SCIENTIFIC SECTION

THE AIMS AND METHODS OF MODERN PHARMACOLOGY.*

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I am glad to have the opportunity to speak on pharmacology to-night as it is a subject which is coming more and more to the fore and in this country is also one very much misunderstood, not only by the chemists but even by some medical men and by most pharmacists. We are dealing here simultaneously with one of the oldest of sciences and also one of the newest, because pharmacology on the one hand was confused by the ancients with pharmacy which, of course, is as old as medicine is itself, and on the other hand, because modern pharmacology in its most highly developed state is especially concerned with the relation existing between the physical and chemical properties of various substances and their action on functions of living matter, in the most intensive and extensive sense of the word. To give a definition of pharmacology is not an easy task as is the case with all definitions; indeed many well-known textbooks on the subject such as Sollmann's in English, Poullson's in Scandinavian and Meyer and Gottlieb's in German, avoid doing so altogether. The two most prominent and authoritative books on the subject in English, however, define it quite satisfactorily in the following way. Cushny states that "Pharmacology is the study of the changes induced in living organisms by the administration in a state of minute division of such unorganized substances as do not act merely as foods." A much more comprehensive and I believe more accurate definition is that given by Prof. W. Dixon, of Cambridge, who speaks of pharmacology in its broadest sense as that "science which deals with the alteration of function in living matter brought about by changes in its environment." This broad definition of pharmacology which appeals to me very much can be put more clearly in the following way. Pharmacology in its broadest sense is that great department of knowledge on the border line between biology and chemistry which deals with the relations of the two. If by the term biology we understand all the sciences dealing with living organisms whether they be of plant or animal origin, we can conveniently subdivide the consideration of its subject matter under four headings. The first is *Morphology* which deals with the anatomy, histology and finer structure of all living organisms. The second is *Physiology* which concerns itself with the normal functions of living matter whether of plant or animal origin. The third is *Pathology* which treats of the changes anatomical or physiological produced in living matter by disease. The fourth is the very extensive branch of *Biology dealing with the alterations* in living organisms or tissues *produced by all matter*, in the chemical sense of the word. This is the domain of pharmacology. At the present stage of its development in view of the fact that physical and chemical phenomena are no longer to be separated, pharmacology may be stated to be that science which deals with the effects of physico-chemical forces on the physiological functions of living matter. This broad definition of pharmacology expresses, I am quite sure, the conception of the subject held by

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most of the prominent pharmacologists in America and abroad. In subdividing the subject of biology as I have done, it is evident at once that there is a certain amount of over-lapping between the various subdivisions. This is especially true of the relation between pharmacology and pathology. A great many, if not most, diseases or pathological conditions are produced in their final analysis by chemical, *i. e.*, pharmacological agents and therefore it is not surprising that many a problem of pathology is undertaken and often solved by the trained pharmacologist. No better evidence of this could be furnished than the name of the oldest and leading pharmacological journal in the world, namely, *Shmiedberg's Archiv für Experimentelle Pathologie und Pharmakologie.* A number of synonyms and pseudonyms for pharmacology have crept into our language in the long course of its development. The older physicians often spoke of pharmacology as part of the all-embracing subject of Materia Medica. Materia Medica by these older authorities was used to include all sciences dealing with medicaments. At the present time this phrase Materia Medica is generally employed in a much more restricted sense, and really denotes a catalog-like description of the pharmaceutical and chemical properties of official drugs and other medicaments. In order to lay stress on the physiological aspects of pharmacology dealing as it does with the effects of drugs or chemicals on physiological functions the term *pharamacodynamics* has been coined. This, however, is not synonymous with pharmacology because the latter includes not only pharmacodynamics but also a study of the chemical, botanical, pharmacognostic and even pharmaceutical properties of various substances or chemicals employed in therapeutics or the treatment of disease. What are the purposes and aims and methods of approach characteristic of this science?

Before proceeding further it is well to rectify some misconceptions which have crept in. The peculiar border line position of pharmacology between physiology and physiological chemistry in medical schools has led to a certain paternalistic attitude on the part of physiologists on the one hand and of chemists on the other towards this comparatively new department of medical science. It is not so long ago that pharmacology was classed as a subdivision of physiology and the action of a few drugs on animals was demonstrated by instructors in physiology. Even now while most of our great universities and all of the European ones have well established independent chairs for pharmacology there are some schools in these United States in which the subjects of physiology and pharmacology are still being lumped into one and the same department. Even though the head of such a department were qualified to teach both, the ramifications of pharmacology have grown to such an extent that it is physicially impossible for any physiologist to do justice to both at the same time—the combination figuratively speaking makes too great a mouthful for even the man of gigantic proportions to swallow.

Even more curious in this day of medical specialization is it to find pharmacology as a subordinate to the department of biological chemistry; yet such a curious phenomenon is actually existing in certain parts of the United States. Of course, phenomena like these are but anarchronisms, and belong to the age when anatomy was taught by the practicing surgeon and the teaching of Materia Medica and thereapeutics was the prerogative of the practicing physician.

A misconception of pharmacology of quite a different sort and of a perhaps more

pardonable character is that entertained by certain organic and other chemists, who are beginning to realize that pharmacology and toxicology play an important rôle in connection with the manufacture of synthetic chemicals which have come into use in medicine or which at least have a certain therapeutic value from the commercial point of view. Some of these gentlemen seem to entertain an idea that the pharmacologist is a sort of a simple slot-machine or a music-box convenient to have for testing drugs. Given a new chemical compound all that is necessary to gage its market value is to push it into the slot and presto a card flies out predicting its medicinal complexion and its future value in dollars and cents. Unfortunately, to carry the simile a little further, if the pharmacologist be likened to a music-box, the answer to the chemical inquiry will not be so simple and if the coin is of real value the tune that will be played by the musician will probably not be a very simple one but on the contrary a complicated symphony requiring time and study for its full appreciation.

Still another distorted conception of the scope of pharmacology is that entertained especially in America, by some manufacturing pharmacists and druggists who have also come to realize that pharmacology is something deserving of a place in their establishments. Among such the conception of a pharmacologist is something in the nature of a specialist in biological assay or testing of drugs. All that they expect of such a specialist is to poke a few syringefuls of a medicament into a rat or guinea-pig and see how much it takes to kill; or possibly to test the action of a medicament on the contractions of a piece of uterus; and if the tester can perform a blood-pressure experiment with a highly expensive Kymographion to make a tracing and show that ergot raises the pressure, he is regarded as a wizard. This conception of pharmacology is about on a par with a conception of chemistry which limits its scope to a determination of nitrogen and carbon of a new compound without any attempt at the elucidation of its more complicated chemical structure. Such a technical automat is very useful as far as it goes and the live pharmacologist employs such automats as technicians in order to carry out the very necessary and important assays which may be deemed necessary in the course of his work. But the mere testing of a drug by such simple methods without a broader and more profound interpretation of the results obtained and without a further and more extensive pharmacodynamic analysis of its action is but a small chip in the very complicated mosaic composing the puzzle or problem which confronts the true pharmacologist in the broader sense of the word. The problems which confront the research pharmacologist are as extensive and varied as the whole field of medicine and biology on the one hand and chemistry on the other. This is at least the conception of that science entertained by its leading exponents in Europe and America.

In order to convey an adequate idea of the task confronting the pharmacologist it may be well to take a concrete example. Let us inquire broadly into the pharmacology of digitalis which is still the most important heart drug employed in medicine. Fox-glove or *Digitalis purpurea* has long been known in medicine as a remedy for dropsy. As is the case with a large number of our most important drugs the use of digitalis leaves for medicinal purposes originated in folk medicine and was practiced by the laity long before it was taken up by physicians. It was not until the end of the 18th century that this old wives' remedy

attracted the attention of a Shropshire physician, William Withering (1741–99), who was the first to examine it critically in a real scientific way. Withering's studies were almost entirely of a clinical nature, but his scientific insight and acumen were of such a lofty quality that his empirical deductions concerning the therapeutic action and poisonous effects of digitalis revealed more critical well-balanced judgment than that exhibited by many a modern physician or pharmacologist. His "Account of the Fox-glove" (1785) remains one of the most fascinating pharmacological and medical classics on record. It was long after Withering's work was published that the pharmacology of digitalis and allied drugs in the modern sense of the word began to be studied, and we may state at once for your information and delectation that our knowledge of the pharmacology of digitalis at present is perhaps more incomplete than it was fifty years ago. This, of course, implies that heart drugs are beginning to receive serious attention on the part of scientists, and that they are just beginning to find out how little they know.

In order to investigate the pharmacology of a cardiac drug belonging to the digitalis group, and there are quite a number of such drugs both of plant and animal origin, we must turn our inquiries in several distinct directions. Inasmuch as pharmacology rests upon the fundamental bases of chemistry on the one hand and physiology on the other, attention is directed first to the chemistry of digitalis. What is the active principle or principles in the digitalis plant responsible for the very interesting and sought-for medicinal effects produced by the crude drug? Here we touch upon one of the cardinal objectives of the pharmacologist, *the Search for Active Principles.*

The desirability of isolating a definite chemical body from a crude drug is obvious. Such a pure body can be studied accurately in regard to its pharmacodynamic properties and the results thus obtained will not be distorted by the combined effects of other bodies present or of impurities. Standards of assay and more accurate dosage will be thus obtained and furthermore it is only when a definite chemical principle is isolated that the research chemist may hope at least to solve its structure, and point the way to new synthetics. The chemistry of digitalis has been the subject of study on the part of some of the most eminent men in pharmaceutical chemistry and pharmacology. Many active principles mostly of the glucoside type have been isolated from the digitalis plant but very few of these have as yet been completely studied and but little is known as to their chemical structure. While all such studies are largely chemical in nature the search for active and pure principles of drugs is the legitimate prerogative of the pharmacologist, for hand in hand with all such work must go the study of their action on living things. Quantitative analysis of the various ingredients of the digitalis leaves and seeds must also be made. Further studies on his part are directed towards examination of other cardiac drugs which belong to the digitalis group pharmacologically, and an inquiry as to the relation of their active principles if such can be obtained towards those of digitalis. This leads to the discussion of the second cardinal objective in pharmacology—*The Study of Pharmacodynamics.*

Having obtained a reliable preparation of digitalis the pharmacologist proceeds to study the action of such preparations (or if possible of active principles) on living tissues. Here another word of caution may be stressed. Everyone in this assembly has heard of digitalis and everyone of those here present is quite

familiar with the fact that the principal if not the only use of digitalis preparations is for the treatment of cardiac conditions or disturbances of circulation. In what does the pharmacodynamic study of digitalis consist? Obviously the uninitiated would say, in the study of its action on the heart and circulation. The drug tester or biological assayer would take a new heart drug and examine its effect on the frog's heart by injecting some of the substance into a frog's lymph sac; or he would perhaps perform an imposing blood pressure experiment and see what the drug does to the blood pressure. If he is very ambitious he might further determine the killing-dose of the drug not only for a frog but also for a cat. On the basis of data thus obtained he would render his verdict. Such a superficial study of a heart drug is not the kind that the real pharmacologist would undertake in the case of a drug which is worth while. He knows full well that every drug while showing some striking physiological effect on some particular organ or tissue will also influence either directly or indirectly, to some extent, all other functions of a living body. It is a platitude to say that the body is one. Every cell in the body is more or less connected by physical or chemical or biologic bonds with every other cell. The complete study of the heart drug will, therefore, not only include study of its effects on the circulation but also on the respiration, on the kidneys, which by the way are very intimately connected physiologically speaking with the heart, on the nervous system, on the blood, on the gastro-intestinal tract and indeed on every other organ of the body. Let us, however, confine ourselves for a moment to the effects of a drug on the circulation. A so-called cardiac or heart drug must be studied even in that special field of physiology dealing with the circulation from various angles and the results obtained must be compared and weighed before passing intelligent opinion on its value. In studying the circulation one must inquire into the effects of a drug firstly on the heart, secondly on the blood vessels, thirdly on the nervous system. Let me briefly mention what such a study means; and let us begin with the nervous system. Circulation is profoundly influenced by variations in the nervous apparatus of the body, both the peripheral and central nervous systems playing a rôle. A drug like digitalis not only exerts an influence on the heart muscle itself but also acts upon the heart in marked degree through various nervous centers. The slowing of the heart produced by digitalis is a result of its action on the so-called cardio-inhibitory or vagus center in the medulla. The inhibitory effect is produced by impulses traveling from the center down the vagus nerve to the nerve terminals of the vagus in the heart substance itself, thus producing a slowing of the heart rate. Digitalis and other heart drugs may also influence the circulation profoundly though indirectly through their effect on the cerebrum. The vasomotor center in the medulla may also be affected by such drugs, and last but not the least the circulation can be changed to a large extent through changes in the autonomic nervous system.

The effect of heart drugs on the circulation will differ again to a great extent with the state of the blood vessels. Such drugs must therefore be observed as to their action on the arteries, capillaries and veins. Here the pharmacologist stumbles upon a most fascinating phenomenon, namely: he learns that various vessels are affected by the self-same drug, in very different ways. The same pharmacological agent may produce a constriction of the splanchnic vessels and at the same time a dilation of the vessels of the skin so that a complete study of the

effects of any drug on blood vessels must include separate studies of individual arteries and veins.

If we now turn to the effect of digitalis on the heart, the data now obtained from simple blood pressure experiments are not at all complete. In the first place the blood pressure curve gives only an indirect and incomplete indication as to the action of a drug upon the heart itself. In studying the effect of a drug on the heart in a true and thoroughgoing pharmacological way the investigator must inquire into the action of such a drug on: (1) the dromotropic function of the heart, that is its conductivity, (2) the bathmotropic properties of the heart muscle or its excitability, (3) the chronotropic property, that is the regulation of its rhythmicity, (4) the inotropic properties or contractility, (5) the tonus of the muscle wall and (6) the circulation of the heart muscle itself, or coronary arteries. He may extend his studies further and study the effect on various heart ganglia; and with all such data in his hands he will begin to realize that he has advanced but very little towards the complete understanding of the action of the drug on the heart. In the first place these studies will have to be carried out not only on the frog's heart but upon the hearts of various higher animals. It has been found that various animals react very differently to the effects of the same drug. The study of the drug on the heart will have to be carried on not only in situ in the intact animal but also on the isolated heart, and perhaps on isolated heart strips in order to study the reaction of muscles for various parts of the organ. With the advances of modern physiology the study of the heart effect will furthermore not be complete without some work with the electrocardiograph. Yet with all data thus obtained the practical pharmacologist is far from being in a position to apply them to clinical practice, because of a very important point too often lost sight of, both by the pharmacologist and the practicing physician. I am referring to the circumstance that the vast majority of the experiments performed by the pharmacologist in his laboratory are made on normal animals and it is a well-known fact that pathological organisms and tissues will often react to certain drugs very differently from the way they react in normal state. We have learned to appreciate the fact that many drugs in ordinary doses may exert no appreciable pharmacological action on normal organisms and yet the same drugs even in smaller doses will produce profound changes in the diseased animal or pathological organ. This is a trap into which many a conscientious physician has fallen. The careful medical investigator must bear in mind the part played by "*vis medicatrix naturae*" in all pharmacological and therapeutic experiments and clinical observations. It may be stated as a general law that there is a tendency on the part of nature to restore abnormal or pathological states of living organisms to normalcy, so that the effects of pharmacological agents which tend to exert their action in the same direction are more evident or more pronounced when applied in pathological states than under normal conditions. To illustrate, we cannot reduce much the temperature of a higher animal by administering even large quantities of so-called antipyretic drugs, under ordinary circumstances; yet when the temperature is above normal, that is when the animal or the patient has fever, even a small dose of such an antipyretic will promptly tend to lower the temperature. Again, there are certain antispasmodic drugs such as the alkaloid papaverin and certain Benzyl Esters which exhibit the remarkable property of lowering the tonus and inhibiting

the peristalsis of various smooth muscle organs. Such drugs exhibit this peculiar antispasmodic property on smooth muscle in normal animals to a considerable extent, but where such smooth muscle organs are in a state of abnormal tonicity or peristaltic movement the sedative effect is much more marked. This is especially true of angiospasm, or spasm of the blood vessels. Some years ago I found that the simple and innocuous esters, benzyl benzoate and benzyl acetate, produced a distinct fall in the blood pressure of rabbits, dogs and also human beings. Such a fall in blood pressure is, however, not at all as marked when the observations are taken on normal subjects than when they are made on cases of abnormally high blood pressure due to spastic condition of the arteries. These observations have recently been confirmed in a very ingenious way by two Rumanian investigators who studied the effects of benzyl benzoate and benzyl acetate on man by Plethysmographic methods under both normal and pathological conditions. While the fall in blood pressure after intramuscular injections of solutions of these drugs was not very great in normal health, these authors have noted a marked and long-lasting fall in blood pressure in cases of true hypertension due to a distinct vasodilatation produced by the drug. (1). Another example is the action of opiates and other analgesic or pain-relieving drugs. Their specific action can certainly not be appropriately studied on normal animals, because they obviously do not suffer from pain. So with digitalis and other heart drugs. One cannot appreciate fully either the pharmacological or therapeutic significance of a heart drug by studying its effects on the healthy and strong heart. It is self-evident that an ordinary heart muscle cannot contract much more powerfully than it is intended by nature to contract. When, however, the subject is suffering from myocardial insufficiency or weakening of the heart muscle, administration of Digitalis will draw the flabby heart together and strengthen its contractions in a truly wonderful manner.

These pharmacological studies of Digitalis which I have just briefly outlined do not by any means exhaust the topics involved in an adequate study of that drug. I have not touched upon the influence of Digitalis on the respiration, a subject which must always be considered in connection with the circulation. Nor have I dwelt upon the gastro-intestinal effects which are of particular interest in connection with the therapeutic uses of this drug. Again it is absolutely imperative for the complete knowledge of the action of any drug to obtain definite information concerning its absorption and excretion and fate in the body. This in case of digitalis is of especial importance on account of the remarkable phenomenon of cumulation which it exhibits and which virtually involves a biochemical study of the combination myocardium or heart muscle plus digitalis and the interaction of digitalis glucosides and blood and is inseparable from the subject of *Toxicology*, which is the next cardinal line of inquiry to be pursued by the pharmacologist.

Toxicology is really only one phase of pharmacology because we have come to appreciate more and more that every drug is also a poison as the etymology of the words for drug and poison in different languages clearly shows. The old English "to drug" and the Greek ΦΑΡΜΑΚΟΝ denoted both medicine and poison. It may be stated as a general principle with hardly an exception that every drug that is *worth while* is also a poison, and in order to employ it intelligently for the production of a desirable effect, the physician must be familiar with its toxi-

cology as well as with its pharmacodynamic properties. Toxicological studies of course, just as pharmacological ones, involve both chemical and physiological experimentation, into a discussion of which we cannot here enter. The pharmacologist must learn not only to recognize the clinical signs and symptoms of a poisonous nature, but also to detect by chemical examination the presence of the poison in various tissues, secretions and excretions. Such a discriminating difference between a desirable medicinal effect and a deleterious one, which is the basic principle of all therapeutics and is expressed by the ancient maxim "Nolle Nocere," demands an exhaustive study of the various *Conditions Modifying Drug Action* which is a fourth cardinal topic of inquiry confronting a pharmacologist.

The conditions or factors influencing the action of drugs are very numerous but for pharmacological discussion they may be divided into three classes: (1) those depending upon the drug itself, (2) those depending upon the animal or patient to whom the drug is administered and (3) certain external factors indirectly connected with either the drug or the experimental subject. Factors playing a rôle in determining the poisonous or therapeutic effects of a pharmacological agent which depend on the drug itself are very numerous. In the first place *the dose* of the drug obviously plays an important rôle. The same substance which, given in small quantities, may produce a very desirable therapeutic effect will, when given in larger doses, produce death, as for example is the case with hydrocyanic acid. This acid which is known as one of the most virulent and rapidly acting poisons will not produce, under certain conditions, any poisonous effects at all. When it is administered in very minute quantities to higher animals the drug or poison is taken care of by the living organism which combines it with certain amounts of available sulphur, forming harmless compounds. As soon, however, as a given limit is reached the poison paralyzes the respiratory center and produces death through interference with the normal functions of the red blood cells. The *penetrating properties* of various drugs, that is their property of penetrating through the cell membranes, is of extremely great importance in connection with their pharmacological action. Some drugs may be taken by mouth with perfect impunity and yet the same substances when injected into an animal produce severe poisoning or even death. Thus for instance potassium salts may be and are freely taken by mouth by normal as well as diseased individuals and no harmful results follow such a procedure because, when the kidneys are normal, these salts are rapidly absorbed and just as rapidly excreted in the urine. When, however, a potassium salt is administered intravenously, the characteristic effect of the potassium ion on muscle, and particularly on heart muscle, manifests itself and produces a slowing and sometimes arrest of the heart. Magnesium sulphate taken by the stomach acts as a so-called saline purgative, the purgation being produced through certain peculiar properties of the magnesium ion. Magnesium ions are absorbed through the gastro-intestinal mucosa only to a very slight extent. When, however, magnesium sulphate is injected into an animal either through a vein or even subcutaneously, the characteristic depressant effects of the magnesium ion for the central nervous system are produced, causing a paralysis of the respiratory center. (2). The arrow poison curare introduced into the stomach of a rabbit produces absolutely no deleterious effect. When, however, a minute quantity of this drug is injected into its skin or muscles it is rapidly absorbed, producing

a paralysis of the motor nerve endings and leading to the death of the animal. More interesting still it has been recently observed by Mautner and Koref that if the rabbit be given an injection of insulin previous to the administration of curare by stomach, another change in permeability of tissues is brought about and the same poison is now absorbed through the gastro-intestinal channel producing characteristic signs of curare poisoning. (3). The *physical properties* of the drugs administered to animals and human beings play also a rôle in respect to their pharmacological action. Thus the solubility of various medicaments such as arsenic, phosphates, etc., will make a difference in regard to their therapeutic and toxic effects. Bile for instance is necessary for the proper action of certain anthracene purgatives. The reaction of the various body secretions and juices will, of course, affect the chemical and pharmacological properties of various medicaments. The concentration of the drug will also play an important rôle. The presence of colloids in the stomach will affect the action of various drugs. Many a victim has been saved from the fatal effects of a poison by having taken it on a full stomach. Such a substance as common salt when taken in isotonic solutions will produce no harm yet when a concentrated solution of brine is introduced into the stomach it may produce shock and even death. The Chinese are said to have used this method of dispatching their criminals.

The action of a drug will vary a great deal depending upon the animal or patient to whom it is administered. Different kinds of animals often react very differently to the same pharmacological agents. A rabbit requires some fifty times as much morphine to kill as a man does. (4). The salamander will not be paralyzed by thirty times as much curare as a frog. Digitalis bodies are not very toxic for the toad's heart and yet are extremely toxic for the frog. Not only do different kinds of animals vary in their susceptibility to various drugs and poisons but it has been found that even two species of the same genus will react quite differently. Thus caffeine injected into *rana esculenta* will produce its chief effect upon the nervous system, whereas caffeine injected into *rana temporaria* will exert its action upon the skeletal muscles. The age of animals plays a very important rôle in connection with the action of drugs. Sex under certain conditions will also produce a difference in both intact animals and also in isolated surviving organs. Again epinephrin or adrenalin exerts an entirely different effect on the isolated pregnant uterus from that produced on the virgin organ. An extremley important rôle in determining the action of a pharmacological agent is played by various pathological conditions. I have already touched upon this. The same drug acting on a diseased animal or organ may produce a very different effect from that obtained by observations on the normal animal. Another illustration may emphasize this point. Some years ago Dr. Giu Ching Ting collaborating with me on a research concerning the action of various drugs on the Bronchi made a very interesting observation. (5). The action of various drugs was studied on isolated surviving fresh bronchial muscle obtained from the lungs of pigs obtained from a nearby slaughter house and used within an hour after death. It was noted invariably that under certain conditions the muscle preparations while perfectly fresh failed to respond to treatment with various pharmacological agents. An inquiry into the causes of this peculiar phenomenon revealed that in all such cases the animals from which the preparations were obtained were suffering from broncho-

pneumonia. It was evident that the toxin produced in that disease affected the normal response of bronchial muscle. Microscopic sections of normal and diseased lungs obtained in this connection confirmed these deductions. Many other illustrations of the rôle played by the individual or the animal and even in connection with the action of drugs may be cited.

We are just beginning to realize more and more the profound influence exerted by various external factors on the action of drugs. Thus for instance seasonal variations have been noted in connection with the reaction of frogs to various medicaments. Temperature may make an important difference in the action of some drugs. For example when the alkaloid colchicine is injected into a frog's lumph sac little or no effect may be noted if the animal is kept in a cold place. When, however, the animal is taken into a warm room, symptoms of poisoning develop very rapidly. The explanation in this case is not far to seek. It was found that the alkaloid colchicine at higher temperatures decomposes rapidly producing another alkaloid which is responsible for the toxicological effects. The effect of light on the action of drugs is extremely interesting. Not only does light affect the keeping qualities of certain medicinal substances but we know now also that certain rays, especially the ultraviolet, may potentiate or increase the activity of certain drugs. Dr. Teagarden and myself a few years ago published some experiments concerning the effect of ultraviolet rays on the activity of quinine and quinidine sulphates for frogs and rats. (6). These solutions which are fluorescent are much more toxic in light than in the dark. Paramecia have been known to live for a long time in solutions of eosin if kept in the dark. When, however, the same solutions with the animalcules were exposed to sunlight, the little creatures rapidly perished. Bacteria are known to influence the action of a great many drugs and may indirectly produce poisoning under certain circumstances. For instance, insoluble compounds of bismuth such as the subnitrate are often given in gastro-intestinal diseases to act as sedatives to the mucous membranes. Occasionally, through the action of certain bacteria present in the intestines, these compounds are decomposed, forming soluble salts of bismuth which are absorbed producing the characteristic poisonous effects of bismuth ions. Many more illustrations could be adduced concerning the various conditions affecting the action of drugs but we cannot dwell on this subject any longer in this place.

Having studied as far as possible the various conditions affecting drug action, the careful pharmacologist who is examining a new or unknown drug with an ultimate view of applying it in clinical practice must turn his attention to another cardinal line of inquiry. He must consider certain *Therapeutic Data* concerning it. Even after the pharmacological, chemical and physiological properties of a new substance have been thoroughly investigated a great many questions must be answered before proceeding to administer it to patients. The keeping qualities of the drug must be carefully studied and methods for its assay, which very often are purely biological, must be established. This is particularly true of the illustration which I have cited in this discourse, namely, Digitalis. It is well known that preparations of Digitalis are extremely variable in potency and keeping qualities and it is also well known that in order to produce a satisfactory therapeutic effect with this drug a sufficient quantity of a potent preparation must be administered. Having determined to satisfaction the dosage of a drug, its

method of administration must be studied. Drugs may be administered through various channels and the effects produced may vary with the method of administration.

One of the pit-falls of the pharmacologist as well as of the clinical practitioner is the confusion between local and systemic effects of drugs. A medicament such as atropine may be applied to the eye for a purely local effect but it may be absorbed by the lymph sac and blood vessels of the organ and carried into the general circulation, producing symptoms of atropine poisoning. Vermifuges or anthelmintics are given patients in order to expel intestinal parasites. The absorption of such medicaments by the intestines is undesirable and should be avoided. When administered improperly, as for instance in case of the male-fern resin together with oil, absorption may be promoted and serious poisoning will result. Drugs have been used in vaginal douches for purely local effects, but they have been absorbed into the circulation and produced poisoning and even death. Individual susceptibility of patients or so-called idiosyncrasy must receive proper consideration. The therapeutic application of drugs requires furthermore a preliminary inquiry into the possibility of cumulative effects, tolerance, habituation and drug addiction which may result from their use. All these problems come within the sphere of activity of the expert pharmacologist. Many more topics in this connection could be discussed but we must refrain. It is particularly on account of the ultimate therapeutic applications of the results of pharmacological research, that it is very desirable, nay, according to many prominent pharmacologists, it is essential for the well-rounded and well-grounded pharmacologist to have a medical education. I would rather trust my body when sick to the physican, than swallow any medicament urged upon me by ever so learned a chemist, druggist or even a physiologist or biologist.

The enormous number of nostrums, quack remedies and new synthetics flooding the drug market are certainly not to be laid to the activity of pharmacologists. These dangerous or useless articles are foisted upon the public by thoughtless or rapacious chemists or druggists on the one hand, and are prescribed by the insufficiently trained and crude practitioners or charlatans on the other. In almost all such cases there is to be found a lack of pharmacological knowledge concerning them. The well-trained physician knows full well, that the conscientious and thorough pharmacologist will hesitate to urge the therapeutic use of any substance, before he has studied it from every angle, and that, he will even first try the drug himself, before administering it to fellow man.

(To be continued)

OFFICERS-ELECT OF THE AMERICAN PHARMACEUTICAL ASSOCIATION.

The Board of Canvassers of the AMERICAN PHARMACEUTICAL ASSOCIATION, composed of Henry J. Dusterberg, Otto Kistner and J. T. Lloyd, all of Cincinnati, O., has announced as the result of the vote for officers of the ASSOCIATION the election of the following:

President, David F. Jones, Watertown, So. Dakota.

First Vice-President, A. W. Pauley, St. Louis, Mo.

Second Vice-President, W. H. Zeigler, Charleston, So. Carolina.

Members of the Council, H. C. Christensen, Chicago, Ill.; H. A. B. Dunning, Baltimore, Md.; S. L. Hilton, Washington, D. C.

These officers will be installed at the 1928 meeting of the ASSOCIATION.