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PART II-III

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PART TWO: Drugs not official in The United States Pharmacopeia, British Pharmacopœia, International Pharmacopoeia or The National Formulary

IN THIS section are included medicinal agents not recognized in the official compendia which provide the basis for inclusion in Part One; also certain formerly official drugs and various other agents, some of which may be only of toxicological interest. Included as well are general articles on (a) pharmacological and (b) pharmaceutical classes of drugs.

Abrus. *Abrus Seeds. Crabs' Eyes. Indian Liquorice. Jequirity. Jumble Beads. Liquorice Bush. Love Pea. Prayer Beads. Red Bean. Rosary Pea. Wild Liquorice.*—The seeds of this plant, *Abrus precatorius* L. (Fam. *Leguminosæ*), which grows in India and also in Brazil and Florida, are ovoid, from 5 to 8 mm. in length, smooth, shiny and bright scarlet, having a black marking at the lower, or hilum, portion. They contain *abric acid,* a toxalbumin called *abrin,* and also L-*abrine,* which is N-methyltryptophan. The toxalbumin abrin is a yellowish powder, soluble (with turbidity) in solutions of sodium chloride. It is highly toxic, the lethal dose for animals being claimed to be 0.01 mg. per Kg. of weight. Both Ehrlich and Calmette succeeded in immunizing rabbits against abrin, and obtained an antitoxic serum. Ingestion of a single bean, if chewed, may cause severe vomiting, diarrhea, convulsions, and even death. Symptoms are usually delayed for hours in onset. In addition to catharsis and supportive measures, arecoline has been recommended in treatment. The root of Abrus, known as *Indian liquorice,* possesses the toxic properties of the seeds and should not be used in place of licorice. According to Hooper, it contains *glycyrrhizin* (*Pharm. J.,* 1894).

Abrin has been used, in a concentration of 1 in 500,000, in treating certain chronic diseases of the eye, especially corneal opacities and trachomatous pannus. It excites a purulent inflammation of the conjunctiva, which appears to cause an increase of local circulation, thereby promoting absorption of inflammatory exudates. The substance may be harmful in unsuitable cases. Infusion of jequirity was formerly employed for the same purposes but the possibility of its causing an uncontrollable inflammation which in some instances entirely destroyed vision led to its abandonment as a therapeutic agent. For further information see *U.S.D.,* 23rd ed., p. 1237.

Absinthium. *Wormwood. Madderwort. Wermuth. Mugwort. Mingwort. Warmot. Magenkraut. Herba Absinthii.*—Absinthium or wormwood was formerly officially recognized as: "The dried leaves and flowering tops of *Artemisia Absinthium* Linné (Fam. *Compositæ*), without the presence of more than 5 per cent of foreign matter." *N.F. IV.*

Wormwood is a shrubby, more or less herbaceous, finely canescent plant, growing to a height of 2 to 4 feet. The leaves are 1 to 3 pinnately divided, the lobes being lanceolate or obovate, the basal leaves being petiolate while the floral ones are linear and entire; the flowers are all fertile, tubular, yellowish, in hemispherical panicled heads. The plant is a native of Europe, Asia, and Northern Africa, and is to some extent cultivated in the United States. Gathered in July or August, during flowering, the plant yields the greatest quantity of volatile oil. For a pharmacognostic description see *U.S.D.,* 21st ed., p. 182.

Wormwood yields a volatile oil which is usually dark green, but is sometimes yellow or brown or even blue, having a strong odor of the plant, an acrid taste, and a specific gravity of 0.925 to 0.950. It contains thujone (*absinthol*); thujyl alcohol, both free and as esters of acetic, isovaleric, and palmitic acids; phellandrene, and possibly pinene; cadinene; and a *blue oil* fraction which is probably azulene (Gildemeister and Hoffmann, *Aetherische Oele*). The *absinthic acid* found by Braconnot appears to be succinic acid. Wormwood also contains a yellowish glycoside, with an intensely bitter taste, called *absinthin.* Bourcet described this compound (*Bull. soc. chim.,* 1898, 19, 537) as having the formula $C_{30}H_{40}O_8$, and occurring in white lustrous needles melting at 68°, soluble in water, alcohol, and ether. Adrian and Trillat isolated another crystalline principle, *anabsinthin,* $C_{18}H_{24}O_4$ (*Pharm. J.,* 1899, 1, 75). The old *salt of wormwood* (*sal absinthii*) was impure potassium carbonate, made from the ashes of the plant.

Wormwood, formerly popular as a stomachic tonic, antiperiodic, and anthelmintic, is now seldom used. Patoir *et al.* (*Compt. rend. soc. biol.,* 1938, **127,** 1325) found that an aqueous extract of the leaves produced in rabbits dyspnea, hematuria, gastroenteritis, and death. The volatile oil is an active narcotic poison. It causes trembling, stupor, and later violent epileptiform convulsions, with involuntary evacuations, unconsciousness, and stertorous breathing, which may or may not end in death. A half-ounce (15 ml.) of it caused, in a male adult, insensibility and convulsions, though the patient recovered under the use of emetics, with stimulants and demulcents (*Lancet,* Dec. 6, 1862). *Dose,* of entire wormwood, 1.3 to 2.6 Gm. (20 to 40 grains); of the infusion (one ounce in a pint of boiling water), from 30 to 60 ml. (1 to 2 fluidounces); of the oil, 0.06 to 0.12 ml. (1 to 2 minims).

Absinthe is a liqueur containing oils of wormwood, angelica, anise, and marjoram. *Absinthism* differs from ordinary alcoholism in its manifestations; its characteristic symptoms are restlessness at night, with disturbing dreams, nausea and vomiting in the morning, with great trembling of the hands and tongue, vertigo, and a tendency to epileptiform convulsions.

Acalypha, *B.P. Add. 1900. Indian Nettle. Kuppi. Dadaro.*—The fresh or dried euphorbiaceous plant, *Acalypha indica* L., is said to have expectorant and emetic properties similar to those of ipecac. In the form of fresh leaves, native Indian practitioners are reputed to use it as a poultice for ulcers, as a vermifuge and as a suppository for constipation in children.

It contains an alkaloid *acalyphine* and also a cyanogenetic glycoside which, according to Steyn (*Chem. Abs.*, 1938, **32**, 7572), is actively poisonous.

The *liquid extract* (*Extractum Acalyphæ Liquidum, B.P. Add. 1900*), made with a menstruum of 90 per cent alcohol, was given in *doses* of from 0.3 to 2 ml. (5 to 30 minims).

The *A. virginica* L. (*mercury weed, three-seeded mercury*), which grows in the eastern United States, has been used as an expectorant and diuretic.

Acetal. *Diethylacetal.* $CH_3CH(OC_2H_5)_2$.—*Ethidene* (*Ethylidene*) *diethyl ether,* a limpid volatile liquid resulting from the interaction of alcohol and acetaldehyde. It boils at 102.7°, has a density of 0.8254 at 20°, is sparingly soluble in water, and readily soluble in alcohol. It has been used in both human and veterinary practice for its hypnotic action.

Acetaldehyde. *Acetic Aldehyde. Ethyl Aldehyde "Aldehyde."* CH_3CHO.—Acetaldehyde may be prepared by controlled oxidation of alcohol; commercially it is made by hydration of acetylene in dilute sulfuric acid, in the presence of a mercury salt. Acetaldehyde is a colorless, mobile, flammable liquid, having a decidedly pungent, ethereal, and suffocating odor. Its specific gravity is 0.790 at 15°, the boiling point is 21°. It is miscible with water, alcohol, and ether, and is rapidly oxidized to acetic acid on exposure to the air. Acetaldehyde possesses very marked antiputrescent properties.

Supniwski (*J. Pharmacol.*, 1927, **30**, 429) found the intravenous lethal dose of acetaldehyde for rabbits to be 0.3 Gm. per Kg. Small doses stimulated the respiration; larger, but non-fatal, doses caused narcosis and fall of the blood pressure (see also *Disulfiram*, in Part II). Fatal doses arrested the respiration. Koppanyi (*Anesth.*, 1945, **6**, 603) has studied the anesthetic effect of acetaldehyde on dogs. Applied locally, acetaldehyde is very irritating.

A condensation product of ethyl aldehyde, known as *"aldol,"* $CH_3.CH(OH).CH_2.CHO$, *β-hydroxybutyraldehyde,* has been recommended as a hypnotic and sedative.

Acetophenolisatin. *Endophenolphthalein. Isacen. Bisatin. Diacetyldiphenolisatin.* 3,3-Bis-(*p*-Acetoxyphenyl)oxindole. $C_{24}H_{19}NO_5$.—This laxative compound occurs in white, odorless, tasteless crystals or powder; it is insoluble in water and slightly soluble in alcohol. Its laxative property was first observed by Guggenheim (*Schweiz. med. Wchnschr.*, 1925, **55**, 16); this and subsequent studies are briefly reviewed by Sanders *et al.*, who observed no adverse effects from large doses in the rat (*J. A. Ph. A.*, 1951, **40**, 340) and who also found a diphenylisatin in a concentrate of California prunes (*ibid.*, p. 348). In his report of a study of the laxative activity of triphenylmethane derivatives, Loewe (*J. Pharmacol.*, 1948, **94**, 288) called attention to the high laxative potency of diacetyldiphenolisatin, which he estimates as about 17 times that of phenolphthalein on an equal weight basis. The compound acts on the intestinal mucosa; it is completely excreted in the feces. The usual adult *dose* is 5 mg. (approximately 1/12 grain).

Acetylene. $CH{\equiv}CH$.—Acetylene, discovered by Davy in 1836 and synthesized in 1859 by Berthelot, is prepared on a large scale by the decomposition of carbides, such as calcium carbide, or by methods involving the reduction of higher hydrocarbons.

Acetylene is a colorless gas of ethereal odor, slightly soluble in water, more readily in alcohol and ether, and abundantly in acetone. It ordinarily burns with a very smoky flame, but from a burner with a fine slit gives a clear white flame. It forms an explosive mixture with air, also a series of explosive carbides with copper, silver, and other metals. Acetylene finds extensive use in industry for oxyacetylene welding and in organic syntheses.

Inhalation of high concentrations of acetylene causes unconsciousness. Under the trade-name *narcylene* it was at one time suggested as a surgical anesthetic. According to Wieland its stupefying action is due to interference with the utilization of oxygen by the body and its use as an anesthetic has been practically abandoned. (For literature see *J.A.M.A.*, 1923, **80**, 1383 and Mallebrein and Maier, *Deutsche med. Wchnschr.*, 1925, p. 1521.) It is employed clinically for determinations of cardiac output (Chapman, *J. Clin. Inv.*, 1950, **29**, 651).

Acetyl-*p*-aminophenol. *Apamide* (Ames). *N-Acetyl-p-aminophenol. p-Hydroxyacetanilid.* $CH_3CO.NH.C_6H_3(OH)NH_2$.—This compound occurs as a white, crystalline powder, odorless, and with a bitter taste; it is soluble in approximately 73 parts of water at room temperature.

N-acetyl-*p*-aminophenol is the principal metabolite when either acetanilid or acetophenetidin is administered to humans; it is probably directly responsible for the analgetic effect of the latter drugs. Flinn and Brodie (*J. Pharmacol.*, 1948, **94**, 76) demonstrated that equivalent doses of N-acetyl-*p*-aminophenol and acetanilid produce equivalent analgesia as measured by elevation of the heat-pain threshold. Higher and more rapidly attained plasma levels of N-acetyl-*p*-aminophenol were obtained with that substance than with acetanilid (Brodie and Axelrod, *ibid.*, 1948, **94**, 29; no methemoglobin resulted from ingestion of the acetyl-*p*-aminophenol. The drug has been used, according to unpublished clinical reports, in a variety of conditions in which an analgetic of the type of acetophenetidin or acetanilid may be used. The range of adult *dose* is 300 to 600 mg. (approximately 5 to 10 grains) every 4 hours.

Acetylphenylhydrazine. $C_6H_5NHNHCOCH_3$.—This substance, first introduced into medicine in an impure form, under the name *pyrodin,* has since been used in the pure condition under the name of *hydracetin.* It forms colorless, inodorous crystals, melting at 128°, soluble in 50 parts of water and readily soluble in alcohol. It is a powerful antipyretic but is a dangerous remedy because of its destructive action on the red blood cells. It has been used for polycythemia (McCance and Widdowson, *Quart. J. Med.*, 1937, **6**, 277; McAlpin and Smith, *New York State J. Med.*, 1938, **38**, 101). *Dose,* from 60 to 120 mg. (approximately 1 to 2 grains). For further information see *U.S.D.*, 20th ed., p. 1226.

Acetyltannic Acid. *Acidum Acetyltannicum, U.S.P. XI. Diacetyltannic Acid. Tannyl Acetate. Tannigen* (Winthrop). *Acetannin.*—This compound is prepared by heating tannin with acetic anhydride in the presence of glacial acetic acid. The substance is apparently not a definite chemical compound as different samples vary in color, solubility and acetyl content (see Corfield and Short, *Chem. Drug.*, 1924, **101**, 195).

The U.S.P. XI described it as follows: "A yellowish-white, or a grayish-white powder which darkens on exposure to light. It is odorless or has a slight, acetous odor. Acetyltannic Acid is only slightly soluble in water and in alcohol, but is soluble in ethyl acetate. It is soluble with gradual decomposition in aqueous solutions of alkali hydroxides and carbonates. It is also soluble in aqueous solutions of sodium borate and of sodium phosphate." For tests see *U.S.D.*, 23rd ed., p. 1240.

Acetyltannic acid has a very mild astringent effect due to the presence of a small amount of free tannic acid. In alkaline solutions it is slowly hydrolyzed, liberating tannic acid which exerts its characteristic astringent effect. According to Sollmann (*J. Pharmacol.*, 1921, **17**, 87) this decomposition takes place rather slowly, the astringency reaching its maximum in about 2 hours. This may be interpreted to mean

that the drug would exercise very little astringent effect in the stomach or duodenum; that in the lower part of the intestinal tract it would exert a mild and continuing effect as it is gradually hydrolyzed. Acetyltannic acid was used in the treatment of diarrheas of various types, such as chronic enteritis, cholera infantum, dysentery, and even in relieving symptoms of intestinal tuberculosis. The *dose* is 0.3 to 1 Gm. (approximately 5 to 15 grains). V

Achillea, *U.S.P. 1870.*—The flowering tops of *Achillea Millefolium* L. *Milfoil,* or *yarrow,* is a perennial herb, very common both in Europe and America. It is also known by the names of *ladies' mantle, nosebleed, thousand-leaf* and *noble yarrow.* The plant is from 12 to 18 inches in height, and is specifically distinguished by its doubly pinnate, downy, minutely divided leaves, with linear, dentate, mucronate divisions, from which it derives the name of milfoil, by its furrowed stem and involucre, and by its dense corymbs of whitish flowers, which appear throughout the summer, from June to September. *Achillea nobilis* L., and *A. moschata* Jacq., or *iva* of Europe, are sometimes used as substitutes for *A. Millefolium.*

Both the flowers and leaves of *A. Millefolium* have an agreeable, though feeble, aromatic odor, and a bitterish, astringent, pungent taste. The plant contains volatile oil, tannin, *achilleine, achilleic acid* (apparently identical with aconitic acid) and a bitter principle called *ivain.* The volatile oil is blue (from the presence of azulene) and consists largely of cineol (Schimmel, *Ber.,* 1894, p. 50). Graham (*J. A. Ph. A.,* 1933, **27**, 819) showed that the azulene is formed during distillation of the volatile oil. Gisvold (*J. A. Ph. A.,* 1935, **24**, 1071) found *stigmasterol* and *sitosterol* in milfoil. For data on other constituents see McMurray (*Am. J. Pharm,* 1933, **105**, 573). A number of other species of achillea have been distilled for the volatile oil, including *A. coronopifolia* Willd., *A. moschata* Jacq., *A. nobilis,* and *A. ageratum* L.

Milfoil has been used, chiefly as a folk-remedy in the form of a "tea," as a sudorific and in amenorrhea. Miller and Chow (*J.A.C.S.,* 1954, **76**, 1353), calling attention to the use of yarrow as a hemostatic, found that the alkaloid achilleine, which they confirmed as being present, reduces the clotting time of blood in rabbits, the action lasting for 45 minutes and being without observable toxic effect. Achillea has been used in doses of 2 to 4 Gm. (approximately 30 to 60 grains); the volatile oil has been used in doses of 0.6 to 1 ml. (approximately 10 to 15 minims).

ACS. *Antireticular Cytotoxic Serum.*—This preparation is an antiserum obtained by immunizing lower animals, usually horses or rabbits, with extracts of human spleen and bone marrow. According to Bogomolets (*Am. Rev. Soviet Med.,* 1943, **1**, 101) and other Russian proponents, proper doses of ACS stimulate hypothetical physiological functions of the connective tissue. In mice, the Russians claim complete disappearance of large carcinogenous tumors and a diminishing influence on metastases to the lungs. In rabbits, they observed an acceleration of healing of experimental fractures and rapid growth of normal bone callosity.

First used in human patients in 1936, the Russian clinical work was climaxed in 1946 by a combined report on 2500 cases at Ufa. At this conference ACS was declared therapeutically effective in gunshot wounds, fractures, sepsis, several infectious diseases, traumatic and infectious diseases of the nervous system, certain psychoses, and other diversified disorders.

In the United States, published clinical evidence has not been extensive or conclusive. Pomerat and coworkers demonstrated (1) the inhibitory phase of ACS with tissue culture technic (*Science,* 1944, **100**, 456), (2) some evidence of stimulation with small doses (*Fed. Proc.,* 1945, **4**, 56), (3) depression of hematopoiesis in rats and mice with large doses (*Fed. Proc.,* 1945, **4**, 111; 1946, **5**, 176), and (4) no effect on trypanosome infections in mice (*Fed. Proc.,* 1946, **5**, 177). The interesting observation has been made that acute bartonellosis in rats may be induced by "blocking" doses of ACS. Nickerson *et al.* (*Fed. Proc.,* 1946, **5**, 196) reported no stimulating effect of small doses on the healing of experimental fractures in rats but did not consider their results conclusive. On the other hand, Strauss (*J. Immunol.,* 1946, **54**, 163) reported an accelerated rate of healing in experimental fractures in rabbits.

It would appear that stimulating doses of ACS give promise of clinical utility in speeding the healing of fractures. Davis (*Am. J. Med.,* 1947, **3**, 123) administered the serum to 62 patients with far advanced cancer; although it cannot be said that any lives were prolonged, 10 patients experienced a marked relief from pain, a gain in weight, an increased appetite, and a sense of well-being. Eleven more patients noted moderate benefit. Of 21 cases of rheumatoid arthritis, 12 obtained pronounced relief. A patient with myeloid leukemia responded dramatically to repeated injections; patients with osteoporosis had complete relief from pain; others with Hodgkin's disease, multiple myeloma and lupus erythematosus disseminatus obtained moderate benefit.

Rogoff and associates (*Am. J. Med. Sc.,* 1947, **214**, 395) found ACS therapy of no benefit in the great majority of patients with rheumatoid arthritis; in the few cases apparently improved, benefit was usually transient. Samitz and Stritzler (*Arch. Dermat. Syph.,* 1949, **59**, 493) reported ACS to be beneficial in four cases of chronic ulcerations of the leg, but of no value in the cases of scleroderma, exfoliative dermatitis, generalized psoriasis and pemphigus which they treated with the serum.

The equivocal results in these hopeful trials have discouraged further evaluation pending identification of an active principle and information on its action.

Adenine. *6-Aminopurine.* $C_5H_5N_5.3H_2O$.—This is one of the purine base components of the nucleic acids (*q.v.*) found in animal and plant tissues; it occurs as white crystals, slightly soluble in water. Adenine may apparently be incorporated into the purine moieties of polynucleotides (of the rat) not only as the adenine component but also in the form of guanine (Brown, *Ann. N. Y. Acad. Sc.,* 1954, **60**, 185), suggesting that there can be transformation of one purine into another. Several structural analogs of adenine have been investigated to determine whether they may serve as antimetabolites having ability to alter characteristics of growth, notably inhibition of neoplastic tissue growth. The most effective of these analogs, especially in the treatment of acute leukemia, is *6-mercaptopurine,* which is discussed under this title in Part II. The compound *2,6-diaminopurine* has also been used therapeutically to antagonize adenine in the metabolism of leukemic cells (Burchenal *et al., Cancer,* 1951, **4**, 549).

Adenine has been reported to influence diuresis, muscle activity and the central nervous system much like the bases of the xanthine group (Yoshimuro, *Ztschr. physiol. Chem.,* 1913, **88**, 334). *Adenine sulfate* has been used in treating agranulocytosis by intravenous injection of 1 to 2 Gm. in 30 to 60 ml. of isotonic sodium chloride solution (see also *Pentnucleotide,* under *Nucleic Acids*).

Adenium.—In southern Africa a number of native tribes used as arrow poisons various species of the genus *Adenium* (Fam. *Apocynaceæ*). Of these the poison known to the natives as *echuga* (*echuja*) comes from the *A. Boehmianum* Schinz. Bohm (*Arch. exp. Path. Pharm.,* 1889) isolated from this species a crystalline glycoside *echugin* and a resinous

body *echugon*. He found that it had a digitalis-like effect on the heart but also caused tetanic convulsions. *A. Coetaneum* Stumpf, according to Krause (*Berl. klin. Wchnschr.*, 1910, p. 1699), also contains a glycoside whose physiological action is essentially the same. From *A. honghel* Hunger and Reichstein (*Helv. Chim. Acta*, 1950, **33**, 76) isolated the cardiac glycosides *honghelóside A* and *honghelóside B*, while Frèrejacque and Hasenfratz (*Compt. rend. acad. sc.*, 1949, **229**, 1949) reported isolation of a glycoside which they called *honghéline*. From *A. multiflorum* Hunger and Reichstein (*Helv. Chim. Acta*, 1950, **33**, 1993) isolated the same glycosides as they did from *A. honghel*, except for a further enzymatic splitting of the former.

Adenosine-5-monophosphate. *Muscle Adenylic Acid. My-B-Den* (Bischoff). $C_{10}H_{14}N_5O_7P$.—This natural constituent of muscle tissue is a mononucleotide yielding on hydrolysis a molecule each of adenine, D-ribose, and phosphoric acid.

In the course of its trial in the treatment of patients suffering from Hodgkin's disease, for which disease it is not effective, adenosine-5-monophosphate was found to relieve pruritus (Rottino, *J.-Lancet*, 1949, **49**, 285); such antipruritic action has been confirmed by Kennedy (*N. Y. State J. Med.*, 1950, **50**, 1609), Matt (*South. M. J.*, 1951, **44**, 537), and Sussino (*Am. Pract. Dig. Treat.*, 1951, **2**, 491). The compound has also been used effectively in the treatment of tendinitis (Rottino, *J.-Lancet*, 1951, **71**, 237; Sussino and Verdon, *J.A.M.A.*, 1954, **154**, 239); multiple sclerosis (Lowry *et al.*, *Am. J. Med. Sci.*, 1953, **226**, 73), varicose veins (Lawrence *et al.*, *Angiology*, 1951, **2**, 405), and phlebitis (Rottino *et al.*, *Angiology*, 1950, **1**, 194).

Adenosine-5-monophosphate has been variously administered, as by intramuscular injection of 20 mg. (as the sodium salt) hourly for a total of 5 injections per day for 3 consecutive days, or orally in the form of 20-mg. tablets for sublingual absorption, given at hourly intervals for 5 to 7 doses daily for 4 to 7 days, after which 2 to 5 tablets daily are administered.

My-B-Den is available in 20-mg. sublingual tablets, in 1-ml. ampuls containing 20 mg. (as the sodium salt) in aqueous solution, and in 10-ml. vials containing a sustained action vehicle (gelatin-base) with 20 mg. per ml. of adenosine-5-monophosphate (as the sodium salt).

Adhatoda, *B.P. Add. 1900.* (Fam. *Acanthaceæ.*)—The fresh and dried leaves of *Adhatoda vasica* Nees (*Justicia Adhatoda* L.). *Malabar Nut Tree.* The leaves contain an alkaloid, *vasicine*, $C_{11}H_{12}N_2O$ (apparently identical with *peganine* from *Peganum harmala*), and an organic acid, *adhatodic acid*. Vasicine, according to Chopra and Ghosh (*Indian Med. Gaz.*, 1925, **60**, 355), produces in experimental animals a mild but persistent dilatation of the bronchi. The claim is made that it exerts a powerful toxic influence upon lower forms of vegetable and animal life, but is not poisonous to the higher animals. The leaves are used in India as an expectorant and antispasmodic, especially in the treatment of asthma. The B.P. Add. 1900 recognized the *liquid extract* (*Extractum Adhatodæ Liquidum*), made with alcohol and given in *doses* of from 1.3 to 4 ml. (20 to 60 minims); and the freshly *expressed juice* (*Succus Adhatodæ*), *dose*, from 4 to 15 ml. (1 to 4 fluidrachms).

Adlumia.—Species of this papaveraceous genus contain some of the same alkaloids which are found in corydalis. In *A. cirrhosa* are found *adlumine, adlumidine, allocryptine*, and *protopine* (Watkins, *Pharm. Arch.*, 1903, **6**, 17). In *A. fungosa* Greene, Manske (*Can. J. Research*, 1933, **8**, 210) found adlumine, adlumidine, protopine and *bicuculline*. For further information concerning these alkaloids see under *Corydalis*.

Adonis, *N.F. VII. Adonis Vernalis. Pheasants-eye. Spring Adonis. False Hellebore.*—"Adonis is the dried overground portion of *Adonis vernalis* Linné (Fam. *Ranunculaceæ*)." *N.F. VII.*

Adonis vernalis is an erect perennial herb a little less than one foot high, with light green, pinnatified leaves and conspicuous yellow solitary flowers and achene fruits. It is a native of northern Europe and Asia. Its rhizome has occurred in commercial black hellebore as an adulterant. For descriptions of unground and powdered adonis, see *U.S.D.*, 23rd edition.

Adonis æstivalis L., or *summer adonis*, has been substituted for *A. vernalis*. It may be distinguished from the latter by its crimson flowers and by its stem which, unlike that of *A. vernalis*, is branched at the top.

Constituents.—In 1882 Cervelo obtained an active principle from the plant, to which he gave the name *adonidin*. This is, however, a complex material, containing a mixture of glycosides and *adonic acid*. Koch (*Deutsche Apoth.-Ztg.*, 1939, **54**, 442) stated that the activity of *A. vernalis* is due to two glycosides: *adonivernoside*—almost insoluble in water, having, in addition to cardiac activity, a spasmolytic and diuretic effect—and *adonidoside*, a yellowish white, hygroscopic powder easily soluble in water. According to Mercier and Macary (*Compt. rend. soc. biol.*, 1938, **128**, 228) the latter is twice as powerful as adonivernoside. The drug contains also *adonitol*, pentahydroxypentane, occurring as white crystals which melt at about 102°. For a review of the investigation of the glycosides of *A. vernalis* by Karrer, see *Festschrift*, Emil C. Barell, 1936, p. 238.

Other species of adonis seem to possess similar properties. *A. cupanianus* Guss., found in Sicily, is described by Gatto (*Arch. farmacol. sper.*, 1939, **67**, 226), who found its therapeutic action to be similar to that of *A. vernalis*. Tahara (*Ber.*, 1891, **24**) found an allied glycoside *adonin* in the *A. autumnalis*, and Inoko (*Arch. exp. Path. Pharm.*, 1890, **28**) a glycoside also related to adonidin in the *A. amurensis* of Japan.

Uses.—Physiologically, adonis slows the heart by stimulating inhibition and in lethal dose the frog's heart is arrested in systolic spasm. For physiological studies see Schmidt (*Am. J. Pharm.*, 1920, **92**, 702), and Mercier and Delpaut (*Compt. rend. soc. biol.*, 1938, **129**, 319). Adonis was introduced as a cardiac tonic by Bubnow, in 1879, with the claim of advantages over digitalis in that it was more prompt in its action and had less cumulative tendency. While favorable reports of its clinical use have appeared, Hatcher and Haag (*J. Pharmacol.*, 1933, **47**, 217) came to the conclusion that it is distinctly inferior in its therapeutic action to digitalis because of the irregularity of absorption. The drug is rarely prescribed in this country.

Bechterew found that adonis was a useful adjuvant to the bromides in the treatment of epilepsy. Masslow (*Arch. exp. Path. Pharm.*, 1926, **111**, 114) found that it antagonizes such cerebral convulsants as cocaine and picrotoxin. Under the name of *panadonine*, a preparation of the Japanese *A. Davurica* was introduced into medicine not only for its cardiac effect but also as an analgesic in neuralgia.

The N.F. did not provide an assay for adonis. Mercier and Macary (*Compt. rend. soc. biol.*, 1939, **132**, 529) found the guinea pig unsuited to the assay of the drug, while Munch and Krantz (*J. A. Ph. A.*, 1934, **23**, 988) stated that adonis and its preparations, assayed by the 1-hour frog method, should have the same potency as digitalis and its corresponding preparations.

The *dose* of adonis is from 60 to 300 mg. (1 to 5 grains). The glycoside adonidin, referred to under *Constituents*, has been given in *doses* of 5 to 15 mg. (1/12 to 1/4 grain).

Adrenergic Blocking Agents.—SYNONYMS.—Anti-adrenergic agents, adrenolytic agents, sympatholytic agents, sympathicolytic agents.

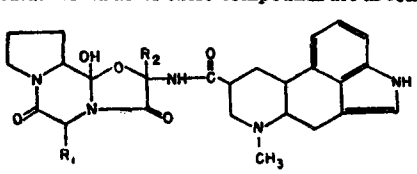
DEFINITION.—An adrenergic blocking agent is a compound the predominant pharmacodynamic action of which is to block certain physiological responses to the injection of epinephrine or to sympathetic (thoracolumbar autonomic) stimulation.

PHYSIOLOGICAL BASIS.—The predominant regulation of blood pressure by the nervous system is mediated through the sympathetic or thoracolumbar division of the autonomic nervous system. Stimulation of sympathetic nerves causes a constriction primarily of the arterioles to produce an elevation in systemic blood pressure. Sectioning of the sympathetic nerve supply to an area of the body results in an immediate vasodilatation within that area. A fall in blood pressure is also seen to follow the paralysis of the sympathetic innervation to the blood vessels innervated by that portion of the autonomic system below the site of spinal anesthesia.

The chemical mediator of sympathetic impulses across the neuromuscular junction between the sympathetic (adrenergic) nerves and the arterioles has been demonstrated to be *arterenol* (*norepinephrine*) or *epinephrine* (*adrenaline*) (von Euler, *Pharmacol. Rev.*, 1951, **3**, 247; Bülbring and Burn, *Brit. J. Pharmacol. Chemother.*, 1949, **4**, 245; Burn, *Irish J. Med. Sc.*, 1951, **308**, 345; Bacq, *J. Pharmacol.*, 1949, **95**, 1). Thus, injection of norepinephrine or epinephrine produces the same general effects of cardio-acceleration or increase in systemic blood pressure that may be seen to follow reflex or direct stimulation of the sympathetic nervous system. Likewise, stimulation of the adrenal medulla to liberate epinephrine causes an increase in systemic blood pressure as well as the other effects of injecting epinephrine.

It is the action of adrenergic blocking agents to abolish the excitatory effects of epinephrine or the adrenergic mediation of sympathetic nervous stimulation. In blocking this action, the compounds have been considered to have potential utility in the management of local or general neurogenic vasoconstriction (Nickerson, *J. Pharmacol.*, 1949, **95**, 27; Goodman and Nickerson, *Med. Clin. N. Am.*, 1950, **34**, 1; Hoobler and Dontas, *Pharmacol. Rev.*, 1953, **5**, 135).

CHEMISTRY.—The ability to block the pressor response to epinephrine is resident in several types of chemical compounds. Perhaps the oldest group of agents wherein this epinephrine-reversal effect was noted is in the ergot alkaloids. For many years it has been known that ergotamine and ergotoxine were capable of reversing the pressor response of injected epinephrine to one of overall vasodilatation (Dale, *J. Physiol.*, 1906, **34**, 163; *ibid.*, 1913, **46**, 291). More recently, because of intensification of work in this field resulting both in the resolution of individual components of ergot alkaloids and in the hydrogenation of several of these components, more active adrenergic blocking agents have been developed (Stoll and Hofmann, *Helv. Chim. Acta*, 1943, **26**, 2070; Rothlin, *Bull. Schweiz. Akad. d. med. Wissensch.*, 1947, **2**, 249). The more promising of these compounds include dihydroergotamine, dihydroergocornine, dihydroergocristine and dihydroergocryptine (Brügger, *Helv. Physiol. et Pharmacol. Acta*, 1945, **3**, 117; Rothlin and Brügger, *ibid.*, 1945, **3**, 519). The structural formulae of these compounds are as follows:

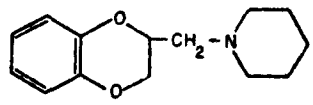


Basic Structure

Dihydroergotamine: $R_1 = C_6H_5CH_2$; $R_2 = CH_3$
Dihydroergocornine: $R_1 = (CH_3)_2CH$; $R_2 = CH(CH_3)_2$
Dihydroergocristine: $R_1 = C_6H_5CH_2$; $R_2 = CH(CH_3)_2$
Dihydroergocryptine: $R_1 = (CH_3)_2CHCH_2$; $R_2 = CH(CH_3)_2$

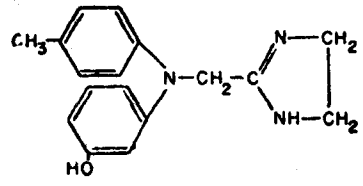
A pharmaceutical combination of the latter three agents is marketed under the trade-mark *Hydergine* (Sandoz).

The first of the generally recognized synthetic adrenergic blocking agents were the Fourneau series of benzodioxanes of which Compounds 933F and 883F have been the more intensively studied (Bovet and Simon, *Arch. internat. pharmacodyn. therap.*, 1935, **52**, 413; *ibid.*, 1937, **55**, 15; Vleeschhouwer, *ibid.*, 1935, **50**, 251; Bovet and Bovet-Nitti, *Medicaments du Systeme Nerveau Vegetatif*, 1948, S. Karger, Basel). One of these (933F) has been marketed under the name of *Benodaine;* its chemical structure is as follows:

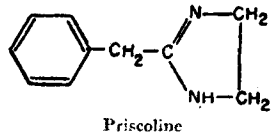


Benodaine

A generally useful type of adrenergic blocking agent is found in the imidazolines. Examples of these compounds include *Priscoline* (Hartman and Isler, *Arch. exp. Path. Pharm.*, 1939, **192**, 141; Chess and Yonkman, *Proc. Sc. Exp. Biol. Med.*, 1946, **61**, 127; Ahlquist *et al.*, *J. Pharmacol.*, 1947, **89**, 271) and *Regitine* (Meier *et al.*, *Proc. S. Exp. Biol. Med.*, 1949, **71**, 70; Moyer *et al.*, *J. Pharmacol.*, 1953, **108**, 240), the latter being the more recently introduced compound. The structural formulae of Regitine (official as *Phentolamine Hydrochloride*) and of Priscoline (official as *Tolazoline Hydrochloride*) are:

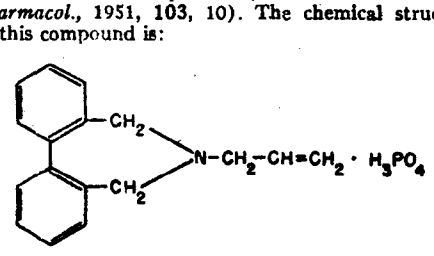


Regitine



Priscoline

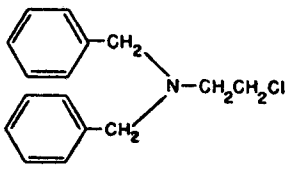
Recently a series of dibenzazepine derivatives have been described as having adrenergic blocking action. The compound identified as Ro 2-3248 (*Azapetine, Ilidar*) has been described as an outstanding example of this class of compounds (Randall and Smith, *J. Pharmacol.*, 1951, **103**, 10). The chemical structure of this compound is:



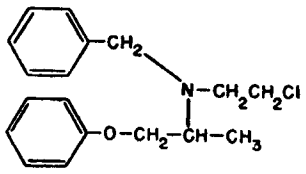
Ro 2-3248 (Ilidar)

Ilidar has been compared pharmacologically with Regitine and Priscoline and was found to be of the order of activity of the latter and 1/10 that of Regitine (Johnson *et al., J. Pharmacol.,* 1953, **108,** 144). Its clinical utility has not yet been established broadly.

The group of adrenergic agents that has received the greatest attention over the past several years is the β-haloalkylamines. Among these compounds are the most potent adrenergic blocking agents and those having the longest duration of action (Nickerson, *J. Pharmacol.,* 1949, **95,** 27). The best known of these compounds is *Dibenamine* (Nickerson and Goodman, *J. Pharmacol.,* 1947, **89,** 167). The one currently receiving most attention in therapeutics is *Dibenzyline* (Woodward *et al., Fed. Proc.,* 1952, **11,** 404; Bannon, *Proc. Mayo,* 1952, **27,** 475; Bakke and Williams, *Am. J. Med.,* 1953, **14,** 141). The chemical structures of Dibenamine and Dibenzyline are as follows:



Dibenamine



Dibenzyline

Yohimbine has been recognized for many years to have adrenergic blocking action (Raymond-Hamet, *Compt. rend. acad. sc.,* 1925, **180,** 2074), but since its utility has been limited to laboratory investigations, primarily, it will not be discussed further in this monograph.

Site of Action.—Principally these compounds block stimulating or excitatory actions of epinephrine and norepinephrine. Thus, the agents will block the rise in blood pressure that follows injection of epinephrine, or the effect of the compound on the nictitating membrane of experimental animals. These agents do not block the inhibitory effect of epinephrine on gastrointestinal activity, the uterus, or the bronchodilator action of epinephrine. Neither do they block the cardio-accelerator action of epinephrine or its effect on the force of contraction of the heart. These two actions of epinephrine are known respectively as its chronotropic and inotropic effects. Thus, the utility of these compounds is limited to the fields of neurogenic hypertension, the relief of localized arterial spasm as in Raynaud's or Buerger's disease, and as diagnostic agents for pheochromocytomas. Another potential utility of several of these compounds is for the inhibition of the development of cardiac arrhythmias that occur spontaneously under chloroform or cyclopropane anesthesia or following the injection of epinephrine or arterenol during surgery. Although all of these agents have these common attributes (Nickerson, *J. Pharmacol.,* 1949, **95,** 27; Goodman and Nickerson, *Med. Clin. North America,* 1950, **34,** 1; Hoobler and Dontas, *Pharmacol. Rev.,* 1953, **5,** 135), they differ markedly among themselves with respect to their other actions, their durations of effect and oral efficacy.

Mode of Action.—The mode of adrenergic blocking action of the ergot alkaloids and their derivatives is not well understood. Actually they have been reported to be potent antagonists to the hypertensive effect of serotonin (Woolley and Shaw, *Fed. Proc.,* 1953, **12,** 293; Fingl and Gaddum, *ibid.,* 1953, **12,** 321). (It will be recalled that serotonin is the hypertensive agent from clotted blood—see under *Sympathomimetic Amines,* in Part II). This lack of specificity of the ergot alkaloids (ergotoxin and dihydroergotamine) would indicate that their effect may be on the mechanism(s) of fundamental importance to the overall metabolism of the tissues affected by epinephrine.

The mode of action of the Fourneau compounds is not understood, although it has been proposed that they alter the permeability of tissue to epinephrine.

The action of Priscoline and Regitine appears to be a mixture of histamine-like, cholinergic, direct vasodilator effect, and a blocking of the excitatory effects of epinephrine (Hermann *et al., Compt. rend. soc. biol.,* 1941, **135,** 1653; Chess and Yonkman, *Proc. S. Exp. Biol. Med.,* 1946, **61,** 127; Yonkman *et al., Fed. Proc.,* 1946, **5,** 216; Ahlquist *et al., J. Pharmacol.,* 1947, **89,** 271; Trapold *et al., ibid.,* 1950, **100,** 119).

The mode of action of Dibenamine and Dibenzyline appears to be due to their cyclization to intermediate ethylenimmonium ions (Nickerson *et al., Fed. Proc.,* 1946, **5,** 195; Nickerson and Goodman, *ibid.,* 1948, **7,** 397), following which these structures hydrolyze to yield inactive compounds. Apparently the onset of action of the agents is determined by their rate of cyclization, which in some instances is very slow (Nickerson and Gump, *J. Pharmacol.,* 1949, **97,** 25). Presumably, the duration of action of the compounds may be due either to their complexing as alkylating agents at the site of action of epinephrine (Nickerson and Gump, *J. Pharmacol.,* 1949, **97,** 25) or to their slow release from fat depots for distribution to the receptor mechanisms (Brodie *et al., Fed. Proc.,* 1951, **10,** 283). The fact that a rearrangement of the compounds is required for their activation can be demonstrated by the parallelism between their *in vitro* rate of titration with thiosulfate and their delayed *in vivo* onset of anti-adrenergic action. That they are strictly anti-adrenergic in action in that they compete with epinephrine for a receptor mechanism can be demonstrated by the ability of prior injections of large amounts of epinephrine to block the action of the anti-adrenergic agents (Nickerson and Gump, *J. Pharmacol.,* 1949, **97,** 25). The ability of Dibenamine to block sympathetic stimulation and norepinephrine effects on blood pressure appears to be less than its ability to reverse the response to epinephrine (Nickerson and Goodman, *J. Pharmacol.,* 1947, **89,** 167). However, it is claimed that this difference is more apparent than real, for epinephrine has a greater vasodilator component to its action than does norepinephrine, which is presumably the mediator of adrenergic impulses at most neuromuscular junctions. Thus, if the adrenergic blocking action of a compound on epinephrine, norepinephrine and other sympathomimetic amines is equated on the basis of vasoconstrictor component of action of the compounds, it is claimed that the blocking action is essentially the same for the several agents (Nickerson and Nomaguchi, *J. Pharmacol.,* 1953, **107,** 284; Nickerson *et al., ibid.,* 1953, **107,** 300).

Pharmacodynamic Actions.—Although the ergot alkaloids have been recognized as adrenergic blocking agents for many years, their clinical utility for this purpose is limited. Indeed, it is doubtful whether they produce any epinephrine blocking action at dosages that do not have other systemic effects (Freis *et al., J. Clin. Inv.,* 1949, **28,** 1387; Barcroft *et al., J. Physiol.,* 1951, **112,** 273). The dosage of the agents is determined more by the tolerance of the patients to

the drug than by the amount which must be administered to produce a therapeutic effect. Thus, the most troublesome side effects of the dihydro ergot alkaloids are nausea and vomiting (Bluntschli and Goetz, *S. African Med. J.*, 1947, **21**, 382; Freis *et al.*, *Am. J. Med. Sc.*, 1948, **216**, 163). It is said that hypertensive patients are more sensitive to these "toxic effects" of the agents than are normal individuals. Although the compounds can be administered orally the dosage must be very carefully adjusted to the individual patient. Apparently, only a small number of hypertensive patients respond to dihydroergotamine (Wilkins *et al.*, *J.A.M.A.*, 1949, **140**, 261). Resistance to the sympatholytic action of dihydroergocornine develops in some patients during long-term oral therapy (Moister *et al.*, *J. Pharmacol.*, 1949, **96**, 21).

The benzodioxanes are less potent adrenergic blocking agents than either the ergot alkaloids or the β-haloalkylamines (Bovet and Simon, *Arch. int. pharmacodyn.*, 1937, **55**, 15; Hermann *et al.*, *Compt. rend. Soc. de Biol.*, 1939, **131**, 282). Although the onset of activity is rapid, their duration of action is limited to 2 or 3 hours. These compounds must be administered intravenously to be effective (Emlet *et al.*, *Am. J. Med.*, 1951, **11**, 241). Consequently, their utility in the treatment of hypertension is strictly limited. Their greatest usefulness has been as an aid to the diagnosis of the pheochromocytoma. The pheochromocytoma is a tumor of the chromaffin tissue of the adrenal medulla, which secretes, intermittently or continuously, excessive amounts of norepinephrine and epinephrine. Consequently, there may be intermittent attacks of severe hypertension or the blood pressure may be sustained at high levels. The administration of Benodaine to these patients usually produces a prompt fall in both systolic and diastolic pressures to or below normotensive levels (Goldenberg *et al.*, *J.A.M.A.*, 1947, **135**, 971; Cahill and Aranow, *Ann. Int. Med.*, 1949, **31**, 389). This is due to the ability of the compound to block the constrictor action of epinephrine and arterenol secreted by the tumor on the receptor mechanism of the arterioles.

The imidazolines, Priscoline and Regitine, are weak adrenergic blocking agents (King, *Fed. Proc.*, 1947, **6**, 345; Goweley, *Brit. J. Pharmacol. Chemother.*, 1948, **3**, 254). Among the imidazolines are compounds that have mixed types of adrenergic, cholinergic, adrenergic blocking, and histamine-like activity (Craver *et al.*, *J. Pharmacol.*, 1944, **82**, 275; Ahlquist, *Am. J. Physiol.*, 1948, **153**, 586; Friedlaender and Friedlaender, *Ann. Allergy*, 1948, **6**, 23). Their principal attribute is that they may be administered orally for the relief of localized arteriospasm. It is likely that their ability to relax blood vessels is due to their histaminic vasodilator action as well as to their adrenergic blocking action. These agents have been used particularly in the treatment of peripheral vasospasm, Buerger's disease, Raynaud's disease, frostbite and causalgia (Kohlmayer, *Wien. klin. Wchnschr.*, 1939, **52**, 1155; Schnetz and Fluch, *Ztschr. klin. Med.*, 1940, **137**, 667; Rogers, *J.A.M.A.*, 1949, **140**, 272). The response to the compounds is not universally good, but they give relief in a sufficient proportion of cases as to warrant their recognition, especially since they may be administered orally.

The β-haloalkylamines, Dibenamine and Dibenzyline, have been studied considerably from the standpoint of their clinical utility. Dibenamine produces gastric irritation and must be administered intravenously to be effective. There is a delay of one or more hours following injection before the compound becomes effective in reducing blood pressure, but its duration of action may persist for 48 hours, or more. Its low solubility requires that it be administered slowly in a large volume by venoclysis. It is most useful in hospitalized patients, for it produces orthostatic hypotension sufficient to produce syncope on standing. The earliest noted effects of the compound include miosis and nasal stuffiness or vasodilatation. If the compound is administered rapidly it may cause profound hypotension, salivation, nausea and mental confusion. Since these haloalkylamines are very irritating, some incidence of thrombophlebitis and phlebothrombosis has been reported (Hecht and Anderson, *Am. J. Med.*, 1947, **3**, 3; Wunsch *et al.*, *Ann. Int. Med.*, 1950, **33**, 613; Goodman and Nickerson, *Med. Clin. North America*, 1950, **34**, 1; Barnett, *Med. J. Australia*, 1951, **1**, 939).

The advantage of Dibenzyline over Dibenamine is said to be its useful order of oral efficacy. This difference in oral efficacy of the two compounds is strictly a quantitative one. The oral utility of these drugs is influenced in large measure by their production of nausea and vomiting. Dibenzyline has a lower propensity to produce these manifestations of gastric irritation than does Dibenamine. Dibenzyline seems to be quite active when administered intravenously. When administered orally the dosage of the compound must be adjusted carefully to the patient. Its effect is said to diminish over the course of administration of several months. Some 87 per cent of patients receiving the compound report nasal congestion. Over half of the patients may experience some indigestion, anorexia, nausea or vomiting. Thus, while utility has been demonstrated for the agent it must await further investigation before its general acceptance clinically can be ascertained. Like Dibenamine, Dibenzyline has a duration of action as long as several days (Haimovici *et al.*, *Proc. S. Exp. Biol. Med.*, 1951, **77**, 477; Moser *et al.*, *Arch. Int. Med.*, 1952, **89**, 708; Bakke and Williams, *Am. J. Med.*, 1953, **14**, 141).

Toxicity.—The toxicities of adrenergic blocking agents relate (1) to their anti-adrenergic activity *per se*, and (2) to their collateral chemical or pharmacodynamic attributes.

Thus, nausea and vomiting produced by the ergot alkaloids are their most frequent drawbacks. As was indicated above, it is unlikely that in dosages in which they are employed in therapy they produce useful adrenergic blocking effects (Goodman and Nickerson, *Med. Clin. North America*, 1950, **34**, 1).

The reactions to rapidly administered Benodaine (benzodioxane) include palpitation, peripheral vasodilatation, excitement, fright or confusion, and hypotension (Goodman and Nickerson, *ibid.*, 1950, **34**, 1). When used as a diagnostic agent it is difficult to divorce the reactions to the sudden fall in blood pressure from those of the compound *per se*. The use of such diagnostic agents for pheochromocytoma is attended by some risk.

The imidazolines may actually produce an elevation of blood pressure and palpitation in some patients. Apparently because of the histaminic action of the compounds they may produce increased gastric acidity (Thiele, *Klin. Wchnschr.*, 1940, **19**, 620; Nasio, *Am. J. Digest. Dis.*, 1944, **11**, 227).

The reactions to Dibenamine and Dibenzyline are mostly referable to their adrenergic blocking action. Thus, they produce profound orthostatic hypotension which in young individuals may be compensated satisfactorily. Older patients do not compensate as well for the orthostatic hypotension and so usually should be confined to a bed during therapy. Nasal stuffiness, dizziness, occasional tachycardia and salivation are manifestations of their adrenergic blocking propensity. The nausea and vomiting may be referable to the irritating action of the compounds when administered orally or perhaps to the redistribution of blood as it accompanies the adrenergic action of the agents.

Toxic reactions to the compounds can be terminated by withdrawing therapy.

Undesirable side effects may be minimized by careful adjustment of dosage and by the slow administration of those agents which must be given by venoclysis.

Hereunder are described the several non-official drugs of this class; the others mentioned above are discussed further in Part I.

Non-official Compounds

Azapetine Phosphate.—*Ilidar* (Roche).—Azapetine is one of a series of dibenzazepine derivatives synthesized and described by Wenner (*J. Org. Chem.*, 1951, **16**, 1475); it is 6-allyl-6,7-dihydro-5H-dibenz-[c,e]azepine (see formula, p. 1527). Pharmacologic studies of 18 of these compounds were published by Randall and Smith (*J. Pharmacol.*, 1951, **103**, 10), who pointed out that the more potent derivatives of dibenzazepine have many of the pharmacodynamic properties common to imidazoline and benzodioxane derivatives. Azapetine was reported by Randall and Smith (*loc. cit.*) to have an acute intravenous toxicity in mice of 26 mg. per Kg. and in dogs of 50 mg. per Kg. Sublethal doses produce central excitation, disorientation and tremors. The principal attribute of this compound as it represents this series is its ability to block adrenergic vasoconstriction. Thus, the compound blocks effectively the pressor action of epinephrine and of arterenol, the pressor response to carotid sinus stimulation, and the nictitating membrane response to epinephrine, arterenol and electrical stimulation of the superior cervical ganglion of the cat. Like other adrenergic blocking agents, it has no significant effect on gastrointestinal motility as measured *in vitro* on isolated intestinal strips and on the motility of the Thiry-Vella intestinal loop in dogs.

In isolated heart preparations azapetine is reported to be a vasodilator of roughly the same order of activity as papaverine. Like other adrenergic blocking agents, azapetine blocks the effect of epinephrine-induced cardiac arrhythmias under chloroform anesthesia. It does not block the accelerator effect of epinephrine on heart rate to any appreciable extent. It is claimed that more nearly the same dose of azapetine is required to block both epinephrine vasoconstriction and that produced by sympathetic stimulation, whereas with the other classic adrenergic blocking agents substantially higher doses are required to block sympathetic stimulation than epinephrine vasoconstriction.

Page and McCubbin (*Am. J. Physiol.*, 1953, **173**, 411) and Handley and Moyer (*J. Pharmacol.*, 1954, **110**, 277) are agreed that azapetine produces a renal vasodilatation and an increase in renal blood flow, in spite of the decrease produced by the compound in mean systemic blood pressure in the dog. Azapetine is active when administered orally in contrast to most adrenergic blocking agents, but the duration of action persists for only an hour or so. Moore *et al.* (*J. Pharmacol.*, 1952, **106**, 14), Johnson *et al.* (*ibid.*, 1953, **108**, 144) and Griffin and his associates (*ibid.*, 1954, **110**, 93) studied azapetine and compared it to phentolamine (Regitine) and benzazoline (Priscoline) for adrenergic blocking action in innervated and denervated vascular beds to the skin and muscle. In general, they found azapetine to have the same order of activity as benzazoline, and both of them to be 1/6 to 1/10 as active as phentolamine.

Green and DuBose (*Circulation*, 1954, **10**, 374) studied the effects of azapetine in some 86 patients with peripheral vascular diseases. They found it to produce symptomatic benefit in about 1/3 of the patients having arteriosclerosis obliterans and to be a useful agent in the relief of spasm occasioned by sudden arterial occlusion, thromboangiitis obliterans, Raynaud's disease and post-phlebitic syndrome.

The side effects of azapetine include a moderate postural hypotension occasioned by sympathetic blockade and accompanied by weakness, dizziness, fatigue and nausea. These side effects may be minimized by careful adjustment of dosage. Azapetine is usually contraindicated in patients having a history of asthma, in incipient shock or in conditions in which postural hypotension may exist. It is recommended that the agent be used with caution in patients having a history of respiratory distress or peptic ulcer.

Dose.—Azapetine is available in coated tablets containing 25 mg. of azapetine in the form of its phosphate. Two or three tablets (50 to 75 mg.) may be administered 4 times daily. The dosage should be adjusted carefully to the patient in order to produce an optimal hypotensive effect with minimal side effects such as would be produced by profound sympathetic blockade.

Dibenamine Hydrochloride (Smith, Kline & French).—This substance, N,N-dibenzyl-β-chloroethylamine hydrochloride, is a sympatholytic and adrenolytic agent; it is structurally related to the nitrogen mustards. This compound was the first of this general class of adrenergic blocking agents, of which Dibenzyline is the available example on the market. The pharmacologic properties of Dibenamine were described first by Nickerson and Goodman (*J. Pharmacol.*, 1947, **89**, 167; *ibid.*, 1949, **95**, 27). Its adrenergic blocking action is characterized by a delayed onset requiring an hour or so following its intravenous administration for full effect. It must be administered intravenously and in large volume slowly because of its necrotizing effect. Consequently, it cannot be administered subcutaneously or intramuscularly safely. The compound is not active when administered orally. The duration of action persists for 36 to 96 hours in man. The compound causes a reversal of the pressor effect of intravenously administered epinephrine and depresses the pressor response to the injection of norepinephrine or to the stimulation of sympathetic innervation either directly or reflexly. The adrenergic blocking action of the agent pertains to the effect of epinephrine on the vascular system and not to the gastrointestinal responses to that sympathomimetic agent. These general attributes have been reviewed most adequately by Nickerson (*Pharmacol. Rev.*, 1949, **1**, 27).

The fact that the compound is not active when administered orally and is tedious to administer intravenously has precluded its general clinical use. The agent has not been made available on the open market and is only available for clinical investigation. It has been found to have little effect on the normotensive individual with respect to blood pressure, heart rate and electrocardiogram. In the presence of neurogenic vascular spasm the compound produces an increase of peripheral blood flow and an elevation in skin temperature due to the blocking of sympathetic innervation of the cutaneous vessels. The translation of this pharmacodynamic attribute to the clinic has shown it to produce vasodilatation beneficial in Buerger's disease, Raynaud's disease, frostbite and acute arterial occlusion. The agent has been employed preoperatively in an attempt to predict the result of surgical sympathectomy (Consolo, *Am. J. Med.*, 1948, **5**, 164). Also, it had been employed successfully in diagnosis and preoperative care of pheochromocytoma (Griswold, *New Eng. J. Med.*, 1948, **239**, 736). There has been some interest and claim for the utility of Dibenamine in the management of schizophrenia and anxiety states (Medinets *et al.*, *Proc. S. Exp. Biol. Med.*, 1948, **69**, 238; Sulli-

van, *Gastroenterology*, 1949, **13**, 564). There is a substantial literature with respect to the utility of this agent on an experimental basis. Unfortunately, its physical and secondary pharmacologic attributes are not conducive to its general use.

The compound causes orthostatic hypotension, nasal congestion, miosis and loss of time perception in some cases. Too rapid infusion may cause nausea, vomiting and central nervous system excitation or tremors. Direct intravenous infusion of the 5 per cent solution may cause thrombosis. Extravasation of the solution may cause local tissue necrosis.

A single *dose* for an adult is 4 to 6 mg. per Kg. of body weight; the single total dose should not exceed 500 mg. The solution of the compound should be added to 300 to 500 ml. of sterile isotonic sodium chloride with or without 5 per cent dextrose. The rate of flow should be adjusted so that the volume is administered over a total period of 45 to 60 minutes. The dose may be repeated 2 to 3 times weekly.

DIBENZYLINE HYDROCHLORIDE (Smith, Kline & French). — This substance, N-phenoxyisopropyl-N-benzyl-β-chloroethylamine hydrochloride (see formula, p. 1528), is an adrenergic blocking agent for which oral as well as intravenous efficacy for the reduction of hypertensive blood pressure has been claimed. The results of its trial in hypertensive patients have been variable. Moser *et al.* (*Circulation*, 1953, **8**, 224) described it as orally effective, moderately potent, and as having a long duration of action. On the other hand, Corcoran, Taylor and Harrison (*Proc. S. Exp. Biol. Med.*, 1952, **80**, 265) reported it to be ineffective in their hands in the treatment of essential hypertension. Whereas Gill *et al.* (*Am. J. Med. Sc.*, 1953, **226**, 249) did not consider Dibenzyline to be satisfactory in the treatment of arterial hypertension when administered orally alone, they found that when combined with low-sodium cation exchange resin therapy a fall in blood pressure could be induced. Moser and his associates (*Ann. Int. Med.*, 1953, **38**, 1245) reported Dibenzyline to be more potent than Priscoline in vasospastic and causalgic states, but only occasionally was it superior to the latter drug in thromboangiitis obliterans and arteriosclerosis. They caution that in older arteriosclerotic patients Dibenzyline should be used with care. Bakke and Williams (*Am. J. Med.*, 1953, **14**, 141) indicated that in spite of their observations that about one-third of the patients had a decrease in blood pressure during initial course of Dibenzyline therapy, only 13 per cent of the patients reported subjective improvement. These patients were relieved of headache or angina pectoris.

When administered orally, and especially so when administered intravenously, the most common complaint of patients was nasal congestion. Dizziness, especially as associated with upright posture (orthostatic hypotension) is also a common complaint. Consequently, most patients are more comfortable when confined to bed during therapy. Indigestion, nausea and anoxia are frequent undesirable signs, but they are not of serious consequence.

The oral *dose* of Dibenzyline is said to be 30 to 240 mg. daily. This dosage must be adjusted carefully to the needs of the patient if it is to be effective without undesirable manifestations or side effects.

HYDERGINE (Sandoz).—This preparation consists of equal parts of a mixture of 3 hydrogenated ergot alkaloids (see also under *Ergot*, in Part I), these being dihydroergocornine, dihydroergocristine, and dihydroergocryptine, in the form of their methanesulfonate salts. Hydergine is used in peripheral vascular diseases such as Raynaud's syndrome, Buerger's disease, frostbite, thrombophlebitis, arteriosclerosis obliterans; for varicose ulcers, and in essential hypertension.

Dihydroergocornine (DHO 180, Sandoz) has received extensive clinical trial but is marketed only in combination with the two other hydrogenated alkaloids. Like ergotamine, ergocristine and ergocryptine, ergocornine has adrenergic-blocking action (Goetz and Katz, *Lancet*, 1949, **256**, 561); ergonovine does not have such action. In addition to this action, these alkaloids stimulate smooth muscle directly and have complex excitant and depressant effects on the central nervous system. Hydrogenation increases the adrenergic-blocking action and decreases the direct muscle action but DHO 180 retains some oxytocic action. Its adrenergic-blocking action is second only to that of Dibenamine in animals when used in adequate doses (Nickerson, *J. Pharmacol.*, 1949, **95**, 27) but in man the blocking action cannot be obtained because nausea, vomiting and malaise limit the dose to 0.3 mg. intravenously or 20 mg. orally.

Its clinical effects are chiefly on the central nervous system (Goetz, *Lancet*, 1949, **256**, 510). It lowers blood pressure in some hypertensive patients (Fries *et al.*, *Am. J. Med. Sc.*, 1948, **216**, 163) when given parenterally or orally, but tolerance develops rather rapidly (Josephs, *Am. Pract.*, 1949, **4**, 71; Moister *et al.*, *J. Pharmacol.*, 1949, **96**, 21). Tolerated doses do not affect blood pressure in normotensive persons. In the hypertensive patient it causes a decrease in both the systolic and diastolic blood pressure, a decrease in heart rate, a slight increase or no change in cardiac output, a transient decrease in hepatic and renal blood flow, an increase or no change in blood flow in the arms and legs, a rise in skin temperature, and elimination of vasomotor reflexes (Wilkins *et al.*, *J.A.M.A.*, 1949, **140**, 261; Freis *et al.*, *J. Clin. Invest.*, 1949, **28**, 1387; Hays *et al.*, *ibid.*, 1949, **28**, 615). Oral administration of dihydroergocornine for 3 to 9 months gave favorable results in 12 of 25 patients with arteriosclerosis obliterans, 2 of 14 with vasospastic disorders, but not in a patient with embolic occlusion (Popkin, *California Medicine*, 1950, **72**, 108). It did not cause angina pectoris or changes in the electrocardiogram in patients with enlarged left ventricles (Scherf *et al.*, *Proc. S. Exp. Biol. Med.*, 1949, **71**, 420).

Presently the combination of the 3 hydrogenated alkaloids is marketed because it is cheaper to produce, it has been shown to be equally effective, and it is perhaps less toxic in doses of equivalent action. In hypertension, Hueber and Wohlrab (*Münch. med. Wchnschr.*, 1951, **93**, 2157) reported subjective improvement without change in blood pressure in 4 of 10 aged, hypertensive patients. Both subjective and objective improvement was recorded in 12 menopausal, hypertensive cases, and in 3 of 9 cases of essential hypertension. No improvement was observed in hypertensive patients with nephritis and in those with malignant hypertension. Intramuscular administration was the most effective route, and sublingual tablets were several times as effective as oral administration. Using oral administration, supplemented with intramuscular doses if needed, Odenthal (*Deutsche med. Wchnschr.*, 1951, **76**, 1107) reported relief from symptoms of headache and dizziness in 122 of 218 ambulatory patients with hypertension, although only 19 per cent of hospitalized cases were relieved of symptoms. The average decrease in systolic pressure was about 25 mm. and of the diastolic pressure 13 mm. of mercury. Wilbrandt (*Angiology*, 1953, **4**, 183) used subcutaneous injections daily or on alternate days for 10 to 20 doses, followed by sublingual administration; among 100 patients with stage I or II hypertension (graded according to the changes in the retinal vessels) symptoms were relieved in 80 per cent but blood pressure decreased in only 5 per cent; among 100 patients with severe hypertension, stage III or IV,

symptoms were relieved in 52 per cent and blood pressure was decreased in 31 per cent. When a placebo was substituted the patients relapsed; no tolerance to the drug was observed to develop.

Tandowsky (*Circulation*, 1954, **9**, 48) evaluated the parenteral use of this preparation for 2 weeks to 1 year in 100 patients and concluded that the transitory effect on blood pressure and pulse rate made this preparation impractical in ambulatory patients but in 22 cases with manifestations of early cerebrovascular derangement, such as headache, brief hemiplegia, sudden loss of memory, etc., the parenteral use, particularly by intravenous injection, of Hydergine relieved the manifestations.

Snyder *et al.* (*Am. Pract. Dig. Treat.*, 1954, **5**, 299) treated 20 patients with essential hypertension with sublingual tablets 4 times daily, commencing with 0.3 mg. and increasing the dose until therapeutic response or incapacitating side effects appeared. On the average these patients received 12.8 mg. daily, with a range of 2.4 to 30 mg. Only 3 of 20 patients showed a decrease in blood pressure and side effects, including nausea, vomiting, headache, dizziness, blurring of vision, skin rash, anorexia and abdominal cramps, preventing continuation of treatment. In another 20 patients, Hydergine was injected subcutaneously, commencing with 0.3 mg. every 6 hours and increasing this dose to effectiveness or tolerance; in 5 there was a reduction of mean blood pressure of 20 to 30 mm. of mercury and 5 decreased more than 30 mm.; when sublingual therapy was substituted all but 1 patient returned to the pre-treatment blood pressure level. It was ineffective in cases of malignant hypertension but it was recommended for short-term use parenterally in moderately severe hypertension complicated by renal failure since precipitous drops in blood pressure which may aggravate renal failure are seldom caused by Hydergine. Numerous reports of symptomatic benefit with Hydergine in patients with hypertension have appeared (Josephs, *Am. Pract. Dig. Treat.*, 1949, **4**, 71; Nuzum, *Ann. West. Med. Surg.*, 1950, **4**, 781; Schultz, *Am. Pract. Dig Treat.*, 1953, **4**, 330; Grenfell, *ibid.*, 1954, **5**, 532). The last-named gave injections 3 times weekly for 2 weeks, then twice and later once weekly for 2-week periods each, and finally every 2 weeks; both decrease in blood pressure and relief of symptoms resulted.

In peripheral vascular disease, Zeman and Finkemeyer (*Deutsche med. Wchnschr.*, 1951, **76**, 1207) reported improvement of intermittent claudication in 14 of 30 patients following oral or parenteral use of Hydergine. Ehren (*ibid.*, 1334) reported marked improvement in 3 of 18 cases with arteriosclerotic peripheral vascular disease, 18 of 33 with endarteritis obliterans, 24 of 31 with vasospastic peripheral vascular symptoms, and in all 6 patients with symptoms following frostbite. Roberts *et al.* (*Am. J. Med. Sc.*, 1952, **224**, 431) used 0.5 to 2 mg. orally 4 times daily in 72 patients and observed significant improvement in those with organic vascular disease, particularly those with ulceration, but little benefit in those with spastic vascular disease. Luke and Marien (*Can. Med. Assoc. J.*, 1953, **68**, 221) described marked improvement in 8 of 10 patients with arteriosclerosis obliterans with 0.5 to 1 mg. sublingually 4 times daily. Eichler and Heinzel (*Arch. klin. Chir.*, 1954, **278**, 568) reported on 157 patients studied over a period of 5 years. Twenty-five of 60 cases of Buerger's disease had good results; 20 who had been subjected to sympathectomy without relief were benefited by Hydergine therapy. Amputation was avoided in 16 of 27 cases. Of 44 cases with arteriosclerotic peripheral vascular disease, 10 obtained good and 17 satisfactory results. Seven of 12 cases with arterial embolism were benefited. Eleven of 13 cases with Sudeck's atrophy of bone, 11 of 13 with Raynaud's syndrome, and 4 of 11 with indolent leg ulcers were benefited. Mild cases received 0.5 to 1 mg. sublingually 4 times daily; moderate cases received 0.3 to 0.6 mg. subcutaneously daily in addition to the sublingual dose; severe cases also received 0.3 to 0.6 mg. by intraarterial injection daily in addition. July and Babilliot (*Semaine hôp. Paris*, 1954, **30**, 4369) reported improvement in patients with peripheral vascular diseases with oral and subcutaneous therapy and intraarterial injections of Hydergine dissolved in 10 ml. of 1 per cent procaine hydrochloride solution.

In patients with migraine, Bercel (*Am. Pract. Dig. Treat.*, 1955, **6**, 348) used dihydroergotamine in treatment of attacks but Hydergine daily sublingually as a prophylactic measure with a decrease in incidence of headaches of 71 per cent. Popkin (*ibid.*, 1952, **3**, 532) used Hydergine effectively in the relief of a variety of symptoms in aged patients.

Dose.—The usual dose sublingually is 2 to 3 mg. daily in divided doses every 4 to 6 hours. Subcutaneously or intramuscularly, the usual dose is 0.3 to 0.6 mg. daily or on alternate days. Oral administration is rather ineffective. Intraarterial injection is used (*v.s.*).

Hydergine is available in sublingual tablets of 0.5 mg. and in 1-ml. ampuls containing 0.3 mg.

Piperoxane Hydrochloride. *Benodaine Hydrochloride* (Merck), Compound 933F.—This substance is 2-(1-piperidylmethyl)-1,4-benzodioxane hydrochloride (see formula, p. 1527), an odorless, crystalline powder, freely soluble in water. Its solutions may be autoclaved, are stable to light and on storage.

Piperoxane hydrochloride is an adrenergic-blocking agent of short duration of action which has come into use as a diagnostic test to distinguish between essential hypertension and the hypertension due to an epinephrine-secreting tumor (pheochromocytoma). In the test a solution containing 2 mg. per ml. is injected into the tubing through which a slow intravenous infusion of normal saline solution is being administered to the patient; the dose of piperoxane hydrochloride is 10 mg. per square meter of body surface (about 0.25 mg. per kilogram of weight, or about 20 mg. for the average adult). If the patient's hypertension is due to an epinephrine-secreting tumor, a significant drop in blood pressure occurs in about 4 minutes and persists for about 10 minutes; in other hypertensive patients the pressure is unchanged or may rise. Drill (*New Eng. J. Med.*, 1949, **241**, 777) reported rises to 300 mm. systolic pressure, with nausea, headache, dizziness, and precordial pain, in two hypertensive patients. Negative tests have been obtained in patients with tumors, while positive tests in patients in whom no tumor could be found have been reported (Taliaferro *et al.*, *J.A.M.A.*, 1949, **140**, 1271). Before operating on the basis of a positive test this should be compatible with clinical features and should be checked with the histamine test (Roth and Kvale, *Am. J. Med. Sc.*, 1945, **210**, 653), the methacholine test (Guarneri and Evans, *Am. J. Med.*, 1948, **4**, 806), and/or the tetraethylammonium ion test (LaDue *et al.*, *Ann. Int. Med.*, 1948, **29**, 914).

The more recent indications that some pheochromocytomas may contain a predominant amount of arterenol or noradrenaline have provoked a re-evaluation of the reliability of the piperoxane test for this laboratory diagnosis. The reason for this concern has been the relative insensitivity of arterenol to adrenergic blocking agents generally. However, Goldenberg *et al.* (*Arch. Int. Med.*, 1950, **86**, 823; *J.A.M.A.*, 1950, **143**, 1139) and others confirmed the utility of piperoxane for this diagnostic purpose even when the gland content of pressor amine was found on extirpation to be predominantly norepinephrine (arterenol) (Koffler *et al.*, *J. Clin. Endocrinol.*, 1950, **10**, 897; Conference on Therapy, *Am. J. Med.*, 1954, **16**, 574).

Aerosol Antiseptics.—The term "aerosol" signifies minute particles—liquid or solid, organic or inorganic—dispersed in air; the liquid droplets are usually from less than 1 micron to 2 microns in diameter. Unfortunately there is some confusion of this term with the surface-active agents known as Aerosol, as *Dioctyl Sodium Sulfosuccinate.*

A true liquid aerosol does not wet surfaces which it touches, regardless of the rate at which it flows or the quantity of liquid at the outlet of the generator. Moreover, such an aerosol offers considerable resistance to dissolution in the solvent serving as the vehicle for its dispersion; thus, an aerosol dispersed from an aqueous solution of eosin or fuchsin or toluidine blue and then splashed into or through successive flasks containing water will color it only slightly or not at all (Dautrebande, *Physiol. Rev.,* 1952, **32,** 215).

The idea that it would be possible to kill bacteria floating in the air by spraying antiseptic solutions was originally applied by Lister in 1867 in the operating room. The phenol which he used for this purpose, however, proved so toxic to the surgeon that the method was completely abandoned. In 1938 Masterman showed that an atomized solution of sodium hypochlorite would kill air-borne bacteria when present in as small a proportion as 1 Gm. of NaOCl in 40,000 liters (1400 cu. ft.) of air. A considerable number of other antiseptics has been tried.

Studies by Robertson and his colleagues at the University of Chicago, first reported in 1941, indicated that both propylene glycol and triethylene glycol vapors are highly bactericidal against many organisms, including their spores. Triethylene glycol had come to be the agent of choice for aerial disinfection of environments occupied by human beings, for as little as 1 ml. of glycol in several hundred million ml. of air proved to be lethal to the common respiratory bacteria, pathogenic and non-pathogenic, as well as to the viruses of influenza, psittacosis and meningopneumonitis (see Robertson, *Am. J. Med.,* 1949, **7,** 293). Germicidal concentrations of the vapor are odorless, tasteless, non-irritating, non-toxic, invisible (except for production of a Tyndall beam when a mist is produced) and have no deleterious effects on walls, fabrics, books and other objects.

A fairly wide use of triethylene glycol for air sterilization in hospital wards, military barracks, schoolrooms and other public places indicates that the glycol may be effective in controlling air-borne infections, although some of the results are inconclusive (Robertson, *loc. cit.;* Sahyun, *Stanford M. Bull.,* 1948, **6,** 457). Nagy and Mouromseff (*Science,* 1950, **112,** 593; 1951, **113,** 698), studying the effect of vaporized or atomized propylene glycol and triethylene glycol on *E. coli* dispersed in air, concluded that the glycol vapors are not germicidal but simply accelerate the rate of settling of the bacteria. Lester, Dunklin, and Robertson (*ibid.,* 1952, **115,** 379), reporting their own experiments showing that the vapors of the glycols are bactericidal against *E. coli,* infer that insufficient glycol was used in Nagy and Mouromseff's experiments; the former investigators did find, however, that triethylene glycol vapor acted more slowly and produced a considerably lower rate of kill of organisms than did propylene glycol, an observation apparently contrary to earlier findings as to the relative efficiency of the glycols for a number of different kinds of bacteria (Robertson *et al., Science,* 1943, **97,** 142). The concentration of propylene glycol used by Lester and his co-workers ranged from 0.2 to 0.4 mg. per liter of air (equivalent to 1 to 2 times saturation), while the concentration of triethylene glycol ranged from 10 to 25 micrograms per liter of air (equivalent to 2 to 10 times saturation). A relative humidity between 15 and 40 per cent is essential for optimum activity of the glycols.

The term *aerosol therapy* or *inhalation therapy* refers to the use of a dispersion of liquid particles (though sometimes also of a dispersion of solid particles) in a gas for inhalation treatment. Various drugs may be thus administered, a suitable nebulizer being essential. For an excellent discussion of this type of therapy see Dautrebande (*Physiol. Rev.,* 1952, **32,** 214), Rooth (*Acta med. Scandinav.,* Supplement 228, 1949, "Inhalation of Liquid Aerosols," in English), also Cobe (*J. A. Ph. A., Prac. Ed.,* 1949, **10,** 88).

Æsculus. *Horse-chestnut.*—The *Æsculus hippocastanum* L. (Fam. *Hippocastanaceæ*) or horse chestnut tree seems to have been originally a native of Asia but is now grown as an ornamental tree in Europe and America. The seeds or "nuts" contain about 49 per cent of starch and nearly 4 per cent of oil. They have a very bitter taste and are probably poisonous in the raw state but it is said that they are used after roasting by the Indians as a food. In Germany the oil is being extracted commercially.

The bark contains considerable amounts of a strongly hemolytic saponin (*escin*) which has been suggested as a substitute for quillaja (*Deutsche Apoth.-Ztg.,* 1939, **54,** 416) as an emulsifying agent. The most interesting constituent of the bark is a glucoside, *esculin* (*æsculin*), also called *polychrome, bicolorin, enallochrom* and *esculinic acid.* It has been identified as 6,7-dihydroxycoumarin-6-glucoside; on hydrolysis it forms *esculetin* (6,7-dihydroxycoumarin) and glucose. Aqueous solutions of esculin and esculetin show a blue fluorescence when the pH is above 5.8. Several other principles, such as the glycoside *argyræscin* and *capsulæscinic acid,* have been reported but are of little importance.

Following intravenous administration of *Venostasin,* an extract of horse chestnut, an increase in capillary and erythrocyte resistance and an apparent increase in plasma antithrombin activity were noted in most of the 20 patients thus treated by Perlick and Bödecker (*Münch, med. Wchnschr.,* 1951, **93,** 1465). In 40 patients, Enders (*Die Medizinische,* 1953, **22,** 755) used this extract for venous stasis with benefit; embolism was not observed in patients with thrombosis in the legs.

Esculin is used in about a 4 per cent solution or ointment to protect the skin from sunburn. It has the property, like other fluorescent substances, of absorbing ultraviolet rays.

It is probable that our native species, which are popularly called *Buckeye*—such as *Æsculus glabra* Willd. and *Æ. Pavia* L.—have similar properties although we know of no definite proof.

Agaric. *Agaricus, N.F. V. Agaricus Albus. White Agaric. Larch Agaric. Touch-wood. German Tinder.* "Agaric is the dried fruit body of *Polyporus officinalis* Fries (Fam. *Polyporaceæ*) deprived of its outer rind." *N.F. V.*

The term "agaric" is more properly applied to the fungi of the genus *Agaricus,* but the majority of medical writers limit it to the fungus from *Polyporus officinalis* Fries (*Boletus laricis* Jacquin; *B. purgans* Persoon), which is found upon the old trunks of various coniferous trees of the eastern and western hemispheres. It varies in size, from that of the fist to that of a child's head, and is hard and spongy, externally brownish or reddish. As found in commerce, it is deprived of its exterior coat, and consists of a light, white, spongy, somewhat farinaceous, friable mass.

Impregnated with potassium nitrate, and afterwards dried, it constitutes *spunk, punk,* or *tinder* (*amadou* of the French), capable of absorbing liquids, and flammable. Punk is said to be prepared also from various other species of *Polyporus,* as *P. ungulatus, P. ribis,* etc.

Microscopically, powdered agaric is characterized by numerous non-septate, narrow, mycelial threads and

few prismatic or cubical crystals of calcium oxalate from 0.010 to 0.040 mm. in diameter.

The most interesting constituent of the plant is *agaric acid* (also called *agaricin, agaricic acid, laricic acid*). This tribasic acid is α-n-hexadecyl citric acid, $C_{19}H_{36}OH(COOH)_3.1\frac{1}{2}H_2O$. It forms odorless tasteless crystals, melting at 142°, which are slightly soluble in water.

The chief physiological effect of agaric acid is to stop secretion of sweat. There has been considerable discussion of the mechanism of this antihydrotic effect. Because it antagonized the effect of pilocarpine on the sweat glands but not on the salivary, Hattori (*Ber. gesam. Physiol.*, 1934, 86, 671) concluded that its action was directly on the gland structure and not through the parasympathetic nerves. McCartney (*J. Pharmacol.*, 1917, 10, 83) proposed the remarkable theory that the antihidrotic effect is due to spasms of the muscular layers of the skin. In large doses agaric acid has also an action on the medullary centers, at first increasing blood pressure and respiration and later depressing them. In overdose it also causes vomiting and purging, probably from local irritation of the alimentary mucous membrane.

Agaric and agaric acid were formerly used in the treatment of the colliquative sweats of wasting conditions, such as tuberculosis. Opinion differed as to its value.

Under the name *agaricin* were marketed preparations containing the active agaric acid, with larger or smaller amounts of impurities. The pure principle was administered in a *dose* of 10 to 30 mg. (approximately 1/6 to 1/2 grain).

Dose, of agaric, 0.3 to 1 Gm. (approximately 5 to 15 grains).

Fungus chirurgorum. Boletus chirurgorum. Boletus igniarius. Oak-agaric.—Surgeon's agaric is formed by *Polyporus fomentarius* (L.) Fries, growing upon the oak and beech trees of Europe. The inner part of the fungus, beaten to a soft texture and sterilized, was formerly used by surgeons for arresting hemorrhage, being applied with pressure. Its hemostatic effect was probably purely mechanical. *P. ignarius* (L.) Fries and *P. marginatus* Fries yield similar products.

Agave. *Agave americana* L. *American Aloe. Century Plant. Flowering Aloe. Spiked Aloe. Maguey.* (Fam. *Amaryllidaceæ.*)—An evergreen succulent plant, indigenous to Florida, Mexico, and other parts of tropical America, and cultivated, for hedges in Spain. Botanists have described 50 species of the genus, *Sisal grass* or *sisal hemp* and *Tampico hemp,* also known as *Pita hemp* or *Pita fiber,* are the most important of the various fibers obtained from the agave leaves. From a number of species of *Agave* are produced in Mexico large quantities of a fermented liquor, known as *pulque,* and distilled liquors known as *mescal* or *tequila.* All of the pulque agaves have thick leaves. When they are about to bloom the central bud is cut out, leaving a large cavity into which the sap (*aguamiel* or *honey water*) exudes rapidly. At first clear green, yellowish or whitish, this sap soon by fermentation becomes milky and acquires a cider-like taste or, if the process is allowed to go on, is rapidly converted into vinegar. Pulque is said to contain about 7 per cent of alcohol, and is used as a beverage. The juice has in it an optically inactive reducing sugar, *agavose,* $C_{12}H_{22}O_{11}$. The juice and also the herbage of the agave contain a saponin and are used in Mexico in the place of soap. For chemical and physiological study of this saponin see Jones *et al.* (*J. A. Ph. A.*, 1932, 21, 787).

Agrostemma. *Corn Cockle. Purple Cockle. Corn Rose. Corn Campion. Crown-of-the-Field.*—The *A. githago* L. (Fam. *Caryophyllaceæ*) is an annual herb with a few erect branches and densely pubescent throughout; it bears linear lanceolate leaves and red flowers about 2 inches broad. It is a native of Europe but has been naturalized in this country where it is a troublesome weed in the winter wheat fields. It contains two saponins known as *githagin* and *agrostemmic acid.* These saponins are absorbable from the alimentary canal and may produce systemic poisoning. Besides gastrointestinal irritation, severe muscular pains and twitching, respiratory depression and coma may occur. Poultry and live stock are poisoned by the seeds of the corn cockle. Wheat may sometimes contain these seeds. (See Muenscher, *Poisonous Plants of the United States,* Macmillan Co., New York, 1951).

Albumin Tannate. *Albumini Tannas, U.S.P. XI. Tannin Albuminate. Albutannin.*—Various compounds of tannin with protein substances have been introduced into medicine under proprietary names. The substance *Tannalbin* (Bilhuber-Knoll) is said to be made by precipitating egg albumin with tannic acid (see Ott, *Pharm. Ztg.*, 1927, 68, 388).

Albumin tannate is a "yellowish-white, odorless powder. It is almost insoluble in water, in alcohol, in chloroform, and in ether. It is decomposed by aqueous solutions of alkali hydroxides and carbonates." *U.S.P. XI.* For results of tests of the solubility of different brands of tannin albuminate see Leach (*J.A.M.A.*, 1920, 75, 1129).

Although, as shown by Sollmann (*J. Pharmacol.*, 1921, 17, 63), most commercial preparations of albumin tannate are more or less soluble in water and slightly astringent, this effect is probably due to presence of uncombined tannin as an impurity. When submitted either to peptic or pancreatic digestion the compounds are gradually hydrolyzed, liberating tannic acid, which exercises its characteristic astringent effect. The digestion by pepsin is, however, so slow that under ordinary conditions it is not probable that any considerable amount of tannin will be liberated in the stomach. Therefore, the astringent effect is felt mostly in the intestinal tract. Pancreatic digestion is also very slow, so that an astringent action will be continued through almost the whole of the alimentary canal. As the tannin is liberated gradually the astringency will evidently be comparatively mild in its effect.

Albutannin was used in medicine as an astringent in the treatment of diarrheas, having the advantage over vegetable astringents in that it is much less likely to produce gastric disturbances. It was used in chronic enteritis involving the lower portions of the small bowel and colon. V

Dose, from 1 to 4 Gm. (15 to 60 grains) 3 or 4 times a day.

Aldrin. 1,2,3,4,10,10-Hexachloro-1,4,4a,5,8,8a-hexahydro-1,4,5,8-dimethanonaphthalene. $C_{12}H_8Cl_6$.—Pure aldrin is a white, crystalline solid, substantially odorless at room temperature but having a mild pine-like odor when warm, insoluble in water but soluble in many organic liquids; the melting point of the pure material is about 104°. The commercial grade of the substance is required to contain not less than 95 per cent of pure aldrin. The stability of aldrin in the presence of alkalis is notable among halogenated insect toxicants.

Aldrin and its chemical relative dieldrin both function as contact and stomach poisons toward a wide variety of insects, appearing to be substantially more potent than other insecticides in common use. A critical evaluation of their effectiveness requires more extensive trials of the products under different conditions of use. For data on relative toxicities of aldrin and other insecticides on different insects see Lidov *et al.* in *Agricultural Control Chemicals,* American Chemical Society, 1950, p. 175.

When administered in edible oil to albino rats, the acute toxicity, expressed as LD_{50}, is 40 to 50 mg. per Kg. of body weight. Since aldrin is a chlorinated hy-

drocarbon it may be expected that cases of human poisoning which may occur will show symptoms typical of intoxication by chlorinated hydrocarbons, namely stimulation of the central nervous system and disturbance of the gastrointestinal system. These have been discussed under *Chlorophenothane* and *Toxaphene;* the treatment is essentially identical. For a more detailed discussion of the probable symptoms and treatment of poisoning by aldrin or dieldrin see *J.A.M.A.*, 1951, 146, 378; there is no specific antidote. [V]

Aletris, *N.F. VII. Stargrass. True Unicornroot. Unicorn Root. Starwort. Blazing Star. Colic Root.*— "Aletris consists of the dried rhizome and roots of *Aletris farinosa* Linné (Fam. *Liliaceæ*)." *N.F. VII.*

Aletris farinosa L., or *true unicorn root,* is a perennial acaulescent herb indigenous to sandy and grassy woods of the eastern United States and extending westward to Arkansas and Minnesota. It is characterized by possessing a horizontal to slightly oblique grayish-yellow to grayish-brown rhizome, from the sides and lower face of which emanate many tough, wiry, pale yellow or whitish, fibrous rootlets. From this rhizome there arises a spreading rosette of thin lanceolate foliage leaves and later, through the center of the rosette, a naked slender scape, bearing a spike-like raceme of small, white, tubular flowers. The fruit is an ovoid, beaked capsule inclosed in a roughened, mealy looking perianth.

Probably because of the fact that the English names "blazing star" and "starwort" have been applied to the aletris as well as to the chamælirium or *false unicorn root,* which yields the drug *helonias,* aletris is often confused with the latter herb. For a detailed description of aletris, see *U.S.D.*, 24th edition, p. 1312.

Marker and co-workers (*J.A.C.S.*, 1940, **62**, 2620) isolated the steroidal sapogenin, *diosgenin,* which had previously been obtained from *Dioscorea tokoro* (see under *Dioscorea*). Costello and Butler, in a report to the Scientific Section of the Proprietary Association (May 19, 1947, Atlantic City, N. J.), stated that aletris contains a pharmacologically active volatile oil and an active resinous material.

As suggested by its popular name "colic root," aletris was formerly used, especially in domestic practice, for expelling flatulence. It has been claimed to be of value in the treatment of various uterine disorders, and Costello and Butler (*loc. cit.*) attributed to its volatile oil and resinous material depressant action on the uterus.

Dose, 1.3 to 2 Gm. (20 to 30 grains).

Alkaloids.— Alkaloids are naturally occurring, basic, organic nitrogen compounds possessing, generally, marked physiological activity; the term is generally applied to substances of plant origin but by some authors it is also given to certain bases from animal sources. Most plant alkaloids contain the nitrogen in a cyclic structure though some, as for example ephedrine and other phenylalkylamines, are open chain bases, for which reason the latter are by some not considered to be true alkaloids. The classification of alkaloids can only be arbitrary; it is not possible on any basis to define exactly what constitutes an alkaloid notwithstanding the fact that for convenience in discussing them they are often classified as derivatives of certain fundamental organic nuclei. The property common to alkaloids is that they are nitrogenous bases, and may be considered to be substituted ammonias.

Plant alkaloids are almost exclusively found in phanerogams; rarely do they occur in cryptogams. They generally exist as salts of naturally occurring organic or inorganic acids; sometimes they are present as the free bases, or as esters, or as amides, or even in glycosidic combination. Individual plants contain more than one alkaloid, as a rule; cinchona contains more than twenty. Extraction is effected by means of various solvents; aqueous solutions of dilute acids often extract the alkaloid as a water-soluble salt, alkalinization of the plant material generally permits extraction of the alkaloid base with organic solvents.

The complexity of the structure of most alkaloids renders difficult the problem of determining their constitution. A supply of pure alkaloid is, of course, essential for a structural study but a not uncommon difficulty encountered at the outset is the possibility that in the process of extraction of an alkaloid from a plant it may have undergone hydrolytic decomposition or racemization, as when hyoscyamine is converted to atropine in the course of alkaloidal extraction of belladonna. After determining the empirical formula and optical rotatory power of the alkaloid (most alkaloids are optically active), an attempt is made to determine the character of the molecule. Phenolic groups may be identified through solubility of the alkaloid in fixed alkalies, color reaction with ferric chloride, alkylation and acylation. Alcohol groups may be detected by their reaction with phosphorus chlorides or thionyl chloride, by acetylation, or through oxidation or dehydration reactions. Presence of carboxyl groups may be demonstrated through solubility in ammonia or by esterification. Methoxyl is tested for by reaction of the alkaloid with concentrated hydriodic acid, followed by a quantitative determination of the amount of methyl iodide formed. Methylenedioxyl groups may be determined by reactions involving the elimination of formaldehyde. Several different reactions are utilized in determining whether the nitrogen in cyclic structures is secondary or tertiary. Finally, the alkaloid is subjected to several different types of degradation reactions, by which treatment it may split into more readily identifiable molecules.

The alkaloids are generally colorless crystallized compounds, containing carbon, hydrogen and oxygen, in addition to nitrogen. Some, however, are liquids as, for example, coniine, nicotine, arecoline and sparteine; these as a rule contain no oxygen. A few colored alkaloids exist; the yellow berberine is an important example. Most alkaloids combine with acids, without any liberation of hydrogen, to form well-defined salts; some principles (such as caffeine and other xanthines) which are so weakly basic that true salts appear incapable of existence, are by some also classed among the alkaloids. Many of the alkaloidal salts are soluble in water and, to a lesser extent, in alcohol; in other organic solvents they are generally insoluble. The free bases, on the contrary, are as a rule insoluble in water but soluble in organic solvents. There are, however, some exceptions to these generalizations.

Detection and identification of alkaloids are effected through the use of various reagents which produce precipitation or color reactions, or both, that are characteristic for individual alkaloids. Quantitative determinations of alkaloids are based on weighing of the separated alkaloid or some definite compound of it, or on the volumetric measurement of the acid-combining power or some other stoichiometric reaction of the alkaloid.

The similarity of alkaloids in any one of the several series of these principles found in plants appears to indicate that plants have the ability to synthesize a variety of alkaloids from a common parent substance through such fundamental chemical reactions as oxidation and reduction, condensation, methylation, decarboxylation, etc. Starting compounds for these syntheses are amino acids and their derivatives, formaldehyde, formic acid, and methanol. The function of alkaloids in plants is uncertain. They are variously regarded as plant metabolism products, reserve materials for protein synthesis, plant stimulants, detoxication products, or protective substances against ani-

mal or insect feeding. Many alkaloids have been synthesized, and a few are largely produced in this manner.

The large variety of structures occurring in alkaloids has made it thus far impossible to systematize their nomenclature. Names of specific alkaloidal bases are often derived from the botanical name of the plants in which they are found; in general such names end in *ine*, but it must not be assumed that all substances having names ending thus are alkaloids. Names of alkaloidal salts continue in their antiquated and illogical usage. The salts which quinine, for example, forms with hydrochloric and sulfuric acids are called quinine hydrochloride and quinine sulfate, respectively, and their formulas are written to indicate an apparent addition of one or more molecules of acid, thus, $C_{20}H_{24}N_2O_2.HCl$, and $(C_{20}H_{24}N_2O_2)_2.H_2SO_4$. Salt formation in these instances is analogous to that by which ammonium chloride is formed from ammonia and hydrochloric acid, for which compound the term ammonia hydrochloride and formula $NH_3.HCl$ were long ago abandoned. The quinine salts, therefore, should be called *quininium chloride* and *quininium sulfate*, respectively, and their formulas should be written to indicate transfer of the proton (H^+) of the acid to the alkaloidal base.

Henry, in describing most of the plant alkaloids in his book *Plant Alkaloids*, classifies them as derivatives of the following fundamental groups, the more important members of which are also given.

Chemical Classification of Alkaloids According to Fundamental Groups

Pyridine Group.—Piperine, arecoline, coniine, pelletierine, the lobelia alkaloids, the tobacco alkaloids.

Tropane Group.—The solanaceous alkaloids, the coca alkaloids.

Lupinane Group.—Sparteine, anagyrine, cytisine.

Isoquinoline Group.—Including the alkaloids of the following plants: Cactus, hydrastis, corydalis, opium and other papaveraceæ, ipecac, berberis, and curare. This group includes several sub-groups.

Phenanthridine Group.—The Amaryllidaceæ alkaloids.

Quinoline Group.—The cinchona alkaloids.

Indole Group.—Including alkaloids of the following: Harmala, yohimbé, quebracho, ergot, calabar, nux vomica and other strychnos species.

Pyrrolidine Group.—Carpaine.

Pyrrolizidine Group.—The senecio alkaloids.

Quinazoline Group.—Vasicine.

Glyoxaline Group.—Alkaloids of the pilocarpus species.

Alkaloidal Amines.—Including the alkaloids of the ephedra species, the brassica species, the colchicum alkaloids, and muscarine.

Steroidal Alkaloid Group.—The solanum alkaloids, the aconite alkaloids, the delphinium alkaloids, and the veratrum alkaloids.

Alkaloids of Undetermined Constitution.—Alkaloids of species of alstonia, aristolochia, gelsemium, lycopodium, rauwolfia and some others.

The *purine* bases, including caffeine, theobromine and theophylline, while often considered as alkaloids, are perhaps more frequently referred to as purine derivatives and are generally described under this heading. In this connection it should be noted again that the selection of substances comprising the group of alkaloids follows no rigidly defined rules.

From both living and decomposing animal tissues there have been isolated a number of basic substances, relatively simple in chemical composition, which are sometimes spoken of as animal alkaloids. From decomposing flesh have been isolated such substances as methylamine, dimethylamine, trimethylamine, putrescine, cadaverine, choline, muscarine, and neurine; these are sometimes called *ptomaines*, and many of them are poisonous. Bases obtained from living tissue are called *leucomaines*.

For a discussion of specific alkaloids or alkaloid-containing drugs reference should be made to the individual monographs in this book. Other reference works include Henry's *Plant Alkaloids*, 4th edition, 1949; Manske and Holmes' *The Alkaloids*, Vol. 1, 1950, Vol. 2, 1952; Hamerslag's *The Technology and Chemistry of Alkaloids*, 1950.

Alkanet. *Alkanna Root. Alkanet Root. Orcanette. Spanish Bugloss.*—This is the root of *Alkanna tinctoria* Tausch. or *dyers' alkanet*, an herbaceous perennial plant, of the Fam. *Boraginaceæ*, indigenous to Asia Minor and southeastern Europe. It is not to be confused with the allied bugloss (*Anchusa*) formerly official. The root contains a coloring principle called *alkannin* (or *anchusin*) which is most abundant in the cortical regions; there is present also a small amount of a wax, carnaubyl cerotate. Alkannin is brownish red in color with a coppery luster, but with metals forms salts which are usually blue. It is almost insoluble in water but soluble in alcohol, ether and fixed oils. For further information concerning the chemical structure and physical properties of the compound see Brockman (*Ann. Chem.*, 1935, **521**, 1).

Alkanet is somewhat astringent, and was formerly used medicinally; it is now employed only to impart a red color, as to oils, fats and waxes.

Allantoin. *Glyoxyldiureid. Cordianine.* $C_4H_6N_4O_3$. —Allantoin is a product of the oxidation of uric acid. Certain animals—but not man—possess an enzyme, known as *uricase*, which is capable of causing this transformation. Allantoin occurs as a white crystalline powder, odorless and tasteless, sparingly soluble in cold water; optically active and racemic forms of it exist. In World War I it was noticed that severe wounds, especially those involving osteomyelitis, which became infested with maggots healed with unexpected promptness. This observation led to the widespread use of the so-called maggot therapy (see Buchman, *Ann. Surg.*, 1934, **99**, 251). In 1935 Robinson, of the United States Bureau of Entomology, presented evidence that the beneficial action of maggots was due to the presence of allantoin in their excretion. Following this allantoin was widely employed by surgeons for the purpose of accelerating cell proliferation in sluggish wounds, especially in osteomyelitis. Greenbaum (*Med. Rec.*, 1940, **151**, 8 and 286) confirmed an earlier observation of Macalister that when allantoin is introduced into the circulation either by intravenous or by oral administration it causes a definite increase in the neutrophile leukocytes and that it is practically non-toxic. An extensive review of the chemistry and therapeutics of allantoin is provided in an article by Greenbaum (*Am. J. Pharm.*, 1940, **112**, 205). Its use in cosmetics is discussed by Mecca, *Drug Cosmet. Ind.*, 1955, **76**, 768.

Allantoin is used, most frequently in combination with other substances, as a local application to various infections and wounds in strengths of 0.4 to 2 per cent. Allantoin has also been suggested as a remedy for gastric ulcer to be given in *doses* of from 30 to 130 mg. (approximately ½ to 2 grains).

Allergens. *Allergenic Extracts.*—Allergy is an altered reaction of the tissues, in certain individuals, to agents which in similar amounts are innocuous to other persons. The agents which produce allergy are called antigens or allergens and stimulate the production of specific antibodies within a sensitive organism. The antibodies so produced may be humoral and freely circulating in the blood stream or sessile, that is, firmly attached to tissue cells. It is the interaction of the allergen with sessile antibodies that produces allergic symptoms. The theory most widely held is that the injured cells from this interaction release

histamine which produces the allergic reaction. In many instances there is a familial tendency toward allergy.

The principal symptoms of allergy are "hay fever" (a misnomer since the symptoms are not necessarily related to hay nor is fever present), asthma, gastrointestinal disturbances, urticaria, angioneurotic edema, eczema, coryza, arthralgia, etc. Hamilton and Bendkowski (*Brit. M. J.*, 1954, 1, 1069) surveyed the incidence of these disorders in general practice.

Innumerable substances may cause allergy. An allergic individual may be sensitive to one or a multiple of allergens. Allergens are generally classified as follows: *Inhalants* include the allergens causing symptoms in the respiratory tract—pollens, fungi, animal epithelial emanations, various dusts, smoke, cosmetics, perfumes and strong odors. *Foods* may be the cause of symptoms. Among the common offenders are wheat, eggs, milk, chocolate, fish, nuts, pork and strawberries. *Drugs* may act as an allergen. Penicillin and aspirin are common offenders along with vaccines and serums. *Infectious agents* include bacteria, fungi, parasites and viruses. *Contactants* include plants, flowers, furs, leather, jewelry, cosmetics, insecticides, many industrial chemicals, etc. *Physical agents* are represented by heat, light, cold and pressure.

For the diagnosis and treatment of allergy there are available allergenic extracts which are aqueous (usually glycerinated) extracts of the specific proteins of the substances responsible for allergy. These solutions are standardized usually on the basis of pollen or nitrogen units depending upon the manufacturer. Some of the diagnostic allergens are prepared in dried powder or paste form. Most are in the liquid form ready for injection. There are also available oral preparations of pollen for prophylaxis or treatment.

DIAGNOSIS.—The diagnosis of allergy is made in several ways. An accurate, careful history is of paramount importance. Relationship of attacks to the season of the year, environment, changes in occupation, eating of foods, etc. is often indicative of a particular sensitivity. Diagnosis may also be made by one of several test methods using specific allergenic extracts applied by (a) intracutaneous injection, (b) cutaneous scratch, (c) cutaneous patch test, (d) indirect skin testing (passive transfer) using a nonallergic individual, (e) mucosal application to either the conjunctival sac, inferior turbinates or by aerosol to the bronchial mucosa. Allergenic extracts vary in concentration depending upon the manufacturer and the recommendations accompanying the product used should be followed closely. Sheldon *et al.* (*J.A.M.A.*, 1953, 151, 785) discussed the significance of skin tests. Tuft and Heck (*J. Allergy*, 1954, 25, 340) found that skin sensitivity persists for many years regardless of the treatment employed.

TREATMENT.—The most successful treatment of allergy is the avoidance of contact with the offending agent. In many cases this is impracticable and treatment consists of desensitization. This is done by injection of the specific allergenic extract in a series of gradually increasing doses. Suitable preparations are usually available as stock solutions although prescription preparations may be obtained to fit individual cases. Various combinations of extracts may be made, on prescription, so that a patient may be desensitized for several allergens simultaneously. There are three methods of desensitization generally employed: (1) The *coseasonal method* depends for successful treatment upon frequent administration of small doses for the purpose of reducing symptoms. Treatment is not begun until symptoms are evident and is discontinued when symptoms have been relieved and not resumed until symptoms reappear. (2) The *preseasonal method* of desensitization consists in starting treatment approximately 2 months or more preceding the usual initial attack. The injections are given weekly or twice weekly, depending upon the general reaction toward the extract. (3) The *perennial method* is now followed by many allergists. The principle of perennial treatment is to keep the tolerance of the patient near its maximum throughout the year. It has been found that perennial treatment yields a higher percentage of satisfactory results than preseasonal desensitization. In perennial treatment the dosage of the extract is reduced to a maintenance dose, approximately one tenth of the maximum desensitizing dose, and is administered monthly or semimonthly throughout the year. House dust is perhaps the most important cause of perennial allergy and, since complete avoidance is impossible, perennial treatment is the method of choice. Use of antihistaminic drugs for symptomatic relief is discussed under *Antihistaminic Drugs*, in Part II; the treatment of severe allergic syndromes is also discussed under *Cortisone Acetate*, and *Epinephrine*, in Part I.

Rapid desensitization in cases of serum sensitivity may be attempted in emergencies where it is necessary to administer antitoxin or immune serum as therapeutic agents (see *Serum Reactions* under *Diphtheria Antitoxin* in Part I).

In the treatment of allergies, precaution must always be exercised and the patient kept under a physician's care for at least half an hour after the administration of a dose so that in the event of an immediate reaction epinephrine can be administered promptly. Each patient should be treated individually and under no circumstances should any dose be increased where severe reactions occur from the preceding one.

Stock allergenic extracts are available or may be prepared on prescription for every substance that may cause allergy and a listing of all available would be impractical. Some of the more commonly used preparations are as follows: *House Dust Allergen*, derived from many sources to insure broad antigenicity. *Mixed Grasses Allergen*, including timothy, June, orchard, sweet vernal and red top grasses, which are usually the cause of spring hay fever. *Ragweed Combined Allergen*, prepared from short and giant varieties, the most common excitants of fall hay fever. *Rocky Mountain Formula Allergen*, including pigweed, western ragweed, Russian thistle, sagebrush, the pollens of which are active from July to October. *Southern Formula Allergen*, including Bermuda grass, Johnson grass, giant and short ragweed, the pollens of which are active from April to frost. *West Coast, Early Summer Allergen. West Coast, Late Summer Allergen. Poison Ivy, Oak, Sumac Extract*, which are available as monovalent extracts or in combination for the prophylaxis and treatment of poison ivy, oak, and sumac dermatitis.

Some bacterial diseases in humans produce a state of allergy or sensitivity shortly after the infection occurs, and this sensitivity persists for many years after the disappearance of the infection from the body. These sensitivities, as demonstrated by skin tests, are valuable in the diagnosis of disease. The classic example of this reaction is the tuberculin test for tuberculosis (see *Old Tuberculin*, Part I). Other diseases for which allergic extracts are available for diagnosis are brucellosis, coccidioidomycosis, and histoplasmosis.

Brucellergen is a protein nucleate prepared from smooth strains of *Brucella abortus, Br. suis* and *Br. melitensis* (Huddleson *et al., Brucellosis in Man and Animals*, New York, The Commonwealth Fund, 1943). The test is performed by injecting intracutaneously, on the flexor surface of the arm, 0.1 ml. of Brucellergen. A positive reaction consists of a circumscribed area of erythema and edema from 2 to 10 cm.,

developing in 24 to 48 hours and persisting for as long as 7 days. A mild to severe systemic reaction may follow the injection of Brucellergen. It must be used with caution in persons suspected of extreme sensitivity, for example veterinarians.

Coccidioidin is prepared from cultures of *Coccidioides immitis*. It is used for the diagnosis of infection with *C. immitis*, which produces coccidioidomycosis, most prevalent in the interior valleys of California and also referred to as valley fever, desert rheumatism, San Joacquin fever. In its pulmonary form the disease produces pulmonary lesions difficult to differentiate from tuberculosis.

Histoplasmin is the filtrate from cultures of *Histoplasma capsulatum* and is used in the diagnosis of histoplasmosis, a fungus infection of the reticuloendothelial system. The disease is characterized by ulcerations of the oropharynx and gastrointestinal tract, and often accompanied by lymphadenopathy. The severe form is usually fatal, but a benign form, affecting a high percentage of the population (especially the east central states), produces pulmonary calcifications without symptoms. Histoplasmin is of value, along with tuberculin and coccidioidin in the interpretation of roentgenographic plates showing pulmonary infiltration and calcification. The test consists of the injection intracutaneously of 0.1 ml. of diluted histoplasmin into the flexor surface of the arm. The reaction is read in 24 to 48 hours.

All allergenic products are produced under license from the National Institutes of Health, Department of Health, Education and Welfare. Expiration dates for these products vary from 18 months to 5 years if stored constantly at 2° to 10° C.

Allium. *Garlic.*—"Garlic is the fresh bulb of *Allium sativum* Linné (Fam. *Liliaceæ*)." *N.F. V.*

The genus *Allium* includes a large number of species, of which nearly seventy are indigenous to this country. *Allium sativum* L., or *English garlic*, is a perennial herb with an underground compound bulb composed of numerous bulblets which have a common membranous covering, from the base of which numerous rootlets descend. The compound bulb consists of from 6 to 15 bulblets (sometimes called "cloves") each of which is ovate wedge-shaped and covered with dry membranous scales. When bruised they have a strong odor and an intensely pungent taste. "The membranaceous scales, dry leaf and root remains should be removed before Garlic is used for the manufacture of pharmaceutical preparations." *N.F. V.*

Garlic yields about 0.1 per cent of a volatile oil of brownish-yellow color, with a specific gravity of from 1.046 to 1.057. It has a disagreeable pungent odor. It consists chiefly of allyl disulfide, $C_6H_{10}S_2$, and allylpropyl disulfide with small amounts of higher polysulfides; it contains no allyl sulfide (diallyl sulfide).

Garlic has been reported to have therapeutic virtues which have been variously attributed to the presence of diallyl sulfide, unstable sulfur in alkyl polysulfides, a bacteriophage, acrolein or some similar unsaturated aldehyde, and to a chemically undefined group of substances designated as phytoncides. Walton and Lindegren (*Proc. S. Exp. Biol. Med.*, 1937, 36, 55) reported the presence of enough allyl aldehyde to render the vapors of garlic markedly bactericidal. Lehmann (*Arch. exp. Path. Pharm.*, 1930, 147, 245) reported that garlic juice, in as little as one part in a million, produced methemoglobin when mixed with blood. Cavallito and Bailey (*J.A.C.S.*, 1944, 66, 1950), however, showed that none of the constituents separated from the oil from garlic have the antibacterial activity claimed for them; from an alcoholic extract of clove they did isolate an unstable, liquid antibacterial agent, *allicin*. The substance has been assigned the formula $C_3H_5.S(O).S.C_3H_5$ (*J.A.C.S.*, 1944, 66, 1952). When tested by the cylinder-plate method against *Staphylococcus aureus*, using the technic employed for penicillin, allicin shows an activity equivalent to about 15 Oxford penicillin units per milligram, which is about 1 per cent of the activity of penicillin; allicin is active against both gram-positive and gram-negative bacteria.

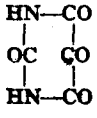
Among the ancients garlic was credited with curative virtues in an extraordinarily large variety of diseases. It has been widely employed in pulmonary conditions such as chronic asthmatic bronchitis and sometimes whooping cough. Minchin (*Pract.*, Feb., 1918) revived the ancient idea of its value as an internal antiseptic. Loeper and DeBray (*Bull. soc. méd.*, 1921, 37, 1032), from experiments upon both human beings and dogs, reached the conclusion that garlic tincture causes a fall in blood pressure which is most marked in cases of hypertension. They also found that it brings about a leukocytosis. There is no doubt that the oil is absorbed through the alimentary tract and eliminated partly through the lungs and partly through the urine. Garlic is also occasionally employed as an anthelmintic, a use which has received some scientific support from the experiments of Rico (*Compt. rend. soc. biol.*, 1926, 95, 1597). Dehydrated garlic has been used for its carminative effect in various functional gastrointestinal disorders (*Rev. Gastroenterol.*, 1949, 16, 411).

Externally it has been employed as a rubefacient and stimulant to the nervous system. In catarrhal pneumonia bruised garlic cloves were sometimes applied as a poultice to the chest.

The expressed juice of garlic has been employed in *doses* of 2 ml. (15 minims) but the most popular preparation was the syrup (*Syrupus Allii*, N.F. V), in *doses* of 4 to 8 ml. (1 to 2 fluidrachms). The oil has been given in *doses* of 0.12 to 0.2 ml. (2 to 3 minims).

Under the name *Allisatin* (Sandoz) an odorless and tasteless tablet preparation of garlic principles adsorbed on vegetable charcoal, which releases the principles on contact with stomach juices, is offered for use as an intestinal antispasmodic. *Allimin* (Van Patten), a commercially available tablet containing a dehydrated garlic concentrate with dehydrated parsley concentrate, is advertised as a vasodilator for use in hypertension.

Alloxan.—This product of the oxidation of uric acid has been known for more than a century, but it has been only relatively recently discovered to have the property of inducing experimental diabetes mellitus, in animals, without surgical removal of the pancreas (Dunn *et al.*, *Lancet*, 1943, 1, 484; 2, 384). Alloxan has the structure represented by:



It occurs as a colorless powder, easily soluble in water and in alcohol. Alloxan acts by destroying the β-cells of the islets of Langerhans, possibly through inactivation of essential sulfhydryl enzymes of the cells, thus resulting in permanent diabetes, commonly without damaging the α-cells or the acinous cells of the pancreas. Following intravenous injection, in rabbits, of 200 mg. of alloxan per Kg. of body weight the substance disappears from the circulating blood within 5 minutes, during which period necrosis of the beta cells, which elaborate insulin, begins. Within 24 hours some of the islets have disappeared entirely, while others exist only as alpha cells. In addition to its effects on the pancreas, alloxan produces cataracts, necrosis of renal tubules, and other less striking changes in the adrenal cortex, pituitary, thyroid, and thymus.