COÖPERATION BETWEEN PHARMACOLOGY AND THERAPEUTICS.*

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It is important that a healthy coöperation should exist between those who are engaged in the scientific study of drug action and those who use drugs for the purpose of curing or alleviating disease; for the problems of pharmacology, like those of pathology, have a very immediate bearing on medical practice. Established modes of treatment frequently form the starting point of scientific studies, and the exact knowledge thus gained leads in turn to greater precision in treatment. Pharmacologic studies have uncovered new therapeutic possibilities that have ultimately proved useful in the clinic. Finally, a clear recognition of the fact that substances of similar chemical structure frequently possess pharmacologic properties that are similar but not identical has opened up a vast field of research. Numerous compounds of a given type are now produced with comparative ease by the organic chemist. While many or most of these may possess no great practical advantage over their original prototypes, yet such studies are constantly leading to improvements in our remedies, and the possibility is always present that the systematic combination of chemical and pharmacologic research will tap important fields that have hardly been suspected hitherto.

Now more than ever before, therapeutic advance depends on an intelligent utilization of the methods, the criticisms and the new discoveries of pharmacology. Older remedies are being restudied, and from the host of newer ones that are constantly being placed before the profession an intelligent choice must be made. Before I undertake to discuss how coöperation between the pharmacologist and therapeutist may be promoted, however, it may be well to point out some of the factors which tend to separate these two classes of workers. In the first place, their attitudes toward their respective problems are essentially different. The pharmacologist contemplates with scientific skepticism that which is unproved, and he proceeds slowly and carefully from the known to the unknown. The therapeutist, on the other hand, brought face to face with a crisis in the life of his patient, cannot refuse to try the unproved when remedies of known efficacy are lacking. Hence he often grasps at straws, being restrained only by the possibility of doing harm to his patient. Such a practice, justifiable in itself, too often leads to those habits of inaccurate reasoning that are reflected in therapeutic literature. Optimism in practice often means an unjustified and uncritical enthusiasm in the interpretation of results.

The pharmacologist and the therapeutist are further separated by the conditions under which their observations are commonly made. In the laboratory the action of drugs is usually studied on normal animals, and toxic doses can be administered with impunity. In the clinic, on the other hand, therapeutic doses alone are used, and the effects of these are often modified by disease. The pharmacologist is permitted to employ methods of study which involve operative or other harmful procedures. The clinician is restricted to those methods of study that can be used without harm to his patient. Finally, the laboratory worker plans a

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series of experiments, and he endeavors to eliminate errors by repetition and by controlling the various factors that might influence his results. In therapeutics the number of observations is necessarily limited by the available clinical material, and the interpretation of results is often hampered by the fact that the effect of other factors, such as the natural course of the disease and the action of the other drugs used, is difficult to estimate and is, indeed, often estimated incorrectly. Under such conditions, years may elapse before even a simple therapeutic problem is conclusively answered.

As I have said, pharmacologic studies are usually made on normal animals. In seeking to utilize the knowledge thus obtained for therapeutic purposes, the following questions arise: 1. Are the effects observed produced by doses that can safely and easily be administered to patients? 2. Will the human organism react in the same manner as the animal studied? 3. How is this reaction modified by disease?

The question of dosage, simple as it may seem, has caused and will probably continue to cause occasional therapeutic stumbles. The fact that large doses of strychnine were known to produce a marked rise of arterial pressure in animal experiments was in part responsible for its extensive use by clinicians in conditions of low pressure. Yet it now seems established that in safe doses strychnine does not raise the blood pressure materially, either in man or in animals. The rise of pressure, therefore, is a toxic effect, and, so far as we know, it is not available for therapeutic purposes. Due consideration must also be given to the fact that in the laboratory intravenous injections are frequently used, whereas in medical practice these are seldom given except in emergencies. Finally, different species of animals may vary in their reactions to a given drug. When the reaction is essentially the same in a variety of mammals, it may be assumed that the human organism will respond in a similar manner; but when the reaction varies, the effect on man cannot safely be predicted from laboratory studies. In practice, moreover, even lesser quantitative variations in response may become of paramount importance, for it is our purpose to secure therapeutic results, and at the same time to avoid unpleasant side effects.

One of the most important methods for helping to bridge over the gap between animal pharmacology and practical therapeutics is the accurate study of the effects produced when drugs are given in the usual medicinal doses to human beings. The methods employed in making such studies must naturally be free from the possibility of doing harm. Fortunately a great variety of new methods have been developed in recent years which may be applied to the study of human functions. Without attempting to name all of these, I mention the following: bloodless determinations of the arterial and venous pressures; graphic records of the gastric contractions, of the arterial and venous pulse waves and of the electric changes accompanying cardiac activity; roentgenographic examinations of the alimentary tract; determinations of the rate of metabolism; chemical analyses of the alveolar air, of small quantities of blood and of excreta, and estimations of the various immune bodies in the blood. Each new method that can be applied to the study of human functions not only advances our knowledge of these functions and of their perversions in disease, but also makes possible more accurate studies on how these functions are influenced by various remedial measures.

In many cases such studies can be carried out on normal individuals, and within a short space of time sufficient data can be accumulated to establish with scientific accuracy certain aspects of drug action.

Ultimately, however, we must answer the question: Are these drug effects of value in combating the disturbances of functions that are encountered in disease? The final answer to this question can seldom if ever be given from studies either on normal animals or on normal men. In certain instances the diseased function is unusually susceptible to drug action. The body temperature of a febrile patient, for example, is reduced more easily by antipyretic drugs than is the body temperature of a normal person. Digitalis in therapeutic doses has relatively little effect on the heart rate when this is controlled in the usual way from the sinus region. Its reputation for slowing the heart of patients is based almost exclusively on observations which were made on those suffering from auricular fibrillation. Diuretics of the caffeine group produce a moderate diuresis in the healthy man, and may be ineffective or harmful in nephritic edema, whereas in cardiac edema they often cause a veritable flood of urine. The dilatation of the bronchi produced by epinephrin is most plainly demonstrable in conditions of bronchial constriction, whether produced experimentally or occurring during asthma. Finally, the treatment of infections can manifestly be tested only on infected animals or human beings.

Not infrequently the remark is made that the value of a therapeutic measure is determined solely by clinical experience. While I have no desire to contradict this assertion, it should be pointed out that ordinary clinical observations are often extremely difficult to interpret, owing to the vagaries of disease and to the many remedies that are so commonly employed in a single case. The past history of therapeutics warns us that in order to avoid error we need as much assistance as possible from every source. Pharmacology may not, indeed, answer therapeutic problems directly, but at least it aids in their solution. It shows how drug action may be made the subject of accurate study, and the critical attitude which it adopts must be carried over into the interpretation of therapeutic results, if progress in that subject is to be placed on a firm foundation.

On the other hand, pharmacologists could, I believe, be of greater help to those who work in the clinic if they would fully realize how their results may be given a form more suited to clinical needs. What, for example, is the effect of a given drug in small doses, especially when given over a long period of time? How are the effects modified when animals have been made the subject of disease? What pharmacologic problems can be studied on man himself, and especially on patients who are taking the treatment usually given for their disease? Work on such lines as these, whether by pharmacologists or by clinicians, will help to maintain contact between the science of drug action and the art of treatment.

CRITICISMS AND COMMENTS ON THE NATIONAL FORMULARY IV.*

BY JACOB DINER.

In the early days of the Formulary it represented a collection of formulae, gathered more or less indiscriminately from all corners, and endeavoring, in a most laudable manner, to unify, as far as possible, the rather divergent composi-

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