SCIENTIFIC SECTION

THE AIMS AND METHODS OF MODERN PHARMACOLOGY.

BY DAVID I. MACHT.

(*Continued from p. 17, Jan.* JOUR. A. PH. A.)

I now come to the consideration of the highest goal of the pharmacologist, namely, the study of *Chemopharmacodynamic Relations*. This is a goal toward which every expert pharmacologist strives to approximate but unfortunately which very few succeed in approaching, and is indeed one from which many a pharmacologist has unwaringly receded. Inasmuch as the chemistry of digitalis bodies has not yet been solved a discussion of such relationships in connection with that drug cannot be made. A few general remarks on the subject, however, may not be out of place. The subject of relationships between chemical structure of various substances and their physiological effects is a fascinating one but is one which has yet been developed to a very limited extent. Large treatises have been published on the subject notably those by Fränkel and Oswald. These have grown in volume with every new edition but an examination of the same reveals that they are for the most part but compilations of many unrelated observations obtained by various investigators which the writers have attempted to correlate according to their fancy. Of course, there are quite a considerable number of definitely established chemopharmacodynamic relationships in pharmacology, but on the whole any attempts at broad generalization in this field are premature and the work along this line by careful pharmacologists has confined itself to chemopharmacodynamic and chemotherapeutic studies within definitely established limits, and with chemical compounds the structure of which is generally thoroughly known. We are not in a position in pharmacology to go so far as physicists used to go in our student days when they delighted in expressing every physical phenomenon by means of formulas in terms of C. G. S. units. Whenever I speak on this subject I cannot refrain from alluding to two anecdotes which serve admirably to warn the uninitiated of the pitfalls in this fascinating field of research.

A young man who had been drafted in the chemical warfare service, on returning to America after the war decided to go into pharmacology. This ambitious young gentleman came to the pharmacological laboratory of Johns Hopkins University to consult with some of the men concerning the following wonderful idea which he conceived. He wanted "to study the relation between chemical structure and pharmacological action." On being asked as to what particular group of compounds he was especially interested in, he replied that his purpose was to take up the study of all organic chemicals that he could pick up in the chemical museum for this purpose. It is ten years since this young man made the above remark and I am sure that his ambitions have since then become more modest. Indeed I am not well aware of his having contributed anything of importance to the subject of chemopharmacodynamic relationships at all. The trouble with him was that instead of confining himself to an intensive study of a small group of chemically related substances he wanted to tackle the correlation of the whole field of chemistry with the whole field of physiology.

In another case a group of investigators undertook to study the relative *toxicity* of a large number of organic and inorganic compounds and to do so they chose for their criterion the killing power for tadpoles. An enormous number of experiments were performed on tadpoles and on the basis of the figures thus obtained they constructed a mathematical formula purporting to convey the relationship between chemical structure of the substances examined on the one hand and the killing power for tadpoles on the other. I am not prepared to question the validity of the formula thus built up from the tadpole experiments although from the pharmacological point of view it is very doubtful that the same formula could be applied to express the toxicity of entirely unrelated chemical compounds. The investigators in question unfortunately went further and actually claimed that the toxicological data obtained from tadpoles and the mathematical formula constructed therefrom could be applied to other animals and even to human beings. Here is another excellent illustration of an insidious trap into which the inexperienced pharmacologist is liable to fall, unless he is thoroughly trained not only in chemistry but also in the biological and medical aspects of such experimentation. Even though a mathematically correct formula could be constructed dealing with the relationship between the chemical structure of any group of compounds and their toxicity for tadpoles, such a formula would only hold good for tadpoles, and even then for only the *particular species of tadpoles* on which the experiments were performed. To apply the same formula to other genera of animals, would be sheer folly, unless new experiments equally as numerous be performed on such animals with the same results. This from the pharmacological point of view is very unlikely because every pharmacologist is well aware that differences in their reaction to drugs are shown not only by different families of animals but even by different species of the same family. To give a concrete illustration of the complexity of this subject I may be permitted to report the findings obtained by me and my co-workers in connection with a toxicological study of certain mercurated fluorescein derivatives.

We have been interested in studying the toxicity of the following compounds. Oxymercuridibromfluorescein commonly known as Mercurochrome-220 Soluble and containing theoretically 26.6% of mercury, dimercury-dioxy-dibromfluorescein containing theoretically 43.2% of mercury, Oxymercurytetrabromfluorescein or mercurated eosin containing 23.18% of mercury, Oxymercurytetraiodofluorescein containing 19% mercury and Oxymercuryfluorescein or Flumerin containing 31.5% of mercury. The toxicity of these compounds was first studied on tadpoles of the frog *rana sylvatica*. This was done by immersing the tadpoles in solutions of the various drugs and noting the killing time. It was found that the relative toxicity beginning with the most powerful of the various compounds was in the following order: Iodo Compound ⟶ Mercurated Eosin ⟶ Mercurochrome ⟶ Dimercury Compound ⟶ Flumerin.

The toxicity of the same compounds determined by intraperitoneal injections into white rats beginning with the most powerful was in the following order: Mercurochrome ⟶ Mercurated Eosin ⟶ Dimercury Compound ⟶ Flumerin ⟶ Iodo Compound.

The relative toxicity for rabbits determined by intravenous injection was in the following order beginning with the most toxic: Dimercury Compound

⟶ Flumerin ⟶ Mercurochrome ⟶ Mercurated Eosin⟶ Iodo Compound.

The toxicity for cats by intravenous injection was of the same order as for rabbits except that it was found that the dimercury compound was extremely toxic for that animal, even more than for rabbits. The toxicity of the above compounds was also studied by phytopharmacological methods on plant protoplasm. This was done on living seedlings of *Lupinus albus* suspended in nutrient Shive solution according to the methods practiced by the author. (7). Such seedlings suspended in solutions of the various mercurated compounds for 24 hours in the dark at room temperature gave the following order of toxicity beginning with the most toxic: Mercurated Eosin ⟶ Mercurochrome ⟶ Dimercury Compound ⟶ Flumerin ⟶ Iodo Compound.

A most remarkable phenomenon was noted in connection with the experiments on living seedlings: namely, the toxicity of the solutions became much greater when the seedlings were grown in them exposed to light and the order of toxicity was changed being as follows: Mercurochrome ⟶ Flumerin ⟶ Dimercury Compound ⟶ Iodo Compound ⟶ Mercurated Eosin.

It is thus evident from the above experiments that the relative toxicity of the various compounds is very different for different plants and animals. Furthermore, it was found that in case of the tadpoles as well as in case of the *Lupinus albus* seedlings the toxicity of the mercurated fluorescein derivatives was greater in the presence of sunlight. A study of the results obtained furthermore revealed another curious observation. It was found that the dimercury compound was extremely toxic to the higher animals, cats and rabbits when injected intravenously and yet the same dimercury compound when injected into the peritoneal cavity of white rats was less toxic than mercurochrome or mercurated eosin. The dimercury compound was also less toxic than some of the other mercurated derivatives when tested on the seedlings both in the dark or in the light. The explanation of this extraordinary phenomenon was not far to seek. When the same dimercurated compound solutions was administered to both rabbits and cats as well as rats by intraperitoneal injection it was not as poisonous as either mercurochrome or flumerin. This was due to the fact that this compound was less penetrating through the tissues and consequently was absorbed with greater difficulty than either mercurochrome or flumerin or mercurated eosin. When injected into the peritoneal cavity the absorption was so slow that the toxic effects came on very slowly and the animal succeeded in getting rid of some of the poison. When, however, the dimercury compound was injected directly into the circulating blood its toxic action on the heart muscle was immediately manifested by the arrest of that organ and death of the animal. This difference in the penetrating power of the various compounds used could be clearly seen by examining the seedlings suspended in their solutions. It was noted, even with the naked eye, that the penetration of the dimercury compound was not as great or as rapid as that of mercurochrome. We further found that when the three mercurated compounds of di-bromfluorescein, di-chlor-fluorescein and di-iodo-fluorescein with the halogens in the resorcin component were studied on gold fish and rats, the index toxicity was again different. These experiments illustrate how many factors may play a rôle in even such a problem as the study of the relative toxicity of a small group of closely related chemical compounds, and which render any sweeping

generalizations concerning the relation of chemical structure to physiological action very risky. All such statements must be based on actual experimental evidence and it is not at all wise to make any greater claims than are actually warranted by one's experiences in this field.

In spite of the difficulties which I have tried to emphasize, the science of pharmacology has been quite fortunate in having discovered a considerable number of important chemopharmacodynamic relationships. I need only cite a few outstanding examples. The Meyer and Overton theory of narcosis is one of the best known generalizations in pharmacology which has been based on an enormous number of experiments with a very large number of compounds. This is a good example of a generalization wide in scope in the chemopharmacological field and for this very reason this theory has not successfully or rather completely stood the test of time, and exceptions and modifications to the original statements of the so-called Meyer-Overton law are cropping up almost every year. A much better example of the classical nature in this field are the studies on cocaine. The chemistry of the cocaine molecule, as is well known to all those here present, has been thoroughly studied and its structural formula has been absolutely established through the work of Willstätter, Ladenburg, Merling, Merck and others. This molecule consists of three components, one of which is a complicated base called ecgonin, the other benzoic acid and the third methyl alcohol. A very careful pharmacological study has been made of the rôle played by each component not only in regard to the local anæsthetic properties of cocaine but also in respect to its delirifacient properties and its action on muscle (8, 9). Following such studies further work was done in regard to simplifying the structure of cocaine-like bodies, at the same time retaining its important therapeutic properties especially as a local anæsthetic. Substitutions were made in place of ecgonin and other components of the cocaine molecule and as a result of such extensive chemopharmacodynamic studies the new local anæsthetic novocaine was synthesized. This discovery as in the case of all such successful outcomes in pharmacological research lead to what we may call researches of secondary degree; in that various modifications of novocaine were put on the market which differed from it only by the introduction of other side-groups. Another classical example of chemopharmacodynamic relationship, is the study of quinine. The chemical structure of this alkaloid has also been definitely established through the work of numerous chemists and pharmacologists, Skraup, Hesse, Claus, Miller, Rohde, Rabe and König. Its molecule was shown to consist of three parts: a quinoline nucleus with a methoxy group in para-position, a so-called loipon component consisting of a piperidine nucleus with two CH_2 groups in bridge position and two connecting side-chains, one having a Vinyl group and the other a H CO H group connected with the quinoline. The brilliant researches of Morgenroth and his pupils in connection with quinine and numerous cupreine alkaloids related to quinine are a very fascinating chapter in modern pharmacology. These authors have shown that by changing slightly the constitution of different cupreine derivatives, various chemotherapeutic agents were produced which exerted specific bactericidal and parasiticidal effects on specific bacteria and protozoa. Another classical example of chemopharmacodynamic relationship are the studies of Ehrlich and his school on various arsenical compounds culminating in the compound 606 or salvarsan.

If I may be permitted to quote still another illustration along this line showing how the discovery of such relationships may result from prolonged and painstaking routine and comparative studies of various chemical compounds, I should cite my humble contributions to the pharmacology of the opium alkaloids. I have been carrying on pharmacological studies on the various opium alkaloids for many years and some ten years ago became especially interested in the peculiar properties of the papaverine group of opium alkaloids which are characterized by their antispasmodic effect on smooth muscle organs and tissues. The alkaloids of the papaverine group are distinguished chemically from the morphine group of opium alkaloids by their containing a double nucleus, one component of which contains isoquinoline the other a benzyl grouping. The morphine alkaloids of opium have an entirely different chemical structure, the molecule being composed of a combination of two very different components namely a phenanthrene group and a piperidine group. Numerous experiments with papaverine and related alkaloids and their decomposition products have led me finally to conclude that its antispasmodic properties resided in its benzyl component. As a result of these studies came the discovery of valuable antispasmodic properties of various benzyl esters which are now familiar to all and are extensively used in medical practice throughout the world (10). Incidentally to the study of the various benzyl esters a pharmacological examination of benzyl alcohol led me very quickly to the discovery of its local anæsthetic properties thus opening up the way to synthesis of a new group of local anæsthetics, much less toxic than cocaine or novocaine. Benzyl alcohol solutions for anæsthesia were found to be at least 40 times less toxic than cocaine (11).

I should like on this occasion to make a preliminary announcement of another discovery, which I have not yet published. I have been carrying on comparative studies concerning chemopharmacodynamic relationships of morphine and related alkaloids. As a result of these studies I have collected undoubtable evidence that the narcotic properties of morphine reside in its phenanthrene component. The piperidine component of morphine I have found played the principal rôle in the action of morphine on smooth muscle, stimulating it. I have dwelt at some length on the problems confronting the broadminded pharmacologist and described the principal lines of inquiry which one must pursue in order to make an adequate study of the pharmacological properties of a drug to the research pharmacologist for the carrying on of original investigations. Let us now consider some other aspects of Pharmacology.

The pharmacologist being able to draw on the store houses of chemistry on the one hand and biology on the other is especially fortunate in having a rich mine to supply him with ore for every conceivable kind of pharmacological and therapeutic research. It is not at all necessary to look for far-fetched and rare subjects to obtain material for original investigations. In pharmacology the investigator can draw first of all on the Materia Medica itself either of the United States or on that of any other country. The pharmacopœias and dispensatories of all nations are abounding in largely unexplored and virgin fields. Many of our most important drugs still require intensive and extensive study from the pharmacological and therapeutic points of view. The very illustration which I have quoted above, namely digitalis, is a very good example. Our knowledge concerning this

drug is more confused at present than it has been twenty years ago because of the many new discoveries in chemistry and physiology. The same is true of almost every important drug in our pharmacopœia. Not only do the principal drugs of our Materia Medica require further research but also many of the so-called obscure and minor medicaments to be found in the medical dispensatory may also yield valuable stuff. Cod-liver oil has been used by the laity and by medical practitioners for the treatment of rickets and malnutrition for many years. With the development of pharmacology some of the cock-sure exponents of that science without further experimental basis were inclined to cast this valuable substance in discard, asserting that cod-liver oil was no more valuable than an equivalent amount of olive oil or other vegetable or animal fat. The recent discoveries concerning vitamines have changed our views entirely concerning the pharmacological and therapeutic properties of this drug, and now on the basis of such studies the pharmacologist goes further and actually *potentiates* his cod-liver oil by irradiating it with a mercury quartz lamp in order to increase the vitamin content.

A second source of available material awaiting pharmacological investigations is, of course, the whole field of organic chemistry. Here again the discriminating pharmacologist must use his wits and experience in the selection of the compounds to be studied. It would obviously be impossible to make a routine examination of all organicals that have been prepared in the chemical laboratories, unless a regiment of pharmacological testers were engaged in examining them in a big factory. Nor is it wise to undertake the study even of a too large single group of chemical compounds without having some special "lead" or as the Germans say "Fragestellung," that is a definite objective. A thorough examination of any large group of chemicals from every pharmacological angle will, of course, in the course of long time lead to some kind of a discovery of interest but such a procedure will be more or less of an accident, and is comparable to the groping of a blind chicken which may occasionally pick up a grain or two. The same may be stated of general floundering about without a definite objective in pharmacological research from the physiological side. The prospects of discovering some definite facts or establishing some chemopharmacological relationships are much greater when the investigator confines himself to some well-defined problem even though it be apparently an unimportant one, because very often the study of such a problem may lead to incidental or accidental questions of much greater interest.

The pharmacologist can approach original research from still another point of view, namely, the therapeutic one. It is here that the investigator trained in medical sciences again scores over his colleagues. The pharmacologist with a medical training, which in the opinion of all leading exponents of pharmacology is absolutely essential, will often think of practical therapeutic problems to be solved in his laboratory. Indeed in my opinion the usefulness of the pharmacologist can be increased manifold through his contact with various clinicians. I for one have collaborated with practically every department of the Johns Hopkins Hospital in investigating the pharmacological and therapeutic aspects of various problems arising in the same. Such a pharmacologist will one day take up a therapeutic problem bearing on internal medicine. At another time he may become interested in the study of anæsthetics, antiseptics or other drugs employed by the

surgeon; at other times again he may collaborate on problems bearing directly on various specialties.

Still another and very attractive store house of material awaiting the alert pharmacologist is the historical one. It is a remarkable fact that almost all of our very important medicaments have had their origin in the remote past and were used by old wives and medicine men. Opium was employed for the relief of pain centuries before Sertürner discovered that it contained the alkaloid morphine. Cinchona Bark was employed by the natives of South America for the cure of ague long before its chemistry or pharmacology was begun to be studied. So with digitalis, so with cocaine and many other well-known drugs. Folk-lore is, therefore, a very large store house of information which can be utilized with much profit by the discriminating scientist who has the gift of separating the grain from the chaff. Only very recently in the past few years a valuable addition to our pharmacopœia was made through a scientific study of a crude Chinese drug, Ma Huang, from which an alkaloid ephedrine has been isolated. Perhaps the most important one source leading to original discoveries in pharmacology, however, is the one which the pharmacologist shares with all other scientific investigators and that is a *systematic and assiduous application* to a careful study of some problem or other, because any such intensive study is bound to open sooner or later new points of view and suggest new problems often of greater importance than the original one. In pharmacology as in other sciences we may well quote the proverb "In all labour there is profit, but talk of lips tendeth only to want." (Proverbs XIV, 23.)

Let us now consider for the moment some of the recent developments in pharmacology. Enormous progress in this science has been made from the time of Schmiedeberg who is generally regarded as the father of modern pharmacology. The advances made in tracing *chemopharmacodynamic relationships* and in chemotherapy may be appreciated by comparing the size of the first edition of Fränkel's Arzneimittelsynthese with the ponderous tome comprising the last edition. Indeed the last edition has become so large that it is unwieldy and unreadable. Numerous facts have been compiled in this work; yet an examination of its contents will soon reveal that after all not so many great contributions of an original character have been made to the subject. Most of the material here found belongs to researches of so-called "second order," that is results of repetitions, amplifications and embellishments, along the several really original lines discovered by the chosen few scientists of the first rank. This will be found to be especially true in connection with studies which have been made concerning hypnotics, local anæsthetics, antiseptics, analgesics and antipyretics. The fundamental discoveries concerning these groups of drugs were certainly the result of brilliant original experimentation; later contributions, however, are simply the grinding out of analogous chemical compounds with slight modifications in their structure. They are mostly new variations of the same old tunes.

During the past decade or more pharmacologists have been giving special attention to the *study of endocrines* and other products of animal origin. The remarkable and brilliant work in this field especially on the hormones of the suprarenal and pituitary glands by Abel and his assistants, the thyroid gland by Kendal and on insulin by Banting, Best, McLeod and Collip, leading to isolation of the crystalline product by Abel are more or less familiar to all and are to be listed

among the great achievements of modern medicine. A third interesting development in recent pharmacology has been the study and greater appreciation of the problem of what may be termed "two or more drugs." It has been found that combinations of two or more drugs administered to animals may produce new and startling effects. Two drugs when given together may produce a simple additive effect. Again such a combination may reveal a *synergistic* phenomenon indicated by the potentiation of the pharmacological action of one drug by others. Thus for instance we have shown that a combination of morphine, the principal alkaloid of opium with small doses of papaverine or narcotine, belonging to the benzyl isoquinoline group of opium alkaloids, will produce a greater analgesic effect than the addition of the two component doses and at the same time such a combination is less depressant to the respiratory center and hence less poisonous (12, 13). The contributions of Prof. Bürgi and Storm Van Leeuwen on this subject of drug combinations are especially noteworthy. One drug may also be influenced by the *previous* administration of another one. The so-called paradoxical phenomenon of Dale in which the pressor effect of epinephrine is reversed after a previous administration of ergotoxin is probably familiar to some of you. A great deal of valuable work has been done in pharmacology of recent years along what I may term *micropharmacological* lines. By micropharmacology I mean the study of minute bits of tissue from various parts or organs of different animals. Such studies have been of great help in establishing for instance the nerve supply of certain organs. A most remarkable illustration may be given from the work of Prof. Hugh H. Young and myself on the physiology and pharmacology of the urinary bladder (14). Differences of opinion have long existed concerning the autonomic innervation of this important organ, and apparently no agreement could be reached on the basis of experimentation performed on various animals with the whole bladder either excised or *in situ*. In making a thorough study of the subject we began an inquiry into the effect of various drugs on bits of tissue from various parts of the same bladder and more particularly a comparative study of the muscle tissue obtained from the fundus of the bladder on the one hand and the *trigonum vesicae* on the other. Here the solution to the puzzle could easily be found. It was noted that the same drugs produced diametrically opposite effects on tissue obtained from the two parts of the bladder. Thus it was found that epinephrine while producing a powerful contraction of muscle tissue from the *trigonum vesicae* produced a very marked relaxation of muscle from the fundus of the same bladder. Again it was found that various drugs of the so-called parasympathetic group affected the fundus and trigonum quite differently. The *trigonum vesicae* muscle did not respond to these drugs (physostigmine, atropine, pilocarpine, etc.) at all, while fundus muscle responded very readily. Much valuable information, some of which necessitates a revision of older ideas, has been contributed of late by studies in *colloidal chemistry* as applied to pharmacology, and in particular by investigations concerning the properties of surface membranes. These obviously play a rôle in relation to the absorption of drugs and toxins. Credit is due in this connection especially to Prof. Handovsky and other pioneers in this new field. Interesting information of clinical value has resulted in the past few years from studies concerning the action of drugs on the psychological functions. This subject to which I have given the name of *psychopharmacology* and which I have been developing

is still in its infancy, but has already yielded valuable information (15, 16, 17, 18). I have been of late especially devoting a great deal of time to a comparative study of the effects of drugs and toxins on animal and plant protoplasm. As a result of these studies a new branch of pharmacology to which we may apply the term of *phytopharmacology* is growing up. Even the few contributions which my collaborators and I have so far made along these lines have yielded extraordinarily interesting and practical results (19). Thus it was found by us that by the use of certain living plant tissues, a number of toxic substances present in blood and other secretions could be experimentally detected, a feat hitherto impossible of accomplishment by ordinary zoöpharmacological methods. In this way I have been able to demonstrate conclusively the existence and to study the properties of a toxin present in the blood serum and other secretions of women at the time of menstruation (20). Similar phytopharmacological methods have been employed by us for the detection of minute quantities of carbon monoxide in the blood (21), and this year I have announced and published some interesting and promising studies concerning the toxin of Pernicious Anemia (22, 23). I have been able for the first time to prove the existence of this toxin, and by phytopharmacological methods I am now able to diagnose this disease, and follow the results of treatment. A new and most valuable contribution of pharmacology in recent years has been the studies of Cushny and others concerning *optic isomers*. Comparative experiments with various stereo-isomers of different alkaloids have revealed differences quantitative, and sometimes even qualitative, in pharmacological action and curiously enough in most cases it has been the levo-rotatory variety which was found to be the most potent. These studies on optic isomers lead me to speak of another development in pharmacology in which I am particularly interested at the present time and to which I like to apply the term of *photopharmacology*. I am referring to the study of the effects of various radiations visible and invisible, on drugs alone and on their pharmacological action. While the influence of ultraviolet and other radiations on chemical action have engaged the attention of chemists for a long time, the effects of light and other radiations on physiological and pharmacological phenomena have been made a subject of study only in the past few years. Studies on the physiological effects of light have already given us better insight into the properties of certain vitamines and have led to most important therapeutic contributions. Studies on what we may term *photopharmacology* are even more recent than those on *phytopharmacology* but promise to be of no less value. The importance of light and the influence of other radiations both ultraviolet and infra red on the keeping qualities of drugs and on the action of various medicaments on living organisms, plant or animal, cannot be overestimated. We have found for instance that ultraviolet radiations and also X-rays and radium emanations produce most remarkable changes in the potency and keeping qualities of digitalis and other medicaments (24). Even more remarkable have been the studies recently first announced by me and by Dr. W. T. Anderson, Jr., concerning the effects of *polarized light* on various drugs. This work, which has been carried on for several years before we ventured to announce it, has definitely shown that not only the very short ultraviolet radiations can produce photochemical and photopharmacodynamic changes but that even the ordinary longer rays of the visible spectrum when polarized may produce profound photo-

chemical changes in drugs leading to alterations in their pharmacodynamic action (25, 26).

The status of pharmacology in our medical schools will depend largely upon the professors of that subject. The scope of pharmacology as I have outlined it to-day touching upon the physico-chemical sciences on the one hand and on the biological sciences on the other is, of course, co-extensive with practically the whole domain of experimental medicine. It is for this reason, as I have already alluded, that the pharmacologist on the medical faculties is sometimes regarded with considerable jealousy both by the physiologist and the bio-chemist and even by those internists or practitioners of medicine who realize that they must know something of therapeutics in order to ply their art. Enough, however, has been said by me to indicate that the pharmacologist occupies a position in science which cannot be filled by other scientific men. The misconceptions concerning this important subject which are so prevalent in these United States are partly the fault of pharmacologists themselves. While the scientific investigator in this department of knowledge may choose to work on any problem he may wish, the course of the true pharmacologist will always be distinguished by two ear marks. The real pharmacologist never looses sight of the following two facts: 'Tis true that pharmacology is based upon the two foundations of chemistry and physiology, *but* the chemistry in which it is most interested is *primarily Pharmaceutical Chemistry or Chemistry of Drugs;* and the physiology in which it is primarily concerned is *Physiologicol Therapeutics* or the action of drugs for the relief of suffering and cure of diseases.

I began my paper with the statement that pharmacology is simultaneously one of the oldest and one of the youngest of sciences. The antiquity of the subject I think can be gathered from what I have already said. One of the best proofs of its young age at least in this our country can be gathered from an examination of the by laws and constitution of the American Society for Pharmacology and Experimental Therapeutics. This constitution is different as far as I know from that of any other scientific society not only in America but in the whole world, in that it contains the following two paragraphs. Article 3, Section 2, "No one shall be admitted to membership who is in the permanent employ of any drug firm." Section 4 (*b*) "Entrance into the permanent employ of a drug firm shall constitute forfeiture of membership." Whatever may have been the motives of the framers for writing such two clauses into the constitution of a scientific society, one inference which is derived from it admits of little doubt. Such articles reveal a lack of confidence and poise on the one hand and exaggerated self reliance on the other, so typical of youth and immaturity. Or, shall I perhaps say such conduct verily reveals the naiveté of childhood, and the impetuosity of youth, who fired with enthusiasm for newly glimpsed fields, forgets the past, neglects his forebears, exaggerates his capabilities and rushes forward—relying only on himself—to find that in the end he must appeal to others for coöperation and aid. He does not understand that scientists as well as those in other walks of life, depend on other men, and consequently have a duty to fulfill to ply their science or their art or trade not only for themselves but also for the welfare of the public and the State.

I have endeavored to convey to you, as best I could, in my peculiar and humble way, what pharmacology is and should stand for. I know not whether I

succeeded; and therefore will conclude with a quotation from an ancient sage.

Rabbi Tarfon: "'Tis not incumbent on thee to complete the work;
Yet art thou not absolved from doing what thou canst."
(*Ethics of the Fathers, II, 21*)

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CAUSES OF DETERIORATION OF STROPHANTHUS SEED DURING STORAGE.*

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Experimental work being done in these laboratories on tincture of strophanthus brought out the information that a sample of Strophanthus Kombé seed which had originally assayed 120 to 133% U. S. P. deteriorated to such an extent during grinding and storage that at the end of one year it assayed only $37^1/_2$ to $48^1/_2$ U. S. P. strength. Since this deterioration was unexpected and unusual in our experience, a thorough search of the literature was made for the purpose of deter-

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