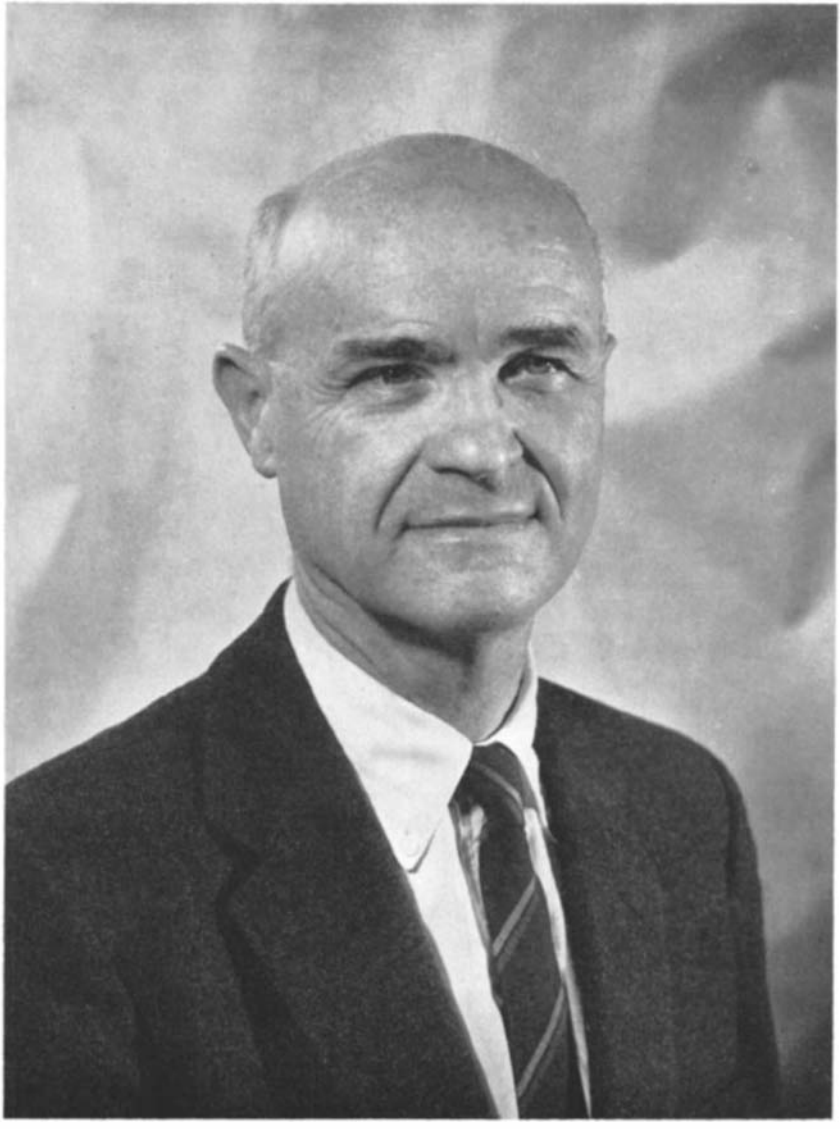

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PHARMACOLOGY IN A CHANGING WORLD

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In one who for many years has been called on annually to bid God-speed to a class of medical students, an invitation to contribute the prefatory chapter to a volume of the *Annual Review of Physiology* arouses familiar emotions. The occasion clearly calls for something out of the ordinary; yet from previous experience one knows that after the event he will look back on it unhappily, wondering why, with all the words he might have used, he chose those particular ones. He cannot take the task lightly, partly because now and then he learns from former students that words which he had long forgotten were thought to have been of value to them at a critical stage of their careers. He knows that the credit for such an impression belongs, not to any words of his, but to coincidental first successes in the performance of adult tasks by young people of such caliber that they would do well in anything they undertook. Yet he realizes that, if some of these in retrospect believe their subsequent success to have been even slightly influenced by his efforts, they must indeed have been eagerly searching for guidance in a confusing world. So he tries again and again to find the winged words and golden thoughts that had eluded him in the past until at last he hands the task on to his successor, realizing that he has been seeking something that will only be found with the Lost Chord.

The present assignment differs from this long-familiar one in that the audience is more numerous, diverse, and sophisticated, and there are no direct assurances from previous listeners that earlier efforts have served a useful purpose. The latter presumably is compensated by the fact that the Editorial Board continues to dedicate precious space in these volumes to such an undertaking. The former intensifies the desire at least to find a theme appropriate to the occasion.

In perusing the prefatory chapters previously contributed by my contemporaries, I find the term "transitional period" frequently applied to the years of our activities. If this is true of physiology as a whole, it certainly is no less true of pharmacology. The author of the prefatory chapter to the preceding volume (1) discussed his experiences during a transitional period in medicine, which he entered by way of the physiology laboratory. It will be interesting to me to attempt a corresponding review of my own experiences in pharmacology during the same period. My justification for doing this in the *Annual Review of Physiology* is that I have always regarded pharmacology and physiology as sister sciences sharing the same basic interests and employing the same methods.

A discussion of transitions in pharmacology is particularly timely be-

cause this year will mark two events that depict the passage of the science into a new phase. One is the appearance of Volume I of *The Annual Review of Pharmacology*. The other is the First International Pharmacological Meeting. The one is scheduled for early summer, the other for August, both in 1961. The latter is the first official international meeting ever to be arranged by pharmacologists for their own purposes.

I cannot speak for the *Annual Review of Pharmacology*, but I know that the First Pharmacological Meeting actually will find pharmacology, not in a state of new and complete independence, but in a position in which it began over a century ago and in the rôle which made it one of the most intellectually stimulating of all sciences. The theme of this meeting is to be the Mode of Action of Drugs, a problem which enlisted the attention of Claude Bernard (2) before 1860 and which was the main incentive for the foundation of modern pharmacology by Rudolf Buchheim (3). Bernard's interest in drugs lay in their ability to serve as "*scalpels chimiques*" for dissecting out physiological mechanisms and thus for making important additions to fundamental knowledge. Buchheim was primarily concerned with learning the facts about what drugs can and cannot accomplish and was aiming directly at better orientation of the physician in his use of drugs at the bedside. Buchheim's illustrious pupil Schmiedeberg, who was called upon to organize the world's first Laboratory of Pharmacology in Strassburg just after the Franco-Prussian War (4), combined both these concepts of the rôle of pharmacology into a discipline so exciting that it attracted a group of young men of extraordinary brilliance. A partial list of these includes such names as Dale, Richards, Cushny, Abel, Wallace, Dixon, Meyer, Gottlieb, Magnus, Trendelenberg, Ehrlich, Fühner, Heubner, and Fourneau. Men such as these would have been welcome in any field and would have made it great. They chose pharmacology because at the time it was the most intellectually stimulating of the medical sciences.

The time was the first decade of the twentieth century, when the Western Hemisphere was just beginning to establish chairs of pharmacology. Epinephrine (adrenaline) had been isolated, chemically identified, and recently synthesized. Tyramine was found to be related chemically and physiologically to epinephrine, and the concept of sympathomimetic amines had just been propounded (5). The similarity between the effects of adrenaline and those of stimulation of the sympathetic nervous system had been noted, and Elliott (6), then a student at Cambridge, made the proposal that sympathetic nerve impulses might act by liberating this chemical agent. Dixon (7) was making a similar claim for muscarine (the actions of which were discovered by Schmiedeberg some years before) as a parasympathetic transmitter. Langley was using nicotine to map out the autonomic nervous system (8), and Cushny had recently shown (9) that the long-familiar pulsus irregularis perpetuus is referable to atrial fibrillation, which he could produce in experimental animals by electrical stimulation. The chemical in-

dustry was turning out considerable numbers of new compounds, and some of these (acetanilid, acetophentidine, antipyrine, barbiturates) were finding permanent places in therapeutics. Meyer, Overton, Traube, Lillie, Verworn, and others were diligently searching for a general theory of narcosis (10). Perhaps most exciting of all was Ehrlich's undertaking to create specific chemotherapeutic agents according to biological and chemical theory (11).

These and other scintillating events were transpiring in the area previously assigned to materia medica, which hitherto had been the least progressive of all medical disciplines. It was also the last to succumb to the invasion of traditional medicine by the scientific method. There had been a long period of revulsion against the injudicious therapeutic practices of preceding generations. Clark (12) cites some of these and quotes the comment "*il est mort guèri*" which sometimes appeared at the end of case histories. According to Buchheim (13), the man who was called pharmacologist in the old days often was assigned the task of performing autopsies, both because he was not as busy or as important as his colleagues and because the major purpose of the autopsy was to convince the family that the patient died of the disease, not of the drugs. During this period, research in materia medica had been aimed at finding mixtures and manipulations which would bring out the virtues of a drug and attenuate its shortcomings—a tradition which still survives in the terms "adjuvant" and "corrective" in prescriptions. According to Schmiedeberg (3), Hahnemann believed that both these aims could be achieved by simple dilution, which was one of the main features in his Homeopathic Doctrine.

The revulsion against therapy was accelerated by the emergence of pathology as the accepted route to success in academic, scientific medicine. Pathology took over the autopsy service and made it do much more than protect unsuccessful therapists against legal action. Clark (12) quotes the following from the leader of the rise of modern pathology, Rudolf Virchow: "Therapy is in an empirical stage cared for by practical doctors and clinicians and it is by means of a combination with physiology that it must rise to be a science, which today it is not."

Virchow's advice actually was even then being followed by Buchheim and his colleagues. But the leaders of the transformation of medicine from unverified tradition to a science were, with few exceptions, trained in pathology until the changes outlined by McLean (1) began about 1920. It is scarcely surprising that men whose viewpoint on the possibility of favorably influencing the course of a disease was derived from the study of lost therapeutic battles in the autopsy room should take a dim view on drug-giving.

The preponderant motives of the brilliant group who, just one generation ago, were called upon to become the first professors of pharmacology all over the world, clearly did not include the prospect of material advantages, scientific prestige, or immediate benefit to humanity. The chairs of pharmacology during the first two decades of this century were poorly supported, and

the newly appointed professors in many if not most cases were viewed with condescension by their colleagues in the older scientific disciplines, with indifference, hostility, or contempt by the clinicians. The immediate reason for adding them to the medical faculties seems to have been a determination on the part of a few energetic faculty members and alumni to bring the institution abreast of this latest trend in medical education. Sometimes the newcomer supplanted a professor of pharmacology and materia medica whose approach had been the traditional one of materia medica. In such cases one of the immediate results was a series of complaints from the clinical faculties that the students no longer were being taught anything about drugs, and from the students that they were at a disadvantage in competition with their contemporaries in other institutions because they no longer were given lists of time-honored prescriptions.

This was the situation at Pennsylvania when I entered the medical school in 1914. A. N. Richards had been appointed Professor of Pharmacology in 1910, and after a term in Schmiedeberg's laboratory he began to organize a course along the new lines. By the time I took this course in 1915 he had established a reputation as a splendid teacher with a fetish for perfection. His insistence on valid evidence and his emphasis on critical examination of the method made a deep impression on his students, including myself. When I was offered an instructorship in his department at the close of my internship in 1919, I was glad to accept.

As I look back, I realize that this was near the end of the era which Schmiedeberg (3) called the Negative Phase of Pharmacology. This period began with the revulsion of the medical profession and the public against prevailing practices of drug-giving, was accelerated by the therapeutic nihilism resulting from the pathological orientation of the leaders of the rising science of medicine, and was climaxed by the accomplishments of the new pharmacologists who tested the available drugs and in many cases found them wanting. Apart from Ehrlich's triumph with the arsphenamines (which many other workers unsuccessfully tried to duplicate with other metals and in other types of infection) and tissue-sparing antiseptics such as Dakin's solution, the organic chloramines, and the organic mercurials, there had been no notable additions to the therapeutic armamentarium for more than ten years. The new generation of pharmacologists had aroused serious doubts about the real value of many widely used drugs but they had not yet provided anything better. These negative findings were appreciated by scientifically minded clinicians, who were thus enabled to avoid deceiving themselves even when they thought it proper to go on deceiving their patients, but the challenge which kept the pharmacologists at work under often discouraging conditions was the one which had first attracted Bernard, Buchheim, and Schmiedeberg, viz. the explanation of how and why drugs do what they do. Nowhere, as far as I know, was there any suggestion that the pharmacologist was expected to do anything but learn the facts about fundamental mechanisms. As a matter of fact, in so doing he was providing

two essentials for the next phase, viz. the methodology for studying new drugs, and an attraction to good young people to enter this fascinating field.

Shortly after my entrance into pharmacology in 1919 began a Positive Phase, in which important new drugs were introduced in rapid succession. The first of these was insulin. Then came ephedrine, important not so much in itself, but rather as a trigger for intensive efforts toward the synthesis and testing of drugs affecting the autonomic nervous system. One of the major reasons for this outcome was that a single drug company, more enterprising than its competitors, sought to secure an advantage over them by cornering the Chinese market on Ma Huang, the vegetable source of ephedrine. As a result the competitors were driven to resort to synthesis of compounds related to ephedrine, and a large variety of these were made and tested. One company found a product that sold so well as to enable them to finance a research organization of their own, which subsequently became quite large and now is very active and productive. Others came up with a variety of new compounds with a spectrum of activities wide enough to permit choice of the agent having a minimum of undesired features for almost any situation. Perhaps all these things would have happened if the natural source of ephedrine had been shared among the manufacturers, but they certainly were accelerated by the attempt of one of them to gain a monopoly.

Then came such events as the mercurial diuretics (intended originally as antiluetics of the arsphenamine type), the nonnarcotic anticonvulsants, the synthetic adrenergic and ganglionic blocking agents, standardized curare and synthetic curariform agents, the sex and adrenal steroids and their derivatives, the clinically useful anticoagulants, the antihistaminics, and finally the sulfonamides and antibiotics. The newer anesthetics, the synthetic analgesics, and the muscle relaxants were utilized by new groups of medical anesthesiologists in an enterprise that was stimulated and nurtured by pharmacology. More recently have come the tranquilizers, psychic energizers and hallucinogens, and the orally effective potent diuretics.

When I entered pharmacology in 1919, the physician who went through life depending entirely on the drugs used by his teachers was not doing much harm, either by omission or commission. Three years later the situation had already changed with the introduction of insulin. Like many of my contemporaries, I saw some instances of the early misuse of this drug by practitioners who had not bothered to familiarize themselves with its capacities for doing harm. Similar episodes subsequently arose with the potent diuretics, the sulfonamides, the antibiotics, the intravenous anesthetics, and many others. These new drugs were not like the tonics, alteratives, emollients, demulcents and derivatives of the old days, which might or might not do any good but were unlikely to do harm. They were potent agents and they usually were given in dosages intended to build up and maintain an effective concentration in the body. The physician who used them had to know something about their capacities for harm as well as good, and for this the first step was an awareness of the questions he should have asked and answered before

he went ahead. This is where a modern course in pharmacology enters the picture as the only way of preparing a medical student for life in a constantly changing scene.

For change it certainly will. According to Beckman (14), an average of 400 new prescription items now is being introduced in this country every year, and some fifty of these are new chemical entities. Another source (15) places the total at 3000 in the last ten years and estimates their average life at three to five years. The recent volumes of the *U. S. Pharmacopoeia* are no larger than their predecessors, and the newest (XVI) is actually a little shorter than XV. Obviously the new agents are replacing an equal number of older ones, and the statistics for life expectancy, mortality, and morbidity, as well as the obviously greater usefulness and comfort conferred by some of the new drugs (antidiabetic, antihistaminic, antiarthritic, antiepileptic, tranquilizing, antihypertensive, etc.), all indicate that the public is better off in this respect than ever before.

Where does pharmacology fit into this picture? This question can be directed into the past, the present, and the future. It is now a far cry from 1919, when my accession to the Department of Pharmacology at Pennsylvania increased its numerical strength by fifty per cent, i.e. from two to three. Richards had already started his investigations on kidney function, which were undertaken for the purpose of enabling him to give his students a better explanation for the diuretic effects of caffeine than was then possible. He and Cecil Drinker (while a medical student) had made a perfusion pump which could duplicate the normal pulse pattern and, on perfusing a rabbit kidney with it, had found that the addition of a minute amount of epinephrine produced: (*a*) rise in perfusion pressure which, since the pump output was constant, indicated vasoconstriction; (*b*) swelling of the oncometer-enclosed kidney, which indicated vasodilation; and (*c*) diuresis, which suggested increased glomerular filtration. The best explanation Richards could find for this strange state of affairs was a selective constriction (by epinephrine) of the efferent glomerular vessels, and he set himself and his associates the problem of finding an experimental means for testing this hypothesis, which then was completely new. While perusing Cushny's then-recent monograph (16), we happened to see an inconspicuous allusion to some experiments by Ghiron (17), who reported that he had been able to make microscopic observations of the glomerular circulation in the kidney of a living mouse. After unsuccessful attempts at duplicating these observations, we turned to the flat kidney of the frog, and here we found the preparation Richards had been seeking. Actually it was only after several years of extraordinarily productive work that the preparation was used to determine whether the original hypothesis was valid or not; the answer was affirmative (18).

The next direction of the experiments was determined by a suggestion by Wearn (19) that it might be possible to withdraw glomerular fluid directly from Bowman's capsule by an adaptation of the microdissection technic then being developed by Robert Chambers. These experiments yielded the

first unambiguous evidence ever secured on the nature of kidney function, for the glomerular fluid contained a chloride and a reducing sugar while the bladder urine contained neither (19). Obviously these normal constituents of the blood had left the circulation to enter the glomerular space and had been reabsorbed somewhere between the glomerulus and the bladder. The result was regarded as strong confirmation of the filtration-reabsorption concept of Carl Ludwig. Quantitative studies on other normal blood constituents subsequently indicated that the glomerular fluid is essentially a colloid-free ultrafiltrate of the blood plasma (20). The finding that this is true of easily measurable creatinine furnished the basis for now-familiar clearance studies and thus for the entire mass of modern renal physiology. I like to recall that it all began out of an attempt to improve the teaching of medical students. It seems to me that a young physiologist or pharmacologist who seeks to advance more rapidly by avoiding teaching and concentrating on research is missing a most powerful incentive to get his thoughts arranged in proper perspective.

The work on frogs came at a time when Richards had secured a little money from a friend to enable him to pay for some animals and to buy some needed supplies (including hirudin, the only anticoagulant then available other than citrate and oxalate). Shortly afterward I went to China, and when I came back in 1924 the department was a beehive of activity on the kidney project. Richards had secured support for this from several foundations and the period of poverty was over. He urged me not to jump on the renal bandwagon, but to work on my own problems. I therefore returned to my first interest, which involved an explanation of certain effects of morphine and other drugs on respiration (21). Actually I had never forgotten this problem, and my first days in Peking were spent on trying to isolate hirudin from the heads of Chinese leeches so that I might get on with my plan of measuring cerebral blood flow in relation to respiration. I had expected that my first year in China would be spent in working with Bernard E. Read, the head of the Department of Pharmacology; and for the second year Reid Hunt, Professor of Pharmacology at Harvard, was to be present as visiting professor. What actually happened, however, was that Dr. and Mrs. Hunt arrived a few weeks after I did and a year earlier than Read and I had expected. Read thereupon made a rapid readjustment and left for his sabbatical a year earlier than he had planned. Before he left he outlined his plans for studying Chinese drugs, gave me a list of supposedly important ones, and urged me to have a try at investigating them.

Some of my experiences in this connection have been recorded elsewhere (22). If it had not been for a series of coincidences that led us to ephedrine (my writing to Chen before he came to Peking telling him of my unpromising experiences with Chinese drugs, his telling something of this to an uncle at a family reunion in Shangai and getting a recommendation to look into Ma Huang, and our trying a hasty aqueous extract of this drug in a preparation for a student experiment), my two years in Peking would have been

highly interesting but scientifically unrewarding. Ephedrine however brought these years from the Negative to the Positive Phase.

By 1925 money was becoming available for research work and we were able to afford occasional cross-circulation and perfusion experiments. Solid heparin had appeared, but it was so expensive (or our fund so small) that we had to resort to repeated bleedings, defibrinations, and reinjections to make it cover as many experiments as possible. We were able to buy the glass parts of some new Van Slyke-Neill blood-gas analyzers, but we had to mount them ourselves and we did our own analyses after the experiment had ended, sometimes spending the entire night on this after a day of complex dissection and experimentation. Apart from an interlude devoted to addiction to morphine [a study undertaken out of a sense of public responsibility but surprisingly interesting from the scientific viewpoint (23)], my work dealt with the interrelations among circulation and respiration which had been revealed by my first independent efforts (21). The results led me to a concept similar to that popularized by Gesell (24), but actually advanced many years earlier by Rosenthal (25) and subsequently by Winterstein (26) and Pearce (27), viz. that the chemical control of breathing depends on the concentration of stimulant chemical material in the cells of the center, and since these are continuously producing such agents by their own metabolism, their activity can be modified by changes in their blood supply. This was the origin of my interest in the cerebral circulation.

The reports by Heymans and his associates (28) on the respiratory effects of reflexes from the carotids and aorta directed my interests into this area and subsequently toward other reflexes. The results forced a reevaluation of the interplay between chemical and reflex factors in respiratory control, a process which is still going on. Similar processes are now beginning in circulatory control (29, 30).

With World War II the days of financial stringency definitely ended. One of the pleasantest episodes of my career was the opportunity afforded by our activities in aviation research to create a climate in which Kety (31) could conceive and develop his method for measuring cerebral blood flow and metabolism in man, and in which means for testing the hypothesis concerning respiratory control were immediately available. It is noteworthy that this situation, like that which brought about Richards' work on kidney function, was the result of a pervading desire for a better understanding of a familiar action of a well-known drug (21).

Schmiedeberg died in 1921. If he and his teacher Buchheim could see the changes in the therapeutic scene in the subsequent forty years, they would have good cause for gratification with the quality of the seed they planted. For all the important drug discoveries during this period were made in research laboratories dedicated to the task on which they and their pupils had worked, viz. to study the actions of drugs by any or all methods that seemed appropriate. They could not have foreseen the rapid increase in financial support of medical research in this country that followed the ex-

ample set by John D. Rockefeller, Sr. just before 1920. Nor could they have anticipated the expansion of the chemical industry and the rapid growth of research among the drug manufacturers. But they would have no cause for surprise at the dramatic results of providing more opportunities for good people to develop and test their ideas in laboratories. Buchheim had this to say in 1857 (3): "Wer imstande ist den schwierigen Teil, die Fragestellung, gut auszuführen, wird mit Leichtigkeit die für seine Untersuchungen geeigneten Methoden auffinden können." He and his pupil Schmiedeberg might smile a little at the recent rediscovery of the importance of new questions to be fed into our modern research machine.

The unprecedented and uninterrupted series of discoveries of new drugs, however, has caused a drastic change in the place of pharmacology among its sister sciences. Its original twofold aim of adding to basic scientific knowledge by using drugs as physiological reagents, and of orienting physicians on the proper uses of their drugs at the bedside, now has been supplemented by a third, viz. to discover and evaluate new agents of therapeutic value. Actually this assignment was familiar even in Buchheim's day (3), but the agents to be tested were so few and infrequent that such activities could be taken more or less in stride with the other functions of the laboratories. Now, however, this certainly is no longer the case. The 400 new drug items introduced every year, and the associated continuous turnover of drugs alluded to above (page 6), represent only the survivors of a much larger number of preparations that had to be tested. This has come to be much more than an appendage of pharmacology.

Such developments have obscured in a golden glow of practical accomplishments the traditional objective of pharmacology, which was to provide facilities and intellectual climates in which gifted young people would want to work and would be encouraged to follow up their ideas by any suitable method. It has always been the prerogative of academic departments of pharmacology to find these people and to prepare them for their careers, and I know of no plan for changing this situation in the future. But in these days of emphasis on research, of mutterings of discontent over "teaching loads", and of freely available fellowships for young people who, under the caption of "graduate training program", can be made to perform tasks which seldom are of the caliber which once made pharmacology exciting, it is becoming increasingly difficult for the director of such a laboratory to have a clear objective at which to aim his policies.

It seems to me that his best objective is to attract into pharmacology a fair share of the young people who are going to be the leaders of the medical sciences in the future. There is now a large and well-supported program for promoting graduate study in the individual medical sciences (including pharmacology), but I wonder how many of the best candidates are going to choose pharmacology rather than biochemistry or physiology. Many science teachers in high schools and colleges have done work in the latter disciplines and are properly enthusiastic over them, but I have yet to hear of one who

is able to speak for the intellectual rewards of pharmacology. These are comprehensible only after a student knows enough about the other medical sciences to appreciate the possibilities of the interdisciplinary approach of pharmacology.

It seems to me that the better place to search for the leaders of pharmacology of the future is among the medical students. These already are a carefully selected, sophisticated group, and if one can attract and hold their respect (by making one's teaching as interesting and challenging as possible), one has at least made a start. In the past we used to measure the success of our teaching program by the number and caliber of the young medical graduates who sought to work in the department. The development of the residency training program has drastically altered this situation, for a young man offered a residency during his internship must come to a decision while close to the attractions of the clinic but remote from the laboratory disciplines. He can cross over subsequently from clinic to laboratory, but the reverse step is seldom possible. We once were able to offer him the enticement of an intellectually stimulating experience in teaching and research, but the modern clinical departments have come to be at least our equal in this respect, and they have the added attraction that the young man remains within the clinical hierarchy and is working toward his specialty certification. Thus the clinical departments hold nearly all the winning cards in the competition for the best young medical men, and this means to me that they are going to have the leaders of the medical sciences of the future unless something is done to alter the present arrangement.

I wish to make it as clear as possible that I do not regard a medical training and degree as essential for success in pharmacology or any other medical science. Such a claim would be ridiculous, not only because the medical course is too rigid, too brief, too shallow, and too diversified to be anything but a preparation for further education, but also because the example of men like Richards, Fenn, Bard, Bronk, and many others shows that distinguished careers are not appreciably hampered by the lack of medical training.

We clearly are entering an era of salaried positions for all connected with the medical sciences, clinical and preclinical. The disparity in salary between the two groups already is narrowing and it may narrow further if the presently-rumored governmental support for medical education materializes.

The basic medical sciences have a greater attraction than ever before for the better young medical graduates, and clinical departments in major medical centers are becoming complete, self-contained medical schools. This is one of the early results of the attraction into these departments, by means of the residency training programs, of the young physicians who once turned to the basic science departments for a year or two of research and teaching before they settled down to clinical careers. Such young people provided an annual transfusion of eager young blood for a department such as ours, and now and then (often enough for our limited resources) one of them would

decide to remain in pharmacology. Since the advent of the residency programs, the young physicians get their research and teaching experience in basic science within the framework of the clinical departments, which now are retaining the strengths they once shared with us.

A department such as ours then may: (*a*) seek some arrangement which will again enable it to secure a regular rotation of the best young physicians; (*b*) develop some means for recruiting nonmedical personnel of a caliber equal to that of the better medical students, whom it is going to teach; (*c*) reconcile itself to medical graduates who could not obtain good residencies and to applicants for graduate training who could not enter medical school; or (*d*) recast its objectives and activities to fit the new order of things, i.e., allow the clinical departments to take over the most interesting and most exciting features in modern medicine.

I have listed these in the order of their apparent desirability. It is unlikely that (*a*) can be accomplished by any but the most forceful intervention, for the whole structure of a modern university hospital has come to depend on this source of excellently trained, highly motivated, and poorly paid young men. But we are dealing here with a matter that transcends the convenience of hospital administrators and the ambitions of department heads inclined toward empire building. The real question is the best allocation of the young people who are going to be the leaders of the future. If our entire residency training program were critically reëxamined with the view of making the best possible use of the precious young human resources with which it deals, the basic medical sciences might be greatly strengthened.

It is too early to tell what will eventually happen to these departments when the process of development of independent clinical units described by McLean (1) runs its allotted course and the clinical teachers regard themselves as fully competent to teach all the basic science the students need to know. They may be quite right in this, but the problem will come when the goose that laid the golden eggs is to be replaced. Alternative (*b*) would be ideal if these people could be found in sufficient numbers and with sufficient regularity to make this a dependable source of desirable young personnel. As noted above, pharmacology is at a disadvantage here because the interdisciplinary features that made it attractive to brilliant young men in the past cannot be appreciated until the other sciences have been thoroughly sampled.

The recent and current trend toward a biochemical approach to pharmacology is another manifestation of this long-familiar phenomenon. There can be no doubt about the possibilities of this approach. But it should be recalled that the first entry into pharmacology by Buchheim and his associates was essentially chemical. One of his colleagues (Carl Schmidt by name) was responsible for discovering the free acid of the gastric juice, the presence of chitin in the shells of insects, and the partition of sodium and potassium between red blood cells and plasma (3). Schmiedeberg quite early in his career demonstrated the formation of urea from ammonia in the liver (4).

At that time studies such as these were regarded as part of physiology, not as a separate and competitive discipline. Before Schmiedeberg occupied his permanent chair in Strasburg, he went to round out his repertoire for pharmacology by a term in Ludwig's laboratory of physiology. Richards was trained in biochemistry and was sufficiently esteemed to be asked to edit the *Journal of Biological Chemistry* quite early in his career, but before he settled down he went to Schmiedeberg to learn physiological technics. The accomplishments for which both these men are best known are a combination of chemistry and physiology, and a similar statement can be made about Dale, Meyer, Abel, Ehrlich, and many other great pharmacologists of the past.

For as I see it, the strength of pharmacology has always lain in its broad scope and diversity. It is no longer possible for the director of a laboratory of pharmacology to become a master of all the experimental technics available in all the biological sciences, but he can at least keep his department from specializing in one particular approach, thereby becoming only another department of physiology or biochemistry or microbiology. The distinctive feature of pharmacology is not that it has any methodology peculiar to itself, but that it is ready to use any or all methods to elucidate the mode of action of chemical substances on living systems. The more types of activity there are in a department of pharmacology, the better are its prospects of living up to the traditions of Buchheim, Schmiedeberg, Dale, Richards, Cushny, Abel, and their counterparts. It is not necessary, or even desirable, to go any further than to create a climate to which some of the keenest young minds will be attracted as they were in the past. If this is done, pharmacology will be well served in the future. If not, it probably will be reduced to service functions such as screening programs, toxicity studies, and bioassays, and the other sciences will take over its intellectual appeal.

There are signs of a determined effort to recapture some of the formerly intimate relationships between physiology and biochemistry, at least at the international level. A liaison committee between the International Union of Physiological Sciences (IUPS) and the International Union of Biochemists (IUB) was appointed in 1959 for the purpose of arranging a series of joint programs between the two disciplines. The First International Meeting of Pharmacologists mentioned on page 2 is being held under the auspices of the IUPS, through a new Section on Pharmacology organized in 1959. An attempt at making this the first joint program between the IUPS and the IUB, while viewed favorably by a majority of the officials of both unions, could not be consummated because of limitations of time. The preponderant flavor of the meeting, however, is to be biochemical.

The theme of this meeting—The Mode of Action of Drugs—actually is one which has stimulated outstanding efforts of distinguished workers, not only in pharmacology, but in physiology, including general physiology, biophysics, endocrinology, and radiobiology; biochemistry, including physical chemistry, histochemistry, enzymology, and nutrition; and pathology, in-

cluding microbiology, immunology, oncology, and toxicology. Dealing with an explanation of the effects of chemical substances on living systems, it represents as close an approach as one can find to a common interest among all branches of experimental biology. Pharmacology still has the same opportunity and challenge it has had since Buchheim and Schmiedeberg, of serving as a final common pathway for all the medical sciences. It can live up to these only by diversification, not by specialization in one type of approach or methodology.

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