methyl ketoxime followed by hydrolysis of the methoxy group with mineral acids. The free base then may be liberated with alkali and, after extraction, be converted into the salt by treatment with hydrobromic acid.

Description—White, crystalline powder; solutions are slightly acid to litmus, having a pH of about 5; melting range 180° to 192°.

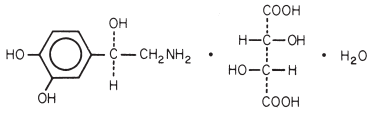
Solubility—1 g in about 1 mL water or about 2.5 mL alcohol; slightly soluble in chloroform; insoluble in ether.

Comments—Used topically as a mydriatic and vasoconstrictor in the eye. It has much less ability to penetrate the blood-brain barrier and, therefore, has fewer CNS side effects than other amphetamines. In addition, it does not cause vasoconstriction when injected intradermally and has minimal effects on the bronchioles and gastrointestinal (GI) system.

Most other indirect agonists, such as the amphetamines, methylphenidate, and pemoline, are useful for their CNS effects, as opposed to their sympathomimetic effects. The CNS effects are covered in Chapter 85. However, the peripheral side effects of these agents are largely predictable and interpretable in light of their ability to increase norepinephrine release in the sympathetic nervous system.

NOREPINEPHRINE BITARTRATE

1,2-Benzenediol, 4-(2-amino-1-hydroxyethyl)-, (*R*)-[*R*-(*R,*R**)]-2,3-dihydroxybutanedioate (1:1) (salt), monohydrate; Levarterenol Bitartrate; Noradrenaline Acid Tartrate; Levophed Bitartrate**



(−)-α-(Aminomethyl)-3,4-dihydroxybenzyl alcohol tartrate (1:1) (salt) monohydrate [69815-49-2] $C_8H_{11}NO_3 \cdot C_4H_6O_6 \cdot H_2O$ (337.28); *anhydrous* [51-40-1] (319.27).

Preparation—By the synthetic procedure given for *Epinephrine* (page 1311), using ammonia in place of methylamine; the base is then converted to the bitartrate and resolved.

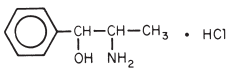
Description—White or faintly gray, crystalline powder; odorless; slowly darkens on exposure to air and light; solutions are acid to litmus, with a pH of about 3.5; melts, without previous drying, between 98° and 104° to form a turbid melt.

Solubility—1 g in about 2.5 mL water or about 300 mL alcohol; practically insoluble in chloroform or ether.

Comments—An α and β_1 agonist with relatively low affinity for β_2. It is an endogenous transmitter at sympathetic nerve terminals. Its main use is in treating shock after volume restoration.

PHENYLPROPANOLAMINE HYDROCHLORIDE

(±)-Benzenemethanol, (*R,*S**)-α-(1-aminoethyl)-, hydrochloride**



(±)-Norephedrine hydrochloride [154-41-6] $C_9H_{13}NO \cdot HCl$ (187.67).

Preparation—By reacting benzaldehyde with nitroethane to form α-(1-nitroethyl)benzyl alcohol and then reducing this nitroalcohol to the corresponding amino compound, which is then converted to the hydrochloride. US Pat 2,151,517. For an improved industrial process, see US Pat 3,028,429.

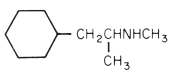
Description—White, crystalline powder with a slight aromatic odor; affected by light; melts between 191° and 196°; pH (3 in 100 solution) between 4.2 and 5.5; pK_{a1} (0.10) 9.04; pK_{a2} (0.005) 9.06.

Solubility—1 g in 1.1 mL water, 7.4 mL alcohol or 4100 mL chloroform; insoluble in ether.

Comments—A nasopharyngeal and bronchial decongestant. It also is used to treat urinary incontinence and retrograde ejaculation.

PROPYLHEXEDRINE

Cyclohexaneethanamine, (±)-*N*,α-dimethyl-, Benzedrex; Dristan



(±)-*N*-α-Dimethylcyclohexaneethylamine [101-40-6] $C_{10}H_{21}N$ (155.28).

Preparation—As described in US Pat 2,454,746, a solution of cyclohexylacetone in formic acid is reacted with *N*-methylformamide by heating for 4 hr at 160° to 180°. The resulting formyl derivative of propylhexedrine then is hydrolyzed by refluxing with 50% H_2SO_4, and the hydrolysate is extracted with ether to remove acid-insoluble material. The aqueous solution then is rendered strongly alkaline with NaOH, and the propylhexedrine is extracted with ether and purified by distillation under reduced pressure.

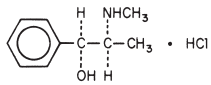
Description—Clear, colorless liquid, with a characteristic, amine-like odor; volatilizes slowly at room temperature; solutions are alkaline to litmus; absorbs CO_2 from the air; specific gravity 0.848 to 0.852; boils about 205°.

Solubility—1 g in >500 mL water, 0.4 mL alcohol, 0.2 mL chloroform, or 0.1 mL ether.

Comments—A nasal decongestant with no CNS effects.

PSEUDOEPHEDRINE HYDROCHLORIDE

Benzenemethanol, [*S*-(*R,*R**)]-α-[1-(methylamino)ethyl]-, hydrochloride; *d*-Isoephedrine Hydrochloride**



(+)-Pseudoephedrine hydrochloride [345-78-8] $C_{10}H_{15}NO \cdot HCl$ (201.70).

Preparation—(−)-Ephedrine hydrochloride is acetylated to produce (+)-*N*-acetylpseudoephedrine hydrochloride, which is then deacetylated to yield the official article. Ephedrine and pseudoephedrine are diastereoisomers, the former having the *erythro* and the latter the *threo* configuration.

Description—Fine, white to off-white crystals or powder with a faint, characteristic odor; melts between 182° and 186°; pH (1 in 20 solution) between 4.6 and 6.

Solubility—1 g in 0.5 mL water, 3.6 mL alcohol, 91 mL chloroform, or 7000 mL ether.

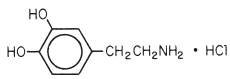
Comments—A nasal and ocular decongestant with weaker cardiovascular and CNS effects than ephedrine.

DOPAMINE DRUGS

Dopamine and fenoldopam mesylate are the only two dopamine agonists currently used clinically for their peripheral, sympathomimetic effects.

DOPAMINE HYDROCHLORIDE

1,2-Benzenediol, 4-(2-aminoethyl)-, hydrochloride; Dopastat; Intropin



3,4-Dihydroxyphenethylamine hydrochloride [62-31-7] $C_8H_{11}NO_2 \cdot HCl$ (189.64).

Preparation—Dopamine, which is 3-hydroxytyramine, may be prepared from tyramine by successive nitration to 3-nitrotyramine, reduction to 3-aminotyramine by catalytic hydrogenation and diazotization to 3-hydroxytyramine.

Description—White, crystalline powder; decomposes about 241°; to avoid oxidation of the hydrochloride injection, the air in containers is replaced with nitrogen; yellow or brown discoloration of solutions indicates decomposition of the drug, and such solutions should not be used.

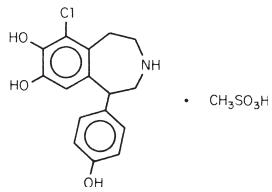
Solubility—Freely soluble in water; soluble in alcohol; practically insoluble in chloroform or ether.

Comments. Acts on dopamine and α and β receptors to exert its sympathomimetic effects. Its affinity for the different receptor classes is dopamine > β > α. It increases heart rate and contractility and, therefore, cardiac output by stimulating β receptors in the heart. Dopamine activation of α receptors produces vasoconstriction, whereas its D1 dopamine receptors in renal, splanchnic, coronary, and cerebral vascular beds produce vasodilation. Theoretically then, dopamine increases blood pressure while maintaining perfusion of these vital organs. Although this characteristic of dopamine has been cited as a rationale for its preferred use in the treatment of shock, the extent to which it is therapeutically superior to other vasoconstrictors, such as norepinephrine, remains controversial. Stimulation of D1 dopamine receptors in the kidney inhibits the reabsorption of sodium and water, resulting in natriuresis and diuresis. Because of these properties, dopamine is used in the treatment of heart failure associated with cardiac decompensation after heart surgery, congestive heart failure, or MI when there is significant hypotension (ie, cardiogenic shock). Dopamine also is used in the treatment of septic shock and other types of shock to restore blood pressure after volume replacement.

The side effects associated with administration are related to excessive β-mediated stimulation of the heart and α-mediated vasoconstriction. It is contraindicated in patients with *pheochromocytomas,* in patients with *uncorrected tachyarrhythmias* or *ventricular fibrillation,* and in patients on *MAO inhibitors* or *tricyclic antidepressants*.

FENOLDAPAM MESYLATE

1*H*-3-Benzazepine-7,8-diol, 6-chloro-2,3,4,5-tetrahydro-1-(4-hydroxyphenyl)-, methanesulfonate (salt); Corlopam



[67277-57-0] $C_{16}H_{16}ClNO_3 \cdot CH_4O_3S$ (401.86)

Preparation—Reduction of 3,4-dimethoxyphenylacetonitrile affords the corresponding amine, which is treated with 2-(4-methoxyphenyl)oxirane, opening the ethylene oxide ring through nucleophilic attack to form 2-[2-(3,4-dimethoxyphenylethylamino)]-1(4-methoxyphenyl)ethanol. With strong acid this latter compound yields the trimethoxylated benzazepine ring structure; this is demethylated with BBr_3 to the trihydroxy derivative, oxidized to the orthoquinone, and treated with 9*N* HCl to form the basic product.

Description—Melts about 274° with decomposition.

Comments—A selective D1 agonist used for the IV management of severe malignant hypertension in a hospital setting.

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