SYMPOSIUM

THE EVALUATION OF NEW DRUGS

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The development of synthetic organic chemistry has brought with it profound changes in our mode of living, not least in the field of medicine. A glance at the 1958 British Pharmacopoeia, as compared with the first edition of a hundred years ago, serves to illustrate this point. An additional striking feature is the diversity of chemical types that find employment in this way. There is no such thing as a favoured molecular species, and although this widens the scope for investigation, it vastly increases the task of those concerned with the search for new drugs. Fortunately, parallel advances in experimental biology and scientific medicine have aided the process of selection, and it is of interest to survey the current position.

Basically, the discovery of a new therapeutic agent, using this term in its broadest sense, has three distinct phases:—

1. The discerning of a potentially useful biological effect in a chemical compound, either synthetic or natural in origin.

2. The determination of the comparative safety of the compound using laboratory animals.

3. The tentative trial of the compound in man or domestic animals.

This scheme is an over-simplification, but those engaged in this kind of work will identify each of these stages with the three major obstacles that have to be surmounted before success can ultimately be achieved. Other disciplines such as pharmacy and biochemistry all have important contributions to make; the former in presenting the drug in its safest, most effective, and most convenient form, and the latter in arriving at a mode of action, perhaps thereby aiding a more intelligent application.

It is possible to formulate an idealised flow-sheet to cover the discovery and development of a new drug, but in practice very few examples taken from the vast number of agents now available will be found to have conformed to it. The pattern, however, is reasonably standard for the progression of a new drug in the immediate pre-clinical stages, although the final decision still depends heavily on human judgment and on a compromise between extreme caution, and the natural desire to bring the work as rapidly as possible to a useful conclusion. In this communication it is proposed to outline and discuss, sometimes using specific examples, as many as possible of the factors which have to be considered.

The discovery of drugs is not a monopoly of any one institutional or industrial section of the community. Instances can be quoted which had

their beginnings in all manner of university and hospital laboratories. But in recent years the main concentration of effort has been in organisations based on the industrial pattern, and although it might be said that the authors are biased in this matter, there is every reason to suppose that research carried out under these circumstances is conducted with at least the maximum economy and speed, if only because of the highly competitive nature of the pharmaceutical industry. Be that as it may, the course of events when the main function of the unit is the search for new therapeutic agents is much the same, wherever they may occur. This is true whether the end product is an antibiotic or synthetic substance, although this paper will deal almost entirely with the latter.

The Chemico-Biological Approach

At the outset, the organic chemist must have a chemical lead of some kind. This might be provided by knowledge, possibly incomplete, of the structure of a substance showing something of the biological effect he is looking for. The prototype molecule may have arisen from a chance observation in the laboratory or clinic, or the behaviour in a given assay of a compound prepared for another purpose, not necessarily even therapeutic, or it might be that of a substance contained in and isolated from a native remedy. Alternatively, the molecule could have been designed on a more rational basis in an attempt to disorganise or modify the function of an essential chemical factor within the target cell, be the latter parasitic, or a normal component of the animal body. Given such a lead, the chemist can begin almost immediately to devise and then synthetise potentially improved structural variants of the prototype. If constructive progress is to be made, however, it will be necessary to have the new compounds assayed by a test sufficiently precise to show up small changes in biological activity in a statistically significant manner. The development of such a test is the prime function of the biologist member of the team. It may take the form at first of an assay *in vitro*, but it is essential to augment or replace such a method as soon as possible by a replica of the particular condition under investigation in laboratory animals, the smaller the better, thus enabling the maximum experimentation to be made with the quantity of material available. In practice, the evolution of the biological assay method is usually the most time-consuming and the most expensive aspect of chemotherapeutic research. The problem is at its simplest when it concerns infectious diseases caused by micro-organisms and particularly those that can be cultured *in vitro*. The initial screening can then be directly on the causative organism, and a few mg. of the agent is all that is required. But even so, there are uncertainties apparent which make it undesirable to place complete faith in such a procedure. For example, what level of growth-inhibitory concentration should be used to define positive activity? It would be unwise to fix this too rigidly since if the figure is to be related to the limiting tissue concentrations thought to be essential for a corresponding therapeutic effect in the infected animal, then the chemical and physical properties of each substance will need to be taken into account, because

these, at any rate in part, govern the absorption and distribution characteristics *in vivo*. Likewise it is sometimes necessary to distinguish between mere inhibition of growth and an effect leading to the actual death of the disease incitant. This in turn involves the contribution that can be expected from the defence mechanisms of the host animal, which may differ from species to species. Then the growth of some micro-organisms is more easily suppressed than others. For example, the tubercle bacillus will cease to multiply at concentrations measured in a few parts per million, of a large number of simple phenols and aromatic amines, especially those that oxidise with facility to quinonoid structures. Yet not one of these substances is known to be effective *in vivo*. There is good reason to suppose that the tubercle bacillus in the infected animal differs from the same strain in the culture tube, and amongst other things in its response to the action of drugs[1]. Finally, an assay *in vitro* cannot take account of metabolism of the test substance in the animal body. It is well-known that the sulphonamide drugs would not have been discovered in the way that they were if Domagk had not proceeded early to an examination in infected mice of the azo precursors, themselves having only marginal action *in vitro*. In this sense, the administration of any single organic compound to an infected animal can be regarded as an experiment made in fact with a number of related substances.

Some infective disease conditions can only be studied away from the animal host with great difficulty. For example, it is not possible to cultivate malaria parasites or trypanosomes *in vitro*, although it has been found possible under carefully controlled conditions to maintain the viability of these protozoa in isolation for a sufficient length of time to study the effect of drug action upon them. In at least one case, that of the antimalarial drug proguanil, such a technique was of value in directing attention to the formation *in vivo* of an active metabolite[2]. Fortunately from the point of view of facilitating the chemotherapeutic study of these diseases, elegant and comparatively simple methods have been worked out for producing controlled infections in laboratory animals.

Perhaps the most difficult of the infective diseases to study experimentally are those due to viruses[3]. In the first place, inactivation of virus *in vitro* is far too easily achieved by a variety of agents to have any significance as a method for sorting drugs. Experiments using tissue cultures have been of greater value in elucidating the mechanism of drug action but have not helped in developing any new effective agents, due mainly to difficulties associated with technique. Many viruses will multiply in contact with the chorio-allantoic membrane of the chick embryo and the influence of chemical compounds on the process can be measured either by introducing them on to the chorio-allantois or into the yolk-sac. Both routes are open to criticism, but the latter can be regarded as approximating to a therapeutic assay *in vivo*. It has been common experience, however, that results obtained in tissue culture and chick embryo are rarely transferable to animals such as the mouse, or even to the hatched chick, from which it follows that for progress in the chemotherapy of the virus diseases direct medication in an infected animal

is necessary. This in turn brings its own snags and complications, not least those arising from the lower rate of virus multiplication observed in animals made weak or sickly from toxic drug action. Research in this field is extremely costly, and the continued insusceptibility to drug action which now seems characteristic of these diseases is in itself a source of discouragement to all but the hardier spirits. Nevertheless, it does go on.

Until perhaps the middle of the last decade, the bulk of chemotherapeutic research effort, for a number of reasons, was directed towards the diseases of micro-organismal origin of the type that have just been considered. Although there are notable exceptions, intensive work in laboratory animals on non-infectious diseases, for example those of organ-dysfunction, has only begun in comparatively recent times. This has required an almost complete re-orientation of outlook in many of the longer-established research units and with the new entrants into the field, has in turn been reflected in the current shortage of pharmacologists who are now urgently needed in increasing numbers for this kind of investigation. This statement is not so flippant as it might seem, because as may be by now apparent, the limiting factor in the search for new drugs is rarely the ability of chemists to produce likely candidates for examination, but more often the absence of a means of testing them. By its very nature, organic disease is often difficult to establish in a test species bred to be intrinsically healthy, and when it concerns the higher functions such as the central nervous system it may not be possible to parallel experimentally the stresses of the higher primates. Thus the very great interest of the present time in sedatives and the so-called tranquillisers has called forth a tremendous amount of work on all manner of ingenious test procedures. Similarly, although a wide range of anti-epileptic drugs is available to medicine today, there is still no experimental method which will distinguish with precision between substances acting on the two principal forms of epilepsy, and final judgment has to await the outcome of clinical trial. Malignant disease is also represented by a great variety of laboratory conditions, from the apparently spontaneous development of tumours in the mammae of a particular strain of mice, to the chemically induced, and finally to those grown as the result of subcutaneous implant. Yet no single experimental technique can be relied upon to screen compounds likely to inhibit the growth of a pre-defined malignant condition in man, and in practice a whole battery of methods is frequently used in the cancer research institutions to ensure detection of even the faintest glimmer of activity.

The Biochemist

So far, chemotherapeutic research has been discussed only in its most elementary form of the chemist synthesising a potential drug and the biologist subjecting it to assay. Given ingenuity in devising a hypothesis relating chemical structure to biological activity, discovery can come quite soon in this way and with great economy of effort. Even so, it is the experience of many groups of workers that only one compound in every

thousand synthesised is likely to be even considered as a candidate for clinical trial, and in a well-equipped unit with heavy overhead and maintenance charges the total average cost of preparing and assaying each separate substance can be as high as £200. Expense apart, there is least intellectual satisfaction in proceeding solely along semi-empirical lines even when the so-called rational approach has been attempted. The latter can rarely take count of the differential activity required in chemotherapy between host and parasitic cells which cannot be distinguished biochemically on present-day knowledge except in the crudest of terms. Much less can it explain the catastrophic changes in biological activity that sometimes follow even the subtlest variation in chemical structure, such for example as the almost complete disappearance of trypanocidal activity which results when the two methyl groups, seemingly insignificant in polarity and size, are removed from the large and highly polar molecule of suramin[4]. It follows therefore that the mode of action of most drugs, however evolved, is at best only partially understood at the time of their discovery. It is primarily the task of the biochemist to make good this deficiency, and in so doing to provide background knowledge which might lead to the synthesis of more effective agents.

Conversely, the biochemist is frequently engaged to study a disease as a preliminary to the commencement of chemotherapeutic research proper, in order to provide a starting point for the chemist and the biologist. This notion was behind the work which lead to the isolation and the elucidation of the structure of Mycobactin, a growth factor for the causative organism of Johne's disease, and which was to be found only in acid-fast bacteria[5]. The plan was to devise specific inhibitors which should then have been peculiarly antituberculous or antileprotic agents. Unfortunately, the molecule was so complex ($C_{47}H_{75}O_{10}N_5$) that the chemists found it difficult to devise potential antagonists even on paper, and although many hundreds of compounds were ultimately prepared, not one exhibited antituberculous activity *in vivo*. It is also the biochemist who is usually called upon to study the distribution and fate of drugs in the animal body. Work of this nature has perhaps not been pursued with sufficient intensity in the past, but it is absolutely essential if chemotherapy is to be established upon a more scientific basis. Most of the advocates of the rational approach have in mind only the relationship between the structure of the drug molecule and its action on an isolated cell or an enzyme system contained therein. It is not always appreciated that a therapeutic agent can be described only thus when it is able to exert its influence on the target cell *within the tissues of a living animal host*. Under these circumstances, complex considerations of absorption, distribution, excretion and metabolism, have to be taken account of. We know far less about the relation between chemical structure and these properties (which differ anyhow from species to species) than is known about the association of structure with action on individual cell systems. Until this deficiency is made good, the ultimate design of potential drugs, particularly for systemic medication, will continue to involve a large element of uncertainty.

The Pharmacist

While the potential drug is still in the early laboratory phase, only scant attention will have been given to the form of presentation to the experimental animal. If it is soluble in water, all well and good, while if sparingly soluble it will in all probability have been put up for test as a crude suspension prepared by a standard procedure in a rudimentary type of ball-mill. Since it will be used without delay, little thought need be paid to physical or chemical stability, while often the matter of sterility can be largely ignored, even when subcutaneous or intraperitoneal injection is involved. So soon, however, as interest in the drug reaches the point where clinical or veterinary field trials seem a likely possibility, it is desirable to think in terms of the ultimate forms in which it will be administered. Neglect to do this at an early date can cause delays at later and more critical stages. This is an important function of the pharmacist in the total research effort, and ideally he should begin working and thinking on these matters alongside the chemist and biologist from the time of first indication of promise. He must learn all he can about stability, particularly in the face of the possible need to provide a sterile preparation, and indeed as a guide to the treatment that can in general be meted out to the compound during the manufacture of formulates. He will almost certainly have to assume responsibility for analytical control, and this in turn calls for detailed knowledge of the chemistry of the substance and also of the preparative route so that he can guard against the carry-over of possible toxic intermediates into the final product. Needless to say, analytical procedures must relate to the formulations as well as to the pure drug. Above all, in devising likely formulations he must consider the feasibility of ultimate manufacture in the factory and work out processes that lend themselves to the necessary scaling-up. Suspensions that form a clay-like deposit on storage in bulk or in vials, powders that cannot be dispensed in automatic filling machines, cream preparations that stop the stirrer, and tablets which fragment when handled by the hundredweight, are not popular with production managers. All these are problems which invariably come the way of the pharmacist to solve.

Process Development

In building up a complete, even if sketchy picture of the search for a new drug, it must not be overlooked that works manufacture of the bulk chemical will eventually be required. Initially, the organic chemist will have aimed at the synthesis of the required compound without regard to the feasibility of the processes for large-scale production. Rarely are quantities greater than 5 g. needed for the earliest biological experiments, and in the laboratory he can indulge in Grignard reactions and ether extractions to his heart's content. But the mode of preparation he has employed will often be quite impracticable, and costly beyond reason, for translation to a manufacturing unit. It may not suffice even for the production of the modest few pounds needed for extended toxicity tests and early clinical trial. It is at this point that the process chemists begin

their work, and in well-planned development they can combine the study of alternative manufacturing routes with the provision of useful quantities of the drug for further therapeutic experiments as well as for tentative formulation research. Even so, it is common experience that manufacturing efficiency in the early years of a new drug is comparatively low, and the high initial cost is often a reflection of this state of affairs rather than a deliberate attempt on the part of the manufacturer to charge as much as possible for his product. It also frequently happens that despite intensive and costly process work, a given route has later to be abandoned when it is found to be intrinsically uneconomic, and a fresh start has to be made. This in turn may call for the design and installation of entirely new chemical plant, causing further delay and expense.

Pre-Clinical Requirements

When an active drug has been selected, the next problem is to find out whether it is safe to give to man. The final decision to give a new drug to a human being is always a very difficult one to make. In spite of tests on experimental animals, it is impossible to be quite sure that the human subject will react in the same way; there is always the element of chance, and the possibility that the drug may have unforeseen toxic action. In order to minimise the chance of an unpleasant surprise of this kind, it is essential to make very full toxicity tests in the laboratory. To issue a drug for the treatment of human disease without this safeguard is quite indefensible. It will be remembered that last December[6], a Paris Court awarded 643 m. francs to people who were incapacitated, and to the families of the 102 persons who died after taking an organic tin compound for the treatment of boils. This has been described as the worst disaster ever caused by a drug and it happened only a year ago. Had this drug been given a full pharmacological examination it is doubtful if it would have ever reached the stage of clinical trial[7].

Toxicity Tests in the Laboratory

In the course of tests for activity a rough idea of the amount of drug which is safe to give to animals will have been obtained. It is usual to determine the LD50 of the drug (the dose which kills half of a group of animals) when given by mouth and when injected. Mice are often used for the determination of acute toxicity in this way. This is not sufficient; the drug must be given to animals repeatedly in order to study the effects on their organs when exposed continuously to the drug for a period of weeks or months. The growth rates of treated animals are compared with those of untreated controls, and the blood is examined microscopically and biochemically to detect any effect on the blood-forming tissue and the endocrine glands. At the end of the test the animals are killed and the organs examined histologically. A chronic toxicity test of this kind usually reveals actions which are not seen in animals which are acutely poisoned. The doses given must be high and when the toxic level is found, experiments must be made to determine the safe one.

Rats are also used for preliminary tests of this kind. It is essential to use several species of animal because different species often have different degrees of tolerance to a drug. It is hardly necessary to be reminded of the classical example of the rabbit, which can live on belladonna leaves, because it is insensitive to the poisonous effects of atropine. It would not be satisfactory to use the rabbit alone as a guide to the safety of belladonna alkaloids in man.

It is of value to know the toxic effects not only to rodents, but also to carnivores (dogs and cats), and the final assessment of toxicity must often be made in monkeys, which bear the greatest resemblance to man in their reactions and metabolic processes. Attention must be paid to the toxic effects in the most susceptible species, and when the trial dose for man is chosen, it must be a safe dose for this species. All toxicity tests should be planned and performed in collaboration with the pathologist who is responsible for the examination of the animals and their tissues at the end of the experiment. Often it is possible to detect clinical signs which may be of importance when the drug is tried in man.

All this is, of course, very time-consuming and very expensive. The chemist, the pharmacologist and the manufacturing company are usually all anxious to see whether the drug works in man, because if it does not, most of the work may have been in vain. Nevertheless, the tests must be done.

Clinical Trials

It is reasonable to say that it is legitimate to try a drug in man when the pharmacologist, the pathologist and the chemist, having examined the results of all the tests, are willing to take a therapeutic dose themselves. This criterion does not, however, always apply. If a drug is expected to have an ameliorating effect in diseases such as cancer, which advances inevitably to death, it is reasonable to use something more toxic than would be admissible for the treatment of headaches or malaria.

The first dose of a new drug is always attended with some anxiety. There is always someone who has an extreme sensitivity to any particular drug and it is unfortunate if he happens to be one of the few people chosen to take the first dose of the new drug. Useful remedies have been discarded more than once as a result of misfortunes of this kind. An example of a drug which weathered the storm is chloramphenicol, once said by the medical journals to be safe only for use in typhoid fever (which may be fatal), but now prescribed for much less serious ailments without extensive toxic reaction. An example of a drug which did not stand up to the test in man is one of the pyrimidine antimalarials, which was the precursor of proguanil. It unexpectedly produced severe frontal headaches. This effect could not have been forecast by any of the extensive animal tests to which it had been subjected. The effects of tranquillising drugs, which depend for their activity on their selective effects on parts of the human brain, cannot be finally assessed in any other animal than man. Another unexpected casualty among new drugs was the dye, methylene violet, discovered by Hawking to be effective on

filiarial infections in cotton rats. When tried in Africa it was found to cause the nails of the toes and fingers of the patients to fall out. Fortunately, the nails grew again. Because he had done a great deal of laboratory work on these dyes, Hawking spoke very forcibly of the necessity for early clinical trials in man[8].

As indicated earlier in this paper, every opportunity must be taken to gain knowledge of the way in which a new drug is absorbed and excreted, and before the first doses are given to man, it is desirable to have a method for determining the drug or its breakdown products in the blood and the urine. These methods will have already been worked out for use in experimental animals, but it must be remembered that the doses given to animals are usually large; a method which is suitable for the detection of the drug in a monkey which has been given doses close to the toxic range may be not sufficiently sensitive to detect the small quantities to be found in man after a small therapeutic dose. It is better to be prepared for this, if possible, so that the maximum information may be gained from the first human subjects.

Clinical trials are not always easy to arrange. There are a few hospitals, research institutes and university departments which have specialised in the study of new drugs of particular types, such as hypotensives, local anaesthetics, tranquillisers and drugs for treating neoplastic diseases, and these are usually co-operative. However, it is becoming increasingly difficult to persuade such people to try a drug which can be regarded only as a possible improvement on drugs which are already in use and are reasonably effective. This is a pity because advantage should be taken of any improvement in a drug, such as greater specificity of action, lower toxicity or less liability to produce unpleasant side effects; the proper assessment of such an improved substance requires careful and painstaking work and a great deal of experience. Conditions are even more difficult when a drug is to be used for treating diseases to be found only in the tropics. Medical Officers in tropical countries are always exceedingly overworked; with the best will in the world it is often quite impossible for them to give the time and attention that is necessary for clinical trials of a new drug. There is only one way in which these difficulties may be resolved satisfactorily and that is for a pharmacologist who has been associated with the development of the drug from the start, and who knows from his observations in the laboratory its possibilities and its short-comings and the toxic effects which it is likely to produce, to work with the clinicians who are conducting the trial. If such an arrangement can be made, this kind of team work gives the best chance of discovering the truth about a drug.

The ease with which a clinical trial can be conducted depends upon the nature of the pharmacological or chemotherapeutic properties of the new drug. The simplest tests are those which can be made on groups of volunteers—university students or laboratory workers. Professor Keele at Middlesex Hospital has for several years investigated the relative potency of analgesics by measuring their effects on the pain produced by muscular movements of the arm when the blood supply is interrupted

by a sphygmomanometer cuff[9]. Professor Bain and his colleages at Leeds have made experiments on student volunteers with new local anaesthetics and antihistamine drugs[10]. There is usually no difficulty in obtaining full co-operation from medical students in these investigations, when their purpose and value are explained.

Another fairly simple type of trial to arrange is one upon an infection that is not dangerous to life, provided that the tests for toxicity of the new drug have been adequate. An example is provided by the investigations which have been made at Porton by Andrewes on the effect of drugs on the common cold, using experimentally infected volunteers[11]—an ideal arrangement in which the variables can be controlled with the same precision as in laboratory experiments on experimentally infected animals. However, it is important not to generalise from a single example of a type of drug tried clinically. Andrewes tested an antihistaminic drug on the common cold which happened to have very low activity as an antihistamine. It is possible that with a more potent member of the series, he might have obtained a more promising result[12].

Further examples are the experiments made in East Africa upon volunteers infected experimentally with known strains of the malaria parasite[13], and in West Africa by Bruce-Chwatt on natural malaria infections[14]. In the U.S.A. valuable work was done upon the activity of antimalarial drugs in the State prisons, where volunteers were infected with known strains of the parasite and treated with drugs at different stages of the infection[15]. These experiments, perhaps more than any others on malaria, have given us an insight into the way the drugs act on the tissue forms and the blood forms of the parasite. British Law does not allow the occupants of H.M. Prisons to volunteer for useful work of this kind.

A good deal of thought and enquiry is necessary to determine the best place for carrying out a trial upon naturally infected people. A place must be chosen in which the incidence of the infection is high, otherwise much time and effort may be expended in the examination and rejection of uninfected individuals. For example, a tropical city such as Bathurst in the Gambia is ideal for investigating the action of drugs on roundworms[16]. Here about 60 per cent of schoolchildren have *Ascaris* eggs in their stools on the first examination and there are relatively few other worms present. It does not take long in an area of this kind to accumulate a useful number of subjects for a clinical trial. For threadworms, a children's hospital is the obvious place for trials, and for whipworms, an institution for mentally retarded children, where the habits of the inmates ensure the regular transmission of this parasite. A hospital, school, or institution is always the place of choice for conducting a trial because it is possible there to keep a check on the recipients of the drug and to examine them again days or weeks later to see if the parasite has been eradicated or reduced in numbers.

At the other extreme of human afflictions, the trial of a drug against cancer is relatively easy to arrange because many people are anxious to make advances in this difficult field. Here we are faced with a progressive disease which usually has a fatal outcome, and there are very few drugs

to use against it. The nature of the disease is such that a drug which arrests the disorderly division of cells in the neoplasm is likely also to affect the orderly multiplication of the normal cells of the host. Present-day drugs used in neoplastic disease are therefore by nature poisonous, and the margin of safety is small. Great experience and skill are necessary in those who carry out trials of drugs against neoplasms. The selection of suitable patients for the treatment is not easy; it is necessary to decide whether surgery or radiotherapy would be of more benefit to the patient.

Even greater difficulties are encountered when clinical trials are required in diseases which may be dangerous if left to progress and which already have methods of treatment that are known to be effective. It is inhuman and quite indefensible to allow the condition of a patient to deteriorate during the trial of a new remedy, so that he stands a lesser chance of recovery when treated with drugs of established value. In this connexion, the trials of antitubercular drugs organised a few years ago by the Medical Research Council are models of careful planning and selection of patients[17]. Unfortunately, such resources are seldom available for clinical trials, and the best that can be done is for us to learn from the reports the importance of limiting the variables as much as possible and of recording all relevant information in an experiment which is so designed that statistical methods can be applied to the results.

The overriding consideration for those who are engaged in trials which use man as the experimental animal, must be to take every possible safeguard against causing harm by our activities, and to hope that some good may ensue.

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DISCUSSION

In presenting their paper the AUTHORS commented on some current problems.

DR. ROSE outlined the development of a new antituberculosis substance from ethyl Bunte's salt. Its hydrolysis product, ethyl mercaptan, was a potent antituberculosis agent but had many undesirable properties. The

corresponding disulphide had more favourable properties but was not suitable for clinical use. A non-toxic substance which liberated ethyl mercaptan in the tissues was sought. Eventually the bisethylthiol ester of *iso*phthalic acid (Compound 15688, Etisul) was chosen. It was found to be potent by the percutaneous route, but like ethyl mercaptan and the disulphide had no *in vitro* activity. Attempts to elucidate the mode of action of these compounds had not yielded a great deal of information. The active metabolite was still not known, but he hoped that this unknown substance would come to light and that it was not a mercaptan. Methyl mercaptan and methyl thiobenzoate antagonised the antituberculosis effects of these compounds. Compound 15688 was going to clinical trial in both tuberculosis and leprosy, and would be administered percutaneously.

DR. GOODWIN said he wished to emphasise the importance of toxicity tests, and that the metabolism of a drug should be known before it was tried in man. This was often difficult because drugs now being made approached in structure the metabolites found normally in the body. Adequate controls were necessary in clinical trials, particularly with a drug such as an analgesic. In the tropics a new compound would be tested in well organised communities where it was fairly easy to keep track of the patients, but this was very different from what often happened with a drug given to people in African villages or even in some African hospitals. In such places there must be the shortest possible period between the first examination or treatment and the follow-up examination —often much shorter than was desirable. This meant that a drug for use in tropical areas should if possible be given as a single dose. A new drug may show no undesirable side effects on Europeans, but in a country where the standard of nutrition was low, and the light intensity and the humidity high, unexpected side effects might be seen.

DR. G. F. SOMERS (Liverpool). The synthetic chemist usually began with preconceived ideas of chemical structure and possible relationships to drug action. In any screening programme the search should be wide, otherwise important discoveries were likely to be missed. He wished to underline the importance of the statistician's contribution to this work.

DR. ROSE. His experience was that the active compound was usually found by the man who was looking for it. It was not altogether unexpected that a substance designed for one condition might be more active against another. Chemotherapy provided many examples.

MR. S. G. E. STEVENS (London). There was increasing interest in the effects of metabolites of drugs. In the evaluation of a drug, ought one to consider the long-term effect of such metabolites? In certain parts of America the inmates of State prisons were occasionally used for such tests. Would the Authors be prepared to persuade the Government to allow some work of this sort in this country?

DR. GOODWIN. The metabolic products were very important. One example was proguanil, which had to be metabolised in the body before it

worked as an antimalarial. Similarly, chloroquine was stored in the liver in large quantities. He did not think British law would permit trials on prisoner volunteers.

DR. J. M. ROWSON (Ibadan). The average African appeared to carry half-a-dozen diseases in his blood stream. Hospitals in the bush were usually primitive, and contrasted with the few good ones. There seemed to be a great future for native drugs; in Nigeria hundreds awaited investigation. The stability of pharmaceutical preparations in the tropics needed more control. Packs often deteriorated after only a few months.

DR. ROSE. His own interest in native remedies was to obtain a chemical lead for future synthetic work.

DR. GOODWIN. The place for research on African drugs was in Africa. The universities there had good botanical and pharmacological departments. The administration of drugs to queues of patients in the tropics was a very real problem. A drug which was injected pleased the African very much, but it was a nuisance to the pharmaceutical department. Something given by mouth was therefore very much better, but a tablet was a valuable commodity, and moreover it was not easy for everyone to swallow tablets. Something which was taken as a draught was best for a long line of people.

MR. G. R. WILKINSON (London) and MR. H. J. BRAGG (Folkestone) stressed the need to bring the pharmacist into the research team at an early stage in the development of new compounds.

DR. ROSE. The organic chemist, pharmacologist and biologist should work hand-in-glove with the pharmacist from the very beginning. It might be that the organic chemist, responsible for synthesising the potential new drug, could make changes to its structure to meet pharmaceutical problems.

MR. J. B. LLOYD (Manchester). Had the Authors considered, during this present period of very intense activity in synthetic drugs, having some central bureau for the organisation of clinical trials? Another problem was the legal aspect of administering an inert substance to a patient who because the trials are blind could not be asked to give his consent.

DR. GOODWIN. The Medical Research Council undertook limited special trials. It was usually possible to obtain the patient's consent to receive a new drug. It was certainly possible to obtain the consent of medical students, for example in analgesic or toxicity tests.

DR. ROSE. A clinical trial should be conducted close to the laboratories, because the absorption and distribution of the drug could then be studied if necessary by special techniques.

MR. A. BRAGG (Liverpool). Long term stability tests should be carried out in parallel with long term toxicity tests both on the drug and its formulations.

DR. ROSE. Accelerated ageing tests cannot entirely replace actual storage experiments.

MR. N. HERDMAN (Edinburgh). Would the authors enlarge on the possibility of the increased use of precursors in controlled fermentation or in fertilisers and soils to achieve controlled biosynthesis in plants and animals?

DR. ROSE. What was needed was fundamental study of the way in which Nature built up molecules. For instance, one could feed ^{14}C to a plant.

DR. R. L. BLYTHE (Philadelphia). The procedures for testing new drugs in Britain and America were similar.

DR. ROSE. There was a tendency for the duration of toxicity tests to be increased. If, during the histo-pathological examination, there was any sign of cytotoxicity, tests must be conducted for the lifetime of the animal species used.

PROFESSOR E. SHOTTON (London). The main function of the pharmacist in this work was formulation. If he was an analyst he was not functioning strictly as a pharmacist. Much more work needed to be done on preservation in order to correlate the physical properties of the preservatives with those of the preparations.

DR. ROSE. What the Authors had stated in the Paper was that the pharmacist would almost certainly have to assume responsibility for analytical control but not necessarily have to do the work itself. He maintained that the pharmacist did have the final responsibility for acceptance.

MR. B. B. NEWBOULD (Sheffield). What function should the national Press have in informing the general public of recent advances in chemotherapy? Should communications be issued by or through any particular body to ensure accuracy?

DR. ROSE. So often the lay Press had the wrong end of a story. Sometimes it was the fault of the scientists, who stressed a point which they thought was interesting but which was not the point which interested the lay public. There was no doubt about the interest of the public in discovering new drugs.

DR. GOODWIN. The more reputable papers and journals often carried good scientific articles in which a balanced view was presented.

DR. P. T. CHARLTON (Nottingham). Many micro-organisms could split the S—S link of disulphides, and among the products of metabolism were found considerable quantities of methylated compounds—the methyl alkyl sulphides. There must be a close connection between metabolism in the animal body and the activities of these sulphur compounds against micro-organisms in that body. It seemed possible that methyl mercaptan acted as an antagonist to ethyl mercaptan because it was being used as a more normal metabolite. Micro-organisms could also exert a methylating action on the other compounds in that group, selenium and tellurium. Had Dr. Rose considered using selenium and tellurium compounds in a similar way?

DR. ROSE. It had been their experience that selenium compounds were highly toxic. They had not tried replacing sulphur with selenium in their active substance.

MR. R. E. LISTER (Edinburgh). What was the ethical position in using placebos in controlled experiments and withholding drugs of known value from suffering subjects?

DR. GOODWIN. The suffering of many who required analgesics was of psychological and not organic origin. In such cases a placebo would often do as much good as something more potent and more poisonous. It was extremely important not to withhold adequate treatment from patients, and it was the business of those conducting clinical trials to see that the patient did not suffer as the result of the trial of a new drug. Any trial must not continue for so long that the patient forfeited his chance of benefiting from already established medicine.

MR. C. F. ABBOTT (Liverpool). Industrial pharmacists used kinetic studies to predict the life of a product and to avoid the irksome two-years' delay.

DR. ROSE agreed, but there might be a chain reaction, with several decomposition products. It was often difficult to forecast exactly what the position would be at the end of two years on the basis of a three months' experiment.

MR. V. REED (London). Was the antidote to a new drug always available?

DR. ROSE. The best antidote to a new drug which proved toxic was to withdraw it.

DR. GOODWIN. If the drug was an antimetabolite, they could always have the metabolite available.

DR. ROSE. This underlines the importance of the biochemical study of the action of the drug, which might well suggest a substance which would antagonise the drug and act as an antidote.

MR. S. DURHAM (Sheffield). To what extent did the animals used in the preliminary trials reproduce conditions found in humans? What was the value of clinical tests on the patients of general practitioners?

DR. GOODWIN. The mouse, the rat, the guinea pig and the monkey were, on the whole, more different from man than man in England was different from man in the tropics. A clinical test by general practitioners would have to be carefully arranged with the College of General Practitioners.

MR. J. C. HANBURY (Ware). A great many scientifically trained students were going to the less developed parts of the world, and one of the best services such people could do for the advancement of medicine was to make a serious, scientific appraisal of the traditional native medicines. One of the greatest difficulties to be faced in the future was the provision of adequate facilities and material for the clinical evaluation of the very large number of drugs which would come into service in the next few years.

MR. T. D. WHITTET (London). Statistics issued by the Home Office about experiments on animals were somewhat misleading. By far the majority were simple injections which caused no pain. There could be an improvement in public relations by stressing the simple nature of these experiments.

MR. D. F. SMITH (Bournemouth). Did the Authors consider the present methods of clinical trial adequate, or was it possible for material to be launched on to the market before it had been adequately tested by even the present standards?

DR. GOODWIN. The development of drugs was a continuing process. Much work might go into a compound which was hailed as useful and important, but it might be replaced by something more active as a result of work going on elsewhere. A certain amount of material did reach the market without adequate clinical trial.