Report of

A SYMPOSIUM ON

CLINICAL TRIALS

held at

THE ROYAL SOCIETY OF MEDICINE

LONDON

on Friday, April 25th, 1958
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CHAIRMAN:
PROFESSOR SIR CHARLES DODDS, M.V.O., F.R.S.
FOREWORD

By Dr. A. M. Brunton
Director of Medical Services, Pfizer Ltd.

The growing number and complexity of chemical compounds that are being developed for the treatment of disease is making the problem of clinical evaluation increasingly acute.

To accord a new remedy its due place in medicine is no easy task and often it is only after extensive trial that any definite conclusions can be reached.

The pharmaceutical houses, with their research facilities, play a part in the progress of medicine, not least through the discovery and production of new drugs. Close liaison between the industry and the medical profession is therefore of first importance.

The purpose of the Symposium was to examine the main problems involved in the carrying out of clinical trials with a view to producing, if possible, a general picture of how such trials might best be conducted.

We would like to thank Sir Charles Dodds for the encouragement and help he gave both before the meeting and as Chairman. To all who contributed to the success of the Symposium, by the presentation of papers, in discussion, or by their presence, we are extremely grateful. We would also like to thank those who, although unable to attend, gave the meeting their encouragement and support.

Our special thanks are also due to the Royal Society of Medicine for the excellent facilities provided.

Folkestone, 1958.
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INTRODUCTION

Dr. W. Williams (Pfizer Ltd.) welcomed those attending the Symposium and introduced Professor Sir Charles Dodds as chairman.

The Chairman said: 'We are gathered to discuss what is undoubtedly the most burning question in the whole subject of therapy: the clinical trials of new medicaments of whatever sort. A review of the history of the fine chemical industry as applied to therapeutic substances over the past fifty years shows very clearly that clinical testing has been the real bottleneck in the progress of this subject. During the last fifty years great advances have been made in chemistry, bio-chemistry, and particularly in micro-biology. The animal investigation of the products of these sciences has also shown unbelievable expansion and technical advance; yet the human being as the final test object remains still very much as remote as he was fifty odd years ago. It does not need to be stressed that no animal can ever replace investigation of the effect of the remedy on human beings. Animals cannot describe subjective sensations, nor is their metabolism the same as in the human subject, and before any remedy can be launched on the medical profession and the public it must first pass through clinical tests. That this presents many difficulties to any organisations concerned must be obvious from the outset.

First, there is the difficulty of finding clinicians with sufficient training and, above all, sufficient time and interest to undertake the very arduous and frequently unrewarding work. Assuming that these clinicians can be found, we have to find the facilities at some institution with either an in- or out-patient department or both. This immediately raises the question of a professional responsibility between the administrator of the compounds and the patient. Should the patient be told that he is to be the subject of an experiment? Moreover, there are forensic difficulties here, because the investigator has to consider the position of his institution. The organisation of the institution obviously must be told when any major trial is to be undertaken and permission must be granted from the governing body. Here again, the legal responsibilities to the patients in their institution have to be considered. Finally, there is the question of the remuneration of the experimenter, possibly of the patient or subject and of the institution. But all of these matters will be dealt with by the various speakers in today's symposium.

In no industry is there fiercer competition than in that supplying therapeutic remedies, and in no other industries are the conditions so difficult for the manufacturing firms. For example, a firm manufacturing, let us say, battleships or motor-cars knows that in ten years' time, whatever the advances, they will still be manufacturing some form of battle-ship or some form of motor-car. It is able to plan ahead and to lay down expensive plant.

If we turn to the manufacturers of drugs and therapeutic remedies, the same
set of conditions by no means applies. I think it is safe to say that in no other industry is it possible for a company to go to bed a successful organisation and to wake up in the morning to find itself out of business. One has to think only of the advances which have taken place in the professional life-time of all of us present. One can imagine a successful business, whose success depended on the manufacture of anti-pneumococcal serum, being completely knocked out by the development of the sulphonamides, which in turn were affected, if not completely knocked out, by the introduction of the antibiotics. In each case the technique of production and the discipline is entirely different. When you consider that allowance has to be made for all that, it is perhaps not surprising that funds have not been allocated for the building of large-scale clinical testing units.

Other countries seem to have managed their clinical testing in a better manner, at least quantitatively, if not qualitatively, than we have. This is probably due, particularly on the Continent, to the fact that the heads of clinics are absolute monarchs, able to do exactly what they like with their patients. Very often they do. In America, the drug houses have in many instances built excellent clinical research centres. Many of us here have visited and observed these efforts with admiration.

I believe that I am correct in saying that this symposium represents one of the first, if not the first, attempt to grapple with this problem. It is a problem of fundamental interest to medicine, to mankind and certainly to the economic interests of this country.
AIMS AND ETHICS

A paper on 'Aims and Ethics' was presented by J. G. Scadding, M.D., F.R.C.P., of the Institute of Diseases of the Chest, Brompton Hospital, London.

Dr. Scadding: I approach the task of opening this symposium with considerable trepidation. Several excellent accounts of the general principles underlying clinical trials have been published within the past few years; and most of these have included a discussion of ethical aspects. Among these I may mention the contributions by Professor Bradford Hill (1951, 1954)\textsuperscript{1,2} and the Bradshaw Lecture by Dr. F. H. K. Green (1954)\textsuperscript{3}. I shall assume, therefore, that I need not attempt a complete survey of the aims and ethics of clinical trials, but may digress a little on special points which may give rise to discussion.

The aim of clinical trials can be described in broad terms as the assessment of the value of therapeutic or prophylactic measures in human disease. It should be a pre-requisite of a clinical trial that all possible information has been obtained from animal experimentation, not only about the therapeutic or prophylactic potentialities of the agent to be tested, but also about its toxicity and its general pharmacology. Preliminary pharmacological studies in the human subject will often be desirable also. When observations in the laboratory have produced good prima facie evidence of possible therapeutic value and of lack of toxic effects, a clinical trial is permissible. Usually the first step is to make preliminary observations on a few carefully selected patients in order to judge whether the expectations of therapeutic value are likely to be justified. As soon as suggestive evidence of a favourable therapeutic effect in man has been obtained, a formal clinical trial is usually desirable. Nearly always, this trial should be a controlled one, designed to compare two groups to which patients are allocated randomly, and treated similarly except that in one group they receive the substance under investigation and in the other they do not. This is necessary, firstly because of the variability of the course of disease from individual to individual, and from community to community, and in the case of infectious diseases, from time to time in different epidemics; and secondly, in order to avoid the introduction of bias into the assessment of results by observers, including the patients themselves, who are aware that a new treatment is being tried. The effect of the bias introduced by the patients is particularly noticeable in chronic diseases. For instance, in chronic bronchitis and emphysema with its prolonged, variable, and often disappointing course, it is a common experience among clinicians that a patient will be grateful for any interest shown in his case; and that after an extensive investigation, in itself unlikely to be of therapeutic value from a physical standpoint, many patients say that they feel much better. It is in order to eliminate the observer error introduced by the bias of the physician and of the patient himself that the complicated procedures of 'blind' and 'double blind' controlled trials are necessary; to these Professor Crofton will refer.
The effects of a therapeutic or prophylactic measure can in general not be controlled by past experience of the same disease, untreated or treated in other ways, because of the variability of the course of most diseases. Exceptions to this general rule are constituted by diseases with a known uniformly fatal outcome and no established specific treatment, such as tuberculous meningitis, in which the first authenticated cases with recovery after streptomycin treatment were sufficient to establish the value of this antibiotic; and by diseases with a well-recognised severe course and high mortality such as pneumococcal pneumonia, in which the dramatic response to the first specific agent available, sulphaspyridine, was convincing to those familiar with the course of this disease without a formal controlled trial.

An important aspect of clinical trials is concerned with the assessment of the ill-effects of the agent under investigation. Here again comparison of treated and control groups is desirable to enable a true assessment of the frequency of side-effects to be made. Immediate ill-effects are unlikely to be missed, but should, of course, be sought systematically. Sometimes, however, ill-effects of treatment appear only after a long interval and therefore are not evident in the primary assessment of results of a clinical trial. Moreover, it may happen that in a chronic disease the treated patients show an immediate advantage, which may nevertheless under more prolonged observation prove to have been transient, so that in the long run the untreated patients do equally well or possibly even better. For these reasons, reports of the early results of clinical trials of therapeutic agents in chronic diseases should, wherever possible, be supplemented by later reports of the progress of treated and control groups for as long as is practicable after the end of the trial.

I should now like to say a few words on the interpretation of the results of clinical trials as they affect the practice of the clinician. I think it is insufficiently realised, and not only among clinicians, that a clinical trial can answer directly only the questions which it was designed to answer, though its results may be relevant to some other questions. Many clinical trials are deliberately limited to a narrowly defined type of case, since the acceptance of a wide range of types of case increases the probable variability of the course in both treated and control groups, and therefore makes it likely that a large number of patients will have to be studied before a statistically valid result emerges. If, for one reason or another, the definition of the type of case included in a trial is less precise, comprising a large range of clinical types, a negative result is very difficult to establish, since it is possible that a therapeutic effect in a small number may be masked in the final result by a null effect in the majority. I will quote two examples of trials in which I think this effect was apparent.

During the war years, I made some observations on the effects of sulphonamides in bacillary dysentery in Egypt, culminating in a ‘double blind’ controlled trial of sulphaguanidine (Scadding, 1944, 1945). Most cases of bacillary dysentery seen at the time were mild, and in the controlled trial, no statistically significant differences were apparent between groups of sixty-seven control patients and sixty-six patients treated with sulphaguanidine. These observations were ethically possible in the climate of opinion existing at that time only after it had been demonstrated that an absorbable sulphonamide was at least as effective as, and probably more effective than, the non-absorbable sulphonamides which were fashionable; for this permitted
the introduction of the clinical safeguard in the controlled trial that any patient doing badly on either of the prescribed suspensions might be given an absorbable sulphonamide. In fact, this change of treatment was thought advisable in only one treated and one control patient. When the results in the patients in whom specific types of bacilli had been isolated were analysed by bacterial types, the specific groups were very small. In the group of six cases proved to have been due to Shiga bacilli, there was strongly suggestive evidence of a beneficial effect of treatment, for the three treated cases did better on all counts than the three untreated. In the thirty-four cases proved to have been due to Flexner bacilli, there was no difference on any count between the treated and control groups. It thus became a plausible (but unproved) hypothesis that a favourable effect of treatment in the few severe cases was being masked in the total analysis by the failure of treatment to improve the favourable natural course of the mild cases which constituted the majority.

I think that a similar situation, though for rather different reasons, exists in relation to the recent M.R.C. trial of cortisone in chronic asthma (Sub-Committee on Clinical Trials in Asthma, 1956d). In general the results of this trial were relatively unfavourable to cortisone in chronic asthma, showing that the initial advantage in the treated as compared with the control cases became less apparent as the trial went on, until by the end of the trial there was no appreciable difference between the two groups, as assessed by the various criteria used. The negative answer which the trial gave to the only question to which its design permitted an answer, namely, 'Is cortisone good treatment for the general run of cases of chronic asthma?' was perfectly sound. However, it is difficult to define precisely 'chronic asthma', especially as the greatest aid to precise definition of nosological groups, a knowledge of aetiology, is denied to us in this instance. Almost certainly, this led to the inclusion of a large variety of types of case, probably of very variable causation, in the trial; and I believe that a favourable result in a few was probably being masked by the inconclusive long-term response in the majority.

I have quoted these examples in order to draw attention to a paradox. To ensure that any effect of the treatment under investigation may become evident with as small a number of patients as possible, and that the significance of a negative finding, i.e. failure to find a difference between treated and control groups, shall be as great as possible for a given number of patients observed, it is desirable that the criteria of diagnosis, of severity, and of other variable factors such as age and sex, required for admission to the trial shall be strictly and narrowly defined; but then the result will be directly applicable only to the narrowly defined situation. If the definition of the observed group is loose, either because of the difficulty of precise definition, or because of the inevitable variability of the clinical material, or because it has been made so deliberately in order to secure a rapid intake of patients into the trial, then there is a danger that a favourable effect in a minority of the treated cases may be masked by the lack of effect in the majority. A negative result to a trial based on such heterogeneous clinical material, while providing useful general guidance, may not always be a sound guide to the treatment of the individual patient.

Turning to the ethics of clinical trials, I think there are several points on which there will be general agreement, and which I do not need therefore to elaborate.
Firstly, patients must be willing to enter the trial. Secondly, all patients must receive good treatment by existing standards. Thirdly, no patient should suffer any disadvantage for having been included in the trial either as a treated or as a control case. Fourthly, the protocol must contain a 'conscience clause' permitting the clinician in charge to modify treatment in agreed circumstances. The clinicians who will be in charge of the patients must approve the protocol, and must be satisfied that their own attitude towards the proposed treatment is such that they will find themselves only rarely wishing to take advantage of the conscience clause.

The application of these principles in practice is often difficult. One of the chief difficulties arises when for the first time a drug of apparent value is introduced for a serious disease carrying a high mortality, since it may be felt that a control patient is being denied potentially life-saving treatment. One of the best ways of meeting this difficulty is to ensure that a satisfactory clinical trial of a new drug is carried out at a time when the drug is still scarce. If all available supplies of the drug are in fact being used it can be claimed with justice that no patient is suffering because of the existence of a trial. This was the position in relation to the first M.R.C. streptomycin trial in this country (Medical Research Council, 1948). It is clearly of ultimate advantage to patients in general that the early supplies of a new drug should be used in a well-designed clinical trial at a time when the ethical difficulties can be avoided in this way. A difficulty of another sort appears when an effective treatment for a serious disease is already available, and a new agent which shows promise of being of comparable or even greater efficacy appears. It seems unethical in these circumstances to conduct a controlled trial consisting of a comparison between groups of patients treated with the drug of established value and with the as yet unproved drug. Preliminary observations of some sort are necessary in such a situation to establish the probable efficacy of the new agent. One way in which this may be done is to conduct a trial of the new agent in patients who have been shown to be resistant to the already established effective treatment. This is the situation in which we find ourselves in relation to new drugs for the treatment of tuberculosis; it makes the conduct of controlled trials extremely difficult, both because of the small number of patients available, and because of the inevitable variability of clinical picture which they present.

An important point in relation to the ethics of clinical trials is that ethical judgements in this matter are of necessity subjective. For even with a uniform code of ethics accepted by or imposed upon the entire medical profession, the judgement of the individual physician on the ethical propriety of a controlled clinical trial is dependent upon his personal opinion of the probable value of the procedure under investigation. If he has a strong preliminary impression that the procedure is unlikely to do either harm or good, he will be perfectly prepared to conduct a trial in which half the patients are not subjected to it. If, on the other hand, he starts with the preconceived idea that the procedure under investigation is likely to be of considerable therapeutic value he will be more hesitant about a controlled trial, certainly if it must be conducted in patients with a serious disease. This is another strong reason for the prompt organisation of properly controlled trials of any agent showing promise of therapeutic value in a serious disease, before preliminary reports, based of necessity upon impressions, have so biased the minds of physicians as to
place them in this ethical dilemma; and also for the avoidance of premature publication of impressions derived from uncontrolled observations.

Ethical considerations may sometimes make the ideal ‘blind’ controlled trial impossible. This is the case, for instance, when the method of administration of the drug under investigation is such as to involve the patient in pain or discomfort. Most people would hesitate to subject patients who constituted a control group to a long series of intramuscular injections of inert substances.

In general, the ethical difficulties of controlled trials are greater with serious than with trivial illnesses. For instance, I imagine that no one would hesitate for a moment to embark upon a strictly controlled trial of an oral preparation alleged to have a beneficial therapeutic effect upon the common cold, provided always that this preparation had been shown to be harmless. At the other end of the scale, one may contemplate the ethical difficulties involved in the planning of a trial of radiotherapy against surgery in operable cases of carcinoma of the bronchus. In this instance, there exists a strong preconceived idea that surgery alone offers hope of cure in a proportion of these patients; although the evidence for this opinion has never been obtained, since radiotherapy is usually reserved for those patients whose condition is regarded as inoperable. This example illustrates well the conflict which may exist between the physician’s estimate of the interest of the individual patient and of the interests of the community as a whole who will in the long run benefit by an advance in medical knowledge. In my view, the Golden Rule is, in this as in many other difficult ethical situations, the best guide to conduct. A trial is not ethical unless it is so designed that the physician would allow himself or a near relative to be included in it.

References

CONTROLS

A paper on 'Controls' was presented by Professor J. W. Crofton, M.D., F.R.C.P., of the University of Edinburgh.

Professor Crofton: The word 'control' conjures up an anti-vivisectionist's picture of helpless guinea-pigs foully and unnecessarily done to death by fearful experimental diseases. This stench of saltpetre attaching to the word 'control' has led many doctors, especially on the continent of Europe, to be deeply shocked by the thought of conducting 'controlled trials'. In a recent article an Italian author explained that one of the chief reasons why no controlled trials had been carried out in his country was that Italian doctors did not think it proper to leave a group of patients without treatment! Although these misconceptions may seem merely entertaining to the initiated, it is important to realise that they have a wide currency outside our own country and even within it.

Nevertheless, the ethics of the control group are, of course, fundamental to the whole conduct of a controlled trial. In general the policy is that the control group receives the best treatment previously available. From the patient's point of view it is the safest group to belong to: he may be denied the still unproved advantages of the new treatment, but he avoids its possible side-effects. And, of course, the new treatment may prove to be inferior to the old.

No Controls Necessary

Controls are unnecessary when the disease treated is normally 100 per cent fatal: all survivals will be due to the new treatment. For instance, no controls were required in the first Medical Research Council trials of streptomycin in tuberculous meningitis (Medical Research Council, 1948). But having demonstrated that streptomycin is effective, the use of controls may be necessary to show that any new treatment is superior.

On the other hand, controls are unnecessary if the new treatment is so dramatically effective that it is clearly superior to anything that has gone before. The value of chloramphenicol in scrub-typhus is a case in point (Smadel and others, 1948; Giles and Symington, 1950), even though controls—of an unspecified type—were used in the first of these investigations.

Types of Control

Possible types of control may be classified as follows:

1. Retrospective.
2. Patients treated in other wards, other hospitals, etc.
3. Contemporary controls treated by the same people in the same place.
4. Each patient his own control.

The aim of a controlled trial should be that the control group should differ from the test group only in that the patients in it receive the best treatment previously
available instead of the new treatment under test. It is clear that for this purpose a series of patients previously treated, or those treated in other wards or other hospitals, do not form an adequate control group. Such groups may, of course, be quite useful for comparison with the test group in a preliminary pilot trial. But it is quite impossible to ensure that the selection, composition and other treatment of such ‘controls’ were similar to those of the test group. The only sure way of elucidating the true value of the new treatment is to use contemporary controls treated in the same place by the same people.

The Patient as his own Control

This method is applicable to conditions in which one is assessing the effect of a drug on a symptom, as in the treatment of asthma or of pain, or assessing the side-reactions of drugs. In most cases the criteria of effectiveness are subjective and therefore the trial should be a ‘blind’ or ‘double blind’ trial. A ‘blind’ trial is a trial in which the patient does not know which drug he is receiving, a ‘double blind’ trial one in which neither patient nor observer knows. When the patient is his own control, he should be changed from one treatment to the other without knowing that a change has taken place.

For oral treatment the test and control drugs can usually be given in identical capsules. If the drug has to be given by injections this is best done by a third person, the patient and the observer being kept in ignorance of which drug is being given.

In a ‘double blind’ trial if the treatment is oral each particular kind of capsule may be labelled ‘A’, ‘B’, etc. But by this method the clinician may, because of a direct or a side effect, guess that ‘A’ is one particular treatment. It is better, therefore, for each patient’s capsules to be given a separate serial number, so that the clinician may not be led to compare one group of patients with another and perhaps in consequence be prejudiced in his observations.

Some of my colleagues used the technique of the ‘double blind’ trial to assess the painlessness of several different sorts of streptomycin. The preparations were injected by one worker in a previously determined random order. The amount of pain with each injection was recorded by a second observer, neither he nor the patient being aware of what type of streptomycin had been given (McLeod and Somner, 1962; Sandler and Grant, 1956).8

When isoniazid was first introduced we used a similar technique to investigate gain (Mudie and others, 1954). One group of normal doctors, selected at random, whether, as was claimed, it had any non-specific metabolic effect leading to weight-received lactose dummy capsules throughout the weeks of the trial. The test group received isoniazid most of the time, but were unknowingly switched to lactose for two weeks at one phase. There was no difference in weight-gain between the groups. One doctor who gained 7 lb. in weight and felt wonderful on the drug was in fact receiving lactose throughout!

Some of my colleagues have also used the system of making the patient his own control to compare the effect of long-term prednisolone, long-term cortisone, and dummy tablets in chronic asthma (Grant, I. W. B., and Somner, A. R.: Personal communication). The treatment was changed at intervals without either the patient or the observing doctor knowing which drug the patient was receiving.
Methods of Allocation to Control Groups

One of the early methods of allocation, and a method sometimes still used, is the system of allotting every alternate case to either a control or test group. This has the disadvantage that the clinician knows to which group the next patient will be allotted. If for some temporary reason he is prejudiced against this treatment group, and the patient seems to be particularly ill, he may decide not to admit this patient into the trial. In such a way the type of patient admitted to the control and test group may be different.

The same objection applies to a method frequently used in the United States of allocating the patient to a treatment group according to the last digit of his hospital number. As before, the clinician knows to which group the patient will be allotted and he may in consequence, if he is prejudiced against that group, try to treat the patient ‘off protocol’. It is needless to add that his prejudice may be completely incorrect.

A third method is to provide each centre with a series of envelopes blank except for a serial number. When the patient is admitted to the research series his name is written on the outside of the envelope and the envelope is opened. Each envelope contains a card giving the treatment group for that patient. If this method is carried out according to instructions the clinician’s prejudice cannot influence the matter. Nevertheless, there is the possibility that some less scrupulous clinician may, if he is admitting several patients to the trial at the same time, open several envelopes and allot the cards according to his prejudice.

The method recently adopted is to have a simple list of serial numbers opposite each of which the treatment group is written according to a method of random allocation which will be discussed below. This list is held by a secretary at the office of the co-ordinator of the trial. When the clinician has a patient suitable for the trial, he telephones or writes to this secretary, who takes the details of the patient and only then informs the clinician which treatment the patient is to receive. No prejudice can enter into this arrangement.

The order in which the different treatments are allotted in the series can be determined by a table of random numbers, but it is permissible to alter the laws of chance in the interests of the trial. For instance, it may be desirable to allot a larger number of patients to one particular test group in order to obtain definite evidence about its value. It is often useful also to make the numbers in the different groups even out every ten or every twenty in order to keep the groups roughly equal, without having to collect so many cases that this would happen by pure chance. If seasonal factors, such as weather, are important, as for instance in the treatment of bronchitis or bronchiectasis, it is well that the numbers in the different treatment groups should be equalled out over relatively short intervals.

If there is likely to be considerable variation in the type of case admitted to the trial, it may be a good thing to divide the cases into sub-groups and to randomise each sub-group separately. In this way the control and the test groups are likely ultimately to be composed of a similar range of types of case.

There is a great deal to be said for randomising patients in each hospital separately. In this way it is likely that any one hospital will treat roughly equal numbers of patients in the test and the control groups so that any differences in
treatment, attributable to that particular hospital, will be equalised between the
two groups. On the other hand, if there are a very large number of centres, some of
which are admitting only small numbers of patients, it may sometimes happen that
several of them have rather unbalanced groups. Nevertheless, it is probably safer
to keep a separate randomisation list for each centre.

The Treatment of the Control Group

As already mentioned, the control group will be treated by the best method
previously available. It is well to obtain the agreement of the physicians concerned
as to the best previous method of treatment and to specify it in the protocols. Other-
wise quite a large number of different sorts of treatment may be used for the control
group. These will probably differ in value among themselves. For instance, in the
Medical Research Council trial of chloramphenicol and chlortetracycline in clinical
pneumonia the control group was allowed to be treated by penicillin or sulphon-
amides according to the wish of the clinician. In one particular centre the control
group was treated with relatively small doses of oral penicillin and an undue pro-
portion of the patients with unsatisfactory progress in the control group came from
this centre (Medical Research Council, 1951)7.

If no satisfactory treatment has been previously available then it will have to
be considered whether it is proper to make the trial a ‘blind’ one or a ‘double
blind’ trial. This will often be justifiable if the treatment is an oral one. It is no
particular affliction for the patient to swallow ‘dummy’ capsules and this has certain
advantages. In the first place, any psychological effect of the treatment should be
the same in the two groups. In the second place it enables a much better comparison
to be made of any apparent toxic side-effects of the drug under test. If patients
and doctors know that a new drug is being employed they are likely to be much
more alive to the possible side-effects. With almost all new drugs side-effects such
as paraesthesiae, giddiness, drowsiness and other subjective symptoms have been
reported. Such reports can be better assessed at their true worth if there is one
group of patients who have received dummy tablets without the patient or the
observer knowing whether or not these are different from the tablets given to the
test group. In a trial carried out by the Tuberculosis Society of Scotland (1957)8 on
the use of prednisolone in pulmonary tuberculosis the incidence of rashes observed
on withdrawing the prednisolone was probably unduly large because of a much
more intensive search in the test group than in the control group who were known
not to be receiving prednisolone.

Changes of Treatment in the Control Group

The clinician must always have the right to break the protocol and change
the treatment if it seems clearly in the patient’s interest to do so. Obviously, if this
happens too often the results of the trial are liable to be prejudiced. It is tidier, and
much easier to analyse, if it is possible to lay down in advance what treatment
should be used, both in the control and in the test group, if the patient is not
responding satisfactorily. For instance, if one were trying out long-term tetracycline
against lactose capsules in bronchiectasis, it could be suggested that penicillin, or
penicillin with streptomycin, could be used if necessary to deal with an exacerbation.
In a trial of prednisolone in chronic asthma, conducted by my colleagues and
already mentioned above, it was suggested that any undue exacerbation of the asthma should be treated with A.C.T.H. injections, the doctor not knowing whether the patient was receiving prednisolone or dummies. If at all possible it is much better that the control group should not, during the period of the trial, receive the treatment given to the test group. However, sometimes changes of this kind are not too disastrous for changes of treatment may be found necessary both in the control and in the test group. These can be regarded as an indication of unsatisfactory progress and their relative frequency may be some reflection of the efficacy of the original treatment.

Morale of the Controls

It has already been made clear that patients in the control group are not necessarily at a disadvantage. They should always be receiving the best available previous treatment. Therefore in my experience they normally do not suffer in any way in morale. As far as they are concerned they are having adequate treatment for their condition and at this stage the doctor treating them does not know whether the treatment they are receiving is going to prove to be inferior or superior to the treatment under test.

Conclusions

In many types of clinical trial it is highly desirable to have a control group. This group will normally be treated by the best possible previous treatment in order to determine whether the new treatment under test is superior. It is essential to use a method of allocation to the treatment and control groups which will exclude any prejudice on the part of the clinician. The method of allocation must also be designed to ensure that the two groups contain a similar range of cases.

Summary

1. A control group is essential to a clinical trial designed to resolve a genuine doubt about the value of a new treatment.
2. In general the control group receives the best treatment previously available. This may or may not prove inferior to the new treatment under test.
3. Patients in the control group should be treated at the same time and by the same clinicians as those in the test group.
4. In certain circumstances the patient can be made his own control.
5. Where the criteria of successful treatment are mainly subjective it is best that the trial be ‘blind’ (the patient unaware of the identity of the treatment he receives) or ‘double blind’ (neither patient nor observer aware of the identity of the treatment).
6. Allocation to treatment or control groups should be by a genuinely random method which makes it impossible for the clinician’s prejudice to affect the allocation. Methods can also be employed which should ensure that treatment and control groups contain a similar range of cases.

References

1 Medical Research Council, (1948), Lancet, 1, 582.
CRITERIA FOR MEASUREMENT IN ACUTE DISEASES

A paper on ‘Criteria for Measurement in Acute Diseases’ was presented by Professor R. Cruickshank, M.D., F.R.C.P., of the University of Edinburgh.

Professor Cruickshank: Professor Crofton has reviewed the first and perhaps most important requirements in the conduct of a controlled clinical trial—namely, a well-balanced design and the ‘blind’ or ‘double blind’ control. When this has been organised, the next step is for the participants to define precisely the way in which the new medicament is to be used and agree on the subjective and objective criteria for assessing the progress of the illness that is being treated. The illness itself may also need to be clearly defined.

Treatment

If the treatment is a chemotherapeutic substance, the dosage, the duration and the mode of administration of the new drug is defined in accordance with the available evidence about its pharmacological action. If children are involved, the dosage will have to be adjusted according to the age or weight of the patient. In the case of adult patients, it may be possible to use two or more different dosages, as was done in the trials of P.A.S. in pulmonary tuberculosis and in the early trials of penicillin in subacute bacterial endocarditis. If the drug is very unpleasant, it may have to be given in capsules or cachets, but this form of administration is very difficult with children between one and five years of age, for whom the drug is best given in some very sweet excipient. In infants, on the other hand, a bitter or unpleasant drug does not need any camouflage, as the taste buds are still poorly developed.

It may be necessary with a new drug to ensure that adequate blood levels are being obtained, particularly following oral administration in capsule form, and this means the collection of blood samples at varying intervals after a dose of the drug. Fortunately, with capillary methods of assay, this can often be done with very small amounts of blood. The most important point, however, is to ensure that all the co-operating clinicians adhere to an agreed uniform dosage, irrespective of severity of illness or other factors.

For the control group, the placebo or dummy drug should have some physical resemblance to the active drug. For example, if the active drug is coloured and unpleasant to take, the dummy drug should be of a similar colour and be made distasteful. Pharmacists and pharmaceutical companies can be very helpful in this matter. Sometimes, the control group will be receiving some recognised form of therapy which is quite different in its mode of administration from that of the new drug. For example, in the controlled trial in adult pneumonias, to which Professor
Crofton referred, some of the patients in the control group were given injections of penicillin, while in the treated group the drugs were given orally.

**Criteria of Measurement**

For the assessment of any new therapy to have its greatest value, it is very desirable that the treated and control groups of patients should be closely comparable in the nature and severity of the illness. Thus, in addition to adjustments for age and sex, the type of case to be admitted to the trial may have to be restrictively defined. For example, in the early trials of anti-tuberculous drugs, the cases of pulmonary tuberculosis chosen for admission were defined as ‘rapidly progressive bilateral tuberculosis of recent origin, bacteriologically proved, in patients aged fifteen to thirty years.’ Or, cases may be classified after admission to the trial according to certain criteria of severity; for example, in tuberculous meningitis the duration of illness before admission and the mental state of the patient on admission were important criteria in assessing the effect of chemotherapy. Again, in an acute self-limiting disease like the common cold, the duration of illness before admission is obviously a very important factor in the measurement of any new treatment. The careful assessment and definition of the illness is particularly important where the number of cases to be admitted to the trial is likely to be limited.

The criteria to be used for measuring the effect of treatment must be clearly defined before the trial begins. These criteria will usually consist of: firstly, subjective symptoms or clinical impressions, for example, the severity of the paroxysm in whooping cough or the relief of joint pain in rheumatoid arthritis; and, secondly, objective criteria, such as temperature, sedimentation rate, leucocyte count, X-ray findings, etc. While the objective criteria might seem to be the more reliable, we have become very conscious in recent years of ‘observer error’, and this human fallibility may apply to the interpretation of an X-ray picture as much as to the clinical impressions of the patient’s progress.

**Illustrative Examples**

I feel the best way to deal with the criteria for measurement in acute disease is to take a few examples from clinical trials in common maladies. I shall choose three illustrations from studies with which I have had some association.

The first is the treatment of acute sore throat. This trial was carried out among Army recruits by my colleague, Dr. Brumfitt, in collaboration with a clinical colleague while they were doing their National Service. Its object was to find out whether a four-day course of penicillin, the prescribed Army treatment, had any ameliorating effect on the acute sore throat occurring in young adults. Sore throat is most commonly due to the haemolytic streptococcus, but there may be other causes, and so both clinical and bacteriological criteria of diagnosis and of cure were needed. The criteria of measurement included both clinical impressions, such as pain and redness in the throat, and objective findings such as temperature, leucocyte count, bacteriological data, etc. The findings are set out in Table I and Figs. 1 to 6.
Table 1
COMPARISON OF TREATMENT GROUPS AT START OF PENICILLIN THERAPY

<table>
<thead>
<tr>
<th></th>
<th>Streptococcal</th>
<th>Non-Streptococcal</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Non-Specific Treatment (40 Cases)</td>
<td>Penicillin Treatment (42 Cases)</td>
</tr>
<tr>
<td>Mean duration of sore throat before admission (days)</td>
<td>1.5</td>
<td>1.3</td>
</tr>
<tr>
<td>Mean initial temperature (°F)</td>
<td>101.6</td>
<td>101.8</td>
</tr>
<tr>
<td>Mean initial white-cell count (per c. mm.)</td>
<td>14,400</td>
<td>14,000</td>
</tr>
<tr>
<td>Percentage of cases with exudate</td>
<td>79</td>
<td>79</td>
</tr>
<tr>
<td>Percentage of cases with tonsillectomy</td>
<td>7</td>
<td>13</td>
</tr>
<tr>
<td>Percentage of patients aged 17-21 years</td>
<td>80</td>
<td>82</td>
</tr>
</tbody>
</table>
Fig. 1. Effect of penicillin on duration of leucocytosis (11,000 or more white cells per c. mm.) in streptococcal cases.

Fig. 2. Effect of penicillin on duration of injection (oedema + redness) of throat in streptococcal cases.
Fig. 3. Effect of penicillin on duration of subjective soreness of throat in streptococcal cases.

Fig. 4. Effect of penicillin on duration of pyrexia in streptococcal cases.
Fig. 5. Effect of penicillin on duration of pyrexia in non-streptococcal cases.

NON-SPECIFIC TREATMENT—BLACK COLUMNS [40 CASES]

PENICILLIN TREATMENT—WHITE COLUMNS [42 CASES]

Fig. 6. Effect of penicillin on proportion of patients from whom G.P.A. streptococci were isolated.
My second example is *infantile enteritis*, now, fortunately, a much rarer and less severe infection than it was twenty to thirty years ago. In this trial, paediatricians and laboratory workers from twelve different hospitals co-operated and the principal drugs under test were Aureomycin, chloramphenicol and sulphadiazine. The three main criteria of measurement were duration of diarrhoea, average time to clinical recovery and the proportion of mild cases which became severe. This last measurement meant that cases had to be classified as mild or severe on admission. Of the two antibiotics under test, chloramphenicol was the more effective (see Table II).

<table>
<thead>
<tr>
<th></th>
<th>Mild Cases</th>
<th>Severe Cases</th>
<th>All Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C</td>
<td>R</td>
<td>C</td>
</tr>
<tr>
<td>Total number of cases</td>
<td>138</td>
<td>138</td>
<td>72</td>
</tr>
<tr>
<td>Number of deaths</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Number of survivors</td>
<td>137</td>
<td>136</td>
<td>69</td>
</tr>
<tr>
<td>Average duration of diarrhoea after entry (days)</td>
<td>5.6</td>
<td>8.3</td>
<td>6.7</td>
</tr>
<tr>
<td>Average time to clinical recovery (days)</td>
<td>9.6</td>
<td>13.1</td>
<td>11.5</td>
</tr>
<tr>
<td>Number of mild cases which became severe</td>
<td>4</td>
<td>28</td>
<td>...</td>
</tr>
<tr>
<td>Number of cases which relapsed</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
</tbody>
</table>

However, at one centre, the control group which had been receiving sulphadiazine compared favourably with the chloramphenicol treated group and fresh trials were therefore initiated at a number of other centres which proved that sulphadiazine was at least as effective as chloramphenicol in the treatment of infantile enteritis (see Table III).

<table>
<thead>
<tr>
<th></th>
<th>Mild Cases</th>
<th>Severe Cases</th>
<th>All Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C</td>
<td>S</td>
<td>C</td>
</tr>
<tr>
<td>Total number of cases</td>
<td>171</td>
<td>182</td>
<td>72</td>
</tr>
<tr>
<td>Number of deaths</td>
<td>2</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Number of survivors</td>
<td>169</td>
<td>182</td>
<td>68</td>
</tr>
<tr>
<td>Average duration of diarrhoea (days)</td>
<td>7.1</td>
<td>5.7</td>
<td>7.8</td>
</tr>
<tr>
<td>Average time to clinical recovery (days)</td>
<td>13.5</td>
<td>12.0</td>
<td>16.5</td>
</tr>
<tr>
<td>Number of mild cases which became severe</td>
<td>10</td>
<td>11</td>
<td>...</td>
</tr>
<tr>
<td>Number of cases which relapsed</td>
<td>7</td>
<td>13</td>
<td>7</td>
</tr>
</tbody>
</table>
ANTIBIOTIC TREATMENT OF PERTUSSIS

EARLY CASES (85)

DAY OF OBSERVATION

Fig. 7

ANTIBIOTIC TREATMENT OF PERTUSSIS
EARLY CASES (85)
SEVERITY OF PAROXYSMS AT INTERVALS
DURING OBSERVATION PERIOD

Fig. 8
ANTIBIOTIC TREATMENT OF PERTUSSIS
INTERMEDIATE CASES (147)

CHLORAMPHENICOL
AUREOMYCIN
CONTROL

AVERAGE NUMBER OF PAROXYSMS PER CASE PER DAY
DAY OF OBSERVATION
Fig. 9

ANTIBIOTIC TREATMENT OF PERTUSSIS
INTERMEDIATE CASES (47)
SEVERITY OF PAROXYSMS AT INTERVALS
DURING OBSERVATION PERIOD

PAROXYSMS
ABSENT OR MILD

PERCENTAGES OF CASES
FIRST 4 DAYS
SECOND 4 DAYS
THIRD 4 DAYS
FIFTH 4 DAYS

PAROXYSMS SEVERE

CONTROL
CHLORAMPHENICOL
AUREOMYCIN

Fig. 10

Page 31
ANTIBIOTIC TREATMENT OF PERTUSSIS
LATE CASES (62)

CHLORAMPHENICOL
AUREOMYCIN
CONTROL

Fig. 11

ANTIBIOTIC TREATMENT OF PERTUSSIS
LATE CASES (62)
SEVERITY OF PAROXYSMS AT INTERVALS DURING
OBSERVATION PERIOD

<table>
<thead>
<tr>
<th>PAROXYSMS</th>
<th>FIRST 4 DAYS</th>
<th>THIRD 4 DAYS</th>
<th>FIFTH 4 DAYS</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABSENT OR MILD</td>
<td>PERCENTAGES OF CASES</td>
<td>PERCENTAGES OF CASES</td>
<td>PERCENTAGES OF CASES</td>
</tr>
<tr>
<td>PAROXYSMS SEVERE</td>
<td>CONTROL</td>
<td>CHLORAMPHENICOL</td>
<td>AUREOMYCIN</td>
</tr>
</tbody>
</table>

Fig. 12
My last illustration is whooping cough, a notoriously difficult disease to treat, as is shown by the great variety of recommended therapies, varying from rectal injections of ether to aeroplane trips. In this trial, clinicians and laboratory workers from eight Infectious Diseases Hospitals in Scotland, England and Ireland took part. The disease was defined as uncomplicated whooping cough in children under five years of age admitted within three weeks of onset of symptoms. There were two treatment groups receiving respectively aureomycin and chloramphenicol and one control group. In all, some 300 cases were included in the final analysis and the criteria for measurement of the progress of the disease were the number and severity of paroxysms during the first three weeks in hospital, the incidence of complications and the rate of elimination of Haemophilus pertussis from the upper respiratory tract. Although the overall results did not show any very obvious benefit to the treated groups, when each group was divided into cases admitted at an early, intermediate or late stage of infection, it was found that with early cases the treated groups fared better than the control group, both in regard to the number and severity of the paroxysms (see Figs. 7–12). There was no difference in the incidence of complications in the three groups, but Haemophilus pertussis was eliminated from the respiratory tracts of the treated groups more quickly than was the case in the control group: the percentage of positive results in all cases swabbed on the second, third and eighth days after admission being 38.4, 14.6 and 3.2 in the treated groups and 37.0, 27.8 and 15.6 in the controls.

May I, in conclusion, say, as a laboratory worker accustomed to the careful designing and recording of controlled experiments, that I have been most impressed by the collaborative spirit which clinical colleagues of diverse personality have shown in the conduct of these controlled clinical trials. It has been particularly interesting to watch the metamorphosis from honest doubt to enthusiastic support for a form of scientific medicine which we can proudly claim to be primarily and essentially British.

References

1 Brumfitt, W., and Slater, J. D. H., (1957), Lancet, 1, 8.
2 Medical Research Council, (1953), Lancet, 2, 1163.
3 Medical Research Council, (1953), Lancet, 1, 1169.
CRITERIA FOR MEASUREMENT IN CHRONIC DISEASES

A paper on 'Criteria for Measurement in Chronic Diseases' was presented by Oswald Savage, O.B.E., F.R.C.P., of the Arthur Stanley Institute, Middlesex Hospital, London.

Dr. Savage: Owing to developments in the pharmaceutical industry the physician today has available a large number of powerful agents and some of these can be used in conditions which until recently were considered untreatable. Many of these drugs are capable of doing harm as well as good, and the advantages and disadvantages of their use have to be weighed up. They may also be expensive and this must be taken into consideration when long-term treatment is involved.

Because of this the need for clinical trials, using controls and with statistical evaluation, has become established and I imagine no one would nowadays deny that these are essential wherever possible.

In the acute killing diseases the problem is relatively simple because one main question has to be answered: Is the mortality altered by the drug being tested? I believe that during the war when penicillin was tried out in battle casualties there was no need to wait long for the answer, and so it was not necessary to withhold the drug from control cases for more than a short time.

In the chronic non-lethal diseases the problem is more difficult. Here there are three questions to be considered:

1. Does the drug have any effect on the symptoms and signs?
   This may be called a pilot trial to find out if a prolonged trial should be undertaken.

2. Does the drug cure the disease?
   In a number of trials recently it has become clear that the answer to the first question is yes and to the second is no. That is to say that the signs and symptoms are suppressed, but the disease is not cured. The third question then arises:

3. Is the state of the patient improved by administration of the drug over long periods, perhaps indefinitely?

The first question as to whether the drug is effective is comparatively easy to decide and Fig. 1 shows a short trial of cortisone in the early days when it was given by injection in large doses. It was compared with the inert substance cholesterol. It was clear in a ten-day trial that the symptoms and signs of arthritis were suppressed. With cholesterol there was virtually no change whereas with cortisone the sedimentation rate dropped to normal, rest pain and tenderness were abolished, the grip doubled in strength, the functional tests showed marked improvement and the patients estimated their benefit as 50 per cent. Unfortunately these methods of measurement may only be suitable in a short trial and may be quite useless in a long one.
Fig. 1. Ten days' trial of cholesterol vs. cortisone

The second question as to whether the drug has effected a cure can often only be answered by withdrawing it after a time, perhaps each month, and seeing if there is a relapse. This decision with regard to withdrawing the drug in order to see if there is a relapse may be a difficult one. In many chronic diseases we have so few objective criteria of activity that reliance has to be placed on measurements which are mainly subjective. In a slow tentative withdrawal in which it is almost impossible to keep the facts from the patient because of the number or size of tablets, he or she may become so apprehensive that fear of relapse on the part of the patient may be difficult to differentiate from a real relapse due to the disease. In an effort to combat this one can point out to the patient the importance of living without the drug, but that will only work once or twice. On the other hand, if sudden withdrawal is followed by severe relapse prolongation of the trial may become difficult or even impossible.

The third question which in effect amounts to: Is the drug worth giving for long periods? is the most difficult one of all. My experience of this has been mainly in connection with rheumatoid arthritis, but I believe this a good example of the problem. I would like to discuss some of the measurements in more detail.

Firstly, it is essential that the physician selecting cases both for the drug and
the control, and the assessors, should have experience of the disease, for in any chronic disease there are periods of remission and periods of relapse which may continue for a short or long time. In selecting cases for a trial it is clear that those in whom there are physical signs to measure will be chosen. The drug is therefore always started in a period of relapse. In an individual case there is no way of knowing whether a remission is just around the corner. In order to cancel out such a possibility a large number of cases must be included in the trial, probably not less than fifty with the same number of controls. Also to eliminate changes due to natural remission and relapse the trial must continue for a long time, probably two or three years. This raises an ethical question. Is one justified in giving an inert substance for a long time to the control cases in such a trial? If the drug is given by injection the problem is even more difficult. With oral drugs this difficulty has up to date been by-passed by giving the current treatment to the control group and comparing it with the new drug being tested, as in the cortisone-aspirin trials in rheumatoid arthritis8,3,4.

Secondly: The crux of all clinical trials must depend on the validity and accuracy of the methods of assessment used. In many chronic diseases pain is the main symptom and as far as I know there is no satisfactory method of assessing this.

I well remember the first case we took into a trial—a woman with long-standing arthritis. I interviewed her before the start and asked her if she would know if the pain were better in a week’s time. She indignantly replied that as she had had the condition for eighteen years she would undoubtedly be certain. A week later she could not recall with any certainty how bad her pain had been. After that we took to recording our interviews and playing them back to the patients if necessary in order to refresh their memories. We have now given up trying to assess pain as it is too difficult with the present methods available. In the majority of chronic diseases it is only recently that serious attempts have been made to measure changes by objective criteria.

For instance, before the days of steroids very little attempt had been made to measure improvement and deterioration in arthritis. One must bear this in mind when the results of a trial are published.

Many rheumatism departments have worked on this problem in an effort to find the best objective measurements. In aiming at accuracy the early attempts were often over-elaborate. As an example, in one of the earliest trials the patient had to be timed tying a knot in a particular way and this had to be done week after week. After a few months of the trial I noticed how bored everyone was with this test, both patients and assessors, and I am sure the accuracy of this measurement suffered accordingly. This raises the question of the frequency of assessment in a long trial. Too short an interval may mean great inconvenience to the patient, particularly if they are working and too long an interval means that the routine which becomes almost a rhythm may be lost. With my experience up to date I would say measurement should be carried out every month or six weeks, but this question is not yet settled. In a long controlled trial in a chronic disease where the assessments have to be carried out in a number of patients at fairly frequent intervals the measurements should be simple and of a type that can be done quickly, almost in the course of a routine examination. We have gradually discarded most of the battery of tests we have tried, either because they are too elaborate or because they take too much time.
We feel, for instance, that we cannot measure the range of movement of a joint accurately enough to be of value.

Our present method in arthritis is to measure an average range of tenderness which we grade roughly into three points: 1. Where the patients admit tenderness; 2. When they wince; and 3. When they won't let you do it again. We cannot be more accurate.

Fig. 2. Our other measurement is the power of the grip, which is useful as the hands are so often involved in arthritis. We use an ordinary beaumanometer and the rolled blood pressure cuff inserted into a bag 6 × 3 in. designed by Dr. Peter Davis. This is inflated to 30 mm. Hg. The patients squeeze the bag as hard as they can.

Having tried a large number of methods of assessment of joints in rheumatoid arthritis we feel that these two, tenderness and grip, are the best at our disposal and it should be noted that there is a large subjective element even in these. So far, we have not found a satisfactory single test to measure either the joints of the lower limbs or the function of the legs.

The other tests which can be of value in measuring improvement or deterioration in a chronic disease are those of function.

In arthritis certain criteria of function are useful; for instance, whether the patient can achieve such things as dressing or feeding themselves, getting in and out
Name: Mrs. S  
Age 48  
R.A. 6 years

<table>
<thead>
<tr>
<th>Day ... ... ...</th>
<th>0</th>
<th>7</th>
<th>28</th>
<th>84</th>
<th>180</th>
<th>365</th>
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<td>Months ... ... ...</td>
<td>...</td>
<td>...</td>
<td>1</td>
<td>3</td>
<td>6</td>
<td>12</td>
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<tr>
<td>Drug mg. Cortisone ...</td>
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<td>75</td>
<td>62½</td>
<td>50</td>
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<td>50</td>
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<tr>
<td>E.S.R. ... ... ...</td>
<td>60</td>
<td>40</td>
<td>20</td>
<td>30</td>
<td>19</td>
<td>17</td>
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<tr>
<td>H.B. ... ... ...</td>
<td>75</td>
<td>75</td>
<td>80</td>
<td>84</td>
<td>90</td>
<td>90</td>
</tr>
<tr>
<td>R.B.C. million ... ...</td>
<td>4.5</td>
<td>4.8</td>
<td>4.8</td>
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<td>4.8</td>
<td>4.9</td>
</tr>
<tr>
<td>B.P. ... ... ...</td>
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<td>115/70</td>
<td>120/80</td>
<td>120/80</td>
<td>130/80</td>
<td>120/70</td>
</tr>
<tr>
<td>Weight (Normal 9. st 7 lb.) ...</td>
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<td>8.2</td>
<td>8.7</td>
<td>9.2</td>
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<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Round face ... ... ...</td>
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<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
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<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

TENDERNESS
1. Second left interphalangeal joint ... 3 2 2 0 0 1 0
2. Second right knuckle joint ... 2 1 0 0 1 1 0
3. Right wrist ... 3 3 1 1 1 0
4. Left ankle ... 3 2 2 1 0 1

RANGE OF MOVEMENT
1. Right shoulder elevation ... 1/3 3/4 Full 1/2 1/2 Full 1/2
2. Left fist ... 1/3 3/4 Full 1/2 Full Full

GRIP TEST (30 mm.)
Right hand ... 60 80 120 130 135 150
Left hand ... 40 60 100 100 110 112

FUNCTIONAL TESTS
Raising arms in 15 sec. ... 1 2 20 26 25 26
Hopping on left foot in 15 sec. ... 2 4 12 14 16 16
Working ... No No Yes Yes Yes Yes
In and out of bath ... No No No Yes Yes Yes
Kneeling ... No No No No No No
Codeine/diem ... 12 12 6 6 4 4

Fig. 3. Clinical assessment of a patient on cortisone after a year.

of a bath, and most important of all whether they can carry out their work; often in the case of women their ability to do housework. These are most valuable in an individual patient, perhaps the best of all tests. However, they are individual, and so far we have found it impossible to fit them into a trial of a number of patients with controls. Also we have not been able to give figures to such tests, so that they can be of no help to a statistician.

In a long trial in a chronic disease, besides measuring improvement or deterioration it is also necessary to measure the adverse effect of the drug—in fact, to measure the side-effects.

Fig. 3, perhaps, can illustrate my point best. It shows you the sort of assessments we make of patients on a long-term regime of steroids. This is the record of a patient having cortisone for a year. We measure the sedimentation rate, Hb., R.B.C. Next,
the possible side-effects, blood pressure, weight, any oedema, moonface and indigestion. In our old assessments you would next have seen a record of pain but we now omit this. For tenderness we follow through a few joints, as widely scattered as possible, which are tender before treatment and add any outstanding ones which occur during treatment. Range of movement is measured so roughly as to be of no statistical significance. The grip test gives us a figure. Functional tests like hopping tend to become boring and they make the patient conspicuous before others, which he doesn't like, particularly if he is improving. Some tests the patient does automatically in his daily life are a useful index and the number of analgesics is a rough test of pain. Here we have a valuable assessment, but it is an individual one and difficult to fit into a controlled trial. Also, you see, we cannot give a figure for most of them for statistical purposes.

So much for the methods of measurements which have been used in most trials in this country. In my experience they are by no means satisfactory, and we are all searching for improvements.

Fig. 4. An alternative has been used in some recent trials and that is to assess by placing the patient in a work capacity range and seeing if he rises or falls from that category during the trial. With this method there must be considerable improvement or deterioration in order for a patient to change from one category to another. It may be that this type of assessment though comparatively easy to carry out and free from the inaccuracies of more detailed measurement is too severe a test for a new drug.

Frequently experience is required before the optimal method of using a new substance is worked out. Such an assessment demanding major degrees of change might eliminate a useful drug or method of treatment which had not been given in the best way. Perhaps that would not matter, as there are so many new drugs, but it might be important. If this method is used in a long-term clinical trial the fourth group would hardly be relevant, for in these patients there is so much permanent structural damage that it is very unlikely that their condition could be improved.

<table>
<thead>
<tr>
<th>Grade</th>
<th>Definition</th>
<th>Remarks</th>
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<tr>
<td>I</td>
<td>Fit for All Normal Activities</td>
<td>Full employment in usual work</td>
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<td></td>
<td></td>
<td>Full house duties</td>
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<tr>
<td>II</td>
<td>Moderate Restriction</td>
<td>Usual employment with modifications</td>
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<td></td>
<td>Light or part-time work</td>
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<td>All housework save the heaviest</td>
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<td></td>
<td>No dependency on others</td>
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<tr>
<td>III</td>
<td>Marked Restriction</td>
<td>Only very light work or light</td>
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<td></td>
<td></td>
<td>housework</td>
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<td></td>
<td></td>
<td>Some degree of dependency on others</td>
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<tr>
<td>IV</td>
<td>Confined to Chair or Bed</td>
<td>Not capable of any work</td>
</tr>
<tr>
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<td>Completely dependent on others</td>
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Fig. 4. Assessment of work capacity range
In the first group the difficulty is the term 'usual employment'. This involves factors quite outside the medical condition of the patient. For example, if a man who developed arthritis was doing heavy work, and if there was the smallest degree of structural joint damage it is as a rule impossible for him to return to heavy work. On the other hand, if he was doing a clerical job he might manage the work even with a slight disability.

In the second group the first difficulty is the term 'with modifications'. This may depend on the good will of his employer and such factors as the length of time he has worked for a particular firm and the degree of his skill in doing the work.

Another factor here is the state of national employment. If the employers are short of labour they will tend to use a man even if some slight disability is present, whereas if there is local unemployment they will only use the minimum of disabled persons necessary to comply with the law.

And so conditions other than medical ones may play a large part in determining the results of a clinical trial using this method of measurement.

Fig. 5. A third method of assessment in long-term trials has been put forward by Dr. John Glyn. Here all the measurements are expressed as percentages of total disability—objective joint involvement includes the number of joints involved compared
to the total in the body, the degree of tenderness and any limitation of movement. Activities of daily living, perhaps the most important assessment in arthritis comprises the speed and ability of dressing, walking, working, eating, travelling, getting in and out of a bath and climbing stairs. Each is graded from 0 to 4 and the points added up for a total. Functional tests include climbing on to a chair, kneeling, hopping, arm flailing, and the strength of grip. Systemic and laboratory signs include weight, degree of anaemia, sedimentation rate and other pathological tests and the radiological assessment comprises the amount of erosion, osteoporosis and structural damage.

Such an assessment takes time, perhaps an hour for each patient, and so can only be done every few months. It has much to commend it as it gives a good all-round picture of the effect of the disease, and the change of that effect on a particular patient. However, each measurement should be done by the same assessor and this may not be possible in a large controlled trial. In addition to this arbitrary figures are allocated for such measurements as speed of dressing, which cannot be accurate unless the normal is known for the particular patient. These figures may be handed to the statistician and ‘blown up’ to give an entirely false sense of accuracy.

Fig. 6. A fourth method of measurement has been put forward by Dr. John Lansbury of Philadelphia.⁶

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**Fig. 6.** Lansbury's systemic index

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He has divided his measurements into a systemic index and an articular index.
The systemic index is an average figure for a number of measurements including
the duration of morning stiffness, the hours after rising before the onset of fatigue, the
number of aspirin tablets needed each day, the grip strength and the erythrocyte
sedimentation rate. Having given each of these a figure he converts them into a
percentage of their average magnitude in untreated patients.

He claims this average of the systemic index is analogous to the fever in typhoid,
the blood sugar in diabetes and the haemoglobin in pernicious anaemia.

Although this is undoubtedly an ingenious concept and I have no doubt in the
author’s hands is satisfactory, it suffers again from the danger that arbitrary figures
are given to measurements which cannot be accurately determined. For instance,
physicians dealing with rheumatoid arthritis recognise that morning stiffness is one of
the commonest and most important symptoms of the disease, and Dr. Lansbury has
included this in his systemic index. However, it is entirely subjective and so if it is
allocated a figure as a percentage it may well be loaded with an unwarranted accuracy.

The fact that there are in current use at least four different methods of measuring
rheumatoid arthritis will show you that the position is not yet satisfactory. I have
taken this disease as an example, but the same criticisms occur in relation to other
chronic diseases. In so many of them the measurements which are available at the
present time are mainly subjective.

Because of this I am sceptical of accepting without some reserve the results of
a long-term trial in a chronic disease, even though it is sponsored by an august body.

In conclusion I would say that our criteria for the measurements in chronic
disease are satisfactory for answering the first two questions which I postulated. We
can decide whether the method of treatment will have any effect on symptoms and
signs and whether it will effect a cure.

With regard to the third question. If the method is not curative is it worth
using for long-term or indefinite treatment? Here I believe at the moment we are
on less sure ground. Our criteria of measurement in this situation still leave room
for considerable improvement.

This is an exercise which is comparatively young and with more experience of
evaluation of chronic disease better criteria will be evolved. The clinical trial with
controls and with statistical evaluation is undoubtedly a step forward from the old
method of the clinical impression, however experienced or unbiased the observer.

There is no doubt that the introduction of such trials has resulted in attempts to
improve the measurements in chronic diseases. This will eventually result in the
accurate assessment of new methods of treatment. Important as this is, the emphasis
placed on objective measurements has already resulted in more careful and accurate
studies in these chronic diseases and has already produced new observations on the
natural history of conditions such as arthritis.

References

1 Copeman, W. S. C., Savage, O., Bishop, P. M. F., Dodds, E. C., Goulieb, B., Glyn, J. H. H., and Kellie, A.

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DISCUSSION

The Symposium discussed matters arising from the papers presented at the morning session.

Seasonal variations

Dr. D. A. K. Black: How does one deal with a disease in which there are important seasonal variations? In looking at one of the slides, it was not clear to me that the possible effect of seasonal variations had been excluded or allowed for.

Professor J. W. Crofton: Where there is a seasonal variation or likely to be a seasonal variation in a particular disease, it is important to arrange that patients are admitted to trial fairly evenly through the year. It is the only way to deal with the problem in a long-term trial.

Dr. J. G. Scadding: The trial of cortisone and prednisolone in chronic asthma referred to by Professor Crofton (p.17) illustrates that a trial can answer only the question which it was designed to answer. I gather that in that trial you had the patient for one month on cortisone and one month off. No doubt it was valuable in giving an answer to whatever question it was designed to answer, but this was a very different question from that which the M.R.C. trial was designed to answer. The latter trial was designed to answer the question whether, as long-term treatment, cortisone was a good thing for the general run of cases of chronic asthma. This question is very different from any which could be answered by a trial where patients were kept on the treatment for one month and then were off the treatment for one month. Any deterioration taking place in the month off treatment might well be due to the withdrawal of the cortisone. These patients could not properly be used as their own controls for the month in which they were on the treatment.

Professor Crofton: I do not want to go into the trial in great detail, except in so far as it illustrates the value of a blind trial in comparing the progress of patients on and off treatment. The results of the trial are not relevant to the present discussion.

Dr. Scadding: But you must examine very carefully what questions a trial could possibly answer before drawing any general conclusion from it, especially if the trial concerns the value of treatment for a condition with such variability as chronic asthma.

Behaviour of controls

Professor R. Cruckshank: I should like to make one or two comments about controls. Both Dr. Scadding and Dr. Crofton seem to accept that if a drug produces what they call highly dramatic results, a control is unnecessary.

I have very strong recollections of the first trials of the sulphonamides in puerperal sepsis by Colebrook. The results seemed to be very dramatic and they were accepted as indicating that the sulphonamides were effective in treating all degrees of streptococcal puerperal infection. But on making an analysis of our severe streptococcal infections we found that in the previous three or four years the percentage of fatalities had been falling steadily. If we accepted that kind of graph at its face value, we should have said that whether we gave sulphonamides or not there would be a steady fall in the number of patients dying from streptococcal sepsicaemia. Because of that, it seemed to us wrong to accept, without a properly controlled trial, that sulphonamide was as effective as Colebrook and his colleagues had claimed.

Clinical impressions should not be disregarded. I was associated with the serum treatment of lobar pneumonia in Glasgow and after treating thirty to forty cases two very experienced physicians were convinced that the new treatment was effective, although the statistician said significant results could not possibly be claimed on so few cases.

Professor S. Alstead: In dealing with the behaviour of controls, I should like to remind you
of the opportunities which occur from time to time of carrying out clinical trials on a solitary patient where a disease lends itself to this procedure. A trial of the suppressant effects of certain common remedies against coughs was undertaken in Glasgow a few years ago. The patient was most cooperative and allowed the test to go on for a considerable period of time. In brief, the circumstances permitted our applying a stimulus to the laryngeal mucosa while the patient was under the influence of various drugs. When the first batch of results between drugs A, B and C were scrutinised, certain conclusions were drawn, but it was thought wise to repeat this series of tests on the same group of drugs over a period of several months. We were not surprised to find that the results justified current views about the value of cough suppressants. On the other hand we had to record that the apparent effectiveness of the control material as a cough suppressant increased from one series to the next. The periods of testing were necessarily at different seasons of the year, but it seemed unlikely that this provided an explanation of the phenomenon.

Biological controls

Professor R. Cruickshank: Sometimes one can use what one might call a ‘biological control’, if one knows precisely what happens from a large series of cases. In a penicillin trial in diphtheria we had only a limited number of cases, due to the disease having largely disappeared. We were anxious to find out whether penicillin got rid of the infecting organisms more quickly than they would have been got rid of under ordinary conditions.

In one series of sixty-five penicillin treated cases nose and throat cultures were taken at weekly intervals and we had a biological control from an earlier and much larger series which showed a gradual disappearance of diphtheria bacilli. In the treated series penicillin in fact helped to eliminate the organisms much more rapidly than was the case in the ‘biological control’ group.

Dr. J. G. Scaddino: I feel that the example of the so-called biological control is open to some criticism. Is there any reason to suppose that the organisms being treated with penicillin, at the time penicillin was used, were not behaving rather differently from the way in which they behaved in the earlier period?

Permission to carry out trials

Dr. A. H. Douthwaite: From whom should we get permission, if it is necessary to get permission, to carry out these trials? You suggested, sir, that we should ask the Governors of the Hospital. In my view it is no business whatever of the Governing body of the hospital whether clinical trials are carried out and I should not dream of asking permission. Once you put that responsibility on to a lay body you will find that you run into endless difficulties and that your work is hampered all the time by the fear that there would be some legal action if something went wrong.

The responsibility in my view is entirely on the clinician. It rests between the research worker and the patient.

The Chairman: I did not mean to convey that I thought that the clinician should inform the institution or the patient on all occasions. Much depends on how extensive the trial is whether you consult institutional authorities. If you have a very extended trial which may require extra laboratory work and which may increase the cost of administration, I think you would probably have to consult them.

Dr. J. G. Scadding: I agree, in general, with what Dr. Douthwaite said about consulting the Board of Governors, but with some reservations. If a trial does not involve any change in the organisation of the hospital or in the numbers or types of patients admitted, there is no need to inform the Board of Governors, and in relatively simple trials I have not done so. If a trial involves making special arrangements, admitting special patients and possibly taking over certain wards or beds, and extra laboratory work, the Board or Committee of Management should be informed.

Informing the patient

Dr. A. H. Douthwaite: Should we inform the patient that a clinical trial is being carried out? In my opinion this should not be done because it introduces bias in the mind of the patient. It might strike fear in his heart. If anything goes wrong, quite independently of the drug, the patient will immediately assume that it is as a result of the experiment, and legal complications will arise.
DR. J. G. SCADDING: In my paper I was careful to say that the patient must go into the trial willingly. I think the question of how much you need ethically to tell the patient depends very much on what it is proposed to do. If it is proposed to do anything to the patient which involves him in unnecessary discomfort, I think he should be told that observations are being made. You can avoid the use of the word 'experiment' by saying that you are making special observations. The word 'observation' is very useful when talking to patients.

If the patient is being treated by the best possible means and what is proposed does not involve him in any danger or discomfort, then I do not think that it is necessary to tell him that he is being specially observed.

Legal position of volunteers

DR. A. H. DOUTHWAITE: What is the legal position when we have perfectly healthy volunteers? You say, 'Here is a new drug. As far as we know, it is non-toxic. It has been tried on animals. We want to know whether you will take it.' Supposing when it is tried on healthy volunteers some toxic effects arise. What is the legal position in respect of the volunteers, and is it altered according to whether they are paid or unpaid volunteers?

Placebo reactors

PROFESSOR S. J. HARTFALL: Why is it that in the control series we always get 15 to 20 per cent or even 33 per cent who react to the inert substance? What is happening in those people? Is it just a question of psychology and superficial suggestion or is there more in it than that? Is it something to do with the psychological type and the emotional stability of the patient whom we have selected and should we have the people we select assessed in terms of that particular function, or is it something deeper than that? Does the sticking in of a needle and injecting normal saline have some effect comparable with the injection of A.C.T.H.? Does this and even simpler procedures induce an alarm reaction?

DR. J. G. SCADDING: I have always taken the improvements which one gets in control groups to be due to the natural variability of human disease, except in those cases where there is known to be a strong psychological factor in the disease, as in asthma. We all know that with any new treatment for such diseases, many patients improve.

PROFESSOR R. CRUICKSHANK: It seems to me that an 'injection' by itself is something which we ought to take into account and in certain types of disease it can be important. In a trial of autogenous vaccines in asthma, half the patients received carbol-saline injections. At the end of the year 60 per cent getting vaccines were benefited and 56 per cent on carbol-salines were similarly improved. It is obvious that the injection therapy did good in both cases and that the mere psychology of giving injections was valuable.

DR. SCADDING: I suggested that we might be in ethical difficulties in giving intra-muscular injections of inert substances. I think Professor Cruickshank will agree that there is an ethical difference between giving a patient, who is gravely ill with a serious disease, a series of painful intra-muscular injections twice daily over two or three months, and, on the other hand, taking an ambulant patient who is not gravely ill, admitting him to a trial where he knows what is happening and giving him a subcutaneous injection once or twice a week. Many of these ethical considerations are matters of degree. I think the criterion for deciding whether you think the trial justifiable is whether you would feel willing to go into it yourself.

DR. D. F. O’NEILL: Professor Hartfall raised the question of patients reacting to a placebo. Some work has been published which points to the existence of the population of a group of people who react strongly to a placebo—the 'placebo-reactors'.* These reactions are not confined to reports of vague, subjective changes; they may involve almost every organ and system in the body. Quite dramatic changes in mental and physical state, both for the worse and for the better, have been observed. We do not as yet know what proportion of the population belong to this placebo-reactor group, nor what personality traits predispose to an unusual reaction, except perhaps undue suggestibility; but quite plainly if we are trying to appraise the effects of any drug, it is essential to make

some kind of estimate of how many placebo-reactors there are in the series of patients being tested, or even (if this were possible) to screen them out from the series altogether. If no allowance is made for the presence of placebo-reactors, the results of a drug trial that compares ‘patients’ with ‘controls’ are bound to be vitiated.

Throughout this meeting I have been struck by the deference shown to our colleague, the statistician, and to the value of statistics. This does, I think, reflect the enormous prestige which is accorded to ‘Science’ in our society. The ‘scientist’ is the new idol; the man in the street pays attention to the utterances of those whom he regards as scientists and seems really to believe that science can lead him into a new and better world. One need only look back on the recent history of our times to see how far this belief is from the truth; it is based on faith and not reason. I can only suppose that this curious social phenomenon has to do with the decline of formal religion. People need something to worship and what they worship now is ‘science’ and statistics. It is part of the culture of the present day that everything said by the statistician is believed to be true, and everything not passed by him is at once written off.

**THE CHAIRMAN:** How can you recognise placebo-reactors until you have done the test?

**Dr. O’Neill:** I know of no proved method of recognising them. This is a field that requires much fuller investigation. One approach to the problem would be to give an inert preparation to the entire series of patients about to be tested, and see what happens. Some will show unexpected reactions of one kind or another, and this sub-group could then be examined more closely.

When we put drugs to the test in the environment of a hospital, we must allow for the factor of mass suggestion. The physician in his white coat is still regarded by many of his patients as a magical figure. He carries great authority and prestige, and his pronouncements may influence the sick person to a degree which is almost hypnotic; hence, in some patients at any rate, the drug which he gives can produce relief and comfort even when in terms of pharmacology it is shown to be inactive. This applies particularly to drugs given by injection: anything injected into the person and above all into the blood, is certain to have emotional reverberations, whatever physical effects it may have.

**Professor J. W. Crofton:** That is the reason for having a blind trial. If our trials were purely objective there would be no need for blind trials.

**THE CHAIRMAN:** How would a statistician eliminate lactose reactors?

**Dr. I. Sutherland:** In addition to the blind comparison between a treated group and a placebo group you might need to have an untreated group to see what was the natural course of the disease and whether you were getting any psychological or other effects from the dummy treatment. If you cannot use a dummy treatment to which there is known to be no specific response, I should have thought that you might consider eliminating people beforehand who are likely to show a specific response to your dummy treatment in order to make a better dummy.

**Professor Hartfall:** If it is necessary to make some assessment of individuals going into the trial in terms of placebo reactions, ought we not to make a similar reaction assessment in the observers themselves?

**Dr. O’Neill:** There should indeed be an assessment of the observer. Similarly, all contacts between a test series of patients and their doctors must be assessed for their therapeutic value. Simply coming up to hospital and seeing a doctor, even if the doctor does no more than see the patient briefly, will have an effect which, although it will vary from one patient to another, has still to be allowed for.

**Professor Crofton:** Surely from the practical point of view it is a quantitative point. A proportion of the patients in each group may be placebo-reactors. The difference between the results in the two groups will depend on the genuine effects in the remainder. It is quite impracticable in a big trial over a period to get rid of one lot of patients and then admit another lot. They will be eliminated in the final comparison of the two groups. If a high proportion of both groups are placebo-reactors, and the drug under test has no genuine effect, the results will be similar in each group.

**THE CHAIRMAN:** Surely, if you could eliminate these people by some means you would save yourselves a lot of unnecessary work.

**Professor Crofton:** You would be able to manage on smaller groups if the differences between the groups were very dramatic, and that might be convenient. But I do not think there is any technique by which you would be able to eliminate placebo-reactors easily.

**Dr. Scadding:** That would depend entirely on the condition you are treating. If you are
interested in finding out whether given drugs relieve something which is fairly subjective, like headache, it will be desirable to eliminate placebo-reactors. But if it is a question whether a drug produces more improvement in a disease which can be assessed relatively objectively, like pulmonary tuberculosis, where X-rays can be used, you need not worry a bit about placebo-reactors. That is surely a point of considerable importance.

**Trials with children**

**Dr. O. D. Fisher:** May I ask Dr. Scadding whether he has any personal experience of conducting trials among children? If he has, does this raise any additional ethical problems or would he simply lay down the criterion of whether he would permit his own child to take part, bearing in mind that parents are not necessarily of the same mind as ourselves?

**Dr. J. G. Scadding:** I have very little personal experience of trials among children, but my criteria would still apply. The question how far one needs to take the parent into one's confidence would depend on the sort of thing one proposed to do. If one were trying two alternative treatments against each other, each of which had a good reputation, no one would think it at all necessary to make a statement that controlled observations were being undertaken. If one were trying something entirely new, particularly a prophylactic measure, some general statement would be necessary from an ethical point of view.

**Criteria for groups**

**Dr. I. Sutherland:** Dr. Savage suggested that if you are merely observing the presence or absence of a particular quality in an individual—whether he can walk freely or not—this is of relatively little value to the statistician as an assessment. I think that that is true if you are concerned with it as an assessment in one patient only, because then your patient either has or has not got that quality and it gives you no more information about his progress than that. If you are dealing with a group of patients, however, it may be a valuable criterion for comparing the state or progress of that group with another group. You can then calculate the percentage of your patients who have obtained that degree of function and compare it with a corresponding percentage in the other group.

**Dr. O. Savage:** We have to give a figure, otherwise the statistician cannot work, and it is the question of giving a figure which raises the problem.

**Dr. Sutherland:** What is important in assessing the results of a trial is the difference between figures. If the same inaccuracies apply to both groups, then even when the absolute figures may not be accurate, the statistician is in a position to give a fair indication of whether the difference between the two figures is greater than would be expected by mere chance, and you can obtain some information from the comparison.

**Observer errors and inaccuracies of observation**

**Professor J. W. Crofton:** I should like to emphasise what speakers have said about observer errors and inaccuracies of observation. As long as your inaccuracies are not too gross and as long as they are applicable both to the control and to the treatment groups, they do not matter too much. Professor Cruickshank mentioned an error in interpretation of X-rays. Such errors are well known and it is very important when assessing X-rays in conditions such as tuberculosis that the people who make the interpretation of the X-rays should be ignorant of the treatment group of the patient. In trials which we run in Scotland we have a panel which reviews all X-rays on two independent occasions without knowing what it said the first time. If the members disagree with their first interpretation, then they look back and decide which reading is nearest the truth. We hope that in this way we can reduce the inaccuracies.

**Dr. J. G. Scadding:** I can sympathise very much with Dr. Savage in the difficulties which he encounters in rheumatism where the criteria are so largely subjective, either because they depend on what the patient says or because the observations are subjective. Where radiological changes are relevant, evidence can be collected during the course of the trial in the form of X-rays and assessed independently by panels of people who have nothing to do with the conduct of the trial and need not know to which group the X-rays they are examining belong. That is a very valuable method of assessment where it is applicable.

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Running analysis

Professor J. W. Crofton: I suggest that at any rate in certain trials there is a good deal to be said for conducting a running analysis so that you get some idea of what is happening and how the groups are differing as you go along. In this way it is possible to conclude a trial when you have enough cases to reach a definite decision.

Patients as their own controls

Professor J. W. Crofton: Reference has been made to using patients as their own controls. It is important that the order of starting either the control drug or the test drug should be randomised because there may be an effect due to the evolution of the disease.

Double blind trial

Dr. K. S. Zinnermann: I should be interested to hear Professor Crofton’s comments on a variation in a system of control which we were forced to introduce in Leeds. We sought to answer bacteriological questions on a small group of patients during the winter of 1956–57. We obtained inconclusive trends from this trial, which was a double blind trial, and we decided for the following scheme to switch round the controls, to treat the controls and to leave the previously treated patients as controls. This made a blind trial impossible because the physicians knew what they were doing. If we found that the controls in the second year confirmed the trend obtained on the other group of patients in the first year, how far would this situation affect the validity of our findings?

Professor J. W. Crofton: I do not think I can answer that because it very much depends on the criteria of successful treatment. If they were purely bacterial, presumably suggestion would not play much part, but it is very difficult to answer the question. If you decide to conduct a blind trial you must be sure that it remains blind and that you do not have one eye open!

Pilot trials

Professor R. Knox: Could we have some guidance on what exactly are the relative purposes of a pilot trial and a large-scale trial? If the pilot trial is convincing, you may argue in some cases that there is no need for a large-scale trial. On the other hand, if you start a pilot trial you may be criticised and told that you need 500 cases before you have obtained significant results. It would be useful to know what different purposes the two types of trial are supposed to serve.

Dr. I. Sutherland: I do not like the idea of pilot trials—pilot in the sense of a small controlled trial which may or may not turn out to be a large one. You should try to plan your first trial to be large enough to give a decisive answer. I am against experimental trials held to decide whether to do a full trial. With premature results you can get yourself into a position where you are unable to undertake a large trial.

Professor J. W. Crofton: I do not see how we can possibly start off a control trial unless we have done a pilot trial. We must establish at least an a priori case for the new drug and also an indication that it is not going to be unduly toxic.

Dr. J. G. Scadding: In my paper I touched upon this matter of pilot trials only by saying that it is a prerequisite of a formal trial that preliminary observations have established an a priori case. I do not think these preliminary observations need necessarily be in the form of a formal pilot trial. But there must be sufficient clinical observations on patients to indicate that there is something to be investigated, to show that there is an a priori case that the drug has some beneficial effect and to show that there are no unforeseen toxic effects or unforeseen snags in the administration of the drug.

I would call these preliminary observations rather than a pilot trial. If you are to go to the trouble of organising anything which can be called a controlled trial, you might as well organise it so that it can be developed into the final trial.

Intensive observations

Professor R. Knox: To what extent does intensity of observation on a small number of patients, giving fuller information of greater detail, counterbalance the rather more diffuse and perhaps rather less frequent observations on a larger number of cases?
Dr. I. Sutherland: I believe that it makes a great deal of difference. If you are able to assess the effects precisely and in great detail you can manage with a smaller number of patients than if the measurements are less precise.

Dr. J. G. Scadding: Surely the relative role of trials involving the intensive observation of a small number of people and of trials involving less intensive observation of a large number of people depend on what you want to find out and the kind of problem which you are trying to solve.

If the problem is whether a given form of treatment produces a favourable effect on an acute disease, which we know from previous experience to run a fairly well-defined course and have a fairly constant mortality, an intensive investigation of a small number of cases will give the answer. But in dealing with something less precise, because of various limitations such as difficulty in definition or natural variability of disease, then a larger trial will be needed. I do not think you can readily compare the validity of those two kinds of trials because they are applicable in different circumstances. In designing a trial one should decide how precise are the observations which one is likely to be able to make, and on that basis one should decide what sort of trial is likely to be necessary.

Dr. D. A. K. Black: It has been suggested that when the number of patients available is limited one might get more information by making intensive observations on each patient. It seems to me more important to spend effort on precise clinical characterisation of patients admitted to the trial rather than on simply multiplying the observations carried out on each patient during the trial.

Dr. Sutherland: The number of patients you need in the trial is affected not merely by the facts that Dr. Scadding mentioned—the precision with which you are able to assess the disease in the first place and the precision with which you are able to assess progress—but also by the size of the difference in the effects which your two treatments have. That is perhaps the major determining factor. If you are dealing with a treatment which has a very substantial effect in comparison with the control series, then you will need fewer patients in the trial than if you are dealing with a very small difference. However big the effect, there will be a lower limit to the numbers in the trial below which you will not be able to go and still be able to distinguish a beneficial treatment from a chance observation.

Conclusion

At the request of the Chairman, Professor S. Alstead concluded the morning session of the Symposium.

Professor Alstead paid tribute to the start made with discussing the problem of clinical trials and said:

'I wonder whether I might refer back to the question of pilot trials. It seems to me that there is something to be said for establishing what Dr. Scadding described as a prima facie case before embarking on an elaborate and well-designed clinical trial. As you yourself said earlier, sir, the amount of work put into the pharmaceutical industry in all its branches with a view to creating new synthetic remedies is enormous. We as clinicians have to recognise that in our practice we constitute the bottleneck of this great enterprise in that there are so few professional men with the necessary training, aptitude and genuine interest in this kind of work. Yet it is obviously extremely important: one has only to look at the medical world and consider how humanity will progress in its constant battle against disease.

Do we not tend to take too narrow a view of our obligations when we simply consider how we are getting on in this country. We may say that mortality in Britain has been appreciably reduced because we have an excellent pharmaceutical industry working in close liaison with the British medical profession, and the same can be said of America and other countries. But if we take a world view of our commitments and of the obligation of the medical profession towards humanity as a whole, it is reasonable to say that we have merely touched the fringe of the problem, and that it is urgently necessary to bring together pharmacists from industry and clinical scientists so that they can exchange ideas and be mutually helpful.

It is highly important that we should explore together the ways of making the best use of our resources.'

The Symposium adjourned.
STATISTICAL ASPECTS OF CLINICAL TRIALS

A paper on ‘Statistical Aspects of Clinical Trials’ was presented by I. Sutherland, M.A., D.Phil., of the Statistical Research Unit, Medical Research Council, London.

Dr. Sutherland: Statistics, or perhaps I should say quantitative thinking, permeates clinical trials to such an extent that I am uncertain where this contribution should begin and end—unless it begins with ‘aims and ethics’ and ends with ‘finance’. I propose therefore to illustrate first how statistical concepts enter to a greater or less degree into each stage of the planning and execution of what I may call the classical clinical trial, and then to describe some of the variants and developments which have been increasingly used during the last few years.

The clinical trial has developed from two basic principles—that the effects of one treatment can be evaluated only by comparing them with the effects of another treatment, and that, because human beings differ in their responses, several patients must be observed on each treatment if the comparison is to be adequate and the conclusions convincing. Because the idea of comparison is fundamental, I shall refer to comparative trials rather than controlled trials, as this avoids the misinterpretations

ESSENTIALS OF A COMPARATIVE TRIAL

<table>
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A          B

TREATMENT   MANAGEMENT OBSERVATION

TREATMENT CHANGE

DEFAULT FROM OBSERVATION

ASSESSMENT OF EFFECTS

ANALYSIS

REPORTING

INITIAL SIMILARITY ENSURED

... BLIND IF PRACTICAL

... SIMILAR TO AVOID BIAS

... FAILURE OF TREATMENT OR SOURCE OF BIAS

... SOURCE OF BIAS

... OBJECTIVE MEASURED SUBJECTIVE BLIND
of the word 'controlled' which were referred to by Professor Crofton. The aim of a
good clinical trial is simply to make such a comparison, say between an 'old' and a
'new' treatment, used on different series of patients, as precise and as informative as
possible.

This diagram shows the various stages, and indicates essential points to be
observed, in the course of a comparative trial. I should like to comment upon each
of these from the statistical standpoint. The first two stages, which are concerned
with specifying the purpose of the trial, and deciding what treatments are to be
compared, in what type of individual, and in what type of disease, may seem at
first sight to be purely medical, with no place for statistics. I shall refer to these
again, however, since statistical requirements later in the trial often have important
repercussions on these preliminaries.

The next point, the recruitment of enough subjects, raises the question which
the statistician is most frequently asked in connection with any clinical trial, and
to which it is almost impossible to give a simple answer. The only response to the
enquiry 'How many patients shall we need?' is another question: 'What would
you regard as the minimum benefit of the new treatment over the old which would
justify its widespread introduction?' If the clinician can be pinned down to some
numerical indication of what he would regard as a result of practical importance,
the statistician has some hope of ensuring that this result, if it is attained (or exceeded),
will also be of statistical significance (that is, unlikely to be due to chance). The
trouble is that neither the clinician nor the statistician can really answer their
respective questions properly until the results of the trial are known, and by then
the answers are unimportant. The statistician, however, if he errs, must endeavour
to do so on the side of larger numbers. A trial which does not give a decisive answer
is often worse than no trial at all. Impressions of the value or otherwise of a new
treatment will inevitably be formed from the equivocal results, and an ethical
situation may well be created in which any further comparative trial involving
the treatment is quite impracticable. As far as possible, one must avoid the
situation in which either a poor treatment gains currency, or a good one is
condemned, on insufficient evidence; indeed, it is for this very reason that the trial
is undertaken.

Next comes the crux in the design of a clinical trial—the allocation of patients to
the treatment series. Since Professor Crofton has dealt with this aspect very thoroughly,
I will remind you only that unless the treatments are used on similar series of
patients with similar disease, managed in all other respects in the same way, the
comparison will be less precise, and probably very much less informative, than we
wish it to be. In particular, although the results may in fact be quite correct, they
may be largely unacceptable to other workers because of the possible alternative
explanations for the findings. It is for these reasons that, save in exceptional circum-
stances, the old and new treatments must be studied concurrently, and the choice
of which patient is to receive which treatment must not be left to individual preference
—requirements which are now accepted by clinicians with varying degrees of
enthusiasm.

The effect of a properly handled allocation procedure is to provide two series
of patients, ready to start treatment, which are similar in all respects, within chance.
limits. It is desirable to compare the series, at the start, in characteristics such as age, or extent of disease, which may affect the response to treatment; there may occasionally be a large chance difference between the series which will have to be taken into account in assessing the results. As Professor Crofton pointed out, disparity of this kind can often be avoided at the allocation stage—for example, by having separate balancing allocation lists for different types of disease, to ensure equal representation of each type in the two treatment series.

Having obtained two similar series, which are to differ only in their treatment, no further differences must be allowed to enter the comparison. The management of the patients, any ancillary treatments which are given and the methods by which the results are assessed, must all be the same for patients in the two series. A detailed routine for the management and observation of patients, both before and during treatment, is usually laid down in advance in a ‘protocol’ for the trial. Although this degree of specification is regarded as irksome by some clinicians, it is of considerable assistance in avoiding bias in the handling of patients, as well as ensuring the necessary observations on their progress.

Another valuable safeguard against bias, where it is practical, is not to let the patients know which of the treatments they are receiving, by supplying them in units of similar size, colour, appearance and taste—the trial then being described as ‘blind’. It is of equal value to keep the clinician also in ignorance of the treatment, this representing a ‘double-blind’ trial. I once took part myself in what I suppose was a ‘triple-blind’ trial, and found myself analysing the results in ignorance of whether ‘A’ or ‘B’ was the placebo. The exercise was interesting, but not unduly exacting, since the results were practically the same in the two groups. In many trials, however, the identity of the treatments—or at least the fact of a difference—cannot be hidden; one treatment may have to be injected, for example, and the other given by mouth.

It is important to realise that blind treatment does not in itself provide a complete safeguard against differences in management. During the Second World War, the U.S. Navy was anxious to determine the possible value of a new anti-seasickness drug (Tucker, 1954). ‘It was decided to put two lifeboats to sea in rough weather, and give the drug to the men in one boat, and in the other placebos. Care was taken to have the two boats of the same kind and size, manned by crews of the same size and weight, under the direction of men of similar skill and experience’, and, presumably, sent out in the same storm. ‘Preliminary results were encouraging, when it was ascertained that the crew of Boat A, given the drug, observed significantly less seasickness than the crew of Boat B, given placebos. Aware of the possible pitfalls of such a study, however, it was decided to repeat the experiment, this time giving placebos to the crew of Boat A, and the drug to the crew of Boat B. The results were completely contradictory: the crew of Boat A, given placebos, reported significantly less seasickness than did the crew of Boat B, given the drug. The inference was that there must have been more difference between Boats A and B than between the drug and placebo, and so it proved. On careful ‘dissection’ it was ascertained that a leading air-tank in Boat A had permitted water to enter, lowering the boat in the water so that it rode in rough seas in a different manner than did Boat B.’ This source of bias should clearly have been eliminated in the planning.
of the enquiry, by allocating the drug to half the crew of each boat, chosen at random, and the placebo to the other half.

In any trial, but particularly in the case of long-term treatment for a protracted disease such as tuberculosis, changes of the prescribed treatment may occur. Such changes may indicate a genuine failure of one of the treatments, perhaps due to a lack of clinical effect, or to excessive toxicity, which makes it essential for the clinician to depart from the protocol in the interests of the patient, but they may also reflect a lack of faith in one of the treatments, which may not really be justified. Substantial losses from the latter cause may disturb the similarity of the residual series of patients, and consequently bias the assessment, or even make it impossible to draw valid conclusions. The same applies to losses from observation, whether these are complete, the patient refusing to co-operate further, or partial, when necessary observations on the progress of the patients have been missed. Both sources of bias are less potent if treatment has been blind. But the risk emphasises the general principle that, once allocated to treatment, every patient must be accounted for in the results, and changes of treatment or losses from observation kept to the unavoidable minimum. This is another example of the importance of careful planning at the outset. When considering aims and ethics, the nature, dosage, and duration of treatment, as well as the types of patients and disease to be included, thought should be given to the need for as complete a series of observations as possible. This should not merely ensure a successful trial, but is likely also to result in the comparison of more practical methods of treatment.

Whenever possible, objective, and preferably measured, assessments of the progress of patients should be used. It is, however, probable that these will have to be supplemented by subjective assessments. For a valid comparison between the treatments, these must be made in ignorance of the treatment. Sometimes the patient is asked for subjective reports on the effects of the treatment. The results were recently reported of a trial of a reputed anti-smoking drug (lobeline) (Manchester Guardian, 1958a). By the end of a fortnight's course of four tablets a day, one-quarter of the sixty volunteers in the trial had stopped or drastically reduced their smoking and rather more than half were smoking less, the remainder reporting no effect. The volunteers, however, were unaware that only one-third of them were receiving lobeline, the others being given either copper sulphate or a placebo. Moreover, success or failure to stop smoking was not affected by the type of tablet. Clearly one could have placed no reliance on the results if each volunteer had known in advance what treatment he was being given; as he did not, the virtues of the anti-smoking drug were reliably shown to be largely psychological.

A clinician, too, may have to make subjective assessments. If the identity of the treatment is known to the clinician responsible for managing the patient, another clinician should make the assessment; it is, for example, standard practice in trials of tuberculosis treatment to use one or more independent observers to assess changes in radiographic appearances, in ignorance of the treatment of the individual patient.

Of analysis I need say little, as this is usually, and thankfully, regarded as the statistician's private domain. Tabulations and statistical appraisal of the results will also inevitably form an integral part of the final report; and despite their logical basis, the preparation of clear tables and a lucid text is a surprisingly difficult art.
It must be emphasised, however, that should the results show a clear-cut superiority of one treatment over another, it is still incumbent upon the investigators not to accept this result without question. Each step of the trial must be reviewed to see whether there could be any difference between the series, other than the difference of treatment, which could account for the results obtained. As Haldane (1927) has put it, "a good half of most research work consists in an attempt to prove yourself wrong".

I should like now to describe briefly some of the main variants of the basic pattern which I have just outlined.

1. Although I have been speaking, and shall continue to do so, in terms of therapeutics, there is no difference in principle in a comparison of prophylactic agents—the same precautions have to be taken at each stage of the investigation.

2. A trial may, of course, compare more than two treatment regimes.

3. Ancillary problems may be studied at the same time as the main comparison between treatments, without increasing the numbers in the trial. For example, the effect of differences in dosage rhythm may be studied by putting half the patients (chosen at random) in each treatment series on one of the dosage rhythms, and the other half on the other. The results can then be analysed, either as a comparison of the treatments, or of the dosage rhythms, and there will also be some information on whether the choice of rhythm is more important for one of the treatments than the other.

4. A similar design may be used to investigate the possibility of synergism or antagonism between two drugs.

5. It is usual to think of treatment in terms of specific drug therapy. Trials are increasingly being undertaken in which the main comparison is of other aspects of treatment. I am at the moment concerned with two investigations of this type in the field of tuberculosis. In the one trial, the effects of different durations of the same drug therapy are being compared, and in the other, treatment in sanatorium is being compared with treatment in the home, again using the same drug therapy. As effective drug therapy becomes established for a particular disease, attention is bound to be directed towards these more practical problems of administration.

6. Another important trend is the increasing realisation that after the period of prescribed treatment there should be a period of careful follow-up. The immediate results of treatment may not be maintained, and this can only be discovered by a further period of observation. One example arises with the use of A.C.T.H. and cortisone in rheumatic fever; the decrease in erythrocyte sedimentation rate is more rapid with the hormones than with aspirin, but the differences disappear in the course of a period of follow-up without drugs (Medical Research Council and American Heart Association, 1955). Another example is the transient weight gain in tuberculous patients treated with rest in bed, compared with those allowed to continue at work (Tuberculosis Society of Scotland, 1957). As during the period of prescribed treatment, care must be taken during such a follow-up to maintain an absence of bias in treatment, management, and assessment between the series.

7. The precision of assessment can sometimes be enhanced by pairing patients who are similar in initial disease-state and in other factors likely to affect the response to treatment, assigning one of the pair at random to each of the treatments. The
relative progress of the members of each pair then provides an assessment of the benefits of the one treatment over the other. If pairing is not possible at the allocation stage, some form of later matching of patients on their pre-treatment condition is an acceptable alternative. This method has been used to compare the response of tuberculous patients in Britain and in Uganda to similar drug therapy (Fox, et al., 1956).

8. The precision of assessment will be further enhanced if it is possible to apply the two treatments serially, or simultaneously, to the same patient, and to assess their effects separately. This is a logical extension of pairing or matching similar patients—the aim of both approaches being to compare the two treatments on closely similar clinical material. The circumstances in which two separate treatments can be given to the same patient are unfortunately limited; many treatments are systemic, and time, or the first treatment, may cure the disease before the second treatment can be tried. But this valuable approach can be used in the treatment of symptoms (as in asthma), or with local treatments (say for skin diseases), or in studies of local reactions (such as tuberculin tests).

9. Finally, a relatively new technique which appears ideally suited to the clinical trial is the sequential approach, in which each result is scrutinised as it is obtained, and a decision then made on the accumulated results whether to continue the trial, or to accept the treatments, either as equivalent, or as different, in their effects, and to stop the trial (Armitage, 1954). The intake of suitable cases into a trial often proceeds quite slowly, and the prospect of being able to call a halt as soon as a definite result has been obtained is attractive, especially as the average sample size required is less for the sequential than for the corresponding classical procedure. There is unfortunately one main difficulty. The interval between the start of treatment and the assessment of the results for each patient may be much longer than the average interval between the intake of successive patients. If this is so, an unnecessarily large number of patients will have been admitted to the trial by the time it is possible to stop the intake. This may sound like an academic point, but with many diseases, such as tuberculosis, it quite effectively precludes the use of sequential methods for determining the size of the investigation. These methods, however, should be used if it is intended to scrutinise the results as they accumulate. Although this approach has been used only occasionally in the medical field so far (Kilpatrick and Oldham, 1954; Newton and Tanner, 1956; Snell and Armitage, 1957), in part because of this major difficulty, it will undoubtedly find more use as it becomes better known.

References

CLINICAL MANAGEMENT

A paper on ‘Clinical Management’ was presented by F. Dudley Hart, M.D., F.R.C.P., of Westminster Hospital, London.

Dr. Hart: The ethical side of the assessment of therapeutic agents in man has already been very adequately discussed at this morning’s session. Nevertheless I remember a very distinguished clinician opening a debate on this subject some two years ago with the remark that one could not be a good physician and undertake clinical trials. If this be so then clinical trials, which are today essential to medical progress, must be conducted by bad physicians. However, every time this particular clinician whom I have quoted prescribed a new drug he was, in fact, making an experiment on one patient without a control and assessing the result in a highly uncritical manner. Whether we like it or not it is a fact that all new drugs must, after the initial work in the laboratories is finished, be assessed in the wards and out-patient clinics on patients. Before World War II controlled clinical trials were rare in this country, and they are still not very common. The true therapeutic value of many substances is still unknown in spite of many years common usage; gold salts in rheumatoid arthritis are an example. To consider the clinical trial unethical and bad medicine is to hold back the progress of therapeutics in this country, and to make life extremely difficult for chemist, biochemist, bacteriologist and pharmacologist, who, after taking a new discovery as far as they can by careful and critical work in the laboratory then find the cruelest of clinical assessment or even none at all on the patient himself at the end of the line. As a profession we have been rather neglectful of this important duty which we cannot delegate to others; happily the Medical Research Council, the Nuffield Foundation and the Empire Rheumatism Council, to mention only three organisations, have all taken prominent parts in therapeutic assessments, and some of their controlled trials have been examples to the rest of the world.

We have as a nation the reputation of being overcautious and hypercritical, even somewhat nihilistic in our approach to new products; these qualities in this field of medicine and therapeutics amount to solid virtues and fit us perhaps particularly well for the task of therapeutic assessment in the wards and out-patient clinics.

Every trial carries its own particular problems. In the time at my disposal it is impossible to deal with long term and short term, single centre and multicentre surveys in severe, moderate and mild disorders. The question of controls has already been very adequately dealt with this morning by Prof. Crofton. All I will attempt to do is to underline certain general principles which apply in fair measure to all.

General Principles—The Golden Rules

Before embarking on any trial there are certain rules to be rigidly observed. If I may I will illustrate each with an example taken from my own unit:

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Rule 1. There should be absolute ignorance in the ward of which is therapeutic agent and which control or comparison group. Patient, nurse, house physician and registrar—all the regular inhabitants of the ward—should not be in the secret. Better still, they should not be aware that a trial is in progress, but this raises other ethical questions. Today so many new drugs appear every month that patients and staff are not surprised if told there is to be a change from tablets A to tablets B, and so long as there is no enthusiasm or emotional response on the part of the staff little or no notice is taken of such changes. There must always be someone readily available who has knowledge of which substance is being used, either myself—providing I am taking no part in the assessment of the patient—the chief pharmacist, or a colleague in other wards or in another hospital or school. On one occasion in one of our trials a patient was included under a colleague whose firm was not used to the aloof attitude necessary in such trials. The patient had been on an inert substance for a few days, our intention being to get a 'base line' of symptoms and signs before starting the substance under trial. It seemed to me that the house physician on this firm disapproved of these goings on, for when I suggested that the substance in use be continued a little longer he said that the patient had made no progress and implied that she was obviously on the control substance and should now be given the 'Cure'. I appeared to think this over and then said in view of this I would probably make a change. In fact I made no such change but the patient's condition improved dramatically from that moment. Enthusiasm had clearly crept in, houseman and nursing staff had taken sides and the patient was, therefore, taken out of the trial.

Rule 2. Never let enthusiasm, or the opposite, creep in. The attitude of all concerned should be that of a judge or referee, taking no sides and being completely uninvolved emotionally. This lesson was taught us sharply in the early days of the deoxycortone (DOCA) and ascorbic acid therapy for rheumatoid arthritis. This was in November 1949; the U.S.A. was resounding with the miracle of cortisone, British rheumatoids could not get it, and demands were coming in thick and fast. Into this highly electric atmosphere came Lewin & Wassen's claim from Sweden that injections of DOCA and ascorbic acid produced the same effects but more rapidly, within ten minutes of injection of these two substances. The Cure had all this time lain on our own dispensary shelves! I read this article in the Lancet on the Friday morning it appeared. That same day in a lecture to our students, some of whom were clerking rheumatoid sufferers in the wards, I mentioned this paper, saying it would be well worth trying on our patients in the near future as it looked, judging by the Swedish claims, as if interesting results might be obtained. Little did I appreciate the missionary zeal which burns in the breast of the average medical student. On Monday, ten minutes before the round, the two injections were given to four patients. Expecting nothing whatsoever, I was aware when I entered the ward with the students of an extraordinary and electric anticipation. All the other patients were sitting up in their beds, nurses were wide-eyed and expectant, this particular rheumatoid patient stood by his bed quivering with excitement and as I approached he threw his arms high above his head saying with joy, even ecstasy, that this was the first time he had been able to do this for four years. To the astonishment of all of us he then jumped over his bed in one bound, raced to the
door, ran down the corridor and finally reappeared beaming and panting but transported. The students, patients and nurses cheered. Had we made a movie of this it would have put Hench’s cortisone film to shame.

In the out-patient clinic the following week when we gave further injections the atmosphere was that of a revivalist meeting. Patients were leaping to their feet ten minutes after injection and giving demonstrations to the others, who later followed suit. We did, in fact, make a film of one of them. It was too good to last, and as soon as we used critical methods and controls all the hysteria abated and the miracles ceased. It may have been good treatment under these particular circumstances at this time, for nobody got worse and nobody suffered any ill effects, but as an assessment of the effects of these drugs it was totally misleading. It is of interest that the written statements of some of these patients were strenuously denied some months later by the patients themselves. On being confronted with their own handwriting they said they must have been mad at the time to have written such stuff!

Rule 3 is to make only one change at a time in the management of a patient on any new therapeutic substance; any second alteration may be responsible for any change for better or worse—for instance, application of a plaster cast in a rheumatoid or change to a different analgesic. There are too many variables as it is—bad days, good days, sunny days, menstrual periods, days of friction with the patient in the next bed and so on. It is impossible to iron them all out, but variables should always be reduced to a minimum as far as is possible.

Rule 4 is that assessment on a given patient must always be by the same person. Even with the simplest method marked individual variation occurs.

Rule 5 in the assessment of any form of therapy in any chronic condition is to allow adequate time for the patient if an in-patient to be observed beforehand—giving him time to reach his base line, as it were. This applies particularly in assessment of therapeutic agents used in conditions such as arthritis and hypertension, where considerable improvement takes place on bed rest, good nursing and hospital discipline.

Rule 6 is to decide beforehand what questions it is hoped to be able to answer. To try to answer too many will often kill the trial. A statistician or one well versed in statistical methods should be consulted beforehand. The questions to be answered should be particularly carefully considered in the case of the early pilot trial, where the aim is often to see whether a given drug is worth a more elaborate trial. On the first twenty cases or so there is often some indication as to whether it is necessary to proceed to a larger trial or not. A careless assessment or, equally dangerous, a very careful assessment of the wrong factors in such pilot trials may give entirely the wrong emphasis and lead to the dropping of a potentially likely and useful substance. There is a real place for small co-ordinated multicentre pilot trials of this nature, working without knowledge of each other’s results until the end of the short trial, but they must be particularly well and carefully planned.

Rule 7 is to make measurements as accurate as possible and as often as is necessary at the same times in the day. Such measurements must be simple and, more important, they must have been used previously and the method and instruments used must have previously been assessed and found to be efficient and the
results verified when repeated by different observers. The usual measurements in use in the wards are too haphazard and too variable—wasting of a thigh or calf, for instance, is extremely difficult to measure accurately and swelling of a knee impossible by the ordinary ward methods. More important still, it must be appreciated that many so-called objective tests are in fact highly subjective and dependent on the mood of the moment and the degree of discomfort at the time. This applies particularly to function tests of various kinds.

Rule 8. In assessing the effects of a drug in any chronic complaint we make the rule that a positive result must have two components; symptoms and signs must improve after administration of substance X and must also worsen on its withdrawal. So often one has seen improvement take place within a few days of starting a new agent, but steady and continued improvement on stopping the drug shows that this is nature rather than drug at work; it is natural remission, not therapeutic response.

Rule 9. Many trials lie in the comparison of an unknown new substance with a known, well-tried efficient one. In such cases it is of vital importance to work out the correct dose ratio. The history of the past few years contains numerous instances of substances earning undeserved reputations for low toxicity purely because the dose was relatively too small or, conversely, for increased effects, therapeutic and toxic, because the dose was relatively greater than in the control group. This can only be worked out in man by clinical trial. All too often the initial dose of a new substance issued to the public is pitched too high; the therapeutic reputation rapidly won is then marred by the appearance of a host of side-effects soon afterwards, and Jekyll becomes Hyde almost overnight.

The Multicentre Clinical Trial

So far I have discussed only the single-centre trial. There is no doubt that centres which are used to such trials can conduct them more efficiently, if only because any enthusiasm there may have been for them has worn off and they are no longer a novelty, nursing and medical staff taking them as part of the day’s routine. In the arthritis beds in our unit all patients keep a daily record of the essential features of their case—pain, stiffness, analgesic tablets taken, and so on, and the physician in charge of the case makes his independent observations and investigations; this is a routine whether they take any part in a trial or not. All receive the same basic regimen and all have certain assessments made twice weekly at set times of day—joint swelling, tenderness, grip, etc. There is no change in this routine, therefore, when a new trial is started, and the patient is unaware of any change in his treatment unless the new agent under trial produces such change. In multicentre trials, however, planning has to be such as to allow for considerable unit variation, and, therefore, must be simplified to the greatest possible extent. Measurements must be standardised throughout—all units participating in the cortisone/aspirin Trial, for instance, had sedimentation rates done by the same method, all grip-meters used in another trial now under way are issued from one central source; all X-rays are read by the same radiographer using the same criteria for all. The particular value of the multicentre trial is that slight unit differences and attitudes are ironed out, and one can get a fair idea of what substance X does from
the North of Scotland to the South of England. The Medical Research Council trials of steroid therapy in asthma might be quoted as a good example.

A word of warning must be sounded. If such a trial is badly planned then the results and conclusions may be totally misleading and many centres throughout the land may take part in the production of a misleading piece of work. The august name of the organising body responsible for the trial may dazzle the reader and appear to carry a guarantee of verity; a trial organised badly by impartial seekers after the truth can be even more misleading than a more trivial work. It is farther to fall off a cliff than off a cushion.

Conclusions

1. In clinical trials no enthusiasm is allowed. Investigators must be emotionally uninvolved.
2. There must be no expectant attitude: if possible there should be no knowledge of a trial as such in the ward.
3. Repeated trials lead to better and more accurate results as the assessments become routine and cease to attract any attention.
4. Measurements must be accurate, previously well tried out and the results reproducible. They should not be too elaborate or time-consuming.
5. Small pilot trials are of great use in assessing what is to be assessed.
6. Clinical assessments and measurements on individual patients must always be by the same observer; individual interpretations vary even in the most ‘objective’ of tests.
7. In the assessment of the effects of a therapeutic substance in any chronic condition adequate time must be given for a satisfactory ‘base-line’ to be reached before the drug is started. There must be improvement on starting and deterioration on stopping such a drug before a positive result is claimed.
8. Accurate comparable dosage in contrasting two substances is a matter of trial and error. Before arriving at conclusions regarding therapeutic efficacy and frequency and severity of toxic results the comparability of dosage must be seriously considered. As the Chairman has said on a previous occasion, homoeopathy has served as a control to orthodox therapeutics for 150 years and as regards incidence of side-effects it has emerged superior.
9. Multicentre trials are a study in themselves: with many participants measurements must be standardised in all centres and identical methods and instruments used.

These are only a few random remarks concerning clinical assessment. Each trial carries its own particular problems. Each trial answers only a few questions and not necessarily the ones the reader of the report wants. Each trial must be very carefully planned beforehand and results preferably assessed by an outside, disinterested observer. Such trials are today an essential part of practical therapeutics.

I am honoured that I should have been asked to speak on this most important subject today, for never were critical controlled trials more needed than in these days of rapid therapeutic advances.
PRESENTATION OF RESULTS

A paper on 'Presentation of Results' was presented by Maurice Davidson, M.A., D.M., F.R.C.P., of Bromton Hospital, London.

Dr. Davidson: When first I was invited to take part in this symposium, I was a little uncertain as to the exact role I was expected to play. The phrase 'presentation of results' appeared to me to be slightly ambiguous. To whom were the results to be presented; in what form, and at what length? Were they intended for the medical profession only, or were they also for the information of the lay public, and, if so, with what object? Moreover, in regard to this last point, what objections and difficulties might arise out of such popular dissemination of scientific knowledge? These are some of the points which occurred to me in considering the title of my paper; and I must, therefore, at the outset make some attempt to adumbrate them, in order to arrive at a more definite understanding of what the term 'presentation of results' really connotes.

Clinical trials have become a much more frequent task in the hands of many members of our profession in the last few years, since medicine has become less empirical and more scientific in character, and since research in organic chemistry has produced so many new and complex substances to play a prominent part in the treatment of disease. To the pure clinician, especially to one of the older school, in whose mind the holistic view of medicine has, perhaps, been more completely engrained, this multiplication of modern drugs is apt at times to be a little confusing. Indeed, when we look in retrospect upon the application of pure research to practical therapeutics and consider how many once-vaulted preparations have, after a comparatively short career, been replaced by others, and, like Omar Khayyam's loved ones, 'have one by one crept silently to rest,' I think we may be forgiven if we sometimes incline to regard the appearance of the last new remedy with a certain amount of hesitation or even, perhaps, of scepticism.

I hope I shall not be misunderstood when I speak thus critically, perhaps somewhat hypercritically, of research as applied to the treatment of disease. There is, of course, no doubt that the introduction of antibiotics has changed the face of medicine as we knew it half a century ago: the use of penicillin, for example, has enabled us to save many useful lives that would otherwise have been lost. But the advent of the sulphonamides, of penicillin, and of streptomycin, beneficial though they have been, seems to have been a signal for the letting loose of a spate of new drugs which have followed in their wake; and one cannot help feeling that, although a good deal of work has been done, both in the way of laboratory experiment and also by clinical trials in order to test their action, the release of these drugs for general use has sometimes been over-hasty, and that too many patients have then been subjected to intensive treatment with powerful new substances before the full implication of their potentialities has been realised.
The career of a new remedy may be said to exhibit three main phases. When the pure experimentalist is sufficiently satisfied of the action of a drug as demonstrated in animals, and feels that the time is ripe for clinical trial in the human subject, the matter may first be submitted to a thoroughly competent and responsible body such as the Medical Research Council. This, I suggest, is an ideal method of procedure. Next comes the supply—it may be in limited quantity—of the drug to certain selected clinicians holding senior positions on the staffs of teaching hospitals, in order to obtain accurate reports, with proper controls, of the effects of the remedy in suitable cases—again a logical and reasonable step. Finally, the drug may be released on to the market whence it may be procured by the general practitioner, who, as often as not, is harried by his clients, who bombard him with urgent demands for the drug in question, though they have not read the original scientific reports and would not understand them if they had. By the time the lay public have become thoroughly aware of the existence of a new alleged remedy for a particular disease or group of diseases, the original presentation of the results of clinical trials may have become a good deal distorted, and the information which the said public receive may be very different from that originally issued to experts in the early stages of experimental and clinical trial. The ultimate distortion of the true position may be seen in the columns of the more sensational and less reliable varieties of the lay press, from which, as you are all aware, a not inconsiderable proportion of the public glean their ideas of medicine generally and form their own estimate, such as it is, of the value of remedies. I have said enough to indicate broadly the very real need for the utmost care in the presentation of results beyond the stage of tests by laboratory methods and clinical trials. It seems to me that at this point, although experts may be satisfied with results up to date to a sufficient extent to allow release upon the market, the scope and limitations of the remedies in question must still be regarded as to some extent sub judice, and must necessarily remain so until after the lapse of a considerable stretch of time, which alone, I venture to say, can be the ultimate arbiter of their real value.

Now in regard to information broadcast to the public through the columns of the lay press, I must at this point, in fairness to my professional colleagues, explain a little more clearly what I have in mind. I am not, of course, suggesting that any responsible body of medical experts which has undertaken a clinical trial of some new remedy issues a report to anyone outside the medical profession; in cases where a request for such trial has been made to the clinicians by—say—the Medical Research Council, it is to the latter presumably to which they sent their conclusions when the trial has been completed to their satisfaction. Obviously the Medical Research Council cannot deal with the problem of every new remedy suggested by the researches of the pharmacologists—the time which it is possible for the Council to devote to such investigation is clearly not unlimited. What then are the other sources of demands for clinical trials and to whom are reports or results presented? This is a matter on which I am not entirely clear, and it is an important point on which I hope to hear some discussion before we finally close our deliberations. There is nothing to prevent an enthusiastic journalist from reading articles published in medical journals or possibly from getting hold of reprints of these for his own purposes. Whatever the modus operandi, the fact remains that the lay press sooner
or later do, directly or indirectly, acquire a certain amount of information about new therapeutic measures, and publish it with a greater or less degree of the distortion to which I have already referred. Although it does not actually refer to the public press, I may, perhaps, with advantage quote one concrete instance of presentation of results in a manner which, to say the least of it, I regard as far from desirable.

Not long ago I received, doubtless in common with thousands of other doctors, a letter from a large manufacturing firm, whom I will call Messrs. X.Y.Z., enclosing an abstract of an article which had been published in a foreign medical journal and which dealt with clinical trials of a certain drug employed in the treatment of different nervous disorders. These included a considerable variety of neurological conditions, some associated with known anatomical lesions, others of a subjective nature not necessarily attributed to demonstrable organic disease of the central nervous system. The accompanying letter from Messrs. X.Y.Z., couched in language which the writer evidently regarded as ingratiating, suggested that 'of the many problems which I encountered that of the emotionally unstable patient was, perhaps, the most frequent and the most difficult to treat.' After a eulogy of the particular drug, the writer went on to say, 'may we suggest that you should prescribe this for some of your patients? . . . results will be apparent at the end of two weeks, although the drug is essentially a preparation for long-term administration . . . It is particularly suitable for the patient who must continue to do a responsible job during treatment.'

Now I have not the least doubt that this letter and abstract have been circulated to the majority of practitioners in this country, and I regard it as unfortunate that communications of this kind should be thus broadcast to vast numbers of practitioners, many of whom have had no real training in the proper use of medical statistics, nor any grasp of even the elements of real scientific research in medicine. I have, of course, no wish to be censorious, but I cannot help feeling that not a few of the recipients of the letter I have just quoted are of the class of practitioners whose main object—and I am not altogether blaming them—is to ingratiate themselves with their patients by the exercise of what for them is an easy form of empiricism which, as we all know, a not inconsiderable proportion of patients (especially under the National Health Service) are only too ready to welcome and to support.

Just over two years ago I was invited by the Editor of the British Journal of Tuberculosis to write a short epilogue for its Golden Jubilee number, in which various contributors had reviewed the work of the last half-century in regard to this disease. I hope you will forgive me if I quote the closing paragraphs of that epilogue; I do so merely because I think they are germane to the subject under discussion, and perhaps useful as a warning against premature conclusions in regard to new remedies, even when these have undergone a previous subjection to clinical trials by competent observers.

'The introduction of the numerous modern antibiotics has been hailed with enthusiasm as an almost revolutionary advance in treatment. I feel that there is, perhaps, some need of caution and reflection before it can be said that the complete results of their action have been fully assessed. No one who has had to deal with large numbers of cases of phthisis in its various forms can fail to be impressed with the apparently miraculous effects of streptomycin and its attendant remedies in cases in which the prognosis would otherwise have appeared well-nigh hopeless. No
one of judgement, however, can suppose that these drugs are the final answer to the problem of treatment of this disease. The same may be said, on general principles, in regard to the employment of all the other antibiotics for the many varieties of disease of the respiratory organs. Of the immediate effects in a beneficial direction there can be no doubt; the ultimate effects upon the human organism may not as yet be fully understood. It is conceivable that within the next decade problems may be presented to the experts in immunology which may well oblige the clinician to review many of his present ideas on the scope and limitations of chemo-therapy. I put forward this last suggestion for the consideration of our readers, not, of course, with any wish to denigrate the advantages of this latest therapeutic weapon, but rather as a warning against the possible danger of the adoption of a rule-of-thumb attitude in regard to treatment, and as a reminder of the error, to which I have already referred, of regarding knowledge of the immediate action of specific remedies as an adequate substitute for a sense of relative values, and an excuse for “mass production” methods in the treatment of the sick. With this cautionary utterance I must close this review, adding in conclusion a final tribute to our original forebears, upon whose labours much of our advance has been built, and a plea for greater exercise of that remarkable faculty of accurate bedside observation and unhurried clinical judgement which was so conspicuous a feature of their lives and character.

Before actually writing my short contribution to this symposium, I had an opportunity to meet Dr. Williams and to ask him for some little guidance as to the part I was expected to play and the line he wished me to take in discussing the ‘presentation of results’. I suggested that, as a clinician who had had no significant experience in the actual testing of remedies on an adequate scale, I could do little more than discuss the matter from a very wide angle, confining myself to those aspects of the subject which seemed to me to spring from what I regarded as fundamental principles in medicine, and to any ethical corollaries to which such principles must inevitably lead. I was not a little relieved when he told me that he was in agreement with this interpretation and that he felt there was no doubt, not only that the uses of clinical trials were legion, but that there were so many ‘interested parties’, each putting a different shade of meaning on the results. I do feel that this atmosphere constitutes a real practical difficulty in medicine today, and that those who are now entering on a medical career or who are in the early stages of their practice are far more hardly pressed by it than their forebears who learned their art in days when the perimeter of the whole field was so much smaller, and when clinical knowledge was so much more within the mental compass of a single individual. Today, in medicine, as in philosophy or in art or any other intellectual activity, the genuine seeker after truth is often confused by the cross-currents of thought which beset his mind, and, knowing not which way to turn, he sometimes seeks in vain for trustworthy guidance.

‘Now, who shall arbitrate?
Ten men love what I hate,
Shun what I follow, slight what I receive;
Ten who in ears and eyes
Match me: we all surmise,
They this thing, and I that; whom shall my soul believe?’
The well-known stanza which I have just quoted is, I think, apposite in regard to the whole of medical education; I mention it here as not entirely inappropriate to the subject which we have been considering today. There is too much haste in consigning the immediate results of clinical trials to print; too little prior deliberation in order that they may be the better integrated and absorbed into the general body of experience and coherent knowledge. If we of the medical profession are in such a hurry to disseminate ideas which still need further contemplation before they can be adequately digested for useful employment, how can we blame the lay public for the unreasonable and sometimes even dictatorial attitude which they occasionally adopt in the matter of their treatment. I often think of a remark made to me some years ago, in the very early days of the sulphonamides, by that great clinician the late Professor Sir Arthur Hall of Sheffield: ‘You have to be a very strong man indeed to refuse to prescribe M. & B.’

I hope that my hearers will not think that my somewhat disjointed remarks have been merely destructive, and I trust they have not been disappointed in their hope of receiving a more positive contribution from me to this most important topic. If, however, what I have said this afternoon has stimulated some of you to contradict me and to provoke further discussion, I shall feel less diffident than when I first promised Dr. Williams to take part in his programme, and more hopeful that what I have said may have been of some little help to our distinguished Chairman in his task of summing up in his closing address.
FINANCING OF CLINICAL TRIALS

A paper on 'Financing of Clinical Trials' was presented by Professor A. Kekwick, M.A., M.B., M.R.C.P., of Middlesex Hospital, London.

Professor Kekwick: I feel that my own aspect of this subject must strike a somewhat alien note in the light of what has gone before, and I would like to start by saying how much I have enjoyed the discussions up to this point. I assume that the reason I have been asked to speak on this subject is that for the last five years we have had an Institute of Clinical Research at the Middlesex Hospital, to which we have encouraged pharmaceutical houses to bring their products for clinical trials. These trials have been carried out largely by consultants on our own staff and my part in them has been to interview representatives of the pharmaceutical houses and to help in arranging for the trials to be carried out. I have therefore interviewed representatives from many of the pharmaceutical houses whether they have been centred in England, in America or on the Continent, and have had an opportunity of discussing the question of finance with them.

The present position is far from satisfactory. There is a sort of hole-in-the-corner attitude about paying for clinical trials. One keeps hearing stories both from representatives of the houses and from medical men that somebody did a clinical trial for a house and the report was withheld until a large fee was paid; that travellers have used the names of doctors and consultants without their permission and before publication of their results—and other similar tales. Where such stories exist, they represent an unsatisfactory relationship between the parties.

In discussing this question, I wish to start from two major premises. The first is that I believe that pharmaceutical houses want to pay for clinical trials. A number of reasons underlie this wish. Where such trials are well done, they feel it only right and proper to make payment. On the other hand, where the trials are not well done, the pharmaceutical houses feel that they may be able to exercise some degree of control if they pay. Many are more aware of the ephemeral nature of so many of their remedies than a great many doctors.

The second premise is that doctors appear unwilling to accept payment for clinical trials. The reasons for this are somewhat more difficult. There is a longstanding distrust in the medical profession of ethical pharmaceutical houses. This emanates from the old days, when, as Dr. Davidson outlined, the latter were mere pedlars of pills, and some doctors have not yet come to the realisation of what contributions pharmaceutical houses have made and, indeed, are making in the therapeutic field. Another difficulty is that the currency of thought in pharmaceutical houses tends to be one of money, whereas the currency of thought in the medical profession tends to be one of reputation, either among patients or colleagues. These two predominating motives tend at times to clash.

The first step in initiating clinical trials is taken by the pharmaceutical houses
who have the knowledge about new drugs produced in their own laboratories, and who have carried out early pharmacological work. At this stage they approach a doctor or department for aid. The fact that the two parties meeting together start with slightly different motives and a slightly different approach to the problem is the first factor which contributes to the final situation making any discussion of payment difficult or impossible. The second, however, is more important and this is that as they get together, the difficulties tend to multiply rather than diminish and here, I think, the blame must lie, on the whole, with the ethical pharmaceutical houses.

One of the main problems here is misunderstandings about the motive for which the trial is being carried out. Today, we have had discussions on the simplest form of trial; the trial in which the pharmaceutical house requires information. It wants to know whether its product is better or worse than other products, whether it is complementary to existing products, and so on. Each of these trials, it has been pointed out, presents a separate problem, but the important fact as regards payment is that the motive is simple. Such trials are done on the whole in recognised institutions, in university departments or in units in general hospitals. Here there seems to me to be no problem as regards the question of payment. It is right that pharmaceutical houses should bear some of the burden and should pay a fee to the institution carrying out these trials. What happens to the fee within the particular institution does not seem to me to be the business of the pharmaceutical house. In fact, the practice will vary from institution to institution, according to their rules and customs. The only difficulty that arises over this particular type of trial that I have encountered concerns the question of publication. Here, the motive on the part of pharmaceutical houses becomes a little muddled. If they want information, the problem is simple; if they want a promise of publication, they are wanting something quite different. For this type of trial, I feel that there should be no prior obligation, implied or real, on those carrying out the trial to publish. It should be conditional that the fee is for the work and excludes publication of results.

This is the least common type of problem that has been presented to us in the last six or seven years, and I want now to pass on to the other two types of trial where, I believe, the real difficulties arise.

The second type of trial about which we have been approached by pharmaceutical houses is what I call the consumer trial. Here, the house has produced a variant upon an already accepted remedy. It is unlikely that, however thoroughly the clinical trial is carried out, and however statistically it is controlled, any conclusive result will be obtained. This may be because of the nature of the disease for which the remedy is used, or because of the nature of the remedy itself.

What the house wants, it seems to me, is in fact a number of opinions, probably largely from general practitioners, as to whether it is the sort of product that they can usefully employ. As I understand it, they want to hand over their preparation to, say, a number of general practitioners and ask for a report giving their impressions upon it, for which the pharmaceutical houses would pay a fee of, say, three, four or five guineas, comparable, for example, with the report that an insurance company requests on a patient. This may appear a simple matter but from the point of view of the doctors has certain problems.

The prime duty of any general practitioner must remain always to his patients
and his difficulty is his intimate personal relationship with them. If it became known in a practice that the doctor might be receiving a fee, however small and however seldom, for reports on new preparations, I am sure that he would lay himself open to the accusation by lay people of experimenting on his patients. I would have thought that these consumer trials, which apparently have considerable importance to pharmaceutical houses, should not be done for a fee unless the arrangements are made through an official body like the College of General Practitioners.

I have discussed this with one or two people in the College and I am quite sure that if the houses were to approach them, their Ethical Committee would be prepared to consider the matter and see whether some arrangement could be made along these lines. I feel, however, that for this type of consumer trial no payment should change hands unless it is done through an official body such as the College of General Practitioners, or possibly the British Medical Association, so that the practitioner can be protected from any accusation that he has been experimenting.

Even greater problems centre around the third type of trial, which I have heard called a promotional trial. In this case, the pharmaceutical house brings forward a remedy, about which it already knows a good deal and on which a good deal of work and, perhaps, a fully-organised clinical trial has been done. It wishes to farm it out to a number of doctors eminent in the field in which the remedy applies. The pharmaceutical house calls this a clinical trial, but what is wanted is not information but a publication with the man's name behind it. If their motive is publicity, I am quite sure that it is most desirable that the medical people who are approached should be told this frankly in the first instance. I cannot see a medical man, with a reputation of this sort, actually accepting a fee in exchange for giving publicity to a product. This appears to me to be a reasonable attitude. My own feeling is that this type of clinical trial should finish altogether. I do not believe that it is of any value.

I have talked to quite a large number of general practitioners about the literature which they receive to find out how much a particular man's name on certain types of literature means to them. General practitioners are independent creatures and I do not believe that this type of trial is good publicity. On the other hand I have been told by at least two scientific representatives from ethical pharmaceutical houses that they believe it is worth while. If it must continue it will continue to give rise to misunderstandings between the pharmaceutical houses and the medical profession. What the former want is a publication for publicity reasons which they can quote in their literature; if they say this, I do not feel that many people will be prepared to carry out the trial work; if they do not say it they lay themselves open to the accusation of dishonesty.

I have two minor points on the question of payment which have come up from time to time. The first, which arises frequently in interviewing representatives, is the question of payment to patients or volunteers in clinical trials. My personal view is that it is most undesirable. I believe that such payment gives a licence to doctors to carry out procedures which they otherwise would hesitate to do. The same sort of thing happened with blood donors in certain countries before the war when they were paid. Many of them were made invalids for long periods of time because the fact that they were paid gave a kind of licence to the doctor to bleed.
them far too often. I have encountered the same kind of thing in several countries during the last few years when volunteers, particularly among, say, medical students during the summer vacation, are paid a fee. This fee appears to grant a licence to do things which, I am sure, would not be done if the volunteers were unpaid.

One other subject which has come up in interviewing representatives is payment to registrars. It is very important that it should be made clear to pharmaceutical houses that although in fact registrars often carry out a lot of the work of such trials, it is not for the houses to initiate any payment to them. Registrars have different agreements about what fees, etc., they can retain in different places. Once again, I am sure that no question of payment of registrars should be raised by pharmaceutical houses unless it is done with the knowledge of the head of the institution concerned.

To sum up, I believe that we have in this country an opportunity to get a better liaison between the ethical pharmaceutical houses and the medical profession than in any other. One has only to examine the sort of publications that are appearing in countries where pharmaceutical houses are maintaining major payments to hospitals or wards in which they employ their own doctors to do their trials to see that the standard of work is extremely low.

As these trials are initiated by the houses, I believe that the first thing they must get clear in their own minds is exactly why a particular trial is required by them. After that, if they state this to the doctors whom they approach, I believe that the problem of payments will be much simpler and possibly, in many cases, will disappear altogether. The present unsatisfactory position is because of the mistrust which is centred round muddled motives in the promoter—giving rise to situations where accusations of dishonesty can be made.
DISCUSSION

The Symposium discussed matters arising from the papers presented at the afternoon session.

Nature of the trial and evaluation of results

Dr. A. M. Brunton: The whole subject of clinical trials and the assessment of therapeutic agents is an extremely difficult and complex one. It is of great importance to both the pharmaceutical industry and medical profession alike.

Many interesting points have been raised today. One of the questions which may arise in one’s mind is how long should a clinical trial last and how many patients should be included in a trial before the results can be considered valid. This depends, of course, on the disease under treatment and the type of agent being employed.

The question of trials is all important, but it may not always be possible to include controls in certain investigations, which, of course, may make interpretation of the results very difficult. In the assessment of a chronic progressive inflammatory condition, such as rheumatoid arthritis, evaluation of response to treatment is extremely difficult.

Dr. Savage has mentioned that he no longer considers that pain can be used as an assessment of improvement in the arthritic because of the extreme variability of patient interpretation of pain. Evaluating a drug in rheumatoid arthritis is a classic example of the complexity of a clinical trial. Even now the position of corticosteroids versus aspirin in this disease is far from clear. Another disease which also presents many of the same problems is chronic bronchitis.

Dr. Dudley Hart’s experiences with deoxycortone and ascorbic acid, and the resulting enthusiasm generated amongst both patients and staff in the results of treatment obtained, were extremely illuminating. These experiences could also be related to Dr. Davidson’s comments on lay press articles. Many articles printed regarding cortisone in its early days raised false hopes among patients.

Financing of clinical trials

Dr. A. M. Brunton: Professor Kelwick’s comments on trials and the method of paying for them are extremely difficult to discuss fully. I do not agree with him that if general practitioners should be asked for advice or to do some small investigation for a pharmaceutical house, they should not be paid. We often ask the opinion of general practitioners purely for our own information in the Medical Department and we pay them for those opinions or for that advice according to what they have done. I think that the general practitioner can be consulted, as a physician, for his opinion and should be paid as such.

Regarding the question of so-called promotional trials there is an extremely fine dividing line between actual clinical research and what is meant by the word ‘promotional’. For example, had the Medical Research Council trial of cortisone and aspirin in either rheumatoid arthritis or rheumatic fever come out very strongly in favour of cortisone, then the results of this investigation could have been used by pharmaceutical houses manufacturing the corticosteroids in a so-called ‘promotional’ manner, even though the trial was purely a research investigation. Once the trial is completed and published, however, the position may become different.

Concerning physicians and units doing trials with drugs supplied by pharmaceutical houses, I do not agree with Professor Kelwick that publications are unnecessary. One must have reputable names and units with publications in leading British journals in order to substantiate any claims made by pharmaceutical houses about their drugs. Otherwise the medical profession would be sceptical of claims made regarding new remedies. The calibre of the investigator, the unit and the journal are therefore of great importance.

It is rare that a unit actually investigates clinically a completely new drug which has not been tried on any other patient or in any other place. It is possible that it may have been evaluated abroad to a certain extent and, therefore, it is not an entirely new remedy.

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I thank Professor Kekwick for his views on the subject and should like him to consider these specific questions as to whether payment should be made. How would the physician himself feel about being approached on payment? I do not think that the pharmaceutical house would object. On the contrary, they would be glad to get the matter cleared up specifically on the basis of so much payment for so much work done; but it is not quite as easy as that.

Payment of the general practitioner

Professor A. Kekwick: Two points have been raised. Although, on the surface, the problem of the general practitioner and his report is quite simple, it is, in fact, a very difficult one, simply because of his exposed position. If it ever became known in the practice that he was trying new remedies for houses and was receiving payment, I think he would be open to the accusation by his patients that he was experimenting. That is why I suggest that payment should be made only through some official body like the College of General Practitioners. If this can be done, and I understand that they will be prepared to consider it, I think there is every reason why payment should be made. To accept personal payment, however, might expose the general practitioner to a situation in which he would find himself in a very unenviable position locally.

Payment for 'promotional' trials

Professor A. Kekwick: Dr. Brunton’s remarks about the 'promotional' aspect of trials simply underline the whole messy problem. When a house wants the trial to be made for promotional reasons, or if it wants publication from a particular person, I believe that payment is undesirable, because they would be virtually buying a man’s good name. When the trial is wanted for information, then it should be left to the man to decide whether to publish or not. Until there is a clear separation in the minds of the people who call on myself and many others as to which is the prime motive, we will always be slightly distrustful one of another. These two things must be separated at the start.

Payment of registrars

Professor J. W. Crofton: Is it permissible under the Health Service for a company or a research fund to pay an honorarium to a registrar who may do a lot of extra work on research and has no given hours of work?

Professor A. Kekwick: I do not think this is a question of the Health Service, but of the man’s terms of appointment in the institution. I am on the board of an institution which employs part-time registrars on a sessional basis. Clearly, there could be no objection here. I feel, however, that payment must be arranged through the institution and not individually with the registrar.

Professor S. Aisiead: There has been the suggestion that money should be paid to a registrar who conducts research. In my own unit, I am reluctant to agree to such an arrangement. I am willing to delegate the job to a registrar. He can work as a member of a group; and the group will ask him to give a short account of the job he is trying to do and will be trying to criticise. At the end of it, the firm could make a contribution, not to me or to my department, but to the university, and it would be for the university to decide how the money should be used. If they followed my recommendation, the university would use it for the benefit of the man who did the work, and he would benefit by having books put at his disposal or from financial support to cover travelling expenses in connection with professional work.

Payment of university staffs

Dr. D. L. Davies: Regarding payment for clinical trials as it affects university departments, some direct questions arise. In the case of whole-time university staffs is the money to go to individuals or to the institution? or is there to be no money changing hands at all?

In the United States, some whole-time university staffs receive payment for vacation time, and the matter is now being raised in this country. Our university medical staffs are not paid as well as corresponding grades in the Health Service and, generally speaking, it seems churlish to refuse them this extra money and so put the research worker at a disadvantage.

On the other hand, there is no doubt that in course of time, with so much money in the hands of the drug houses and so much less money in the hands of the University Grants Committee, there is a danger that work sponsored by the former will preponderate and tend to take the place of the
work provided by the funds of the latter. We know that in the United States there are university bodies which have become tied to particular drug firms and have suffered in that way.

There is also the effect on the individual worker. It has been pointed out by Professor Whitehorn in the United States that young men who had promising careers in the more general field have often been too early diverted to a specialised field because of the tempting remuneration offered to them. There is no clear answer to this, but I think we must very soon face up to these problems and try to achieve some code of ethics on the subject. I should like to know what Professor Kekwick thinks about it. If his reply is that it is for every individual institution to make up its mind in its own house, I fear that there will be much disparity between different university bodies.

I do think that the people best qualified in many cases to carry out fundamental research for the drug houses are university bodies, because, as has emerged today, the work is very technical. It requires statistical, computational, clerical and laboratory help, which is becoming increasingly concentrated in the hands of whole-time members of university medical departments rather than clinical staff of hospitals. This makes the solution of the problem all the more urgent.

Professor A. Kekwick: I would hate to see anything pertaining either to the old German system or the present systems that operate in some parts of America or in many parts of the Continent, where university departments become all too dependent upon these payments. The advantage of a university department is that it is independent and full-time, which gives it a freedom beyond any price that any pharmaceutical house is likely to pay.

On the other hand, pharmaceutical houses should, I believe, make a contribution in return for information provided. This should be put into general funds, and it is for each university to say what should be done with these funds, but it should not necessarily go back to the clinical department, and probably not to an individual in the department.

The general practitioner

Dr. J. Fry: General practice is, of course, quite distinct from all the other forms of medical practice. The doctor/patient relationships are on a quite different level from those in hospital or in the academic or public health type of practice, and the type of work is quite different. The general practitioner deals with a lot of minor types of disease, but these minor diseases are the ones that are the common diseases of the community.

Again, the patients approach their doctor almost as a friend, and a lot of the barriers which have to be broken down in hospitals are already non-existent.

With regard to drugs, very little work seems to have been done on their prescription and use in general practice. Nor have the habits of doctors as a whole in their use of drugs really been gone into. Where does the general practitioner get his information concerning drugs? Different general practitioners have different sources. Some get it from the reputable journals, others from the advertising put out by the drug firms, and others from the daily newspapers and magazines. They get it, too, from their patients, who also are a very useful source of information.

Research in general practice is very highly specialised and has come to the surface only in the last ten years. One of the major difficulties lies in the fact that it differs substantially from the single-centre type of research mentioned in the investigation of rheumatoid arthritis and other diseases. General practice research either has to be done by individual general practitioners, who have only a limited and specialised or special population at risk, or it has to be done in groups of varying size, when the general practitioners come from all over the country and, due to the nature of their work, do not always have as many opportunities for it as they might wish. One must, therefore, give very careful thought to the organisation of general practitioner research if it is to be a country-wide investigation. The College of General Practitioners has already published the results of two investigations on these lines: into the prophylactic use of antibiotics in measles, and into the signs, symptoms and course of acute chest infections. It is also undertaking many other investigations.

Professor Kekwick's observations were very much to the point concerning general practitioners. The trials raise a certain number of doubts in the minds of many; but if general practitioners can be assured that the patients will be under no serious risks or dangers from them, I am sure that once that is accepted, there will be no problems. There again, however, the doctor/patient relationship is a matter for the individual doctor.
I agree that probably some body like the College of General Practitioners, or the Medical Research Council or a university department, working in its own area with its own group of general practitioners, is the best to organise any wide-scale clinical trial research. I do not think that it should be undertaken by a drug firm because of the difficulties that would be raised. The university department, particularly in a provincial part of the country, has a lot of advantages in its relations with local general practitioners. The professors of medicine or surgery or other faculties could, and should, use general practitioners.

With regard to payment for work done, I do not think one should offer payment except where necessary, apart from expenses. These expenses might be interpreted in a broad fashion, but I do not think it is right for a doctor to be paid for research. I think that anyone who does research or clinical trials does so because he is interested in it. It might be expensive if he had to buy the drugs, but it he could be helped in this way and with expenses for postage and secretarial assistance, that would be all that he would really require. If the drug firms want this type of study, it is up to them to build up a panel or group of general practitioners who are interested in this type of work and get them to do it either individually or through one of the bodies I have suggested.

These points show that there is a lot of scope for therapeutic studies and, of course, other studies in general practice. I am sure that the general practitioner must be considered as a partner and as an important person in the carrying out of these trials.

Clinical Trials Organisation

Dr. R. W. Riddell: I should like to refer to a limited field: that of tuberculosis and the other chest diseases. The problem of the clinical trial is especially important in tuberculosis because suitable cases for investigation are scarce and because drug resistance is likely to develop if inadequate combinations of drugs are used. The importance to the patient is so great that no antituberculous drug should be offered for general use without most strict clinical testing. To deal with the problem the British Tuberculosis Association decided to form a standing sub-committee to be called the Clinical Trials Organisation. Its aims were first, to advise the pharmaceutical firms on the use of new drugs or combinations of drugs in tuberculosis and diseases of the chest; and secondly, to arrange clinical trials of such materials as seemed to warrant further investigation, ensuring that such trials were well planned and fairly accurately reported. The Organisation is now under way and, as far as one can see, is achieving its aims. It has compiled a list of clinicians and pathologists with adequate facilities who are willing to co-operate. When a trial has been planned, the execution of it is handed over to the clinicians and pathologists concerned. They report their findings to the Organisation, which in turn passes them on to the pharmaceutical firm with its own comments on the implications of the work. The Clinical Trials Organisation is a link between the pharmaceutical firms and medical workers. It plans, co-ordinates and finances, but does not execute trials. It reserves the right to publish results of trials unfavourable to the drug tested, if such publication appears to be justified on scientific grounds. Medical staff of the pharmaceutical firms are associated with the trial at all stages and the closest co-operation with them is encouraged.

The important question of finance is dealt with as follows. First of all, firms pay a small registration fee for each project put up for consideration. No fees of any sort are paid to individuals. The Organisation pays all necessary expenses from the funds of the British Tuberculosis Association. The pharmaceutical firms refund to the Association the amounts expended and pay a small percentage charge on the total sum to cover the administrative costs of the Organisation. Thus there is no financial transaction at all between the firms and the individuals who are doing the work for them. Such matters are dealt with through the normal administrative channels of the Organisation.

Ethics of clinical trials

Mr. A. Dickson Wright: I feel also, from an ethical point of view, that this question bristles with great dangers, which will grow and grow to the detriment of the profession and of the manufacturing chemists. I say this with some certainty because we have some awful precedents. In Germany, for example, the problem got completely out of hand. In fact, one man became identified with a medicament to the extent of having his name on the packages while still holding his appointment in hospital or university.

Medical papers were reprinted in tremendous numbers, and the reprints were used by drug
firms, not only advertising their products, but also advertising the man who wrote the paper reprinted. All this is contrary to the fundamentals of ethics and I think it is wrong.

We shall have to exercise tremendous strength of will, especially with the drug firms, because the competition there is fierce. I hope the drug firms will set a very high standard of business integrity in this matter, which is of great importance, because we are dealing with human beings and human lives. It is something which should be grappled with without any delay.

I have been shocked at times by the cold-bloodedness of some of these clinical trials. Is it better to sacrifice a number of patients and get an answer on an important question than do without trials? The whole thing causes me great anxiety, and that is why I am here.

The patient's part of it is something about which the patients are so naïve. They trust us, and they like being experimented on. They like being the centre of attention. But they should be protected from their naivety and not exploited in this way. The patients must be protected, the profession must be protected, and the drug firms must protect themselves.

Professor S. Allstead: If we do not have clinical trials, we are committed to having no trials at all. In fact, when a doctor prescribes without experience derived from clinical trials, he is working empirically. The doctor declares his dependence on the experience culled from his predecessors: this may be good or it may be bad; it is for the doctor to decide and he must exercise his own judgement.

Should the doctor review all the literature in relation to therapeutics over a period of hundreds of years and make this the standard for his therapy? Or should he take cognizance of scientific experiment on the part of his colleagues who carry out clinical trials designed by a group of disinterested workers? Practice at any particular time is bound to be a mixture of 'science' and empiricism: accordingly, it is seldom that therapeutic policy can be defined in simple terms. Certainly few of those who advocate clinical trials will say that such trials provide complete answers to all the doctor's problems. But the clinical trial must be vigorously defended if the only alternative is something approaching random therapeutics.

Professor A. Kerwick: I should like to say how much I agree with Mr. Dickson Wright. He has raised a much bigger problem than that of clinical trials however; the problem of ethics of clinical research. Clinical trials are only one side of this story, the larger issues are much more difficult and are those with which many of us are battling at the present time.

Volunteers

Professor R. Cruickshank: Sometimes we are asked by pharmaceutical companies to try to get more 'clinical pharmacology' on a new preparation—on one of their penicillins, for instance. Indeed, under World Health Organisation regulations some of the penicillins to be used by bodies like U.N.I.C.E.F. must be assayed on human volunteers before they can be accepted.

Inevitably the question arises whether the student or other volunteer should get some recompense for acting as the human guinea-pig, which in this case he is. We had to tackle this at the medical school I recently left, and it was decided that the difficulty might be overcome by giving the student some kind of recognition in the form of a book token after taking part in the trial; but he was not to be 'tempted' beforehand by the promise of money.

Travelling expenses

Dr. E. E. Pochin: Should the patient who comes up for a test receive travelling or other expenses?

The Chairman: I should think that is easily answered. If you do not pay his travelling expenses, he is not likely to come.

Putting drugs on the market

Dr. J. Stanley White: Who makes the final decision as to whether a new therapeutic agent should be issued to the medical profession? We have nothing in this country to compare with the Federal Drug Administration of America, which is extremely strict and insists on the most careful trials.

A brief notice in the Annual Report of the Council of the B.M.A. on the evaluation of new medical products (B.M.J., April 19th, page 182) said:

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'For a considerable time, the Council has been examining the possibility of establishing a scheme for the evaluation of new medical products by laboratory methods. After consultations with the appropriate bodies, it has been informed that the larger pharmaceutical organisations already have their own research departments and it is unlikely that new products would be developed by the smaller firms on account of the extensive and costly research involved. The Council therefore thinks that the proposed scheme for the evaluation of new medical products should be held in abeyance in view of the expense involved and the apparently restricted use which will be made of the services of such an organisation.'

We are, of course, familiar with the Cohen Committee, but that Committee does not compare with the F.D.A.

THE CHAIRMAN: There is no such body. The Cohen Committee is concerned with classification of drugs according to their therapeutic value, irrespective of what they cost. If someone discovered a cure costing £100 a milligramme and it was proved, it would go into the appropriate category.

With regard to putting drugs on the market, the position is that anybody can put anything on the market.

On one occasion when I suggested to the Home Office that a certain substance should be put in some form of schedule before an article about it was published in the Lancet, I had a reply which could be interpreted as saying that until someone had suffered grievous harm, it was quite impossible for the appropriate department to deal with it. That is literally the position today. There is no body corresponding to the Federal Drug Administration at all.

PROFESSOR G. BROWNLEE: The position has perhaps been a little overdrawn. It is worth recalling that the F.D.A. regulations arose because of the major abuses which took place in the United States of America. It is not quite fair to say that we have no safeguards; nor indeed is our position unfavourable with that seen in America under F.D.A. regulations.

The present position, with the spate of new remedies that are coming along, is, of course, creating a different situation, but there do exist the official publications of the Pharmacopoeia Commission. There is the very real method of assessing the value of new drugs by proposing their acceptance by the British Pharmacopoeia or the British Pharmaceutical Codex, and an enormous amount of hard work goes on there. The launching of numbers of compounded remedies, as distinct from the introduction of new drugs, appears to demand some new method of control. I feel that something more is required, but do not think we ought to overdraw the picture.

THE CHAIRMAN: There is no legal method of controlling what is put on the market. You do not have to have your product in either the Pharmacopoeia or the Codex to advertise it. People do not have to ask or get anybody's permission, except in the case of one or two types of drug, such as those controlled by the Therapeutic Substances Act.

DR. A. M. BRUNTON: The Federal Drug Administration is not concerned with efficacy, but only with safety. It is only fair also to mention that reputable pharmaceutical companies investigate thoroughly the toxicity and safety of new products. The question of efficacy is something entirely different. I do not think that any firm in its right mind would put on the market anything about which they were not perfectly sure from a toxicity point of view.

Position of the statistician

THE CHAIRMAN: It has always seemed to me that there has been a desire to push the statistician into positions which, I am sure, he does not really want to occupy. One has heard papers saying that the statistician should begin at the beginning of all research and should plan the original experiments of fundamental research. I am certain that that is entirely incorrect.

PROFESSOR J. W. CROFTON: I am not sure that it is entirely correct that the analysis of the trial should be made purely by a statistician. It is quite reasonable if the statistician has had considerable experience with that sort of trial and disease. Dr. Sutherland, for example, had had great experience of tuberculosis research. In other countries, however, I know from some of my colleagues who have seen the analyses made by statisticians how dangerous it can be when statisticians are dealing purely with forms submitted to them by doctors and do not have the professional knowledge to examine the imprecise or false statements which may be included on those forms. In general, it is wise precaution that some clinician who has a knowledge both of the clinical trial and also of the disease and the problem under consideration, should work with the statistician in the analysis of the trial.
Other types of trials

Professor J. W. Crofton: There is the sort of trial in which it is thought quite possible that the answer will be negative and in which one expects to show that there is no significant or important difference between two methods of treatment. This can be quite useful. For instance, when we were trying out chemotherapy on bed rest against chemotherapy at work in cases of mild pulmonary tuberculosis, we felt that if there were fifty cases in each group and if there was no difference between the two groups, then for practical purposes the inconvenience of bed rests would not be worth while. That is worth consideration when planning a trial.

Another type of trial is to investigate several different forms of treatment at the same time on the same group of patients. The following table shows how the different forms of treatment can be varied among the two groups. To one group can be given, say, drug S, and to the other group drug H, these being allotted on a random basis. At the same time, a trial can be made of, say, bed rest as against treatment at work, these being allocated at random to the members of the first two groups. This affords the opportunity of various comparisons and of separate analysis. The plan of the trial as is as follows: \( S = \) patient treated with drug S, \( H = \) patient treated with drug H, \( B = \) bed rest, \( O = \) treatment at work).

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<tr>
<th>Group 1</th>
<th>Group 2</th>
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<tbody>
<tr>
<td>S B</td>
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<tr>
<td>S B</td>
<td>O H</td>
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<td>S O</td>
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<td>S O</td>
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In the analysis all patients given \( H \) can be compared with all given \( S \), whether they were treated at work or on bed rest. In addition all treated on bed rest can be compared with all treated at work, whether they received \( S \) or \( H \). The great advantage of a trial of this kind is that it is theoretically possible to obtain answers to two or more questions on a fairly limited number of patients. A disadvantage could, however, arise if the effect of one of the drugs was overwhelming. The major objection to this sort of trial is that although perfectly correct logically, to the ordinary person it sounds false.

Conclusion

The Chairman: I do not propose to attempt to summarise today's discussions, because that would take a long time and it would be impossible to do properly.

A number of points have been raised, including the difficult question of payment as it applies to universities. Most universities have a regulation that no college of the university can accept funds without the specific permission of the court of the university. This is a relatively recent ruling and was made because certain institutions were supporting themselves by contract with bodies like the Ministry of Supply, and so on, and the Ministries were getting work of a more or less routine character done in departments that were really subsidised for research.

I think you would find it very difficult, therefore, to get an arrangement with the universities for anything that might be regarded as routine testing. It might go on for a little while, but eventually the court of the university would forbid it.

A number of points have struck me during the discussion today. I was particularly interested in Dr. Savage's paper when he described the attempt to produce figures for the statisticians. He warned us that we must be sure that those figures really meant something. I would certainly like to underline that, because the conversion of movements of joints, etc., into numerals is obviously an extremely difficult matter, and it is really unwise to produce these things and have a lot of elaborate statistical work done on them when, perhaps, the figures themselves do not need to be produced.

On the subject of remuneration, I was interested in Dr. Fry's suggestion that doctors should not be paid. Professor Kelkwick, on the other hand, did not say that they should not be paid, but criticised the method by which they were paid; he also said that if they were paid, it should be done through an intermediate authority which would act as a buffer. The case has to be remembered, however, of the doctor who said he did not want any money but finished up by producing a most expensive piece of research.

I do not think that the payment of expenses is really a good thing. I have had experience of
that and have found that it did not work at all well. The ideal method, I think, is that outlined by Professor Alstead, but I doubt whether many of us could rise to that degree of nobility where the money was paid to the university and probably used in another department.

With regard to the question of payment of volunteers, payment of this kind seems to have been thought of by many people as a sort of passport to do what you would not do unless you were paid. That is perhaps a rather extreme view. The way we have always looked at it is that you pay the person really for his loss of time. In the case of students, you must remunerate them in one way or another or you will not get them.

Professor S. Alstead: On your behalf, I would like to thank Sir Charles Dodds for the gracious way in which he has occupied the chair today and to say, what I am sure is in your minds, that the success of the conference has been in no small measure due to his chairmanship.