BRITISH PHARMACEUTICAL CONFERENCE BLACKPOOL, 1949

Chairman : NORMAN EVERS

CHAIRMAN'S ADDRESS

PHARMACEUTICAL RESEARCH

I PROPOSE, this afternoon, to talk on the theme of pharmaceutical research, its aims and scope and its relationship to research in medicine, chemistry and other sciences. This topic was discussed by Dr. T. E. Wallis in his address to the Conference in 1943, and I feel therefore, that some apology is necessary, but as I propose to approach the matter from a direction rather different from that of Dr. Wallis, who was mainly concerned with academic research, perhaps I may be forgiven for referring to the subject again. In fact, my address is in the nature of an addendum to Dr. Wallis's and will underline much of what he said.

In considering the subject of Pharmaceutical Research, I am immediately confronted by the difficulty of definition. What is Pharmacy and what is Research? The word " research " has become very much overworked in these days. It seems to be applied to almost any type of enquiry. We hear of " listener research," " market research," " packaging research " and even " time-table research." Most people, I think, would hesitate to give the term " research " so wide a definition, but where is one to draw the line? Research cannot be defined according to the importance of the results achieved. The distinction between what is or is not research is something more intangible. Rather, it depends on the attitude of mind with which an enquiry is approached. A problem which appears at first sight to be simple and solvable by known methods and therefore not to be dignified by the name of research may turn out to involve a fundamental investigation into certain phenomena, which raises it to the plane of true research.

When I ask myself " What is pharmaceutical research? " I find it equally difficult to provide an answer. Pharmacy is not a science in itself. It is an art which makes use of many sciences. I would remind you of the words of Daniel Hanbury which were quoted by Dr. Wallis in his address and which I think are worth repetition. He said, " Our art, gentlemen, is ever progressive. All science is interesting to us since almost every scientific discovery may sooner or later, directly or indirectly, yield some results profitable to pharmacy."

It would be going too far to argue from this that all scientific research is pharmaceutical research. Here, I think, we must take into account the objective of the research, and say that pharmaceutical research is research carried out with a pharmaceutical objective, which is rather like saying that an archdeacon is one who performs archidiaconal functions.

What, then, is a pharmaceutical objective? I think that the best way to answer that question is to consider the different types of investigations

tion on a compound having a certain pharmacological action may prove to be valuable for a therapeutic effect of quite a different kind. On the other hand, valuable drugs are sometimes discovered which bear no relation in structure to those previously known. The analgesic, pethidine, is modelled on the structure of morphine, in amidone the relationship is scarcely recognisable. The new antihistamine drugs are of a type not hitherto used in medicine and have a novel pharmacological action. The most remarkable development of recent years has been the discovery of drugs which act selectively on species of living organisms or upon one particular type of cell or enzyme. The antibiotics, antimalarials, antrycide, etc., are examples of drugs acting selectively on certain organisms. Antihistamine, antithyroid, anticholinesterase and curarising agents are examples of selective poisoning of certain types of cells or enzymes. Increased knowledge of chemical constitution and its relation to pharmacological action, of the causes of disease and of the nutritional requirements of organisms makes the task of the organic chemist less subject to chance than it used to be, but we are still a long way from being able to design a new drug like a machine on a drawing-board. The element of luck has not yet been entirely eliminated, but as Pasteur wisely said, "In the fields of observation chance favours only the mind which is prepared." It may have been a lucky chance that led Sir Alexander Fleming to the discovery of penicillin, but unless his mind had been prepared by years of research and thought on such matters, who knows that he would have appreciated its significance?

It cannot be too strongly emphasised that the greatest possible care and the most thorough and exhaustive trials are necessary before placing a new drug on the market. Time and again a drug, which has been thought from preliminary tests to have an irreproachable character and has been launched with a flourish of trumpets, has proved to possess undesirable and even dangerous qualities.

The second type of research to which I have referred deals with the isolation and purification of natural drugs, the determination of their structure and synthesis. Recent discoveries have shown that Nature still has something up her sleeve. A few years ago it might have been thought that it was unlikely that any new natural drugs of value would be discovered and that the future lay with synthetic organic chemistry. Then came penicillin to show us an entirely new type of drug from an entirely new source—a compound with a new sort of structure, and one, moreover, that has not yet been synthesised except in minute quantity in spite of the efforts of some of the finest organic chemists in the world—a blow to the pride of those organic chemists who might have been inclined to think that anything can be synthesised once its structure is known—except, of course, cane sugar. Then, as if to heap coals of fire on the head of the organic chemist, Nature produces chloramphenicol or chloromycetin, a naturally occurring antibiotic with a comparatively simple structure, containing, above all things, a nitro-group and two

chlorine atoms, looking for all the world like a typical product of the organic laboratory, yet it is not among the hundreds of thousands of compounds which have been synthesised. Truly it behoves those who pry into the secrets of nature to preserve a spirit of humility.

Another natural product which promises to be one of the important drugs for the relief of human suffering is known as "Compound E," obtained from the suprarenal gland. The minute amount present in the gland precludes its extraction from natural sources in quantity, and all hopes are centred on a successful synthesis. The known synthesis is long and difficult, even if supplies of raw material from *Strophanthus sarmentosus* are forthcoming in sufficient quantity. The position is a challenge to the organic chemist, and those who solve it will, indeed, have deserved well of mankind.

I do not wish to spend more time on the contributions of organic chemistry to pharmaceutical research. Fundamental as these are, we must in these days regard organic chemistry as a highly specialised art and the organic chemist as a species apart. The pharmaceutical student who intends to become an organic chemist must realise that, henceforth, his whole mind will be steeped in organic chemistry and perhaps in one small section of this vast subject.

I cannot speak with any authority on the third section of pharmaceutical research on my list—pharmacognosy. Dr. Wallis has already done so, nor can I say anything on the fourth item—the cultivation of drugs, so I will pass on to the fifth, the section of pharmaceutical research which most properly merits the name, the preparation of drugs in a form suitable for administration. The introduction of a new drug into medicine entails four steps, (a) the chemical production by synthesis or other means, (b) the pharmacological investigation, (c) the pharmaceutical investigation and (d) the clinical trial. The chemical research should supply information on the physico-chemical properties of the drug, the solubility etc., and on its stability to heat, moisture and oxidation. The pharmacological research should give data on the best means of administration and the probable dose required, and some information about the method and rate of absorption and excretion, whether the effect is transient or prolonged. The clinician can advise from such data on the type of pharmaceutical preparation which is most suitable for administration, whether dosage should be frequent, or whether the action should be prolonged by some such means as the use of an oily medium for the injection. Nevertheless the pharmacist is by no means the least important link in the chain. Failure to provide a satisfactory pharmaceutical preparation may bring a new drug into discredit. The pharmacist out of his experience can and should give valuable assistance to the clinician as to the best method of administration of a new drug.

If an injection is required, a number of questions must be considered, such as—

(a) Is the drug sufficiently soluble and stable in water to make an aqueous injection possible? If not, can any other solvent be used or can

any addition be made to increase the solubility? Would any other form of the drug, such as another salt, be more suitable for injection? If these questions cannot be answered satisfactorily, would a dry ampoule be a suitable method? (b) Is the addition of sodium chloride or other material necessary to make the injection isotonic? If so, how does it affect the solubility or stability of the drug? (c) Is the natural *p*H of the drug suitable for injection, and does it ensure the maximum stability or must the *p*H be stabilised by the addition of a buffer? (d) What is the most suitable preservative, if one is required, and is it likely to react with the drug or affect its stability? (e) What is the most suitable method of sterilisation? Does sterilisation by heat cause any decomposition of the drug or production of toxicity? If heat is unsuitable, does sterilisation by filtration cause any loss of potency? (f) Should the injection be protected from oxidation by filling the ampoule with nitrogen? (g) What is the stability of the injection as finally formulated under ordinary conditions, under tropical conditions or under abnormally cold conditions? (h) If the injection is to be in a rubber-capped container, will contact with rubber affect the injection in any way? (i) Should the injection be protected from light by the use of amber containers?

If the required form is an oily solution or suspension, other problems arise such as— (a) What is a suitable composition for the oily base? (b) If a suspension is required, what is the most suitable particle size of the drug? (c) Does the drug remain easily dispersible in the base? (d) Is the viscosity suitable for drawing into a syringe?

If the new drug is likely to be used in combination with some other drug a study of any possible interaction between the two must be made.

The investigation of all these problems may involve a considerable amount of work. A large number of different formulae may have to be tried and each one checked either by analysis or by pharmacological tests or both. If the drug is a new one, analytical methods may have to be devised in order to detect decomposition. If the drug is administered orally, the problems are not usually so complex. The pharmacist must first consider whether a tablet is a suitable medium of administration or if not, whether a capsule would be a better form. If a tablet is chosen, the compatibility of the drug with the usual diluents or lubricants must be considered, and the amount and the type of diluent necessary to give effective disintegration of the tablet, the possible effect of the granulation process on the drug, and the stability of the drug in tablet form.

New drugs may sometimes call for new methods of administration. I should like, if I may, to take an instance from my own experience of what I regard as an example of pharmaceutical research, which called for all the resources of the pharmacist as distinct from the chemist, and in my opinion, was a type of problem which the pharmacist can tackle better than anyone else. I refer to the production of a chewing-gum containing penicillin. Here was a problem which was quite new. It was not a question of adding penicillin to the ordinary chewing-gum base, because the ordinary chewing-gum base contains water, and penicillin

would not last in it for more than a few days. A completely new type of water-free base had to be produced, and the penicillin had to be incorporated in such a way that it was liberated over several hours of chewing. The chief asset of the pharmacist, as I said in my address last year, is his knowledge of the properties of materials. It is said that the organic chemist with the aid of some coloured balls and bits of wire can design a new detergent and confidently prophesy its properties before the compound is made. A chewing-gum cannot be designed in this way, since so little is known of the effects of constituents on the rheological properties of solids. Many experiments had to be made before the right consistency was reached and the desired slow release of penicillin was attained, involving many lengthy chewings by rather unwilling human guinea-pigs and the taking of many samples of their saliva for penicillin assay. Not only must the desired consistency be attained, it must be retained under a variety of storage conditions, for the margin between chewing-gum which is too soft and sticks to the teeth, and chewing-gum which breaks up when chewed is a very narrow one. There is also the problem of flavouring to be considered; this, too, must be liberated slowly and must not react with the penicillin. Problems such as this can only be solved when the accumulated knowledge and experience of the trained pharmacist is brought to bear upon them.

Drugs which are used by external application provide some of the most interesting problems for the pharmacist. Many of the physical problems which arise in the formulation of such products were mentioned in my address last year, and I do not propose to repeat them now.

Much of the research in industrial laboratories is concerned with methods for large-scale production, not merely of new drugs, but of pharmaceutical preparations. Advice must be given to the production department on the most suitable type of plant and for this purpose batches of a size comparable with a production batch must be carried through. Transfer from the laboratory bench scale to the manufacturing scale is rarely achieved without difficulties, even though an intermediate or "pilot" stage is interposed. The closest co-operation between the research and production staff is essential to ensure success.

But research is not confined to new drugs or to new methods of presentation of drugs. There is a continual stream of problems arising from existing preparations. New ingredients are introduced and reformulation is required to produce a new and improved product. Improved types of plant may require a modification of a production process. Contact with the production department may lead the research worker to suggest an improvement in the production process which will give greater efficiency or reduce the cost. Existing formulae may be found to be unsatisfactory when subjected to certain conditions, or some slight alteration in the composition of one of the constituents may have caused trouble in the finished product. The question of stability provides more problems and more headaches for the pharmaceutical research laboratory than any other. The hospital and retail pharmacist is not so much concerned with this problem, but to the manufacturer it is all important, especially if

goods are to be exported. All sorts of conditions of temperature and humidity must be provided for, and in many cases it may be necessary to use a different formula for tropical countries. Suggestions from clinicians for improvements in the administration of drugs or for new combinations of drugs are a fruitful source of investigation for the pharmaceutical research worker. It is a curious fact, that, no sooner is a new drug introduced, than suggestions flow in for combining it with other drugs. The belief of some clinicians in synergism seems to be unbounded.

The proper organisation of research means a ready access to the published literature on the subject. Much of the research worker's time can be saved by an efficient library service and indexing system. The subject of patents is the bugbear of the industrial research worker. A knowledge of existing patents is essential before undertaking a piece of research. This is not the place to discuss the merits or demerits of patents for medicinal products, but certainly the number of patents granted in this field is increasing and rendering the task of the research pharmacist more difficult. One result of this is the multiplication of new drugs to the confusion of the medical man and the pharmacist. The success of a new drug induces rival manufacturers to produce a similar compound with a modification in structure which avoids the original patent, but may or may not possess any therapeutic advantage. The number of antihistamine drugs which have been put on the market in the United States has forced the Council on Pharmacy and Chemistry of the American Medical Association to refuse to accept new products unless they show a very marked superiority over the old.

Familiarity with recent advances in the pharmaceutical field is a necessary equipment for the research worker, but advances in other industries may provide the key to the solution of many a pharmaceutical problem. The greater part of pharmaceutical research is carried out in the laboratories of industrial firms, though much is done in the Universities and Schools and by hospital pharmacists. The days when the retail pharmacist can spare much time for research work have unfortunately passed; the time when men like Farr and Wright could spend laborious hours on the determination of alkaloids in drugs is no more. Most modern research requires expensive equipment which is not found in the pharmacy. Nevertheless, the retail pharmacist of an inquiring mind must meet many problems which he could solve for himself with some expenditure of time and ingenuity. Doubtless much work of this type is done, but with a few exceptions such efforts remain " unhonoured and unsung." It is to be hoped that the National Health Service will not still further discourage such efforts. Pharmacy must not become mass produced. The spirit of inquiry which is, or should be, engendered in pharmacists by their scientific training should not be stifled when they engage in practice.

Much of the work done in industrial laboratories necessarily remains unpublished. Consequently there is undoubtedly much duplication. A great deal of unnecessary effort could be avoided by a proper organisation

of pharmaceutical research by a committee such as was envisaged by the Executive Committee of this Conference in their report to the Council of the Pharmaceutical Society. Such a body, composed of men of distinction in pharmacy and the allied sciences, could do much to influence the direction of research towards the most pressing problems and to ensure co-operation between those interested in the same problem from different points of view. There seems to be a need for increasing the amount of research work which is carried out on behalf of the British Pharmacopœia and the British Pharmaceutical Codex. Pharmaceutical research must always be the hand-maiden of medical research, but this does not mean that it must be entirely dependent upon it. In fact, the introduction of new or improved pharmaceutical products can and does influence methods of administration. A method of prolonging the action of a drug by altering the form of presentation may so reduce the number of doses required that treatment is much less irksome to the patient.

I have not left much time to deal with the sixth item on my list—research on the chemical and biological standardisation of drugs. The discovery of a new drug is dependent on some method of testing its efficacy. The isolation of an active principle from a vegetable or animal source is dependent on some method of assaying its potency. New drugs require new methods of assay, whether chemical or biological. New methods of manufacture may introduce new impurities. Methods of testing are continually being improved. In parallel, therefore, with research proper must go research on methods of control. Such work can be just as fascinating as other types of research, though the prizes may not be so valuable.

The ideal type of research worker is rare and it is unlikely that all members of a research team will have the true research mentality. The laboratory might not be a very pleasant place to work in if they had. The plodder is needed as well as his more brilliant colleague. There is a general and laudable desire among students of science nowadays to become research workers. The first-class research worker must be a person of ideas, but ideas alone are not enough. He must have the capacity of sorting out the ideas which are practicable and those which are not. He must have the capacity for perseverance and concentration which are necessary to carry an idea into effect. He must be an enthusiast and be able to inspire enthusiasm in others, but his enthusiasm must not carry him so far that he ignores unpleasant facts. He must be prepared to meet continued failure and rise with head "bloody but unbowed." Above all, he must know when to stop. He must be prepared to accept much of his reward in satisfaction with work well done. He should be able to say, as was said by an old chemist a few hundred years ago, "The chymists are a strange class of mortals impelled by an almost insane impulse to seek their pleasure among smoke and vapour, soot and flame, poisons and poverty; yet among all these evils, I seem to live so sweetly. that, may I die, I would not change places with the Persian King."