THE DISPENSATORY OF THE UNITED STATES OF AMERICA

1960 Edition

NEW DRUG DEVELOPMENTS VOLUME

ARTHUR OSOL, PH.G., B.S., M.S., PH.D.

PROFESSOR OF CHEMISTRY AND DEAN OF SCIENCE, PHILADELPHIA COLLEGE OF PHARMACY AND SCIENCE; MEMBER OF THE EXECUTIVE COMMITTEE OF THE COMMITTEE OF REVISION OF THE UNITED STATES PHARMACOPEIA

ROBERTSON PRATT, A.B., PH.D.

PROFESSOR OF PHARMACOGNOSY AND ANTIBIOTICS, UNIVERSITY OF CALIFORNIA SCHOOL OF PHARMACY

With

KARL H. BEYER, JR., B.S., M.D., PH.D.

VICE PRESIDENT, MERCK SHARP & DOHME, RESEARCH LABORATORIES; LECTURER IN PHARMACOLOGY, GRADUATE SCHOOL OF MEDICINE, UNIVERSITY OF PENNSYLVANIA, AND TEMPLE UNIVERSITY SCHOOL OF MEDICINE

GEORGE E. FARRAR, JR., B.S., M.D., F.A.C.P.

MEDICAL DIRECTOR, WYETH LABORATORIES; ASSOCIATE PROFESSOR OF MEDICINE, TEMPLE UNIVERSITY SCHOOL OF MEDICINE AND HOSPITAL

G. VICTOR ROSSI, B.S., M.S., PH.D.

DIRECTOR OF THE LA WALL MEMORIAL LABORATORY OF PHARMACOLOGY AND BIOCHEMISTRY, AND ASSOCIATE PROFESSOR OF PHARMACOLOGY, PHILADELPHIA COLLEGE OF PHARMACY AND SCIENCE

HEBER W. YOUNGKEN, PH.M., PH.D., SC.D.

RESEARCH PROFESSOR OF PHARMACOGNOSY AND BOTANY, MASSACHUSETTS COLLEGE OF PHARMACY; MEMBER OF THE EXECUTIVE COMMITTEE OF THE COMMITTEE OF REVISION OF THE UNITED STATES PHARMACOPEIA

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PREFACE TO VOLUME TWO

In recent years between 40 and 50 new medicinal agents, exclusive of their many dosage forms, have been introduced annually. Thus, since the 25th Edition of THE DISPENSATORY was published, nearly 5 years ago, somewhat more than 200 new drugs have come into use.

One purpose of this NEW DRUG DEVELOPMENTS VOLUME, which constitutes Volume 2 of U.S.D. 25, is to provide information about these new therapeutic substances.

Another is to give new information about certain drugs already described in the main volume of U.S.D. 25.

A third purpose is to provide general survey articles on certain categories of medicinals—such as Antibiotics, Antibiotics with Antitumor Activity, Hypoglycemic Sulfonylureas and Biguanides, Psychotherapeutic and Psychotomimetic Drugs, and Saluretic Agents. Altogether, 209 completely new monographs are included in this book. Either in this volume or in the 1955 edition of U.S.D. 25, all the therapeutic agents of U.S.P. XVI, N.F. XI, B.P. 1958, and the International Pharmacopoeia, including the First Edition Supplement, are discussed. This NEW DRUG DEVELOPMENTS VOLUME is, therefore, a companion book to U.S.D. 25 and extends its usefulness over the interim between complete revisions of THE DISPENSATORY.

In preparing this volume the editors have been mindful of the increasing need, by the large majority of users of THE DISPENSATORY, for information about actions, uses, doses, and side effects of drugs. Accordingly, greater emphasis has been placed on supplying pharmacologic and clinical data, and less on standards and tests. The factual substance of this work was selected from over 25,000 issues of more than 400 periodicals reviewed during the past 5 years.

Today no nation has a monopoly in developing medicinals, as is clearly evident when the national origins of the therapeutic agents of world-wide usage are identified. To be well informed about new drug developments the services of an international editorial board are now needed to gather all the information that must be reviewed in preparing a work such as THE DISPENSATORY. This need has been met by the appointment of a group of international editorial correspondents, whose names appear in this volume.

The help of many contributors has been necessary in preparing this volume; to all who participated, grateful appreciation is extended. Mrs. Eleanor E. Buckley, Staff Writer of the Medical Department of Wyeth Laboratories, made a number of editorial contributions to this work. Dr. Alfonso R. Gennaro, Associate Professor of Chemistry at the Philadelphia College of Pharmacy and Science, helped materially in obtaining chemical data, and Mrs. Elizabeth W. Johnson, Librarian at the same college, maintained the extensive literature files for THE DISPENSATORY. As so many times before, Dr. Walter Kahoe, Director of the Medical Department of J. B. Lippincott Company, ably guided the editorial undertaking from its manuscript stage through to the production of the printed book.

ARTHUR OSOL
Editor-in-Chief

NEW GENERIC NAMES FOR DRUGS DESCRIBED IN VOLUME 1, U.S.D. 25 (1955)

New Generic Name	Name in U.S.D. 25 (page)
Acetaminophen	Acetyl-*p*-aminophenol (1524)
Aminometradine	Aminometramide (1545)
Aminotrate Phosphate	Triethanolamine Trinitrate Fiphosphate (1907)
Azacyclonol Hydrochloride	Frenquel (1808)
Busulfan	Myleran (1760)
Dimethicone	Silicote (1849)
Diphenadione	Dipaxin (1571)
Dyphylline	Dihydroxypropyl Theophylline (1898)
Glucosulfone Sodium	Promin (1882)
Glucurolactone	Glucuronic Acid Lactone (1706)
Heptabarbital	Medomin (1597)
Iophenoxic Acid	Triiodoethionic Acid (1908)
Methscopolamine Bromide	Scopolamine Methobromide (1223)
Noscapine	Narcotine (928-9)
Oxtriphylline	Theophylline Cholinate (1898)
Parethoxycaine Hydrochloride	Diethoxin Hydrochloride (1741)
Phenoxybenzamine Hydrochloride	Dibenzyline Hydrochloride (1531)
Phensuximide	Milontin (1853)
Pipenzolate Methylbromide	Piptal (1790)
Piperidolate Hydrochloride	Dactil (1788)
Sulfamethizole	Sulfamethylthiadiazole (1881)
Sulfisomidine	Sulfadimetine (1881)
Thiazolsulfone	Promizole (1883)

THE DISPENSATORY OF THE UNITED STATES OF AMERICA *1960 Edition*

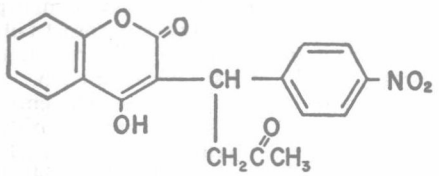
VOLUME TWO

In which are described new drugs, official as well as nonofficial, introduced during the period of 1955-60; also certain drugs for which important new data have recently become available.

New Drug Developments Volume—1960
The listing is alphabetical. A complete Index to this volume will be found on pages 237 to 240

ACENOCOUMAROL. N.N.D.

3-(α-Acetonyl-4-nitrobenzyl)-4-hydroxycoumarin; G 23350; Sintrom (Geigy)



Acenocoumarol, chemically related to bishydroxycoumarin, cyclocumarol, ethyl biscoumacetate, and warfarin (see articles describing these anticoagulants in *U.S.D. 25*), was first synthesized by Stoll and Litvan (*Thrombosis and Embolism,* Proceedings of the First International Conference, Basel, 1954, published by Benno Schwabe & Co., 1955, p. 244; see U.S. Patent 2,648,682 (1953)). Among anticoagulants it is unique in having a nitro group, on the phenyl ring.

Description.—Acenocoumarol is a white, crystalline powder, practically tasteless and odorless; it is slightly soluble in water, the solubility increasing with pH through formation of water-soluble salts of the weak acid. It melts between 191° and 192°.

Actions.—Acenoucoumarol is the most potent of the anticoagulants of the substituted coumarin series; it is about 12 times more active than bishydroxycoumarin and 40 times more potent than ethyl biscoumacetate. It disappears from the body rapidly, being excreted by the kidneys without apparent alteration; in this respect its behavior is different from that of ethyl biscoumacetate, which is metabolized to an inactive form. Acenocoumarol is an anticoagulant of intermediate range, acting faster than bishydroxycoumarin but not quite as fast as ethyl biscoumacetate; hypoprothrombinemia can be produced in virtually all patients in 48 hours or less and sometimes a therapeutic response is observed in 24 hours (Rullo *et al., J.A.M.A.,* 1958, **168,** 743). Acenocoumarol maintains its optimal action 15 to 20 hours; recovery from the action of the drug is usually complete 48 hours after its discontinuance, but 72 hours may be required if the prothrombin time is excessively prolonged (over 40 seconds).

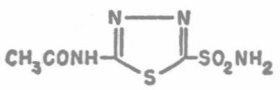
Uses.—Acenocoumarol is used for the prophylaxis and treatment of intravascular clotting, in the same manner as other coagulants (see, in *U.S.D. 25,* the general article on *Anticoagulant Drugs,* p. 1570, and also the articles on *Bishydroxycoumarin,* p. 163, and *Ethyl Biscoumacetate,* p. 553). In 100 hospitalized patients who received the drug, Rullo *et al.* (*loc. cit.*) found it to be dependable and its effects predictable; only 5 patients manifested minor bleeding episodes. No gastrointestinal intolerance was observed. An advantage of acenocoumarol is that it may be given in a single dose daily. Johnson *et al.* (*Can. Med. Assoc. J.,* 1957, **77,** 756) found some cases of "resistance" and others of "sensitiveness" to the drug, *i.e.,* lesser or greater susceptibility than normal, respectively, to the drug; they observed that acenocoumarol does not have the cumulative effect of bishydroxycoumarin, thus lowering the danger of hemorrhagic accidents. No depression of hematopoietic activity appears to occur (Alexander *et al., Ann. Int. Med.,* 1957, **100,** 558).

Dose.—The induction dose of acenocoumarol on the first day of therapy is 16 to 28 mg., followed by 8 to 16 mg. the second day. The maintenance dose is determined by the response of the individual patient, as measured by frequent prothrombin time determinations; the average dose is 2 to 10 mg. daily. Acenocoumarol is administered orally.

Dosage Form.—Scored tablets containing 4 mg. of acenocoumarol.

ACETAZOLAMIDE. U.S.P., B.P.

2-Acetamido-1,3,4-thiadiazole-5-sulfonamide; Diamox (Lederle)



Acetazolamide is described in *U.S.D. 25,* p. 1766. The following article presents the results of more recent studies of the drug, and summarizes its present status.

Acetazolamide may be synthesized from 2-amino-5-chloro-1,3,4-thiadiazole by first acetylating the amino group, then converting the 5-chloro to mercapto, afterwards oxidatively chlorinating to the sulfonyl chloride, and finally treating the resulting acid chloride with ammonia (Roblin and Clapp, *J.A.C.S.,* 1950, **72,** 4890).

Description.—Acetazolamide is a white or faintly yellowish crystalline powder; it is odorless. At 20°, 1 Gm. dissolves in about 1400 ml. of water, and in 165 ml. of alcohol; it is insoluble in chloroform and in ether. Acetazolamide melts at about 258° C.

Actions and Uses.—Acetazolamide was the first of the carbonic anhydrase inhibitors to demonstrate clinical utility. The compound was shown by Berliner and his associates (*Am. J. Med.,* 1951, **11,** 274) to be a powerful inhibitor of renal

carbonic anhydrase and to produce a marked increase in the renal elimination of potassium. Maren and his colleagues (*Trans. N. Y. Acad. Sci.*, 1952, **15,** 53; *Bull. Johns Hopkins Hosp.*, 1954, **95,** 199, 244, 277) described the basic pharmacology of this agent. Acetazolamide increases the excretion of cations, principally sodium and potassium, by inhibiting the ion exchange reaction catalyzed by carbonic anhydrase, which is responsible for the acidification of urine (Pitts and Alexander, *Am. J. Physiol.*, 1945, **144,** 239). This enzyme in the kidney hastens the formation of carbonic acid from carbon dioxide and water, thus controlling acidification of the urine. By retarding in the renal tubule the reversible reaction of $CO_2 + H_2O \leftrightharpoons H_2CO_3$, the administration of acetazolamide results in loss of bicarbonate ion which carries out sodium, potassium and water, rendering the urine alkaline and producing diuresis. Acetazolamide has found considerable use as a research tool for the production of metabolic acidosis in animals (Pitts *et al., Am. J. Physiol.*, 1958, **194,** 125). The acidosis thus produced is characterized by an initial bicarbonate loss and alkaline urine in contrast to the aciduria and hyperchloremic acidosis that follows the administration of ammonium chloride.

The diuretic effect of acetazolamide is related to the excretion of bicarbonate, and as the blood bicarbonate level falls below the renal threshold, the diuretic effect of acetazolamide diminishes and a temporary refractoriness develops in association with acidosis. Following the replenishment of body bicarbonate stores through metabolic processes in a "drug-free" period, a diuretic response may again be obtained upon administration of acetazolamide (Hanley and Platts, *J. Clin. Inv.*, 35, **20,** 1956; *J. Physiol.*, 1959, **145,** 277). For this reason, acetazolamide has found acceptance as a diuretic especially in conditions where an intermittent or short term regimen can be employed, as in premenstrual tension and edema of pregnancy (Assali *et al., J. Lab. Clin. Med.*, 1955, **46,** 733). Ammonium chloride appears to block the diuretic effect of acetazolamide (Maren, *Bull. Johns Hopkins Hosp.*, 1956, **98,** 159). Acetazolamide is distributed substantially into the erythrocytes and other tissues and some of its side effects as well as its utility in glaucoma and epilepsy may be attributable to this property.

Becker (*Am. J. Ophth.*, 1954, **37,** 13) and Grant and Trotter (*Arch. Ophth.*, 1954, **51,** 735) showed that acetazolamide was useful in reducing intraocular pressure in simple open angle glaucoma. In one series, 62 per cent of patients were controlled for periods exceeding 6 months. The high bicarbonate content of aqueous humor and the presence of carbonic anhydrase in the eye suggest that the rate of aqueous formation and hence the intraocular tension are decreased by inhibition of carbonic anhydrase (Friedenwald, *Am. J. Ophth.*, 1955, **40,** 139). Green (*Arch. Ophth.*, 1955, **53,** 478) has confirmed that acetazolamide inhibits the activity of the enzyme in the eye. However, the effect on aqueous formation may arise as a consequence of systemic acidosis (Renner and Tonks, *Brit. J. Ophth.*, 1958, **42,** 732). The clinical utility of acetazolamide in the treatment of simple glaucoma seems well established, especially as an adjunct to miotic therapy.

Clinically, acetazolamide was first employed in the management of edema associated with congestive heart failure, following the observations of Schwartz (*New Eng. J. Med.*, 1949, **240,** 173; *Ann. Int. Med.*, 1955, **42,** 79). Friedberg and Halpern (*Fed. Proc.*, 1952, **11,** 49) and Belsky (*New Eng. J. Med.*, 1953, **249,** 140) found that dosages of 250 mg. to 500 mg. were effective to control the clinical state in mild to moderate congestive heart disease. Dosage higher than that recommended does not increase the diuretic response and may produce drowsiness or mild par esthesias. In patients with congestive heart failure, acetazolamide is an adjunct to treatment with adequate rest, digitalis and sodium restriction.

Acetazolamide has been used in emphysema and chronic pulmonary fibrosis with carbon dioxide retention and dyspnea (Nadell, *J. Clin. Inv.*, 1953, **32,** 622; Heiskell *et al., J.A.M.A.*, 1954, **156,** 1059), in which condition the compound increases bicarbonate excretion and decreases liberation of carbon dioxide at the alveoli by virtue of its inhibition of the carbonic anhydrase of erythrocytes. Animal studies by Millichap *et al.* (*J. Pharmacol.*, 1955, **155,** 251) indicated that the anticonvulsant activity of acetazolamide might be accounted for by its inhibition of carbonic anhydrase in brain. The anticonvulsant activity is independent of the renal action, for it persists in nephrectomized mice (Gray *et al., J. Pharmacol.*, 1957, **121,** 160). Lombroso *et al.* (*J.A.M.A.*, 1956, **160,** 268) found that 47 of 126 epileptic patients were afforded a 90 per cent or better decrease in seizures during daily administration of acetazolamide for periods ranging from 3 months to 3 years. Janowitz has summarized (*Lancet*, 1958, **1,** 1353) experimental studies in which very large doses of acetazolamide decreased the gastric secretion of acid and the pancreatic secretion of bicarbonate in man.

Toxicology.—The nephrotropic action of acetazolamide results in an initial loss of bicarbonate, with a concomitant appreciable loss both of potassium and sodium, and a tendency toward hypokalemic acidosis. The kaliuretic effect is more pronounced than with chlorothiazide. Its use may be contraindicated in the presence of liver cirrhosis, idiopathic hyperchloremic acidosis, in patients in whom there has been serious loss of sodium or potassium or in those with Addison's disease. Upon repeated administration of clinical doses of acetazolamide, the diuretic response may diminish, especially at higher doses or on a regimen of frequent administration. The results of continued treatment of glaucomatous and epileptic patients with acetazolamide for months or years indicates that the mild metabolic acidosis that is produced does not intensify with time. When therapy is discontinued, metabolic balance is regained.

Side Effects.—Side effects include anorexia, paresthesia, tingling of limbs, muscular weakness and excessive fatigue. Pearson *et al.* (*J.A.M.A.*, 1955, **157,** 339) reported a non-fatal case of agranulocytosis. Drug sensitivity reactions may occur and are indications for its withdrawal.

Ureteral colic and renal calculus formation have been noted (Persky *et al., J.A.M.A.,* 1956, **161,** 1625). Renal calculus formation has been induced in rats (Evans and McPherson, *Brit. J. Exp. Path.,* 1957, **37,** 38) during acetazolamide administration, and has been attributed to decreased citrate excretion (Harrison, *J. Clin. Inv.,* 1955, **34,** 1622). Citrate excretion may also be decreased by acetazolamide in man (Gordon and Shepps, *New Eng. J. Med.,* 1957, **256,** 1215).

Dose.—Acetazolamide is the form of the drug administered orally; *acetazolamide sodium,* which is water-soluble, is employed when intramuscular or intravenous injections are to be made, which routes should be used only when oral administration of the drug is impractical. The usual dose of both dosage forms is the same, namely, 250 mg. daily. The usual dose range for acetazolamide is 250 to 500 mg., while for the sodium salt it is 250 to 375 mg. (all dosages are expressed in terms of acetazolamide).

For diuresis in patients with congestive heart failure, from 250 to 375 mg. may be given daily, or every other day, in the morning. For toxemia and edema of pregnancy, 250 mg. is given daily. For premenstrual tension accompanied by fluid retention, 250 mg. is given daily 6 to 10 days before the onset of menstruation. For adjunctive management of obesity the dose is 250 mg. daily. Patients being treated with drugs that cause fluid retention may be given 250 mg. of acetazolamide twice weekly. For treatment of epilepsy as much as 375 mg. to 1 Gm. daily may be required. For acute congestive and secondary glaucoma 250 mg. is given every 4 hours, as an adjunct to miotic therapy.

Dosage Forms.—Syrup containing 250 mg. in 5 ml., and tablets containing 250 mg., of acetazolamide. For preparing injections, *acetazolamide sodium* powder is available in containers of 500 mg.

Methazolamide.—Saturation of the double bond at the acetamido-substituted carbon of acetazolamide, and substitution of a methyl at the carbon atom adjacent to it, produces a derivative, methazolamide, first synthesized by Young *et al.* (*J.A.C.S.,* 1956, **78,** 4649). Methazolamide gives a much higher concentration of carbonic anhydrase inhibitor in the brain of the mouse than does an equal dose of acetazolamide (Gray *et al., J. Pharmacol.,* 1958, **124,** 149).

Like acetazolamide, methazolamide reduces intraocular pressure and is recommended for treatment of glaucoma in cases not satisfactorily controlled by acetazolamide. Methazolamide is marketed as *Neptazane* (Lederle) in tablets containing 50 mg. The effective dosage varies from 50 to 100 mg. 2 or 3 times daily. Side effects and contraindications are similar to those of acetazolamide.

ACETYL SULFISOXAZOLE. U.S.P.

N^1-Acetylsulfisoxazole; Gantrisin Acetyl (Hoffmann-LaRoche)

Acetylation of sulfisoxazole (see *U.S.D. 25,* p. 1364) at the -SO_2NH- group yields a derivative practically insoluble in water and thus especially suited for preparing a tasteless liquid dosage form of the parent sulfonamide. Acetyl sulfisoxazole is hydrolyzed in the intestinal tract and absorbed as sulfisoxazole; hence it has the actions and uses of sulfisoxazole, the only important difference being that approximately 15 per cent more of the acetyl derivative must be used to obtain the equivalent therapeutic effect of a given dose of sulfisoxazole. For uses of this drug, see *U.S.D. 25,* p. 1364, under *Sulfisoxazole.*

As acetyl sulfisoxazole suspended in an oil-in-water emulsion has been found to be absorbed to a greater extent than from an aqueous suspension (Svenson *et al., Antibiotic Medicine and Clinical Therapy,* 1956, **2,** 148), an emulsion dosage form of the sulfonamide has been made available, under the name *Lipo Gantrisin.*

Dosage Forms.—A syrup and a suspension, each containing acetyl sulfisoxazole equivalent to 100 mg. of sulfisoxazole per ml., and an emulsion containing the equivalent of 200 mg. of sulfisoxazole per ml.

ALBOMYCIN

Albomycin, another in the now large series of basic antibiotics derived from actinomycetes, was isolated in 1951 at the Institute for Antibiotic Research of the Academy of Medical Sciences of the U.S.S.R. from culture filtrates of a previously undescribed organism, *Actinomyces subtropicus* (Gause and Brazhnikova, *Nov. Med., Mosk.,* 1951, **23,** 3). A summary of later laboratory and clinical research on the new antibiotic in the Soviet Union has been published in English (Gause, *Brit. M. J.,* 1955, **2,** 1177). The antibiotic *Albomycin* should not be confused with the more familiar *Albamycin,* which is the trademark of the Upjohn Company for novobiocin.

Albomycin strongly inhibits gram-positive cocci, especially pneumococci and staphylococci, including many strains that are resistant to penicillin, erythromycin, streptomycin, and the tetracyclines. It exhibits also positive, but lesser, activity against some gram-negative organisms, including the coli-dysentery group and Friedlander's bacillus. It has been produced by the Soviet pharmaceutical industry for several years.

Chemically pure albomycin sulfate occurs as an amorphous red powder which is easily soluble in water, less soluble in methanol, and insoluble in other organic solvents. It contains 4.16 per cent iron which can be removed by acetone containing appropriate hydrohalogen acids. However, when subjected to such treatment the albomycin sulfate solution loses its bright color and its antibacterial activity is markedly reduced. Addition of a drop of 5 per cent ferric chloride restores the color and the biologic activity. It has been suggested that the iron is attached by a chelate bond to the hydroxy group of the serine moiety of the molecule.

Chromatographic studies have shown albomycin to be a cyclopolypeptide containing ornithine, serine, glutamic acid, alanine, glycine, proline, and a seventh, as yet unidentified, amino acid (Gause, *loc. cit.,* 1955) and to consist of at least four antibiotic components (Stapley and Ormond,

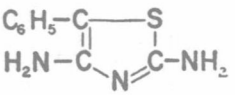
Science, 1957, **125,** 587). The molecular weight, according to Gause, probably is "not less than 1,300." Column partition chromatography led Stapley and Ormond to conclude that "albomycin and grisein are very similar chemically and are identical with respect to antimicrobial activity."

Albomycin is said to be pharmacologically "inactive" and it has been stated that "it is impossible to determine the lethal dose" for a variety of laboratory animals, even following doses of 50 million units/Kg. (Gause, *loc. cit.*). No side reactions have been reported in clinical practice. The drug may be administered subcutaneously, intravenously, intramuscularly, or intrathecally. Major use has been in treating pneumonia, meningitis, post-surgical infections caused by penicillin-resistant cocci, and septic complications of dysentery and measles.

AMIPHENAZOLE HYDROCHLORIDE

2,4-Diamino-5-phenylthiazole Hydrochloride; DAPT; Daptazole (Nicholas)

Amiphenazole base has the structure represented by:



Amiphenazole hydrochloride may be synthesized by refluxing a mixture of α-bromobenzyl cyanide and thiourea in alcohol, the resulting hydrobromide being subsequently converted to hydrochloride. For methods of synthesis see Davies *et al.* (*J. Chem. Soc.,* 1950, 3491), and Dodson and Turner (*J.A.C.S.,* 1951, **73,** 4517).

Description.—Amiphenazole hydrochloride is a white or nearly white crystalline powder. At 20°, 1 Gm. dissolves in about 16 ml. of water and in about 50 ml. of alcohol; it is slightly soluble in ether and in chloroform. Aqueous solutions are said to be stable at room temperature for 24 hours.

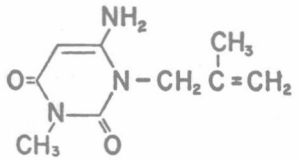
Actions and Uses.—In 1952, Shaw and Bentley, of Australia, reported that a dog completely narcotized with morphine could be restored to normal consciousness within a few minutes by an intravenous injection of amiphenazole (*Nature,* 1952, **169,** 712); it was also shown that the analgesia produced by the morphine was not affected by the amiphenazole. This observation led to the finding that by use of amiphenazole large doses of morphine (up to 200 mg. 4 times daily) could be given to patients suffering from intractable pain in terminal carcinoma without producing drowsiness or narcosis, or antagonizing the analgesic effect of morphine. Moreover, addiction did not develop, so that morphine may be withdrawn at any time without producing withdrawal symptoms. Amiphenazole has little influence on morphine-induced nausea and vomiting. References to a number of publications on the combined use of morphine and amiphenazole are given in a report by Shaw and his colleagues (*Brit. M. J.,* 1958, **2,** 366) in which the hypothesis is advanced that morphine and amiphenazole may combine, probably in the liver, to form a non-narcotic analgesic substance. With regard to mode of action, Shulman (*Nature,* 1956, **177,** 703) cites evidence that amiphenazole, which is related to the thiazole moiety of thiamine, may enter into the pathway of processes involving thiamine metabolism and that this may at least in part be responsible for the action of amiphenazole.

Although amiphenazole has been described as a respiratory stimulant, such action is generally considered to be unsatisfactory; for this reason the drug is useless as a morphine antagonist. Amiphenazole has been used in conjunction with bemegride in the treatment of barbiturate poisoning (*Brit. M. J.,* 1955, **2,** 56, 203, 912).

Dose.—The doses of amiphenazole hydrochloride given by Shaw and his associates (*loc. cit.*) have been variable, ranging from 20 to 60 mg. with each dose of morphine in early trials to as much as 200 mg. in more recent studies, the highest dose apparently being based on the unpublished observation that large doses of amiphenazole relieve mild depressive states.

AMISOMETRADINE. N.F.

6-Amino-3-methyl-1-(2-methylallyl)uracil; Rolicton (Searle)



Amisometradine is a structural isomer of *aminometradine* (*Mincard,* Merrell), originally called *aminometramide* (*Mictine*). The former compound is 1-methallyl-3-methyl-6-aminotetrahydropyrimidinedione, while the latter is 1-allyl-3-ethyl-6-aminotetrahydropyrimidinedione (see *U.S.D. 25,* p. 1545). The synthesis of amisometradine is described in the report of Papesch and Schroeder (*J. Org. Chem.,* 1951, **16,** 1879), also in U.S. Patent 2,729,669 (1956).

Description.—Amisometradine is a white, crystalline powder, odorless and with a slightly unpleasant taste. It is slightly soluble in water, freely soluble in alcohol, and insoluble in ether.

Actions and Uses.—Amisometradine is an orally administered diuretic at least as effective as aminometradine, over which it has the advantage of being considerably less toxic, especially as evidenced by the greatly reduced incidence of gastrointestinal disturbances.

Amisometradine is employed to maintain an edema-free state in patients responding to therapy with a diuretic, and also to initiate diuresis in most edematous conditions except congestive heart failure; mercurial injections may also be required to induce significant diuresis (Wener *et al., Can. Med. Assoc. J.,* 1958, **78,** 200). In a comparison of amisometradine and mersalyl and theophylline injection in the treatment of acute or severe heart failure, Jose and Wood (*Brit. M. J.,* 1958, **1,** 9) concluded that 2.4 Gm. of amisometradine had only 40 per cent of the diuretic strength of 2 ml. of the mercurial injection. Amisometradine has also been used in the

management of water and electrolyte retention during pregnancy and in the premenstrual period.

Continued use of amisometradine does not lead to a state of tolerance. Rarely does the drug produce gastrointestinal disturbance.

Dose.—The usual initial dose, orally for an adult, is 400 mg. 4 times the first day, with meals, and twice daily thereafter. In cases of mild edema, the maintenance dose may be 400 mg. or less daily. In severe cases, the daily dose may be as high as 3.2 Gm. Dosage should be governed by the severity of the edema and the response of the individual as measured by his serial weight record.

Dosage Form.—Tablets containing 400 mg. of amisometradine.

AMPHOMYCIN

In 1953 a new crystalline antibiotic was isolated from several strains of *Streptomyces* isolated from several different soils. The particular strain selected for further study in the Bristol Laboratories was found in a soil sample obtained near Syracuse, New York. The organism was named *Streptomyces canus* and, presumably because of its amphoteric properties, the antibiotic was named amphomycin (Heinemann *et al., Antibiot. Chemother.,* 1953, **3,** 1239). Cultural and morphologic characteristics of the organism, methods of isolating the antibiotic, and its microbiologic and chemical and physical properties were described in the original paper.

In vitro studies indicate inhibitory activity against gram-positive bacteria, especially cocci, but not against gram-negative species or yeasts (Heinemann *et al., loc. cit.*; Reedy and Shaffer, *Antibiotics Annual,* 1956-1957, p. 483). Subsequent *in vivo* work suggests possible usefulness of amphomycin in African sleeping sickness and some other forms of trypanosomiasis.

Chemistry.—Amphomycin is an acidic polypeptide. The isoelectric point is 3.5-3.6. It is soluble in water and lower alcohols but insoluble in nonpolar solvents. Elementary analysis of the acid indicates C, 54.4 per cent; H, 7.19 per cent; N, 14.2 per cent. Titration indicates the presence of a single free amino group.

Neutral aqueous solutions of amphomycin are stable at room temperature for at least a month. The antibiotic has a high degree of surface activity, particularly in neutral or weak to moderately acid aqueous solutions.

Action.—Amphomycin is poorly absorbed by the oral route. Following intramuscular, intravenous, or intraperitoneal injection in dogs, the drug is excreted via the kidneys and about 25 per cent of the daily dose can be recovered from the urine each day (Tisch *et al., Antibiotics Annual,* 1954-1955, p. 1011). However, judging from animal experiments, it is irritating via parenteral injection routes. This might limit its usefulness to topical treatment only.

Uses.—An ointment containing 5 mg. of calcium amphomycin per Gm. was credited by Cronk and Naumann with curing, or causing improvement of, the limited number of cases of impetigo and of infected contact dermatitis on which it was used (*Antibiotic Medicine and Clinical Therapy,* 1956, **3,** 142). An ointment containing 5 mg. of neomycin per Gm. in addition to the amphomycin gave essentially similar results. Neither formulation was effective in acne vulgaris. There was no evidence of skin sensitization with either preparation in treatment periods of from 1 week to 2 months of daily application.

Incidental to their clinical study, it was observed in testing the sensitivity of organisms isolated from the patients that about 200 times as much amphomycin was required to inhibit the bacteria in nutrient broth as in a more complex solid medium. This observation would have an important bearing in assaying amphomycin.

Perhaps potentially more important, because of the scarcity of clinically useful trypanocidal antibiotics, is the report of successful treatment of experimental African human trypanosomiasis (Packchanian, *Antibiot. Chemother.,* 1956, **6,** 684). Mice were infected with lethal inocula of highly virulent strains of *Tr. gambiense* and of *Tr. rhodesiense.* The first therapeutic dose of antibiotic was given 24 hours after inoculation. Trypanosomes soon disappeared from the blood and subsequent examinations at daily or weekly intervals revealed no organisms. Intraperitoneal injection of 125 or 150 mg. for 4 days gave 95 per cent cure in *Tr. gambiense* infection. A dosage of 100 mg. for 4 days cured animals infected with *Tr. rhodensiense.* No relapses occurred during subsequent observation periods of 2 to 8 months. Untreated animals all died with acute trypanosomiasis in from 3 to 5 days. Sodium amphomycin was employed because it is more soluble than the calcium salt in water.

Oral administration of doses as high as 500 mg. per Kg. of body weight daily for 2 days was completely ineffective; 1,000 mg./Kg. daily by the same route for 4 days produced 40 per cent cures and 40 per cent suppression.

Toxicology.—The acute intravenous LD_{50} of sodium amphomycin for mice is reported as 177.8 mg./Kg. (Tisch *et al., Antibiotics Annual,* 1954-1955, p. 1011) and as 120 mg./Kg. (Packchanian, *Antibiot. Chemother.,* 1956, **6,** 684). The former authors reported values of 247 mg./Kg. and 120 mg./Kg. for the ammonium and calcium salts, respectively. Packchanian found an intraperitoneal LD_{50} of 250 mg./Kg. for the sodium salt.

The intravenous LD_{50} for dogs is about 100 mg./Kg. and the oral LD_{50} is in excess of 500 mg./Kg.

Dogs tolerate daily intramuscular injection of 20 to 40 mg./Kg. (5 days per week) for at least 9 months without showing any evidence of changes in blood chemistry or cell counts. Doses greater than 50 mg./Kg., given parenterally, produce renal damage and cardiac effects that are reversible if the daily dose is not too far above 50 mg./Kg.

Given intravenously, amphomycin is irritating, and the same vein cannot be used on 2 successive days without causing damage (Tisch *et al., loc. cit.*).

Summary.—Amphomycin, an amphoteric, polypeptide antibiotic, produced by various strains of *Streptomyces canus,* is active mainly against gram-positive bacteria. It has no significant effect

against gram-negative species but has remarkable activity against *Trypanosoma gambiense* and *Tr. rhodesiense* experimentally inoculated into mice. It has been used successfully in ointments to treat a limited number of cutaneous infections in humans.

The drug is not absorbed appreciably when given orally. It is irritating when given parenterally and may induce renal and cardiac changes if the dose is not carefully regulated.

These facts, together with its antibacterial inferiority to erythromycin and several other antibiotics, reduce the incentive for commercial production.

Animal studies indicate that it might be effective in African sleeping sickness, but careful pharmacologic evaluation in human subjects would be needed. However, its antibacterial action and high degree of surface activity justify further investigation for topical use in animal, and perhaps plant, infections.

AMPHOTERICINS

The amphotericins, A and B, so named because of their amphoteric nature, were recovered in the Squibb Institute for Medical Research in 1955 from cultures of a streptomycete that had been isolated from soil collected in the Orinoco River region of Venezuela (Gold *et al., Antibiotics Annual,* 1955-1956, p. 579). The organism was designated *Streptomyces* sp. (M 4575) in the Squibb Institute collection. Details of its microbiologic features, including carbon and nitrogen nutrition, growth and culture characteristics on different media, and the antimicrobial spectrum of its antibiotics are recorded in the original publication.

Clinical interest in amphotericin (B) stems from its activity against fungi that cause systemic infections. The trade name for amphotericin is *Fungizone* (Squibb).

The amphotericins, which are relatively insoluble in water, can be recovered from either the wet, filtered mycelial residue or from the broth filtrate. They are much less soluble in water and in anhydrous butanol than in water-saturated butanol, and this property is employed in isolation and purification procedures. They are soluble also in lower alcohols (methanol, propanol, and isopropanol). Solubility is improved when the pH is raised to 10.5. Details of various separation and purification technics have been described by Vandeputte *et al.,* who also described the general chemical and physical properties of the crystalline antibiotics (*Antibiotics Annual,* 1955-1956, p. 587).

Amphotericin B, although less water-soluble than A and considerably less stable, is more active *in vivo* (Steinberg *et al., ibid.,* p. 574), and consequently has attracted more interest. Dutcher *et al.* (*Antibiotics Annual,* 1956-1957, p. 866) concluded that amphotericin B is a polyene structure containing a lactone. The basic moiety of the molecule was determined to be an aminodesoxyhexose for which the name *"mycosamine"* was proposed. Mycosamine has been recovered also from degradation products of nystatin and there is evidence which suggests relationship of amphotericins and nystatin to such other antifungal antibiotics as rimocidin, candicidin, filipin, fungichromin, and trichomycin. The authors speculated on a relationship between amphotericins and the xanthophylls and carotinoids. Their studies suggested an empirical formula of $C_{46}H_{73}NO_{20}$. Knowledge of the chemistry of amphotericins and other newer antibiotics up to 1958 has been reviewed (Brink and Harman, *Quart. Rev. Chem. Soc. London,* 1958, **12,** 93).

Stability.—When dry, both amphotericins are stable for "quite long periods of time when stored at moderate temperatures" and protected from light and air (Vandeputte *et al., Antibiotics Annual,* 1955-1956, p. 587). Dissolved in 50 per cent aqueous isopropyl alcohol, amphotericin A is stable for at least 180 hours at pH 6 to 7. In the same length of time at pH 8, about 50 per cent of its activity is lost. The half-life at pH 10 is about 10 hours and 90 per cent of its activity is lost in 4 days. The half-life at pH 4 is about 80 hours. Neutral solutions are reasonably stable at 30° C., but deterioration increases rapidly as the temperature is raised. Time for loss of 15 per cent of initial potency at pH 7.0 and 40° C. is approximately 36 hours; at 50°, 22 hours; at 60°, 15 hours; at 70°, 9 hours.

Solutions of amphotericin B are much less stable. At 30° C. and pH values between 6.0 and 8.0, there is a 15 per cent loss of potency in 48 hours; at pH 4.0 or 10.0 similar loss occurs in about 18 hours; and at pH 12 in less than an hour.

Assay.—Assaying mixtures of amphotericins A and B by broth dilution technics is complicated by the fact that the B component is several times more active than the A against yeasts and yeast-like fungi. In practice, both tube dilution assays and UV spectrophotometry are used to determine the A and B content of mixtures. Details of the methods are given by Gold *et al.* (*loc. cit.,* p. 579) who also described an agar diffusion assay. *Saccharomyces cerevisiae* is used as the test organism in tube dilution assays, *Candida albicans* is used in agar diffusion assays.

A reliable biological assay for amphotericin in biologic fluids has been developed (McNall *et al., Antibiotics Annual,* 1957-1958, p. 131). The accuracy of the method is said to be ± 5 per cent when tests are made in triplicate, and the results are reproducible. The test organism is a strain of *Candida albicans.* Since clinical material often is contaminated with bacteria and since amphotericins do not appreciably affect bacteria, tetracycline is added to the test medium to prevent bacterial overgrowth which would obscure the results. A special method for determination of amphotericin B in serum also has been developed (Taylor *et al., Am. Rev. Tuberc.,* 1958, 77, 1023).

In all of the assays, particular attention must be given to control of pH. Taylor *et al.* (*loc. cit.*) showed that the MIC of amphotericin B decreased from 2.5 μg./ml. at pH 4.5 to 0.02 μg./ml. at pH 8.0. There is a plateau of uniform activity between pH 6.0 and 7.5. Louria has described a modified method which can be used advantageously when very low levels of amphotericin are

expected (*Antibiotic Medicine and Clinical Therapy*, 1958, **5**, 295).

Actions.—Following oral administration, absorption of amphotericin is poor. Louria (*loc. cit.*) gave daily 2.5 to 5 Gm., in divided doses, to 13 patients and found that after 48 hours of such treatment average blood levels ranged from 0.09 to 0.5 μg./ml. The antibiotic was presented in 4 different pharmaceutical forms of varying solubility, but this did not seem to affect appreciably the blood levels attained. Once a given blood level was achieved it declined slowly. After 12 hours, the concentration may drop to from 30 to 80 per cent of the maximum. One instance in which it declined only 40 per cent after 4 days without medication has been observed. Despite the slow drop in concentration when the drug is withdrawn, there is no build-up in concentration with continued treatment, and once a daily dosage of 2 Gm. has been reached, increasing the dosage yields very little increase in blood level of the drug.

In general, the blood levels attained with oral dosage were 4 to 12 times those that are fungistatic for *Candida albicans* and up to 6 times the fungistatic concentration for *Cryptococcus neoformans* in vitro but concentrations in the blood just barely reached levels inhibitory for *Histoplasma capsulatum*. Although mice inoculated with usually lethal doses of these organisms are protected from death when such blood levels are achieved, upon necropsy it has been found that 80 per cent of those inoculated with *H. capsulatum* and all of those inoculated with *C. neoformans* give positive cultures, indicating that infection has not been eradicated.

Louria (*loc. cit.*) concluded that intravenous infusion, which produces blood levels from 1 to 7 times higher than oral medication, is preferable. Not only were the maximum levels attained by this route higher, but even 20 hours after a given infusion the level was generally higher than the maximum achieved with oral administration.

A "considerable amount" of amphotericin is presumably absorbed by the red cells from the plasma (Vogel and Crutcher, *Antibiotic Medicine and Clinical Therapy*, 1958, **5**, 501).

Amphotericin appears rarely, and only in extremely low concentrations (0.015 to 0.03 μg./ml.), in spinal fluid after oral administration of up to 3.2 Gm./day. Intravenous administration of 0.37 to 1 Gm. daily produced significant spinal fluid levels. The ratio of peak blood levels to peak spinal fluid levels may be from about 30:1 to 50:1, and these ratios are maintained as the blood level falls.

On a daily intake of 5 Gm. of amphotericin B (tablets), the total urinary output of the drug in 24 hours may range from 100 to 300 μg. Patients receiving a combination of amphotericins A and B put out about 400 μg. in 24 hours. When the drug is administered intravenously, about 5 per cent of the total daily dose may be recovered in the urine. However, urinary excretion continues over an extended period, as would be expected in view of the slow disappearance of the drug from the blood. Even 4 to 7 days after discontinuance of infusion of amphotericin, blood levels may still be as high as 16 to 20 per cent of the maximum, and the cumulative urinary output of drug may be as high as 40 per cent. Despite the low rate of urinary excretion and long-maintained blood levels, continued daily infusions do not result in cumulative increase in blood level. Taylor *et al.* (*Am. Rev. Tuberc.*, 1958, **77**, 1023) could not detect the drug in serum of patients at any time after intramuscular injection.

Uses.—Study of experimental *Aspergillus* infections in rabbits led Evans and Baker (*Antibiot. Chemother.*, 1959, **9**, 209) to conclude that amphotericin B is fungistatic rather than fungicidal against that "opportunistic pathogen," but none-the-less highly effective in clearing aspergillosis, if treatment is started soon enough after infection. They believed that the drug "should be effective in treating selected cases of human aspergillosis." Similar results and conclusions have stemmed from study and treatment of experimental mucormycosis, induced with *Rhizopus oryzae*, in rabbits (Chick *et al.*, *Antibiot. Chemother.*, 1958, **8**, 394).

Clinical evaluation of antimycotic agents in control of systemic or deep infections is necessarily a slow process because of the long follow-up periods necessary to establish proof of cure rather than mere arrest. However, a number of reports on systemic use of amphotericin B administered intravenously appear promising.

Rubin *et al.* reported 6 cases of cryptococcal meningitis which were of from 1 month to 10 years' duration and were clinically rated "poor," "critical," "paraplegic," or "moribund" before treatment (*Antibiotics Annual*, 1957-1958, p. 71). Dosage ranged from 50 to 100 mg. daily and approximated 1 mg./Kg. The daily dose was dissolved in one liter of 5 per cent glucose and administered over a minimum of 6 hours. Total dose varied from 1.4 to 3.7 Gm. The moribund patient died after the seventh dose, but of the 5 survivors, 3 were rated "normal" by clinical criteria and spinal fluid findings, 1 was considered improved, and the paraplegic case was rated "improved" in terms of spinal fluid findings although "unchanged" in clinical status. Follow-up periods were from 5 to 10 months. Successful treatment of 3 other cases was reported by Fitzpatrick *et al.* (*Ann. Int. Med.*, 1958, **49**, 249).

On the basis of results with 14 patients, including cryptococcosis (3 with cryptococcal meningitis and 3 with soft-tissue infection), histoplasmosis (4), blastomycosis and coccidioidomycosis (2 each), Utz *et al.* (*Antibiotics Annual*, 1957-1958, p. 65) concluded that the drug appeared "promising" in treatment of "some systemic fungal infections." Four of the cryptococcosis patients on oral amphotericin (4 to 5 Gm./day) were considered subjectively improved or apparently recovered. One patient with histoplasmosis and one with blastomycosis who failed to respond to oral therapy were rated as "apparent recovery" and "objectively improved," respectively, after intravenous therapy. Greendyke and Kaltreider (*Am. J. Med.*, 1959, **26**, 135) reported the drug useful in histoplasmosis.

Other reports of successful use of amphotericin B include a case of disseminated coccidioidomyco-

sis of 10 years' duration (Klapper and Smith, *J.A.M.A.*, 1958, **167**, 463), others of shorter duration (Fiese, *Calif. Med.*, 1957, **86**, 119; Littman *et al.*, *Am. J. Med.*, 1958, **24**, 568; Hunter and Mongan, *U. S. Armed Forces Med. J.*, 1958, **9**, 1474; Williams and Skipworth, *Arch. Dermat.*, 1958, **78**, 97), 4 cases of North American blastomycosis (Harrell and Curtis, *Arch. Dermat.*, 1957, **76**, 561), and a case of *Candida albicans* peritonitis (Ohlwiler and Bricker, *New Eng. J. Med.*, 1959, **260**, 488).

In all cases, treatment is a prolonged affair, ranging in the instances cited from about a month to 14 months.

Cutaneous candidiasis in the diaper area has been reported promptly cured in 12 out of 15 infants treated with an amphotericin ointment. Steinberg *et al.* (*Antibiotics Annual*, 1955-1956, p. 574) found ointments curative in guinea pigs infected with *Trichophyton mentagrophytes*.

Amphotericin has been reported to be "of some value" in reducing the number of *Candida albicans* in feces of patients concurrently receiving tetracycline: only slight effect was seen on the number of *Candida* organisms recovered on throat swabs, and no effect on the yield from sputum was observed (Childs, *Scottish Med. J.*, 1957, **2**, 400). Halde *et al.* also noted a decreased number of *C. albicans* in the gastrointestinal tract when amphotericin was given to patients receiving tetracycline (*Antiobiotics Annual*, 1956-1957, p. 123). The decreases, which were greater when the initial count was high, ranged from 4.2 to 100 per cent. In most instances the count remained below the initial count for some time after cessation of therapy.

Lepper *et al.* studied 4 dosage levels of amphotericin in infants receiving tetracycline therapy (*Antibiotics Annual*, 1958-1959, p. 672). Results were equivocal but suggested that a dosage level of 10 mg. of amphotericin per Kg. per day should effect significant reduction in *Candida* in infants concurrently receiving tetracycline. A dosage of 5 mg./Kg./day was considerably less effective.

Cohn and Longacre concluded that a combination of amphotericin 50 mg. and neomycin 1 Gm. given every hour for 4 hours and then every 6 hours for a total of 72 hours "can be considered one of the better drugs for preoperative preparation of the colon" (*Antibiotics Annual*, 1958-1959, p. 761).

At a concentration of 20 μg./ml., amphotericin B suppresses the growth of species of *Candida*, *Rhodoturula*, and *Aspergillus* as effectively as 100 μg. of nystatin in monkey kidney tissue culture, and the drug may have an important place in tissue culture for virus propagation (Hemphill *et al.*, *Antibiotics Annual*, 1957-1958, p. 961). There was no evidence of toxicity to the tissues.

For an evaluation of amphotericin B by the A.M.A. Council on Drugs see *New and Nonofficial Drugs*, 1960.

Resistance.—Reports are conflicting regarding induced emergence of resistance to amphotericin. Littleman *et al.* could not induce resistance in *Candida albicans* in laboratory trials but found that *C. tropicalis* developed a 400-fold increase in 50 transfers. Several other species also displayed increased resistance after repeated exposure to sublethal concentrations (*Antibiotics Annual*, 1957-1958, p. 981). However, Sorensen *et al.*, using a different medium, observed that a 3- to 5-fold increase in resistance of *Candida albicans* could be induced in 10 transfers and that then increase in resistance proceeded rapidly. A 2000-fold increase was produced in 58 transfers (*Antibiotics Annual*, 1958-1959, p. 920). They were able to produce about a 10-fold increase in resistance of *Coccidioides immitis*.

Littleman *et al.* (*loc. cit.*) found that exposure of some strains of *Candida* to nystatin increased their resistance to amphotericin and vice versa. No evidence of increased resistance occurring during clinical use has been reported.

Toxicology.—The LD_{50} of a suspension of amphotericin B for mice is 280 mg./Kg. intraperitoneally. The corresponding value for the sodium salt of amphotericin A is 450 mg./Kg. (Steinberg *et al.*, *Antibiotics Annual*, 1955-1956, p. 574).

The intravenous LD_{50} for mice has been calculated, in terms of amphotericin B content, as 4.5 mg./Kg. for an amphotericin B-sodium desoxycholate solution in 5 per cent dextrose and as 11.3 mg./Kg. for a suspension of amphotericin B in 5 per cent dextrose (Bartner *et al.*, *Antibiotics Annual*, 1957-1958, p. 53). In rabbits and dogs there seemed to be little difference in intravenous toxicity of the two forms of the drug. In rabbits infusion of 5 mg. of either form per Kg. was followed by death in 10 to 30 minutes. Dogs were more sensitive because of (an apparently) "specific gastrointestinal" reaction.

Monkeys tolerated the solution given at a dosage of 2 mg./Kg./day, 5 days a week for 3 to 4 months. There was a temporary increase in blood urea nitrogen in rabbits, dogs, and monkeys but, apart from the emesis and anorexia in dogs, no other gross or histo-pathologic symptoms were noted.

Applebaum and Shtokalko (*Ann. Int. Med.*, 1957, **47**, 346) noted a short episode of diarrhea and "transitory impairment of renal function, . . . suggestive of nephrotoxicity" in one patient and attributed this to the drug. Utz *et al.* (*Antibiotics Annual*, 1957-1958, p. 64) noted "mild and reversible" azotemia, in 2 patients, and nausea, diarrhea, and anorexia in 2 others. But most of the clinical investigators who have reported on the drug have noted no untoward effects, either acute or residual. Klapper and Smith (*J.A.M.A.*, 1958, **167**, 463) administered the drug orally to one patient for 14 months (2 Gm. daily). They reported that the drug was "well tolerated, with no subjective or objective side effects. There was no evidence of hepatic, renal, or hematopoietic reactions."

Summary.—Amphotericin consists of two closely related compounds, amphotericins A and B, elaborated by a species of *Streptomyces*. Both amphotericins are active against a number of fungi that cause systemic and superficial infections, but the A component inhibits more species than the B component, although the latter exerts a stronger action *in vitro* and is more effective *in vivo*.

Amphotericin B is a lactone-containing polyene structure with the empirical formula $C_{46}H_{73}NO_{20}$. The basic moiety of the molecule is an amino-desoxyhexose (mycosamine). Amphotericins are related chemically to nystatin, an observation which is compatible with *in vitro* patterns of acquired cross resistance. It is also related to candicidin, rimocidin and several other less well known antibiotics. There may be a chemical and biogenetic relationship between amphotericins and the xanthophylls and carotinoids.

The amphotericins are insoluble in water but are soluble in aqueous lower alcohols. Amphotericin A is considerably more pH- and temperature-stable than amphotericin B in solution.

The antibiotic is poorly absorbed following oral administration, although therapeutic blood levels can be achieved. Slow intravenous infusion is the preferred method of administration. Once a maximum blood level has been reached, the concentration decreases slowly and the drug may be detected in blood and passed in the urine for several days after cessation of treatment. Ratios of blood level to concentration in cerebrospinal fluid after intravenous infusion are in the range 50:1 to 30:1. The drug is not absorbed following intramuscular injection.

Clinical application is primarily in treatment of systemic fungus infections, such as, blastomycosis, coccidioidomycosis, cryptococcosis, histoplasmosis, etc. However, it has been used topically in superficial candidiasis and it has been effective in ointment form in experimental *Trichophyton mentagrophytes* infections in guinea pigs. Given orally, amphotericin reduces the yeast count in the intestinal tract and it has been proposed as an adjunct in tetracycline therapy to prevent yeast overgrowth. It may find an important place as a mycostatic agent in tissue culture for virus propagation.

Amphotericin has low toxicity when used in appropriate dosage. Mild and reversible azotemia is the most serious side effect that has been reported. There may be occasional nausea, diarrhea, or anorexia. The incidence of these symptoms appears to be low.

Dose.—Intravenous doses approximating 1 mg. per Kg. of body weight daily have been found effective. The daily dose should be dissolved in 1 liter of 5 per cent glucose and infused over a minimum time of 6 hours. Oral doses of 2 Gm. daily have been curative in coccidioidomycosis and other disseminated fungus diseases. Oral doses as high as 5 Gm. daily have been used. The daily oral dose is divided. In general, a higher rate of cures or of arrests, as judged by both clinical and laboratory criteria, has been achieved when the drug has been given intravenously.

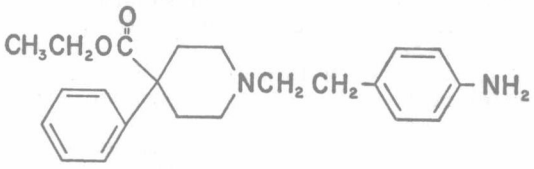
Amphotericin solutions are stable in the presence of small amounts of electrolytes but become turbid in NaCl when the concentration is 0.5 per cent or more. Therefore, dextrose solution is preferred for reconstitution of the lyophilized powder.

Storage.—Both the dry preparation and solutions of amphotericin should be protected from light during storage. Dry preparations so protected are stable at room temperature for at least 8 months and solutions (0.2 mg./ml.) show no loss of potency in 24 hours and only about 10 per cent loss in 1 week at room temperature.

ANILERIDINE HYDROCHLORIDE. N.N.D.

Ethyl 1-(4-Aminophenethyl)-4-phenylisonipecotate Dihydrochloride; Leritine Dihydrochloride (Merck)

The structural formula of anileridine base is:



Anileridine differs structurally from meperidine (see *U.S.D. 25*, p. 797) only in having a 4-aminophenethyl group in place of the methyl attached to the nitrogen of the piperidine ring of meperidine, which substitution more than doubles the analgesic potency of the latter drug. Anileridine may be synthesized by the interaction of *p*-aminophenethyl chloride hydrochloride and 4-phenylisonipecotate carbamate (Weijlard *et al.*, *J.A.C.S.*, 1956, **78**, 2342).

Actions.—Anileridine has an analgesic potency about 2.5 times that of meperidine and 0.25 that of morphine, measured by ability to relieve pain in man. Anileridine, like meperidine, is also mildly antihistaminic and spasmolytic, and is antitussive as well (for detailed pharmacological data see Orahovats, *J. Pharmacol.*, 1957, **119**, 26). It does not have the constipating action of opiates, and in bed patients it does not produce as much dizziness, nausea and vomiting as morphine; in the usual analgesic doses the sedative and direct hypnotic effects are minimal. In doses of equal analgesic effectiveness the respiratory depressant effect of meperidine is of at least the same intensity and frequency as with meperidine (Keats *et al.*, *Anesthesiology*, 1957, **18**, 690; Chang *et al.*, *J. Pharmacol.*, 1958, **122**, 370). Anileridine produces less circulatory depression than does meperidine. The action of ultra-short-acting barbiturates and other central nervous system depressants is potentiated by anileridine. The drug, administered orally as the dihydrochloride, is rapidly absorbed from the gastrointestinal tract, providing analgesia for 2 to 4 hours. Oral administration does not produce as consistent or effective analgesia as does parenteral administration, for which purpose *anileridine phosphate* (a monophosphate), is used. Peak plasma levels are attained within an hour after parenteral administration; the analgesic effect persists for ½ to 1 hour after intravenous injection, 1 to 2 hours after intramuscular injection, and 3 to 4 hours after the drug is given subcutaneously. Anileridine is degraded and excreted principally by the liver and kidney (for further information see Porter, *J. Pharmacol.*, 1957, **120**, 447).

Uses.—Anileridine is used as an analgesic. Among its analgesic uses is that of a premedication for general anesthesia in surgery and as a postoperative sedative. Therien *et al.* (*J.A.M.A.*, 1958, **168**, 2098) found it effective in a wide

variety of medical and surgical situations in more than 600 patients who received over 2,500 administrations of the analgesic; one patient received 552 doses during the course of metastatic carcinoma of the colon, without evidence of addiction. Respiratory depression observed in a few patients by excessive doses was easily counteracted by levallorphan in doses of 1 mg. for every 25 mg. of anileridine hydrochloride. The drug is used also for obstetric analgesia, either alone or in combination with secobarbital or scopolamine (Gross *et al., J. Maine Med. Assoc.,* 1958, **49,** 174). Anileridine is used in the same conditions in which meperidine may be emoployed, and it has the same limitations.

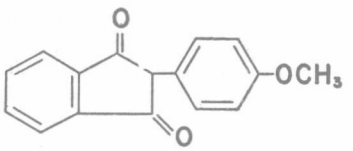
Side Effects.—Respiratory depression and circulatory depression may attend use of anileridine, particularly in older patients or when the drug is administered too rapidly intravenously. Simultaneous use of other narcotics, sedatives or anesthetics is likely to intensify respiratory depression. Significant respiratory depression may be counteracted by nalorphine or levallorphan (see above). Nausea and vomiting, dizziness, increased perspiration, feeling of warmth, xerostomia, restlessness, nervousness and excitement are side effects that may accompany use of anileridine. The drug possesses addiction liability equivalent to that of morphine; unlike meperidine it completely suppresses morphine abstinence, in which respect its addiction liability is, therefore, greater than that of meperidine. It is noteworthy that the amount of anileridine required to sustain addiction is approximately the same as for meperidine, notwithstanding that the equi-analgesic dose of meperidine is 2.5 times that of anileridine. Anileridine is subject to federal narcotic regulations.

Dose.—For oral administration the hydrochloride salt is used, the usual dose being 25 mg., repeated at 6-hour intervals as necessary; for severe pain the drug may be given more frequently, or the dose increased to 50 mg. For subcutaneous, intramuscular or intravenous administration *anileridine phosphate* is employed. Subcutaneously or intramuscularly, the dose is 25 to 50 mg., repeated at intervals of 4 to 6 hours as required; for obstetric analgesia the usual dose is 50 mg., repeated in 3 to 4 hours. When used intravenously in support of anesthesia anileridine phosphate should be given in dilute solution, slowly. A convenient dilution is 50 to 100 mg. in 500 ml. of 5 per cent dextrose injection. The equivalent of 5 to 10 mg. of this solution is infused slowly, and analgesia is maintained by slow intravenous drip at a rate of about 0.6 mg. of the drug per minute, regulated according to the need and response of the patient. The injection dosage form supplied commercially should not be injected intravenously, except in a grave emergency and then at a *very* slow rate (at least several minutes); rapid intravenous injection of more than 10 mg. may cause apnea.

Dosage Forms.—Tablets containing 25 mg. of anileridine hydrochloride (dihydrochloride). Injections containing 25 mg. in 1 ml., 50 mg. in 2 ml., and 750 mg. in 30 ml., of *anileridine phosphate.*

ANISINDIONE.

2-*p*-Anisyl Indandione-1,3; Miradon (Schering)



Anisindione is structurally very closely related to phenindione (see *U.S.D. 25,* p. 1572), differing from the latter only in having a methoxyl group in *para*-position on the phenyl ring. It may be synthesized from anisaldehyde and phthalide in the presence of sodium alcoholate (*J.A.C.S.,* 1936, **58,** 1331); a synthesis is described also in U.S. Patent 2,899,358 (1959). Anisindione is a white, crystalline powder, tasteless, and only slightly soluble in water.

Actions and Uses.—Anisindione, like phenindione, is an anticoagulant; it acts by depressing prothrombin activity of the blood. The average time required for maximal effect with anisindione and phenindione appears to be about the same, being 34 hours for anisindione and 30 hours for phenindione; in the majority of patients, however, anisindione produced some effect upon prothrombin time within 6 hours while 10 hours was required with phenindione (Kellaway, *Brit. M. J.,* 1958, **2,** 889). With anisindione the response to the initial loading dose is narrower than with phenindione and, therefore, the effect of the former drug is a little more predictable (Kellaway). While Lange *et al.* (*Am. Heart J.,* 1958, **55,** 73) found the maintenance dose of anisindione to be rather constant from patient to patient, Connell and Mayer (*Can. Med. Assoc. J.,* 1959, **80,** 785) observed a wide variation from person to person, the range of dose being 25 to 175 mg. daily. Paul *et al.* (*Surg. Gynec. Obst.,* 1959, **108,** 605), in an extensive study of their clinical experience with anisindione, found the dose required to maintain patients at control levels to vary from 50 to 150 mg. daily, given as a single dose; the same investigators reported that liver function tests and bone marrow studies gave no evidence of toxic effects in patients receiving anisindione for periods up to 12 months.

Dose.—Different clinicians have used different dosage schedules for anisindione. Connell and Mayer gave a loading dose of 500 mg. the first day, 300 mg. on the second and third days, 200 mg. the fourth day, and thereafter a daily maintenance dose as established by prothrombin determinations. Paul *et al.* administered 500 mg. the first day, 300 mg. the second day, 200 mg. the third day, and thereafter a maintenance dose of 50 to 150 mg. daily, according to the requirements of the patient. Kellaway's dosage schedule was 300 mg. the first day, 100 mg. the second day, and thereafter a single daily dose as determined by prothrombin time determinations. Vitamin K_1, in 20-mg. doses, either orally or intravenously, may be used to produce a rapid reversal of anticoagulant action.

Dosage Form.—Tablets containing 50 mg. of anisindione.

ANTIBIOTICS*

During the time since preparation of the twenty-fifth edition of the *Dispensatory* several authors have reappraised the position of antibiotics in general practice and in various specialties. And basic problems of the chemistry and physiology of antibiotics have not been ignored. A number of important reviews and thoughtful appraisals dealing with different facets of antibiotic therapy have been cited in monographs on specific antibiotics. But others are of broader scope and apply to several antibiotics or to the total field of antibiotic therapy.

Topics which have received special attention in recent years are: emergence of antibiotic-resistant strains of bacteria; "superinfections" following use of antibiotics; changes in the composition of the intestinal microflora as a result of antibiotic therapy or prophylaxis; anaphylactic and other untoward reactions to antibiotics; mixed antibiotic therapy and joint antibiotic-hormone therapy; and enhancement of antibiotic blood levels, especially of tetracyclines. Use of small amounts of antibiotics in the formulas of premature infants and in diets of older undernourished children, reminiscent of the now well-established practice of using antibiotic-supplemented feeds for young poultry, swine, etc., has been reported successful in limited trials.

Chemistry.—Notable achievements since publication of the 25th edition of the *Dispensatory* are total synthesis of a biologically active penicillin by Sheehan and Henery-Logan (*J.A.C.S.*, 1957, **79,** 1262), recognition of the macrolide group of antibiotics, and elucidation of the structure of erythromycin (Wiley *et al.*, *J.A.C.S.*, 1957, **79,** 6074) and carbomycin (Woodward, *Angewandte Chem.*, 1957, **69,** 50), and advances in knowledge of the chemistry of such polyene antibiotics as fumagillin and nystatin and of such polypeptide antibiotics as bacitracin and polymyxin. These and other highlights and the events leading to them have been reviewed thoroughly and summarized by Regna (in *Antibiotics: Their Chemistry and Non-Medical Uses,* edited by Goldberg, 1959, Van Nostrand, New York). Other important reviews were published by Brink and Harman (*Quart. Revs. Chem. Soc.*, London, 1958, **12,** 93), and Harman (*Trans. N.Y. Acad. Sci.*, 1959, **21,** 469). A survey by Burkholder (*Science,* 1959, **129,** 1457) discusses a wide array of chemical patterns found in antibiotics and is valuable because it draws attention to the structural similarities between molecules of some of the antibiotics and other naturally occurring compounds, some of which are significant in mammalian biochemistry as well as in the functioning of other forms of life. The review is valuable also because it brings together in a single source structures of some of the less well-known antibiotics which have not achieved clinical prominence.

New Antibiotics.—After the discovery of chloramphenicol in 1947, there followed in rapid succession chlortetracycline (1948), oxytetracycline (1950), erythromycin (1952) and tetracycline (1953). Although many new antibiotics have been discovered since that time, the rate of discovery and introduction of clinically useful ones has slackened. Many of the more recent antibiotics have either been shown to be closely related to previously known antibiotics or have limited usefulness because of toxicity or difficulties of administration.

Brief comments on a few of the more important additions to the antibiotic armamentarium follow. For detailed discussion of these and other new antibiotics see the respective monographs.

Phenoxymethyl penicillin (*Pen-V,* Wyeth; *V-Cillin,* Lilly) and its hydrabamine salt (*Compocillin-V,* Abbott), and oleandomycin (*Matromycin,* Pfizer) have been developed commercially. Phenoxymethyl penicillin (and its hydrabamine salt) is almost the equal of benzyl penicillin in clinical activity and has distinct advantages for oral administration. Oleandomycin is a member of the erythromycin family of antibiotics, but in general is less active than *erythromycin* (*Erythrocin,* Abbott; *Ilotycin* and *Ilosone,* Lilly). Reviewing recent developments in antibiotic therapy, Lepper (*Wisconsin M. J.*, 1958, **57,** 207) commented "there was little reason for introduction of oleandomycin," a view which is supported by many physicians. One major objection to oleandomycin is the fact that, because of cross-resistance, use of this relatively less-effective drug may eventually cause erythromycin to become less useful. Another member of the group is *spiramycin* which is available in Europe but is not currently being distributed in the United States. It is probably less desirable than oleandomycin, and the same objections can be made to its wide use as to use of oleandomycin.

Synnematin, discovered in 1951 (Gottschall *et al.*, *Proc. S. Exp. Biol. Med.*, 1951, **76,** 307), was later shown to be D-4-amino-4-carboxy-*n*-butyl penicillin (Newton and Abraham, *Biochem. J.*, 1954, **58,** 103). Like the penicillins in clinical use, synnematin has a very low order of toxicity but it is unique among penicillins in displaying marked activity *in vivo* as well as *in vitro* against gram-negative bacteria, including species of *Salmonella* and *Proteus*. To date, synnematin has not been developed industrially.

Among the antibiotics which have been developed primarily for use against staphylococci resistant to the major antibiotics are *ristocetin* (*Spontin,* Abbott) discovered in 1956 (Grundy *et al.*, *Antibiotics Annual,* 1956-1957, p. 687), *vancomycin* (*Vancocin,* Lilly) reported in 1955 (McCormick *et al.*, *Antibiotics Annual,* 1955-1956, p. 606), and *novobiocin* (*Albamycin,* Upjohn; *Cardelmycin,* Pfizer; and *Cathomycin,* Merck), which was discovered and reported independently by Wallick *et al.* (*Antibiotics Annual,* 1955-1956, p. 909) and by Lin and Coriell (*ibid.*, p. 634). Novobiocin is effective orally, but ristocetin and vancomycin have the disadvantage of being effective systemically only when administered parenterally.

Modifications of tetracyclines have yielded the

* For a general discussion of antibiotics, including definition of the term, brief accounts of the historical background of antibiotic therapy and of sources and methods of biosynthesis, recovery, and purification of these drugs, and alluding to some of their para-medical and non-medical uses, see the *U.S.D. 25* (p. 1551 et seq.).