Remarks

ON

THE OUTLOOK OF RESEARCH IN THERAPEUTICS*

BY

J. A. GUNN, M.D., D.Sc., F.R.C.P.

PROFESSOR OF PHARMACOLOGY IN THE UNIVERSITY OF OXFORD

Research in therapeutics can for convenience be considered from three angles—experimental pharmacology, chemotherapy, and experimental therapeutics—and, in the case of new drugs, investigation generally follows this logical sequence. This has not been, however, in the case of a large proportion of the drugs which are still in use, the historical order. It has been computed that about 50 per cent. of the drugs in our present *Pharmacopoeia* were in use by the Arabic-speaking physicians of the Middle Ages. Many others, like cinchona and ipecacuanha, came to us early from the New World. All these had been first tested by direct observation of their effects on disease in man.

Modern medicine acquired an unwieldy heritage of drugs so introduced. When the new science of experimental pharmacology began, roughly about a century ago, it was confronted with the Augean task of purging the materia medica of an accumulation of inactive and useless drugs. Experimental pharmacology at first led, not to an increase, but to a decrease in the number of remedies in use. What frequently happened was that a reputed remedy, when examined pharmacologically, failed to display such actions as could explain its therapeutic use. This led to a reinvestigation of its therapeutic claims, which were often proved to be ill founded, and it was eventually discarded. It must be admitted, however, that in this process of elimination pharmacology made many mistakes.

FINANCIAL ASPECT OF THERAPEUTIC ERRORS

Drugs cost money, and a drug which fails to produce a certain effect is a dead economic loss. Apart from patent medicines—on which something like £2,500,000 is spent in a single year by consumers in this country—the amount of money spent on useless drugs, and on drugs that, from inactivity, inappropriateness, or incorrect dosage, fail to produce any remedial effect, must run into millions of pounds every year. To take one example: sarsaparilla was rejected from the *British Pharmacopoeia* of 1914, almost exactly 250 years after its introduction into European medicine. Yet nearly a hundred years ago Christison wrote as follows:

"The probability is much in favour of the drug turning out very inferior in virtue to what its admirers imagine. The question is not unimportant. Admitting sarsaparilla does no harm, the subject deserves consideration in an economical point of view. In 1831 the quantity consumed in Britain amounted to 107,000 pounds (Pereira); and in 1821, the apothecary of one of the great London hospitals informed me that he had paid at that time £1,500 for a single year's consumption of it."

In the year 1870 the importation of sarsaparilla into the United Kingdom amounted to 345,000 lb., valued at over £26,000. If we can take the year 1870, which happens to be the only year for which I could find actual figures, and we add to the cost of the crude drug as imported the manufacturers' cost of making galenic preparations, the retail druggist's cost of dispensing, together with the cost of transport, etc., it is probably a conservative estimate that the consumer in this country

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spent in that year £50,000 for sarsaparilla alone. In other words, an amount of money was spent in a year on sarsaparilla which would at that time have sufficed to build and equip an institute of therapeutics and endow the salary of a director.

The questions we have to ask ourselves is whether this process of elimination of useless drugs has proceeded with reasonable speed; whether, if only from the point of view of economy, there has ever been any deliberate and concerted plan to rid medicine of the incubus of spurious remedies. The answer to this question is—No!

TARDINESS OF THERAPEUTIC ADVANCE

It is not only in the discarding of useless preparations that the art of therapeutics has been hesitant. The positive recognition of those with well-substantiated claims was often equally tardy. More than 100 years ago, Quincy, who was not given to exaggerated statements, extolled ipecacuanha as the divine remedy for dysentery; but it was only about twenty years ago when it was decided that its merit lay in the alkaloidal, rather than in the tannin, content of the drug.

When the remedial value of a drug was beyond dispute one might have thought that the determination of the optimum quantity to be administered in a particular disease would have been a relatively simple matter. But this anticipation is not in accord with historical facts. Quinine, as distinct from the preparations of cinchona, has been used in the treatment of malaria for about a century. As long ago as 1842 Christison wrote as follows in regard to its dosage.

"From twelve to eighteen grains divided into four or six doses will be generally sufficient for the ordinary intermittents of Europe; but the severe forms which occur in the south of Europe, and still more those of the Tropics, require thirty-six or forty grains on an average; and in Madagascar Dr. Allan informs me he had not infrequently to use ninety grains divided into three doses."

If the knowledge of quinine had reached that stage of precision in 1842, one would have thought that by 1912 there would be nothing further to learn about its dosage in malaria. But during the war it was necessary to institute special experiments to decide what was the optimum dosage to prevent relapses in malaria. Every administration of a drug may be regarded as an experiment, and the administration of quinine in malaria has been one of the most gigantic biological experiments ever made. Can anyone believe that anything near the maximum amount of information has been obtained from this colossal experiment?

NEGLECT OF THERAPEUTICS

So far as the last half century is concerned, one reason for this delay and uncertainty in estimating the value of reputed remedies is not far to seek. It was simply neglect of, and some lack of interest in, therapeutics. It has been an era during which enormous advances have been made in the pathology of diseases. Contemporaneously there were rapid developments in the recognition of distinct diseases. It was pardonable that during this period the question of the treatment of disease should receive less attention, because it was realized that rational therapy depended, first of all, upon accurate identification of the disease, and, secondly, upon a knowledge of the pathological conditions to be treated. In an address delivered fifty years ago at the opening of the Section of Pathology of this Association at Worcester, Hughlings Jackson began with these sentences:

"Pathology is the basis of every rational system of therapeutics. . . . That, possibly, the greater part of our most effectual treatment is at present empirical I would not deny, but that therapeutics will become rational is what we all hope. . . . It is evident that, for rational therapeutics, we must know what is to be treated."

It was in fact recognized at that time that the first step towards rational therapy was a knowledge of the disease to be treated, and it was logical and inevitable that research should first occupy itself with that necessary precedent.

About the beginning of this century, however, murmurings began to be heard that, both in teaching and in investigation, the treatment of disease was unduly neglected. The object of this discussion is to take stock of the present position and to inquire, without recriminating the past, but merely benefiting from its experience, whether everything is being done that ought to be done to remedy this alleged, and probably actual, neglect of therapeutics.

PROSPECTS OF THERAPEUTIC RESEARCH

I propose therefore, so far as time will allow, to cast a glance at the prospects of therapeutic research at the present time and especially in this country, and for this purpose to adopt the convenient classification of therapeutics into experimental pharmacology, chemotherapy, and, finally, the treatment of disease in man.

Experimental Pharmacology

Pharmacological research presupposes a general knowledge of physiology and of physiological methods. It is in many ways inseparable from pure physiology. For example, adrenaline, being a normal hormone of the body, may justly belong to pure physiology, but ephedrine, a natural plant alkaloid closely resembling adrenaline in chemical composition and in physiological action, belongs rather to the domain of pharmacology.

This close contact or overlapping of physiology and pharmacology at certain points has led some to believe that pharmacology can be adequately regarded and treated as a mere apanage of physiology. This, I think, is a mistake. In the first place, the tendency is for physiological research to become more specialized, but the bulk of the pharmacological research can never become specialized. In the investigation, for example, of new compounds as potential remedies the investigator must run the gamut, as far as possible, of all their physiological actions, at least within the limits of "therapeutic" doses. Consequently, the majority of pharmacologists must possess a wide training in physiological technique, and I think it is fair to say that the tendency at the present time is for the pharmacologist to have to acquire a wider personal experience of physiological methods than is possessed by the majority of physiologists themselves. Secondly, the literature of pharmacology is so vast that no one man can hope to cover it all. *A fortiori* he cannot hope to grapple with the still greater literature of pure physiology as well. Thirdly, unless pharmacology is to become a sterile and detached subject, the professed pharmacologist must, both in the interests of teaching medical students and of research, maintain a knowledge of the use of drugs in diseases and therefore of the diseases themselves. For these reasons, among others, pharmacology makes full demands upon a man's time and energies. In the future it will become less and less possible for one man to be both a physiologist and a pharmacologist. If this is so, and pharmacologists are necessary, there must be careers open to them.

At no period has treatment by means of drugs been so sure a foundation or so amply justified. In spite of the apathy towards pharmacology in this country at the moment, it is quite certain that it will become an increasingly important branch of medicine. I should therefore like to take this opportunity to urge medical schools to make adequate and sympathetic provision for teaching and research in experimental pharmacology.

Chemotherapy

According to strict definition, pharmacology is concerned with the physiological action of drugs, and is consequently more often a basis for the relief of symptoms than for the cure of disease. For example, such important drugs as digitalis, pituitrin, adrenaline, anaesthetics, hypnotics, etc., do not remove the underlying causes of disease. They may, however, sometimes relieve symptoms to the extent of removing disability, and so may be looked upon as curative. It is chiefly in diseases caused by micro-organisms or other parasites that drugs may be definitely curative. Older preparations of this type include, notably, antiseptics, anthelmintics, and "specific" remedies such as quinine for malaria, mercury for syphilis, and ipecacuanha for amoebic dysentery. Until very recent years such remedies were discovered, and could only be discovered, by clinical experiments on persons suffering from these diseases. The action of drugs upon *normal* animals could not provide a basis for the study of the effect of drugs in disease, if in that disease the drug acted, partly or wholly, upon an infective agent. It is true that some indication as to possible "specific" therapy might be obtained from comparative pharmacology. For example, the action of quinine on non-parasitic protozoa might suggest its use in a disease due to pathogenic protozoa.

But it was soon realized that it was of little, or even of misleading, value to determine the pharmacological or toxicological action of a drug on a pathogenic organism as a sole or separate problem. And this for two important reasons. In the first place it was found that the action of drugs on micro-organisms was often highly specific. A drug which would readily kill one micro-organism might have relatively little effect on a very nearly related micro-organism—for example, quinine was less effective in one type of malaria than in another. Consequently the final test of the value of a drug in a parasitic disease had to be carried out strictly on the particular organism causing the disease and on no other. Secondly, it was found that in the case of many, if not most, parasitic diseases in which it was believed that this cure was due to the toxic action of the drug on the causal organism this action was not immediate, simple, or direct, but was modified by the action of the drug on the host. The practical outcome of these discoveries was that the only possible way of determining with any certainty the curative value of a drug in a disease caused by a pathogenic organism was to test the drug in an animal affected with the disease. The action of the drug had to be determined on the complex of host + parasite. The value of quinine in malaria had been so discovered by experiments on men naturally infected with the malarial parasite.

The possibility of investigating the action of drugs on disease as a complex would, however, be for many reasons vastly simplified and extended if experiments could be done on laboratory animals infected with a particular disease; and the nearer such a disease resembled a disease in man the more likely would success be attained in therapeutics. This, which might have been anticipated to be the easiest part of the problem, has often turned out to be the most difficult.

A great stimulus was given to chemotherapeutic research by Ehrlich's discovery of salvarsan, and one is often asked why advance in the treatment of trypanosome diseases has been so rapid as compared with most other diseases. There are two chief reasons. In the first place, trypanosome infections can be readily produced in small laboratory mammals—for example, mice—with a consequent reduction in the cost of experiment and in accommodation required. Secondly, the parasite is easily recog-

nized in the blood and the course of the infection followed; and the most easily observed end-point, death, is with some such infections a very constant time-point. It is relatively easy to decide if a drug has even a slight curative action on the disease. One reason, therefore, for the success of the attack that has been made on the problem of trypanosome diseases is simply the ease of experiment. In other diseases this condition has not been at first forthcoming. For example, human malaria cannot as yet be produced in laboratory mammals, but a type of malarial infection occurs in birds, on which chemotherapeutic research has been carried out which has already borne fruit in the treatment of malaria in man. Similarly, laboratory animals can now be infected with amoebic dysentery, and even, more recently, with leishmaniasis.

For chemotherapeutic research the production of the disease under suitable experimental conditions is, however, not the only necessity. One must also have the potential or reputed remedy. For this second necessity we have hitherto been largely dependent on observations on disease in man. The efficacy of cinchona in malaria and of ipecacuanha in dysentery has been known for centuries. An entirely new plan of attack has, however, been rendered possible by the advances of chemical science. Once the chemical and structural constitution of the alkaloids of cinchona and ipecacuanha were known, it became possible for the chemist to modify these alkaloids in various directions, or to synthesize alkaloids resembling them in certain particulars; and, if these new compounds were chemotherapeutically tested, there was the possibility that some of them might be superior, as therapeutic agents, to the original alkaloids.

Investigations so far have tended to show that the natural alkaloids are superior to artificial alkaloids, whether as therapeutic or as pharmacological agents; so much so, that many have adopted the view that no artificial alkaloid, especially if unrelated to the natural alkaloid, will prove equal to the natural alkaloids as therapeutic agents. While the evidence at present may support that view, I think it is nevertheless fallacious. It was natural that pharmacology and chemotherapy should at first concern themselves with substances which were already known to exert physiological or therapeutic action, and, therefore, in the earlier stages of this science, the great mass of the investigations have been occupied with natural alkaloids or derivatives of them.

What steps have we taken that this country should play a worthy, if not a leading, part in chemotherapeutic research? The answer is that we are doing little that is commensurate with the importance of the subject. It is, I think, beyond dispute that at the present time there is a great waste of opportunity. We have many laboratories actively engaged in making new chemical compounds either for immediately scientific or for commercial purposes. Only a trifling number of such compounds ever receive even a perfunctory pharmacological investigation.

Experimental Therapeutics and Suggestions for Advance

The value of experimental pharmacology and of chemotherapy rests ultimately, however, upon the application of the results so obtained to the treatment of naturally occurring disease in man and other animals. The final and crucial test is the test of the effect of a drug in disease in man. It may therefore be correctly surmised that human experimental therapeutics will require, so far as possible, the same amenities of experiment, the same forethought, skill, and co-operation as the ancillary sciences. The following are some considerations that I venture to put forward.

1. Medical students ought to be taught therapeutics just as thoroughly as they are now taught diagnosis or pathology. They should not only receive oral instruction in the knowledge of therapeutics, but should be taught practically the methods of therapeutic investigation. In connexion with this one might have reason to hope that the general practitioner, who has ample opportunities for observing the therapeutic effects of drugs, might play a more important part in the advance of therapeutics than he has done for the last hundred years. Many observant general practitioners find out, as the result of their experiences, points about the effects of drugs or their side actions which may seem too insignificant to warrant publication. Though these points taken singly may seem of little importance, taken in the aggregate the experiences of the general practitioner, if they could be collected and assessed, would certainly assist greatly in the advance of practical therapeutics.

2. Teaching implies teachers. While perhaps every clinical teacher deals more or less with the treatment of disease, few of them would regard therapeutics as their main business. The University of Edinburgh is, so far as I know, the only teaching medical school in this country which has a whole-time chair of therapeutics.

3. The problem of discarding useless remedies is still with us, because new remedies are thrust on the medical market by drug manufacturers in increasing numbers. Many drug manufacturers in various parts of the world are now actively engaged in investigating new compounds. These investigations are expensive, and the manufacturer rightly looks to recoup himself for the expense by the profits on a new drug, if he can put it successfully on the market. Until we know more about the relations between chemical constitution and physiological action, this type of research must remain largely as a gamble, so far as concerns the discovery of a successful remedy. The testing of a new drug on the therapeutic side has often been perfunctory and done by medical men who have neither the training nor the facilities for arriving at a correct estimate of therapeutic value. This difficulty has recently been at least partly removed by the institution of the Therapeutic Trials Committee of the Medical Research Council. A manufacturer can now submit a new drug for the consideration of this committee, and the committee can, if it believes that the pharmacological indications justify a therapeutic trial, make arrangements for a scientific and thorough investigation of the therapeutic merits of the drug. Of the success of this venture it is too early to speak, but if, as a result of the operations of this committee, drugs will not in future be put on the market without reasonable evidence to justify the claims made for them, the gain will be great.

4. In the provision of teaching and research in therapeutics it might be of advantage to have at least one large hospital in this country which should definitely concentrate its main energies upon therapeutic research and upon post-graduate instruction. It is of course impossible and unthinkable that therapeutics should be separated from the rest of medicine, and no one would suggest that this should be done; but research and teaching need not be on the same plan in all hospitals. At least one hospital might, so far as teaching and research go, take the diagnosis, aetiology, etc., as read, and concentrate its energies upon therapeutic investigation. It might attract the type of man who is interested in this class of work, and a few physicians with this training and interest would help to leaven the whole lump.

5. Some organization is wanted for sifting and promulgating the knowledge of therapeutics. One of the most serious problems that confronts the worker in all sciences at the present time—and perhaps especially medical science—is to keep pace with the accumulations

of knowledge. Medical research is increasing in different parts of the world, and new journals continue to appear. The difficulty of assessing the present state of knowledge is perhaps nowhere greater than in therapeutics, largely on account of the number of publications in which the information must be sought. For instance, there is scarcely any kind of medical publication in which it would not be possible to find some reference to quinine. If a person were to begin to make a complete study of the chemistry, pharmacology, toxicology, and therapeutics of quinine he might have to spend a good part of a lifetime in reading the literature on this single alkaloid. Anyone who begins now to research on such a subject is confronted with the heroic task of ascertaining what has already been done. With the rapid growth of medical research this task becomes more formidable from year to year. It is a realization of this difficulty that has prompted in recent years the creation of special journals devoted to "abstracts" and "reviews." The difficulty of coping with even abstracted literature is becoming increasingly great. These methods of dissemination of knowledge, though a present aid, will before long break down under pressure, and some better method will have to be devised.

I have often wondered whether some such plan as I am about to sketch might not be feasible, though the time may not yet be ripe for it. Every country which engages in medical research should establish a bureau of pharmacology and therapeutics to which would be sent separate reprints of every paper dealing with these subjects. At present, certain privileged libraries in this country receive a copy of every book published in this country. It would be a problem differing rather in degree than in kind to have a similar system internationalized. It would require arrangement with publishers, for it could not be left to authors. Each national bureau would receive roughly as much as it gave. The advantages would be: (1) that the future literature on the subject would be complete in one special library in each country; (2) that it is better to have one complete library on a subject than several incomplete ones; and (3) that it is far easier to extract the desired information from a library consisting of separated pamphlets on one subject than from an ordinary library of volumes of journals, even if the latter are complete. May one go further and prophesy that the time may come when we shall have an institute which will combine laboratories for pharmacology and chemotherapy, a hospital for therapeutic research, and a bureau for sifting and promulgating the advances in knowledge? We have an elaborate organization, with a Ministry, for the prevention of disease; we have no such organization as yet for the treatment of it.

SUMMARY

The past century has been in the main an era of aetiology and diagnosis; the coming century bids fair to be an era of therapeutics. For taking a worthy part in the advances that are certain to be made in the treatment of disease we are in this country none too well organized. We need more laboratories adequately equipped for research in pharmacology and chemotherapy, subjects which will play an increasingly important part in the advance of therapeutics proper. We need more researchers and more careers open to them.

Both in teaching and in investigation more attention must be paid to the assessment of the remedial value of drugs in man. Advance in the treatment of disease might be facilitated by having at least one hospital definitely devoted to research in therapeutics and by the creation of a specialized bureau and library for collecting and disseminating the knowledge of these subjects.

CHOLESTEROL METABOLISM IN DISEASE*

BY

J. A. GARDNER, M.A., F.I.C.

READER IN PHYSIOLOGICAL CHEMISTRY, UNIVERSITY OF LONDON

Cholesterol is an integral constituent of all cells and organs of the animal body. All body fluids contain some cholesterol; even urine contains traces, much augmented in the urine of patients suffering from nephrosis. It exists in the body in the free or alcoholic condition, and also in the form of its esters with the higher fatty acids. These two forms are not equally distributed.

The importance of cholesterol from the point of view of the pathologist was increased by the discovery that under certain physiological conditions—for example, pregnancy—the cholesterol content of the blood might be increased above normal; that in infective conditions at the height of fever the cholesterol of the blood was subnormal—hypcholesterolaemia; that in morbid conditions, such as in various forms of nephritis, cholelithiasis, diabetes, etc., the sterol content of the blood was increased often far above normal value—hypercholesterolaemia. The interest of pathologists was further stimulated by the discovery, I think in Professor Aschoff's laboratory, that the doubly refracting crystals or droplets found histologically in the normal suprarenal cortex, in atheromatous intima, in inflamed kidney, and in other organs, consisted of cholesterol esters; by the observations of Ransom that cholesterol has the property of inhibiting the haemolytic action of saponins; and by the work of the Russian observers, Anitschkow and Chalatow, showing that prolonged feeding to rabbits leads to cholesterol infiltration of the various tissues, the changes in which have been considered to resemble human pathological processes—for example, atherosclerosis.

Space forbids a detailed history of progress in this subject, but I should like, before going on to an account of some recent work, to acknowledge how much we owe to Chauffard and his co-workers in France, and more especially to Professor Aschoff and his school in Germany.

During the past twenty years progress on the chemical side has been more rapid than on the physiological side. Thanks largely to the brilliant work of A. Windaus and of H. Wieland on the oxidative breakdown of cholesterol, and of the bile acids, it has been possible to assign structural formulae, having a high degree of probability, to these substances, and to show that there is an intimate chemical relation between cholesterol and the bile acids.

Cholesterol is an unsaturated secondary alcohol of the molecular formula $C_{27}H_{46}O$, derived from the parent saturated hydrocarbon cholestane $C_{27}H_{48}$. By catalytic reduction the double link is saturated with the formation of bihydrocholesterol or β cholestanol, a saturated secondary alcohol. Coprosterol, which occurs in human faeces, is a stereo-isomer of β cholestanol, the difference depending on a steric rearrangement of the substituent groups at one of the carbon atoms. The parent hydrocarbon, coprostane, is a stereo-isomer of cholestane.

Various artificial isomers of cholesterol have been prepared in the laboratory, the most interesting being the very labile "allocholesterol," which very readily changes into ordinary cholesterol, particularly in acid media. This allocholesterol is readily reduced *in vitro* to coprosterol.

The specific bile acids and cholesterol possess the same carbon structure, except that in the bile acids an isopropyl group $(CH_3)_2CH$ has been eliminated from the side chain.

The bile acids which have been most studied are those of ox bile—namely, lithocholic acid (3 oxycholanic acid) deoxycholic acid (3.7 dioxycholanic acid) and cholic acid

* Read in opening a discussion in the Section of Pathology at the Centenary Meeting of the British Medical Association, London, 1932.