families so informed grasped the impact of the message from the doctor. Even if the patient is intelligent, can he really assess a situation which involved an element of risk, albeit a small one, in relation to the possible benefit he may receive?

A clinician should also ask whether his proposed trial is the best way for finding out an answer to whether this new drug or treatment is effective. The number of properly controlled trials in relation to the total trials of therapeutic agents done is still small, although there has recently been some increase, at least in Britain. The fact that the risk of drug morbidity or mortality is usually highest in the earliest cases treated with a new drug means that it is ethically preferable not to give all the patients a new drug, and that half of these early patients should be randomized into conventional therapy. In my view there are very few exceptions to the rule that pilot trials should not be carried out and the controlled trial should begin with the first randomized patient receiving the new drug. Although setting up a co-operative multicentre trial may be regarded as a chore, and indeed does constitute a great deal of work for all concerned, it is essential if the number of cases being seen is too small to make a properly controlled trial otherwise impossible.

There are two aspects of controlled trials that I believe are unsatisfactory, at least in Britain at present. Firstly, when a new agent is introduced several controlled trials may be set up after the clinical trial certificate has been given by the Committee on the Safety of Medicines, and yet no consideration is given to whether there is a need for several trials, or whether one good trial involving even the whole country would be sufficient. Very often a new trial is set up without knowledge of the results being obtained by other units or investigators.

Although the trials may differ in certain respects, they do need to be co-ordinated, and at present there is no central body to which each investigator may turn. This I think should be a function of the Committee on the Safety of Medicines. Secondly, the results of a controlled trial are so often analysed by the participants themselves at some stage. This is quite wrong: the correct way is for a fully informed advisory board continuously to assess the trial independently of the participants, so that as soon as a significant result is obtained the trial is stopped and all the patients continued on the best treatment.

In this way decisions can be taken at the earliest possible moment and the ethical position of the doctor and the medical research worker can be maintained—namely, to determine the best available therapy for the greater number of patients.

Importance of Controlled Trials

L. J. WITTS

Human experimentation can be divided into therapeutic and non-therapeutic experiments. In the past, appraisal of the value of treatment was left to the judgement of the individual clinician, but the history of treatment by bleeding, purgation, and emetics shows how long an erroneous treatment can survive if it is not subjected to scientific testing. With the rapid introduction of new treatments in the present century, the controlled trial has become an essential instrument of medical progress. In a modern controlled trial half the patients are given the best established treatment for the disease and the other half are given the new treatment. Patents in different centres can be treated simultaneously and the value of a new treatment can be quickly determined.

A similar technique is used in the evaluation of methods of prevention of disease. It is surprising that, though vaccination against typhoid was introduced at the beginning of this century, the right kind of vaccine and its value were not established until field trials were made in Yugoslavia in 1957. On the other hand, the prevention of diphtheria and poliomyelitis was quickly demonstrated by modern methods of trial once the basic knowledge was available.

Non-therapeutic experiments often deal with diagnostic methods such as radiodiagnosis, chemical and physical analysis of the blood, and the establishment of norms. As they are concerned with the advancement of medicine rather than the treatment of the individual, they often present ethical problems.

A large number of codes have been drawn up for the control of human experimentation. None of them is superior to Lord Lister's two desiderata: "First, a warm and loving heart, and secondly, truth in an earnest spirit." In Britain it is generally accepted that experiments should not be carried out on the dying or on prisoners, but few would accept a total ban on trials on children or the insane, as suggested by some codes. Practically all codes demand the "informed consent" of the subject but many experiments are difficult to explain to people without medical knowledge. Patients commonly agree because of loyalty to the doctor. Most hospitals, therefore, now have a special committee to which all plans for clinical research investigations can be referred for approval. A final safeguard is acceptance of results for publication. Researchers are unlikely to carry out experiments if they cannot publish their results, and editors of some medical and biological publications in Europe have agreed not to publish the results of human experiments unless the ethical standards are immaculate.

Appointments of Speakers

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Discussion

CHAIRMAN: I'd like to start by asking how ethical committes are working in practice. Dr. Eilenberg?

DR. EILENBERG: I can't of course, speak for other hospitals, but at Northwick Park the ethical committee was started in April 1970. It's composed of four consultants recommended by the medical executive to the hospital management committee; the director of the Clinical Research Centre; representatives of the non-consultant staff and of the general-practice division; the chief nursing officer; and a layman member of the hospital management committee. Finally, the group secretary acts as committee secretary. We make recommendations and are accountable to the hospital management committee and are therefore wholly independent of any medical establishment within the hospital. We have attempted to concentrate on the ethical aspects of any propects and not on its scientific worthiness—this latter is done by a separate committee, who submit their judgements to the ethical committee.

DR. WILLIAMS: Are these people chosen for their personal qualities or as representatives?

DR. EILENBERG: The consultants are chosen from those members of the staff who have no paid research sessions—they've no vested interests.

DR. WILLIAMS: Our committee at King's College Hospital is a small one and includes the dean of the medical school and the chairman of the joint research committee of the hospital and medical school. So far no representatives of the nursing or paramedical staff have been appointed.

PROFESSOR WITTS: At Oxford the ethical committee has only come into action since I retired; it is quite small, with the professor of medicine, a member of his staff, and also a member of the general consultant staff. It meets three to four times a month, gets through its agenda expeditiously—and so far satisfactorily. It considers all ethical questions referred to it. I think there's one bad fault: any ethical committee must have lay representatives, because justice must be seen to be done. The question of nursing or paramedical staff representation is more controversial; certainly they can be helpful but one doesn't want the committees to get too big. It must be able to work fast and not hold research up.

So far there have been no disagreements among the members of the Oxford committee—if there were I suppose the first step would be for the board of governors to set up an ad hoc committee. If this did not resolve the problem then I think it should be possible to refer it to some central body —perhaps set up by the Medical Research Council or the Royal College of Physicians.

DR. EILENBERG: There is a very important public relations aspect in involving the paramedical staff as well as the outside public. But we mustn't forget the registrar and the nurse, who are left to clarify any confusion in the minds of the patients, and to deal with the actual investigations. Finally, ethics musn't be limited to a specific group: the ethical committee should aim to spread its ideas throughout the whole institution.

CHAIRMAN: This is your working paper's point about an "ethical climate"?

DR. EILENBERG: Yes; unless we do create this climate doctors will be pushed into a medicolegal position rather than an ethical one, as already occurs in the U.S.A.—where the patients have to sign a long involved form containing a lot of small print.

CHAIRMAN: Some people have agreed that a committee shouldn't contain a powerful figure, such as a professor.

DR. EILENBERG: Authority is not invested in only one or two people in our ethical committee.

DR. WILLIAMS: If it's a small committee with one powerful figure it's inevitable that he will sway that whole committee, for part or all of the time. I'm interested in the experience of the ethical committee at Northwick Park, a hospital which after all has a heavy research bias. How do you judge the value of the committee's work? Only if the projects have been refused or modified can you say that the committee has had an effective function. Or do you argue that merely having such a setup makes doctors much more careful about their research programmes?

DR. EILENBERG: I place great emphasis on the climate of opinion. A report from our local ethical committee is always on the medical staff agenda, so that they constantly know about our work. Also by having the chief nursing officer on our team all the ward sisters know what is happening. If they are concerned about anything—or don't understand the project—they can go through their hierarchy to the chief nursing officer on our team and find out.

DR. WILLIAMS: Has this happened?

DR. EILENBERG: Yes, but we've always found that it wasn't the investigators at fault—merely that the nurses may easily get confused between highly technical investigations entirely for the patient's benefit and clinical research.

DR. WILLIAMS: But have you had to turn down some projects or modify them?

Value of the Protocol

DR. EILENBERG: We have a very formal two-page submission for any study, which covers all the aspects—the aims, specific procedures, numbers of patients, and exactly what investigations are involved (including the number of venepunctures, etc.). We don't work by turning a project down completely, but we may send the submission back for more details or suggest modifications in the protocol. For example, one study may initially involve 10 venepunctures in a 6-hour programme; we will say "this seems an awful lot of punctures for a patient—can it be done with an indwelling cannula; what is the statistical evidence that so many venepunctures are necessary, or can you reduce the number?" So possibly a quarter of all projects submitted get modified in some way. But once people know we do this, they think harder before they plan their work—it's a mutual learning process.

DR. WILLIAMS: Can we be sure that a lot of work isn't going on all over the country that hasn't been approved of by ethical committees at all?

PROFESSOR WITTS: Ideas are moving rapidly at present. There hasn't been time to ensure review of the procedures everywhere.

DR. EILENBERG: If you ask me "can I be absolutely sure that a consultant doesn't take a patient into a corner for a venpuncture or a skin biopsy and disguise this as part of the clinical investigation" the answer is no. But we've been explicit in stating that the ethical committee is there also to protect the investigator, and so researchers should welcome its help.

DR. WILLIAMS: But it must have teeth.

DR. EILENBERG: The ultimate solution would be for the hospital management committee to withdraw bed facilities from a consultant. But if we ever get to this point, something must have gone wrong.

PROFESSOR WITTS: An ethical committee is not yet a legal necessity, but it almost certainly will be under the N.H.S. Reorganization Act. Its main purpose is to give meaning to that phrase "informed consent"; we know that the average patient can never really understand exactly what is involved but he likes and trusts his doctor and tells him to go ahead. The committee makes sure that the procedure does satisfy certain criteria.

How Informed is "Informed" Consent?

DR. WILLIAMS: Informed consent really is a nonsense. I've never had a patient refuse to have anything done that I've asked him. The patient can't understand what's at stake—as is confirmed by a recent paper. The only real check on ethics is by a committee which does understand.

DR. EILEENBERG: Informed consent is an ideal towards which we're working But it is a complex issue.

PROFESSOR WITTS: You have to begin by getting consent from the patient that you are going to do something that's not strictly necessary for his investigation or treatment. I don't regard this as "informed" consent; as Dr. Williams says, this is where the committee comes in.

DR. WILLIAMS: I think it should be the other way round: sanction by peers on the ethical committee and then consent by the patient, who's told that after expert assessment the project is supported by the committee.

CHAIRMAN: What effect has the existence of these committees had on public opinion?

PROFESSOR WITTS: There's been much less criticism of medical experiments since they were introduced, and sooner or later some sort of sociological research on their work will be very valuable.

CHAIRMAN: How should lay representation be chosen?

PROFESSOR WITTS: It's easy to pick out people on, say, boards of governors, with horse sense, who'd be objective—

possibly one should avoid people who are too interested in the subject.

DR. WILLIAMS: Should ethical committees have standard constitutions all over the counry?

PROFESSOR WITTS: I'm against standardization, but you should have lay or nursing representation—possibly up to a quarter of the committee. I've had a lot of experience of leukaemia treatment trials in a specialist unit. This does place an enormous strain on the nurses because they're confronted with a large number of patients with a bad prognosis who otherwise would have been diffused over several hospitals, with many nurses to share the emotional load. So their advice to an ethical committee is most valuable, as also it is on non-therapeutic research, where the distinction between procedures of benefit to the patient and those that are not can be most difficult.

DR. EILENBERG: Certainly this distinction is difficult, but our committee is often asked to help make it—perhaps at a very simple level. A surgeon may want to try suture material X against material Y, both of them established as safe; is it really research to do a trial, or is it part of clinical trials?

To move to another point: there are times when the procedure is so minor that greater distress results from obtaining consent than in not doing so. Some minor procedures unrelated to patient care—taking a throat swab or an extra ml of blood, or asking him about his diet—might be more upsetting when you ask for consent than otherwise. So we have produced a list of minor procedures.

DR. WILLIAMS: Are all these projects approved by the ethical committees?

DR. EILENBERG: Yes, always.

Unethical Not to Do Research

DR. EILENBERG: I'd like now to talk about the point I make in my working paper that it may be unethical not to do research. By this I mean retesting some traditional treatments that may have been accepted for several years. These treatments may have been unpleasant for patients, and perhaps ineffective as well, so that we need trials to determine this. For example, following on the trial by Ackner, Harris, and Oldham[5] at the Maudsley Hospital we no longer use insulin coma for schizophrenia—which we know had its fatalities.

CHAIRMAN: What about controlled trials? Do we always need them? I'm thinking, for example, of Lord Platt's point[6] that it's impossible to have a proper trial of coronary care units—all the best doctors insist that their patients are treated in one.

PROFESSOR WITTS: I'm not sure that I would. By and large you require controlled trials of any therapeutic procedure. For example, there's the old practice of giving digitalis to patients with pneumonia. This was apparently a sensible idea, and my professor always did it until a controlled trial from the U.S.A. showed that patients treated with digitalis did worse than those not so treated.

One of the major problems is the first trial of a new drug in man. Though the results may have been satisfactory in animals, something totally unexpected may turn up in man. There's also the question of how many subjects you need for a controlled trial. I disagree with Roger Williams in so far as I think you always need a small pilot trial before embarking on a full-scale controlled trial.

CHAIRMAN: What about the number of centres involved?

PROFESSOR WITTS: The pilot trial will probably be done in a single centre, but the results must be reported to a larger body. It is a general rule that a trial should never be the responsibility of a single investigator. If the pilot trial is encouraging, a controlled trial will probably be carried out in several centres. This requires the creation of a committee which includes pathologists, statisticians, and observers not actually treating the patients. It is my experience that non-clinicians are always deeply concerned with the ethical aspects of the trial. A sequential trial enables us to use the minimal number of patients necessary for statistical analysis but there are snags in this—side effects or evidence of heterogeneity of response may not show up if you use small numbers. Where there's not an enormous difference—and you can see that by regular monitoring—100 a side is a good figure to aim at.

DR. WILLIAMS: Professor Witts has described the ideal trial, as run by the M.R.C., with a central expert advisory committee. But it represents probably a rather small percentage of all so-called controlled trials going on in the country. I'm worried about the trials of a particular drug being done by five or six centres. None of the groups knows what the others are doing; the M.R.C. isn't involved; the Committee on the Safety of Medicines has no role—so there's a great need for co-ordination here.

PROFESSOR WITTS: The standard of trials as a whole is rising, but a number of trials are done in general practice, where supervision is at present difficult.

DR. WILLIAMS: The trouble still is that somebody in a London hospital may just be starting a trial of a drug that's already been found not to work in Manchester.

DR. EILENBERG: This leads to a suggestion that the Committee on the Safety of Medicines may have to develop a centralized agency which organizes information on drug trials.

DR. WILLIAMS: I agree. One place where a central ethical committee would be of great help is in drug trials. All such trials, even pilot ones, should be controlled trials and you need machinery for co-ordinating these and avoiding duplication. Pharmaceutical companies have a vested interest, so they may support trials in five or six centres, in the hope that one of them will show worthwhile results—all the other trials are then quietly forgotten.

PROFSSOR WITTS: Yes; some centralization is certainly needed. Such a central body could also monitor the ethics of trials or experiments done outside hospitals, for it would be quite wrong and probably impracticable for the hospitals to monopolize this kind of work. The Royal College of General Practitioners has much experience of research in general practice.

CHAIRMAN: Has the G.M.C. a possible role here?

PROFESSOR WITTS: No. I should suggest the royal colleges and the Medical Research Council.

Non-patient Volunteers

DR. EILENBERG: We haven't touched yet on the non-patient volunteer. There's no legal framework which allows doctors to experiment, but society expects us to advance medicine. One of the areas of particular ignorance is in mental subnormality and psychiatric illness, and yet central bodies—such as the Medical Research Council—are rather diffident about advocating this. Yet the more ignorant we are about something, the more research is needed.

PROFESSOR WITTS: All the safeguards we've mentioned so far apply to the volunteer as well as to the sick patient. The problem is in fact much more difficult when you are doing research in healthy subjects.

DR. EILENBERG: We shouldn't deny the expression of the fund of good will that exists in lay people, which may be shown in their volunteering. But there's no doubt but that any project should go to an ethical committee first.

CHAIRMAN: Do they have ethical committees in, say, university physiology laboratories.

PROFESSOR WITTS: Not yet, but sooner or later they will have to. When I was in the U.S.A. many years ago it was said that one lot of students were paid five dollars to participate in some experiments on work and climate—and 25 dollars afterwards not to make a fuss.

DR. EILENBERG: At Northwick Park, where we have several

non-medical scientists, we have insisted that they must be associated with a medical person. But there are all kinds of trials going on in Britain without any ethical sanction—the effects of altering school meals for example.

Auditing New Techniques of Treatment

CHAIRMAN: Our last topic is perhaps the most difficult—that is, new techniques (such as transplantation) that are risky but solely designed to help the patient. What is the ethical situation about procedures which are pushing the frontiers of medicine away?

DR. EILENBERG: The ethical committee at present is confining itself to an ill-defined area called research. I do not see it taking over a role to monitor the clinical practice of consultants. A consultant who acts in good faith for the patient's benefit, with the consent of the patient and his relatives, is acting within the limits of his responsibility. But this is where the philosophy of Cogwheel and the divisional organization has not been fulfilled—Cogwheel should provide an opportunity to allow a clinical dialogue and mutual criticism of peers within the hospital.

DR. WILLIAMS: I find it difficult to separate these two aspects—if you do two operations of a new type or organ transplant, it's really an experiment.

DR. EILENBERG: But a lot of this is defensible in terms of one's right to practise clinical medicine. There's a danger of setting up administrative bodies to tell doctors what they can and they can't do.

PROFESSOR WITTS: We mustn't inhibit the desire of the individual doctor to carry out a new operation or other treatment. But most departments should have some sort of audit. I think today a senior man can raise a problem of treatment in his division that he couldn't have done thirty years ago.

DR. WILLIAMS: Yes; these issues are raised a lot. The question of heart transplants is a good example. This has been discussed a great deal in various medical committees—some committees have concluded that they should carry on; others that they should stop. Even so, medicine advances by one bright doctor having an idea and pursuing it; we don't want to lose the support for an individual with an idea. But certainly consent of the Cogwheel committee is necessary—because apart from anything else, this new procedure is likely to make more demands on the nurses, the laboratories and other hospital resources.

CHAIRMAN: What about sanctions against a consultant who goes it alone against the wishes of his fellows?

DR. EILENBERG: Ultimately, the hospital management committee has authority to withdraw facilities—though I'm not saying it's used. But if you create a climate of opinion throughout an institution—a total responsibility by the hospital community—then "mad" acts don't happen. If we don't create some such atmosphere, then the politicians and administrators will step in—and ultimately the patient will be the worse off.

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Scientific Basis of Clinical Practice

Bacterial Resistance: Changing Patterns of Some Common Pathogens

J. E. M. WHITEHEAD

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The growth of drug resistance among bacteria has made several antibiotics useless in treating certain infections for which they were formerly curative. Discoveries of new antibiotics or modifications of existing ones have gained a succession of temporary respites in an otherwise deteriorating situation and have tended to obscure its long-term significance for prescriber and patient. Some authorities, however, consider it unlikely that any entirely new antibiotic remains to be discovered,[1] and it is uncertain for how long chemical manipulation of existing antimicrobial drugs will suffice to meet the capacity of bacteria to adapt to them. Those antimicrobials which remain effective must be used wisely therefore—not only in the treatment of individual patients, but also for the ultimate benefit of the community. Sound chemotherapy rests on bacteriological guidance, much of which derives from the continuing observation of the changing patterns of bacterial resistance. This article is concerned with their present trend and its implications for antimicrobial therapy.

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Drug Response of Bacteria

The response of bacteria to chemotherapeutic drugs—the