THE PRESENT TRENDS OF THERAPEUTICS AS ILLUSTRATED BY THE NEW DRUGS RECOMMENDED FOR ADMISSION TO THE PHARMACOPŒIA.*

BY HORATIO C. WOOD, JR., M.D.

The search for new remedial agents has nearly always been guided by certain general principles, or accepted theories of drug action. Thus, in medieval times there was a wide-spread belief that for every disease the devil had let loose on the earth God had provided a specific antidote and that all that was necessary was to test out successively each of the millions of plants in each disease until the specific antagonist was found. In the latter part of the last century the physiological action of drugs was the rallying point of therapeutics, and pharmacologists devoted their time to studying the effects of any plant which seemed to be poisonous with the idea that these physiological studies might lead to the therapeutic use. The type of this investigation was the epoch-making work of Magendie, the father of pharmacology, whose studies of the cause of convulsions produced by the poison nux vomica led to the introduction of strychnine as a remedy.

In every age we find a group of scientists so filled with the conceit of their time that they hold in contempt the learning of the past and mistake the theories of the day for proven facts. The whirligig of pharmacology is an extraordinary manifestation of this evanescence of human logic. It is only a few years ago that the Rabbis of the pharmacological sanhedrim were sneering at the idea of specifics in medicine. To-day, the search for new remedies is frankly a hunt for these contemned curatives. To be sure, they attempt to cover their shame by inventing a new word which is etymologically inappropriate, chemotherapy. Nearly all drugs are "chemotherapeutic" agents; for the word means, if anything, that the therapeutic effect is by chemical action. If the truth be told, chemotherapy, as generally employed, is but another name for what our fathers called "specifics," a term which we have well nigh discarded as meaningless. The proper designation of this group of drugs is the term etiotropic, *i. e.*, turning towards the cause.

ARSPHENAMINE.

The present furore of seeking new specific, etiotropic, agents through experiments on the lower animals may be attributed chiefly to the concept of Professor Ehrlich. Starting with the known toxic effects of arsenic on protozoa he instigated a systematic search for some compound of arsenic that should retain its toxicity for these pathogenic organisms but be harmless to the human host. The most tangible success of his patient research was a compound which was first introduced under its laboratory number 606 and is now known in this country as arsphenamine. The toxic effects of arsenic seem to be not a property of the element arsenium but of the arsenous oxide ion. The compounds containing arsenium in a pentavalent state are apparently non-poisonous, either to man or germs, but many of them are slowly reduced by animal tissues to the trivalent state and become poisonous. If we can find a compound that is more rapidly broken down by the tissues of the protozoa than those of the mammalia we have a drug which can be used as a specific

* Read before Philadelphia Branch, A. Ph. A., October meeting.

curative in infections by this group of organisms without endangering the life of the patient. Although arsphenamine has not completely realized the hopes of its discoverer, of a drug that could be used in large enough dose to cause at once a complete sterilization of the body, it yet represents a great advance in our methods of treating certain of the protozoal infections, notably syphilis and relapsing fever.

The therapeutic and chemical properties of arsphenamine and its various derivatives are so well known that it is needless for me to describe them in detail. I simply call attention to them as illustrative of one of the trends of modern therapeutic investigation.

CHAULMOOGRA OIL.

An agent, another new admission to the Pharmacopœia, whose value, however, was not discovered by experiments on the lower animals but by the old-fashioned method of clinical trial, is the oil of chaulmoogra. The value of chaulmoogra oil in leprosy has been known to the Asiatics for centuries; an ancient legend reports that a king of India, living in the days before the time of Buddha, was cured of his leprosy by eating the fruits and leaves of the kalaw tree. Later the oil of this tree was widely used in Burma, both externally and internally, in the treatment of this dread disease. In 1819 the plant, from the seeds of which this oil was obtained, was described by Brown under the name of *Gynocardia odorata* and this source was commonly recognized for nearly 100 years. In 1899 a French pharmacist, Deprez, first showed that the true chaulmoogra seeds were not derived from the Gynocardia, and the following year an English botanist named Prain attributed them to a new species of *Taraktogenos* which he named in honor of Kurz, who had first collected the plant, as *T. Kurzii*. The investigations of Joseph F. Rock, of the United States Department of Agriculture, have left no room for doubt that the true oil of chaulmoogra, as used in India, is obtained partly from this species and partly from the allied genus of *Hydnocarpus*, trees that are native in Siam and Burma. The Government has issued a bulletin in which Mr. Rock describes most interestingly his field search for the source of this oil with botanical description of the various allied plants.

Of the curative properties of chaulmoogra oil in leprosy there is to-day no room for doubt. The virtues of the oil seem to depend upon peculiar fatty acids of a type which had not hitherto been described in any fixed oil. The two most important of these acids, separated by Dr. Frederick B. Power some years ago, are named chaulmoogric and hydnocarpic acids. Recently, the sodium salts of these acids, which have the advantage of being soluble in water, have been used hypodermically with considerable evidence of success.

CHLORINE COMPOUNDS.

Somewhat allied to the exploration in the field of etiotropic agents of which I have been speaking, is the search for new surgical disinfectants. Nearly all of our germicidal substances belong to what are known as protoplasmic poisons; *i.e.*, they are toxic to all forms of living organisms. They kill, therefore, not only the bacteria but also the tissue cells. The result of this latter action is to lessen the natural resistance of the body to bacterial invasion so that the application of germi-

cidal solutions often does more harm by their destructive action on the human cells than they do good by their effects on the pus-producing germs. An interesting study by Lambert in 1916, upon human connective tissue cells artificially cultured, showed that practically all of the surgical germicides, except iodine and chlorine, were more poisonous to the human tissues than they were to the bacteria and hence their value in disinfecting wounds must be extremely limited.

The activity of chlorine as a disinfectant has long been known but the instability of solutions of chlorine and the difficulty of preparing solutions of definite strengths practically prevented the use of this element as a surgical disinfectant until studies of Dr. Dakin and Dr. Carrell, during the war, led to the introduction of a modification of the old Labarraque solutions. The essential differences between Dakin's solution and the old form of sodium hypochlorite are, first, that Dakin's solution is practically neutral instead of strongly alkaline, and, second, that its content of available chlorine is definitely determined by chemical assay at the time of preparation. One great disadvantage of the solution was the rapidity with which it lost its available chlorine so that it must be freshly assayed almost every day. Exactitude of strength in Dakin's solution is a *sine qua non;* if it be too weak in chlorine it will not exercise the proper degree of antibacterial effect; if it be a little too strong it will destroy the vitality of the tissue cells.

Because of the inconvenience of assaying this chlorine solution Dr. Dakin was led to undertake a research for a compound which would liberate free chlorine in the tissues but that would be stable under ordinary circumstances. This investigation led to the introduction of three sulpho-chloramine compounds. Chlorazene is the sodium salt of toluene-sulpho-chloramine and was first made by Chattaway in 1905. This compound is generally known as chloramine which is unfortunate because the substance NH_2Cl has likewise received this name. Because of the fact that Dakin popularized both the solution of sodium hypochlorite and the sulpho-chloramines there has been some confusion in the minds of many as to the distinctions between these various chlorinated preparations. The importance of distinguishing between aqueous solutions of sodium hypochlorite and of sodium toluene-sulpho-chloramine has been clearly pointed out in an excellent article by Dr. Smyth. The essential difference lies in the fact that sodium hypochlorite is useful not merely because of its power of destroying bacteria but also because of its solvent action on necrotic tissue which makes it of a special use in large wounds where there is much destruction of tissue. For small wounds that are comparatively clean chloramine is preferable, because it is less irritant and more convenient. It is, therefore, of great importance that pharmacists clearly distinguish between these two chlorine compounds as their field of usefulness is quite distinct.

The acid radical, of which chloramine is the sodium salt, is insoluble in water but has been used, under the name of Dichloramine-T, both as a surgical disinfectant and antiseptic application in diseases of the nose and throat, dissolved in liquid petrolatum. Because, however, of the affinity of this latter substance for chlorine it is necessary that it first be saturated with chlorine before being used as a solvent as otherwise it would lead to the decomposition of the dichloramine-T. The Revision Committee have recommended the recognition of such a chlorinated mineral oil.

SILVER PROTEINS.

The value of silver as a disinfectant application to mucous membranes has long been known. Its peculiar usefulness lies in the fact that it retains its germicidal properties to an extraordinary extent, even when greatly diluted and in the presence of protein material. Behring has shown that in albuminous fluids silver nitrate is a more powerful disinfectant than mercuric chloride; he states that a 1 to 10,000 solution of silver nitrate still possesses the power of killing the highly resistant anthrax spores in the blood serum if exposure is sufficiently prolonged. The disadvantages of silver nitrate as a clinical germicide are, first, its local irritant effect and, second, the action of chlorides in precipitating the silver salt. In order to overcome these objections chemists have advised a number of combinations of silver with various protein substances, in many of which the metal is in a colloidal form. The great difference in germicidal and irritant properties of these preparations has been so puzzling that their exact field of usefulness has been settled only as the result of prolonged clinical observations. Why, for example, should argyrol with a silver content of 21 per cent. be so inferior both in disinfectant power and irritant properties to protargol with less than half this proportion of silver?

Twenty-five years ago, Kronig and Paul brought forth evidence that the germicidal power of metallic salts depended not so much upon the actual percentage of metal present as upon the degree of ionization; the action of the salts is due to the free metallic ions. Pilcher and Sollmann have recently attempted to apply this theory to the silver proteinates. From studies on the antiseptic powers of these compounds they deduce the opinion that despite the colloidal nature of the proteinate solutions a portion of their silver is in the ionic condition. Protargol, with a total silver content of 8.3%, contains over 7% of ionic silver, while argyrol although it contains approximately 21 per cent. of metallic silver yields only $^1/_3$ of one per cent. of ionic silver. There is, however, in these silver compounds a small amount of "available" silver, which possesses antiseptic property, besides the easily ionizable metal; so that protargol is only about 15 times as actively germicidal as argyrol, instead of 21 times as would be indicated by the proportion of ionizing silver. Pilcher and Sollmann also found an enormous difference in the germicidal power of different samples of the same brands of silver proteinates; apparently small differences in the process of manufacture threw larger or smaller quantities of silver into the non-ionic form. These authors also believe that the degree of irritation of the silver compounds is likewise due to the proportion of ionizable metal.

If both the germicidal and irritating properties of these silver salts depend upon the proportion of ionic silver, wherein lies the advantage of a protein silver preparation over a correspondingly diluted solution of such an inorganic salt as the nitrate? There is reason to believe that these silver protein compounds are slowly decomposed and may exercise a degree of bacteriostatic action disproportional to their amount of ionic silver. In other words, where a slow, persistent effect is desired an equal degree of antiseptic action is obtainable with less degree of irritation by the non-ionizing forms than by silver nitrate. On the other hand, where a very rapid action is desired comparatively little is gained by the use of the col-

loidal types of silver. The silver proteinates may, therefore, be arranged into groups according to the amount of ionic silver present. Protargol type represents, on the average, about 7% of ionic silver (compared to about 63% of ionic silver in the nitrate), while the argyrol type represents approximately $^1/_3$ of one per cent. of ionic silver.

SOMNIFACIENTS.

Another important pharmacologic trend exemplified in the new Pharmacopœia is the working out of the relationship, which undoubtedly exists, between the chemical structure of organic drugs and their effects on body function. While we are still a long way from apprehending the fundamental laws involved in this relationship we have collected a sufficient number of observed coincidences in certain groups of drugs to be able to formulate certain arbitrary rules that work out more or less successfully in practice.

One of the earliest of these to be practically utilized was the observation that all of the somnifacients contained a single carbon atom found in the open chain arrangement—*i. e.*, they may be regarded as derivatives of methane having for one of its side groups an aliphatic derivative, such as methyl, ethyl, or propyl. Furthermore, it has been noted that the introduction of a carbamic radical greatly lessens the danger of depression of the vital centers in the medulla. The first of this series of important hypnotics was urethane, still official under the name of ethyl-carbamate. Although one of the safest drugs of the class, it has been found to be clinically lacking in power. Recently more complex compounds of this type have been found which exercise a powerful depressant influence upon the higher cerebral centers with similar slight effect upon the vital nervous system.

The first great success of this type was the well-known veronal, or, to give it its American name, barbital. This drug would probably have received recognition in the present Pharmacopœia had it not been for certain legal difficulties. I might say in passing that one of the most gratifying things of the work of the present Revision Committee has been the spirit of coöperation manifested by nearly all the owners of patents on the modern synthetic drugs.

By substituting a phenyl for one of the ethyl groups in barbital we have the substance pheno-barbital or, as it is more commonly known, luminal, which has attracted so much attention. There does not seem to be any convincing evidence that this drug is superior as a hypnotic to the older veronal but it has been found clinically to be a very useful agent in the treatment of epilepsy. While experience is still too limited to make a dogmatic designation of its precise place in the management of this baleful affection, the present evidence indicates that its value is like that of the bromides, a palliative not a curative, and from my own reading I would gather that its effects are on the whole not much, if any, better than those of the bromides. It does afford, however, a valuable alternative for these drugs in those cases in which for any reason the bromides may be unsuited.

A very interesting series of these narcotics contain an atom of bromine in one of their side groups. The thought which was apparently back of the construction of these molecules was that of obtaining the ionic action of bromine, but their effects, while differing very distinctly from those of barbital, are manifestly not due to a bromine action. In the first place, the dose of bromine which is introduced is too

small to exercise any action, and in the second place, Takeda has brought experimental evidence to indicate that they are not broken up in the body. Nevertheless their clinical effects are quite distinct from the other hypnotics. The two important characteristics of these compounds are: first, that they have distinct analgesic properties, which is not true of the hypnotics as a group; and, second, in small doses they produce a condition of euphoria without evident tendency to drowsiness. The representative of this group recommended for official recognition is carbromal, known more familiarly under the trade name of adalin. It has a field of marked usefulness distinct from that of either barbital or luminal.

LOCAL ANESTHETICS.

A number of years ago pharmacologists reached the conclusion that the local anesthetic power of cocaine is due to the presence of a benzoyl radical containing a nitrogenous side group. On this theory chemists have prepared a host of similar anesthetics in the hope of obtaining one which would be free from the dangers of poisoning. While we have not yet obtained complete success in preparing a non-toxic local anesthetic the two members of this group which have been recommended for admission into the Pharmacopœia represent great advances.

Procaine, which was originally introduced under the trade name novocaine, according to the studies of Eggleston and Hatcher, is about $^1/_3$ as poisonous as cocaine, when injected intravenously; when injected hypodermically the difference is still more marked—according to Closson the hypodermic fatal dose of novocaine for guinea pigs is about 10 times as large as that of cocaine. Although novocaine appears to have less power of penetrating mucous membranes than cocaine, when injected either subcutaneously or into nerve trunks, according to Sollmann, it is practically equal in anesthetic power.

The other anesthetic which has been recommended for admission into the Pharmacopœia is benzicaine, more commonly known under its trade name of anesthesin. It has a very different field of usefulness from that of novocaine or cocaine. Its peculiar value depends upon the fact that it is practically insoluble in water and, therefore, when applied to a raw surface is not easily washed away by the body fluids. Moreover, its toxicity on hypodermic injection appears to be less even than that of procaine; according to Closson when benzicaine is injected hypodermically, dissolved in olive oil, the enormous quantity of 1 Gm. per kilo is required to produce fatal results in the guinea pig, which makes it about $^1/_{20}$ as poisonous as cocaine. Anesthesin is used especially for its effects on open wounds, ulcers and other raw surfaces. It may be applied either in the form of a solution in one of the fixed oils or, mixed with some inert substance such as starch, as a dusting powder. It has been used with much benefit to relieve the pains of gastric ulcer in doses of 3 to 4 grains.

BENZYL BENZOATE.

The investigation of the relationship between chemical structure and physiological action led to the introduction of a relatively simple compound that a few months ago created a veritable furore among the medical profession. Dr. Macht, finding that some of the opium alkaloids were active depressants to the involuntary muscles while others were not, sought to find the reason for this difference. Noting

that all those which affected unstriped muscles contained a benzyl group in their molecule he postulated the proposition that their effects were due to the benzyl radical. This observation led him to suggest the possible utility of the simple compounds of benzyl and the introduction of benzyl benzoate. Because of the scientific standing of Dr. Macht and the plausibility of his reasoning benzyl benzoate acquired, with a most extraordinary rapidity, a tremendous vogue for the relief of various spasmodic disorders such as asthma, high blood-pressure, gallstone colic and similar conditions.

The cause of its failure to realize the first high hopes, I believe, lies in a peculiar oversight of a fundamental principle. As the action of benzyl benzoate is directly on the muscle fiber it is manifest that if one gives a large enough dose to paralyze the offending muscle he will produce a similar paralysis of all involuntary muscles. Thus in order to relieve an asthmatic spasm of the bronchi we have to relax also the arteries, causing a marked fall in the blood-pressure, and to relax the intestinal muscles to such an extent as to check the peristaltic movements. In other words, in exorcising one devil we let loose two or three new devils in the body of the unfortunate sufferer.

TANNIN DERIVATIVES.

The two tannin preparations which have been newly admitted are no novelties. Both of them have been used under proprietary names for some years. The idea that was back of the introduction of these compounds may be briefly summed up as follows: astringent action of a drug is the result of precipitation of proteins in the tissues; tannic acid when taken by the mouth will be largely neutralized, *i. e.*, precipitated, by the proteins in the stomach and, hence, exercise little astringency in the intestinal tract; if we can administer some compound of tannin that is insoluble, and therefore non-astringent, in the stomach but is broken up in the intestines it would have great superiority over the other vegetable astringents in the treatment of diarrhea. A large number of compounds have been placed upon the market for which these advantages have been claimed. That they have not entirely fulfilled the theoretical expectations is shown by the fact that the vegetable astringents continue to be largely used; if these insoluble tannins were capable of doing what theoretically they ought to they would have almost driven the old vegetable astringents off the market. The explanation of their partial failure has recently been shown to be that none of them correspond to the claims that the manufacturers have made. For instance, in such a fundamental, physical property as solubility in water Dr. Leech has shown that none of them correspond to the claims of the manufacturers. Every one of the eight such compounds examined was at least partially soluble in water. Their solubility ranged from 2.4 to 20 parts in 100 of water. In most cases they were still more soluble in artificial gastric juice although the claim is made for them that they are practically insoluble in the stomach secretions. Moreover, their solutions in many cases are distinctly astringent. However, Sollmann has shown that they are dissolved so slowly that it is probable that, under ordinary circumstances, they would be mechanically carried out from the stomach into the intestines before sufficient had been dissolved to exercise any considerable astringent action in the stomach. Moreover, the claims made that they are decomposed in the intestinal tract and exert

their full astringent action has also been shown in many cases to be erroneous. The ones that most nearly correspond to the theoretical requirements are the acetic esters of tannin, of which there are two varieties on the market. While he found considerable difference in the individual specimens the best of them approached very closely to the ideal requirements. The hydrolysis of acetyl-tannin in the presence of sodium bicarbonate is, however, so slow that when taken by the mouth the most of the drug would be well down in the intestinal tract before its full astringency would be developed. For this reason it was deemed advisable to admit to the Pharmacopœia not only this derivative, but one of the albumin tannates whose astringent action is most marked in the duodenum.

REFERENCES.

Eggleston and Hatcher, *Journ. Pharmacol. and Exper. Therap.*, 1919, xiii, 433.
Closson, *Journ. Mich. State Med. Soc.*, 1914, xiii, 587.
Lambert, *Journ. Exper. Med.*, December, 1916.
Leech, *Journ. Amer. Med. Assn.*, 1920, lxxv, 1120.
Pilcher and Sollmann, *Journ. Lab. and Clin. Med.*, Feb. 1923, viii.
Power, *Journ. Chem. Soc.*, 1905, lxxxvii, 838 and 884.
Rock, *Bull. No. 1057, U. S. Dept. Agricult.*, 1922.
Smyth, *Amer. Journ. Pharm.*, April 1923.
Sollmann, *Journ. Pharmacol. and Exper. Therap.*, 1921, xvii, 63.
Takeda, *Arch. Internat. de Pharmacod. et de Therap.*, 1911, xxi, 203.

FURTHER STUDIES OF THE RELATIVE RATES OF ABSORPTION OF DRUGS FROM THE LYMPH SAC AND THE MUSCLES OF THE FROG.

BY C. D. HIGLEY AND M. S. DOOLEY.*

In a previous communication[1] it was shown that the digitalis group of substances, as measured by their intensity of action upon the heart, are absorbed more rapidly and evenly from the muscles of the frog than from the lymph sac. Strychnine is also absorbed more readily from the muscles, as judged by the observation that convulsions come on much sooner, from a given sized dose, than if the drug is acting from the lymph sac. Also it was found that the minimal convulsive dose of strychnine, when given intramuscularly, is not sufficient to cause convulsions in the frog when administered by the other method.[1] The present paper relates the results of experiments upon the question of whether this difference holds, when other drugs are introduced by the two methods. Of course only those drugs that induce some definitely measurable outward change in the frog can be used for this purpose. Epinephrin happens to be one of these. Its dilating effect upon the pupil of the frog from systemic administration, as demonstrated by Meltzer,[2] has been used as a basis of comparison.

DESCRIPTION OF METHOD.

The animals were fastened upon a frog board, and, as soon as the pupil maintained a constant diameter, injections were made into the muscles of the thighs or into the lymph sac as a given experiment required. During the first five minutes thereafter readings were taken of the vertical diameter of the pupil at half-minute

* Department of Pharmacology, Syracuse University College of Medicine, Syracuse, N. Y.