Papers and Originals

MEDICAL ETHICS AND CONTROLLED TRIALS*

BY

Sir AUSTIN BRADFORD HILL, C.B.E., F.R.S.

Professor Emeritus of Medical Statistics, University of London

In commemorating the work and character of Marc Daniels it is only natural that this yearly lecture should almost invariably be related to some aspect of the epidemiology, prevention, or treatment of tuberculosis. For herein lay his most memorable contributions to medicine, and herein he displayed at their best his talent and his personality. However—and I think very fortunately—the conditions of the lecture do not limit the speaker to the field of tuberculosis. They permit him to explore any subject in public health, epidemiology, or therapeutics that can be regarded as apposite to Dr. Daniels's own research interests. I need therefore make no apology for departing so far from custom and for devoting myself to a quite general problem in clinical medicine—the trial of a new (or old) treatment.

More important perhaps than terms and conditions, I know well that I am embarking upon a theme which in the early trials of the new drugs in tuberculosis was often in Marc Daniels's thoughts. Not only had he an urge for perfection and accuracy, not only had he a patience and capacity for hard work that enabled him to seek that perfection in every detail—characteristics which are so necessary for the success of an organized controlled trial—but (as I wrote almost 10 years ago) he had an outlook upon the ethical problem which made him pause and reflect at every step. With all his eagerness for the experimental approach no one could have been more humane, more careful of the patient's well-being. These characteristics were fortunately linked with an unusual organizing ability and an unusual share of that statistical common sense that is anything but common.

In a review (*British Medical Journal*, 1948) of the Medical Research Council's first controlled trial of streptomycin in the treatment of pulmonary tuberculosis it was suggested that the trial might well become a model in this field. The prediction was right. Many therapeutic trials in many branches of medicine have been founded upon this early essay. And it is in this development that lies the true memorial to Marc Daniels.

Treatment of Pulmonary Tuberculosis with Streptomycin

When, in 1946, the Medical Research Council's Streptomycin in Tuberculosis Trials Committee set out to investigate the effect of that drug in pulmonary tuberculosis it was faced with no serious ethical problem. The antibiotic had been discovered two years previously, its striking powers *in vitro* and in experimental tuberculous infection in guinea-pigs had been reported; the published clinical results were distinctly encouraging though not conclusive. Yet overriding all this evidence in favour of the drug was the fact that at that time exceedingly little of it was available in Great Britain. nor were dollars available for any wide-scale purchase of it from the U.S.A. Except for that situation it would certainly on ethical grounds have been impossible to withhold the drug from desperately ill patients. *With* that situation, however, it would, the Committee believed, have been unethical *not* to have seized the opportunity to design a strictly controlled trial which could speedily and effectively reveal the value of the treatment. There was no dearth of patients with the type of disease defined (acute progressive bilateral pulmonary tuberculosis of presumably recent origin, bacteriologically proved, unsuitable for collapse therapy, age-group 15–30). There was no possibility of obtaining sufficient streptomycin for them all. There was no other suitable form of treatment for them but bed rest.

Thus, knowing that all the streptomycin available in this country was being effectively used—much of it for two rapidly fatal forms of the disease, the miliary and meningeal—the Committee (1948) could proceed not only without qualms of conscience but with a sense of duty to do so.

It is perhaps not often that such a situation exists—though it recurred in this country a few years later with the introduction of the inactivated vaccine against poliomyelitis—but whenever a newly introduced drug or vaccine is scarce in its early days, then there presents an opportunity of which immediate advantage should, if possible, be taken. With a serious disease in which the old offers very little hope of benefit the new cannot be withheld. The chance of adequately and quickly assessing the value of the latter, if any, may never again occur.

In spite of circumstances so favourable to the therapeutic experiment the Tuberculosis Trials Committee had nevertheless two ethical problems to resolve. About the first—the doctor's responsibility to the patient in his care—there was, of course, no real difficulty. In this trial, as *in all controlled trials,* it was implicit that the doctor must do for his patient whatever he really believes to be essential for that patient to restore him to health. If he believes that it is essential for the patient's well-being that he remove him from a comparative group on an orthodox treatment to a group on a new and unproved treatment (or vice versa), then surely it is his basic duty so to remove him. While such removals may seriously weaken, or even destroy, the value of a trial there can be no other means of meeting the ethical situation. For example, in the specific trial to which I refer, the cases accepted were by definition unsuitable for collapse therapy. Yet it was axiomatic that the clinicians were free to adopt collapse therapy if the course of the disease so changed that they believed such a measure was indispensable and urgent (and it was, indeed, adopted in 11 of the 52 cases).

The second ethical problem was this. All the patients on streptomycin were given four injections of the drug daily for (mainly) four months. What should be the parallel treatment of the control group? The

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Committee again had no difficulty. It immediately rejected any idea of corresponding injections of saline, so frequently and for so long a time, and relied upon a clear answer emerging in so serious a situation from two groups, both on bed-rest, but one injected and one not. It could not for ethical reasons insist upon an exact equality between the groups, the full double-blind procedure. Nor in this instance do I myself believe that procedure to have been required when the success or failure of the treatment rested upon life or death, or in the assessment of *x*-ray changes by persons kept unaware of the treatment given to the patient.

In a controlled trial, as in all experimental work, there is no need in the search for precision to throw common sense out of the window.

The Experimental Approach

In the assessment of a treatment medicine always has proceeded, and always must proceed, by way of experiment. The experiment may merely consist in giving the treatment to a particular patient or series of patients, and of observing and recording what follows—with all the difficulty of interpretation, of distinguishing the *propter hoc* from the *post hoc*. Nevertheless, even in these circumstances and in face of the unknown a question has been asked of Nature, and it has been asked by means of trial in the human being. There can be no possible escape from that. This is *human* experimentation—of one kind at least. *Somebody* must be the first to exhibit a new treatment in man. *Some patient,* whether for good or ill, must be the first to be exposed to it.

What, therefore, is new in the development of the last 20 years is, I would suggest, the most careful *planning* of the experiment in advance, and an experiment that usually, though not invariably, makes the following demands: (*a*) the construction of two (or more) closely similar *groups* of patients observed at the same time and differing in their treatment; (*b*) the construction of these groups by some process of *random* allocation; and (*c*) the *withholding* of a form of treatment from one or other of these groups.

In other words, we have the familiar controlled trial of to-day in which group A is given the new drug or other treatment under test and group B is not given that treatment, and the progress of their illness is then assessed and compared. As an additional, and occasional, feature we may (*d*) use a placebo as the treatment of the control group.

It is by means of such *comparisons* that we hope to avoid the dangers of deduction described so well by a writer in the *Boston Medical and Surgical Journal* a trifle over 100 years ago (Cheever, 1861). "Effects are ascribed to drugs which really flow from natural causes, and are but the usual succession of the morbid phenomena; sequences are taken for consequences, and all just conclusions confused. From the want of this knowledge [of the natural history of disease]; from defective observation, rash generalizations, and hasty conclusions *a priori,* have arisen the thousand conflicting theories which have degraded Medicine from its true position as a science, and interfered with its advancement as a practical art."

To be fair to Dr. Cheever I should add that he thought the experimental approach to be of "doubtful application in the therapeutical art" and had this to say of statisticians in 1861: "All the theorists say to the practitioner at the bedside, 'Do not try, but think; reason, argue, deduce!' Empirical Hunter said, 'Do not think, but try!' So the modern disciples of the numerical method would say to us, 'Neither think, nor try; but calculate!' Meanwhile the patient dies."

However that may be (and Dr. Cheever offers no alternative), the object of the present-day numerical method is to ensure that the patient will die rather less often. Let me return to the planned experiment designed to this very end.

The Controlled Trial

Customarily the situation is this, that from pharmacological and other tests there is reason to believe that a new drug is safe and likely to be beneficial. Neither belief, however, is established and neither can be established without some form of trial in man. Yet a very little experience of medicine shows that very often the beliefs are accepted without adequate trial and that very often they are wrong.

To take, almost at random, a quite simple and recent example from the literature. Thulbourne and Young (1962) point out that "in surgical wards antibiotics are commonly administered prophylactically to patients known to have chronic chest disease, and to those who for some other reason are thought to run a special risk of post-operative chest infection." Critical of this routine, they conducted a clinical trial with 65 patients given a course of penicillin before and after operation and 70 not so treated. It appears that the drug neither reduced the incidence of post-operative chest infections nor lessened their severity. Was it, one may ask in passing, more ethical to continue to use unquestioningly a powerful antibiotic, day in, day out, with no measure of its benefit than deliberately to withhold it from a specific group of patients in an attempt to find out?

A similar question may be posed of the trial by Fraser, Hatch, and Hughes (1962) of aspirin and antibiotics in the treatment of minor respiratory infections. The three randomly constructed groups treated with (1) potassium phenoxymethyl penicillin, (2) oxytetracycline, and (3) calcium aspirin, show no appreciable differences in the number of patients who developed complications, nor in the duration of their illness, fever, and headache. In short, there is no evidence that the antibiotics influenced either the course of the disease or the number or quality of the complications; and the authors are led to conclude that the indiscriminate exhibition of antibiotics has no advantage over aspirin in treating these uncomplicated minor illnesses in young adults.

A more difficult and complex situation was revealed in a trial of long-term anticoagulant therapy in cerebrovascular disease (Hill, Marshall, and Shaw, 1960, 1962). In previous uncontrolled studies there was a distinct if inconclusive suggestion in favour of their use, and sufficient, indeed, to make a trial difficult. Yet when put to the test of a controlled trial with the comparison of a fully treated group and a group given a dose insufficient to interfere with the clotting mechanism, it not only appeared that no protection was afforded against the recurrence of cerebrovascular accident, but there was a small but definite risk of cerebral haemorrhage in the fully treated cases.

Here we have an instance—and by no means unique—of the wheel turning full circle. At the start of the trial was it ethical to withhold the treatment? At its

end was it ethical to give it ? It is very easy to be wise (and critical) *after* the event ; the problem is to be wise (and ethical) *before* the event.

In all walks of life, I fancy, we are not always wise in our reluctance to depart from the *status quo*, our established and yet unproved beliefs. In medicine, to give an example, Sir George Pickering (1949) described how he was taught that iron and arsenic each had a specific effect on blood formation in man. "As a student and house-physician I saw nearly all patients with anaemia treated with a mixture containing 5 grains of iron and ammonium citrate, 2 minims of liquor arsenicalis, and other ingredients to supply taste and colour, which were given long Latin names. This was a time-honoured treatment used in my hospital and generally in this country for many years. I never saw any improvement of anaemia result from this treatment, though the patients were no doubt pleased to be seen from time to time by a considerate doctor. We now know as a result of applying the experimental method that the dose of iron used was quite inadequate, that there is a very common form of anaemia which responds readily to adequate dosage of iron, and which is in fact due to iron deficiency. As a result of applying the experimental method, we are not only now able to help patients that we could not help before, but by having learned the specific nature of the malady we are now able to prevent it in people who would probably have developed it but for our intervention. As far as I know arsenic has never been shown to benefit any form of anaemia."

Sometimes, of course, the difficulties of experiment are very much graver than in that example. When the benefits of streptomycin had been clearly established in young adult phthisis it was not at all easy to devise trials which would measure the relative value of *para*-aminosalicylic acid and isoniazid. Yet whether the experiment was well- or ill-designed it had *somehow* to be made. In looking back, and forward, it is proper to remember McCance's (1951) comment that the physician "forgets, indeed he may not even know, that what he would have regarded as an 'unjustifiable experiment' five years ago may have become one of his standard diagnostic or therapeutic procedures." To take a gloomier view, some of his standard diagnostic and therapeutic procedures of to-day may in five years' time be entirely obsolete.

In short, medical literature abounds with examples to show that the belief that an unproved treatment (new or old) *must* for ethical reasons be exhibited is unwarranted. Some treatments are valueless, some are hazardous. The whole question is how best can we discover those facts. If the clinical trial is the method of choice then the question becomes in what circumstances can the doctor withhold (or give) a treatment while preserving the high ethical standards demanded of his profession ?

There is no easy answer. In my own experience of collaboration with doctors the problem calls for close and careful consideration in the *specific circumstances of each proposed trial.* No doubt, of course, one can enunciate some very broad principles of ethical behaviour, principles which are an intrinsic part of the doctor's training. But I do not myself believe that it is possible to go very much beyond that, that one can reduce the broad principles to precise rules of action that are applicable in all circumstances.

A Draft Code of Ethics

This, however, is not the view of such an authoritative body as the Ethical Committee of the World Medical Association (1962). The results of their deliberations have been set out in a preliminary draft code of ethics on human experimentation which should serve as a guide to doctors.

In criticizing this code and in setting out subsequently my own views on medical ethics in controlled trials I am deeply conscious of the fact that I am a layman. My excuse is that I have participated and studied in some branch of medicine throughout my working life, and in clinical trials for nearly the last 20 years. In the planning and conduct of these trials I have had the good fortune to be associated with a very large number of medically qualified men and women, including many of the leaders of the profession. I have endeavoured to absorb their ways of thinking as well as their knowledge. I have spent many hours reflecting on these critical problems of ethics, and it is my hope that this account of those reflections may be of value. I would beg the reader to keep that in mind when I invade what may appear to be the very special province of the profession itself.

The code of the Ethical Committee of the World Medical Association starts with a precise definition of an experiment on a human being: "an act whereby the investigator deliberately changes the internal or external environment in order to observe the effects of such a change." Such change in the environment, it continues, should be made only if certain conditions are observed, and one of these conditions is that the experiment should be conducted "under the supervision of a qualified medical man." Even as a layman invited to this *sanctum sanctorum* of British medicine I cannot let that pass. In an exceedingly rash experiment that I have so far very carefully avoided I decide to measure the effects of my methods of teaching. I divide the class into two and I instruct these halves in quite different ways. I assess the effects of such a change in the *external* environment. An even rasher experiment—on randomly determined nights I persuade my wife to drink a cup of hot milk before going to bed ; I record her subsequent complaints of insomnia—that is, the effects of a change in the *internal* environment. Am I to be supervised in either of these pursuits of knowledge by a medically qualified man ? Without being facetious (and basically neither of my experiments is facetious) there are scores of experiments—for example, in industrial psychology—which are not the prerogative, or even within the special competence, of the medically qualified.

It may be retorted that such researches are not intended here. Maybe not, but it is what the words say. And if the code is to be helpful to your profession, surely it must be clear as to what it does mean ? Surely it must not be open to argument as to *intention* regarding who, what, when, or where ? If it is thus open to argument and individual interpretation what is its value ?

Another of the general principles that the code sets out in relation to the change in the environment is this: "That the nature, the reason, and the risks of the experiment are fully explained to the subject of it, who should have complete freedom to decide whether or not to take part in the experiment." It is quite clear that

this provision applies to my present subject-matter, since under the heading "experiments for the benefit of the patient" it is said that "controlled trials in therapeutic and preventive medicine should be conducted according to the general and special ethical rules concerning experiments on the individual."

Personally, and speaking as a patient, I have no doubt whatever that there are circumstances in which the patient's consent to taking part in a controlled trial should be sought. I have equally no doubt that there are circumstances in which it need not—and even should not—be sought. My quarrel is again with a code that takes no heed—and in dealing with generalities can take no heed—of the enormously varying circumstances of clinical medicine. Surely it is often quite impossible to tell ill-educated and sick persons the pros and cons of a new and unknown treatment versus the orthodox and known? And, in fact, of course one does not know the pros and cons. The situation implicit in the controlled trial is that one has two (or more) possible treatments and that one is wholly, or to a very large extent, ignorant of their relative values (and dangers). Can you describe that situation to a patient so that he does not lose confidence in you—the essence of the doctor/patient relationship—and in such a way that he fully understands and can therefore give an *understanding* consent to his inclusion in a trial? In my opinion nothing less is of value. Just to ask the patient does he mind if you try some new tablets on him does nothing, I suggest, to meet the problem. That is merely paying lip-service to it. If the patient cannot really grasp the whole situation, or without upsetting his faith in your judgment cannot be made to grasp it, then in my opinion the ethical decision still lies with the doctor, whether or no it is proper to exhibit, or withhold, a treatment. He cannot divest himself of it simply by means of an illusory or uncomprehending consent.

Another general principle of this code lays down firmly "that children in institutions and not under the care of relatives should not be the subject of human experiments." Does pasteurized milk contribute less than raw milk to the promotion of health and growth? Does sugar in the diet influence the incidence of caries? Is gammaglobulin more, or less, effective than convalescent serum in the prevention of measles? Was it unethical to find out in the very circumstances in which it was possible (as well as important for the subjects) to do so? The guide says Yes.

It also asserts that "persons retained in mental hospitals or hospitals for mental defectives should not be used for human experiment," and this would seem to me automatically to condemn as unethical clinical trials in psychiatry. Again, that may not be the intention; but it certainly has that result.

These are just a handful of examples of the proposed "should and should not" that come from high authority. It is said that they are only a "guide to doctors in different parts of the world," but once so formulated and promulgated it would, I suggest, be difficult, if not even sometimes legally hazardous, for a doctor to act counter to them. It is my belief that they may hamper, if not prevent, much research through clinical trials that not only is entirely ethical but can, indeed, be more ethical than the unthinking use—that is, *experiment*—of unproved treatments.

It is, however, easy to be destructive. Let me attempt to be constructive.

The Specific Approach

With every proposed clinical trial there is, in my experience, a whole series of ethical problems that have to be closely considered and solved before the trial is set in train and *within the particular circumstances of that trial.* In other words, my philosophy embodies *general* questions answered in a *specific* setting. Included in these questions will be the following.

1. Is the Proposed Treatment Safe or, in other words, is it Unlikely to do Harm to the Patient?

There can be no categorical answer Yes or No. No one of the enormously beneficial treatments that have revolutionized therapeutics over the last 20 years is free of undesired side-effects or without any hazard to the patient. None could have been introduced if complete safety had been demanded. Similarly, no operative procedure is without its mortality, however small.

With a known hazard of a proved effective treatment the decision to take that risk would obviously be influenced by the risk of *not* giving the treatment; for example, the doctor might well decide to exhibit chloramphenicol in typhoid fever and be reluctant to do so in uncomplicated whooping-cough. The same reasoning will be needed in facing the unknown. With no knowledge of a danger it would be proper to explore the potentialities of a new treatment in a disease of some severity, but not with a mild self-limiting condition.

Similarly, the possible nature and degree of the hazard itself calls for reflection. Taking again the known case, the physician might legitimately accept the transient nausea of P.A.S., but, in given circumstances, reject the irreversible vestibular damage that may follow certain treatments with streptomycin. With the unknown, using as guide all the available pharmacological information, he will need, I suggest, to think on similar lines.

In all clinical trials worthy of the name careful and precise observations are a *sine qua non.* Where any risk from a treatment may be anticipated one will need to think whether any special observations can be made to bring it to light—and possibly more rapidly than by means of haphazard uses of the treatment. Here indeed, I would argue, is one of the advantages—practical and ethical—of the controlled trial, that by its exact comparisons it may more rapidly pinpoint the unsuspected undesirable side-effects of a treatment. I would add, however, that no trial is likely to reveal the rare and disastrous effect that occurs only once in many hundreds of cases.

2. Can a New Treatment Ethically be Withheld from Any Patients in the Doctor's Care?

The basis of the controlled trial of a new treatment compared with the old is, of course, that we are entirely ignorant of the relative values of these treatments. Presumably, however, we shall know something of the absolute value of the older treatment, and the question, therefore, may well be *not* can the doctor withhold the new, but can he withhold the established in favour of what is then quite unproved?

Let us again consider some possible circumstances. At one extreme we may have an orthodox treatment that offers nothing in a disease that is lethal—for example, cancer. It would seem to me that the doctor cannot withhold any new treatment that appears to offer a hope

of success. At the other end of the scale we have an orthodox treatment that offers nothing in a mild self-limiting disease—for example, the common cold. Can we not, at the very least in young adults who are unlikely to suffer complications or to die from a running nose, withhold the latest wonder drug from one group to measure adequately its alleged effects ?

In between these extremes there will be an enormous diversity of circumstances—a diversity both in diseases and their severity and in established treatments and their values, proved or accepted. Surely the question can be answered *only* in terms of those circumstances ?

3. What Patients may be Brought into a Controlled Trial and Allocated Randomly to Different Treatments ?

The essential feature of a controlled trial that determines an answer to this question is that it must be possible ethically to give *every* patient admitted to a trial any of the treatments involved. The doctor accepts, in other words, that he really has no knowledge at all that one treatment will be better or worse, safer or more dangerous, than another. I have already briefly illustrated above how often that is true. If the doctor does not believe that, if he thinks even in the absence of any evidence that for the patient's benefit he ought to give one treatment rather than another, then that patient should not be admitted to the trial. Only if, in his state of ignorance, he believes the treatment given to be a matter of indifference can he accept a random distribution of the patients to the different groups.

In that situation I would, as a statistician, point out that there is nothing unethical in the use of random sampling numbers, though to the uninitiated they may appear a trifle inhuman. If the treatment is a matter of indifference, then how we distribute the patients to each treatment is equally a matter of indifference. It happens that the use of random sampling numbers is usually a better method than the more traditional alternate patient technique.

I would argue, too, that ethically the doctor is in very much the same situation if, more traditionally, he measures the relative effects of treatments by "ringing the changes" *within* patients rather than *between* patients. It was, wrote Lord MacMillan (1937), a wise statesman who said of the law that "where it is not necessary to change it is necessary not to change." The same dictum will apply to controlled trials within the patient, and so, *mutatis mutandis,* we will have to answer just the same questions as I am posing here in relation to trials between patients.

Returning to my question what patients may be brought into a trial, we shall need to think whether certain types should be omitted even though there may be no evidence whatever that one treatment rather than another will be to their benefit—for example, pregnant women with whom in the light of recent knowledge we should obviously deal with ultracaution, patients with complicating conditions and diseases, the very old and frail or the very young to whom any specially required observations and measurements (of, say, the blood) will be unduly vexatious, etc.

All this must be thought upon. By certain omissions from a trial we may limit the generality of the answer given by it, but on ethical grounds that, in my experience, must be accepted. While on this question of omissions I would repeat, and with the utmost emphasis, what I pointed out in reference to the first trial of streptomycin in pulmonary tuberculosis—namely, that it is implicit in all the trials with which I have been concerned that omissions must take place *after* the admission of the patients if the doctor in charge of a patient believes it to be necessary for that patient. This indeed may make extremely difficult the effective trial of treatments in chronic diseases. If the patient does not recover at the exhibition of one treatment, the doctor may feel it necessary to exhibit the other and thus nullify the required strictly controlled comparison. But that, of course, has been accepted at the outset in every controlled trial—that the ethical obligation always and entirely outweighs the experimental. The doctor in practice testing—that is, experimenting with—a new treatment can always change back to the old and orthodox if he thinks fit. Controlled trials should be equally fluid—though they may rightly demand very much more careful observation and reflection before the change back is made.

It is pertinent, too, to point out that the controlled trial almost invariably demands the follow-up and study of *every* patient admitted to it whether on the allocated treatment or not. Once again, therefore, it may be, to my mind, more ethical in its concepts and execution than the uncontrolled haphazard observations of patients, many of whom are quite unconcernedly lost to sight.

4. Is it Necessary to Obtain the Patient's Consent to His Inclusion in a Controlled Trial ?

I have already made clear that in my opinion this question should really be worded, *When* is it necessary to ask the patient's consent to his inclusion in a controlled trial ? At one extreme is the situation in which the patient will be subjected to discomfort or pain on one or more occasions—for example, by an inoculation, or a series of inoculations, with normal saline to measure the value of inoculation with a believed efficacious agent. Here, in face of pain and discomfort which is not an inevitable concomitant of the patient's disease or of its treatment, I would myself wish to have a full and understanding consent.

Going further, I would in particular wish to seek it in the trial of a prophylactic inoculation in which the doctor is not concerned merely to do his best for the patients already in his care, but in which he is *inviting* well persons voluntarily to enter an experiment. In making the invitation it would be proper, as well as prudent, to explain the circumstances to those you endeavour to attract. It is, however, clear that the results of such experiments (for example, the use of an influenza vaccine in patients with chronic bronchitis) may not only contribute to knowledge but be of considerable benefit subsequently to the participants themselves. Trials are frequently made with both motives, and should be thought upon in both respects.

Returning to the problem of the treatment of patients in the doctor's care, the customary situation of the controlled trial is, as I have already described, an ignorance of the relative merits of two (or more) treatments. To dispel that ignorance you decide to give one treatment to one of your patients and the other treatment to another of your patients—for example, corticosteroids and aspirin in some form of rheumatoid arthritis. Having made up your mind that you are not in any way subjecting either patient to a recognized

and unjustifiable danger, pain, or discomfort, can anything be gained ethically by endeavouring to explain to them your own state of ignorance and to describe the attempts you are making to remove it? And what is true of two patients is equally true of 20 or 200. Once you have decided that either treatment *for all you know* may be equally well exhibited to the patient's benefit, and without detriment, is there any real basis for seeking consent or refusal?

Does the doctor invariably seek the patient's consent before using a new drug alleged to be efficacious and safe? If the answer is No, then what process, one may ask, makes it needful for him to do so if he chooses to test the drug in such a way that he can compare its effects with those of the previous orthodox treatment?

5. Is is Ethical to Use a Placebo, or Dummy Treatment?

The answer to this question will depend, I suggest, upon whether there is already available an orthodox treatment of proved or accepted value. If there is such an orthodox treatment the question hardly arises, for the doctor will wish to know whether a new treatment is more, or less, effective than the old, not that it is more effective than nothing. For instance, the U.K./U.S. international trial of corticosteroids in the treatment of rheumatic fever in children contrasted their effects with those following the administration of aspirin, the accepted treatment of the day. Those in charge of the trial believed that it would have been unethical to withhold aspirin, however tenuous its claims may have been. On the other hand, if there is no orthodox treatment, then surely in certain circumstances one may ethically invent one?

In the treatment of the common cold in young adults the trial was designed to contrast the antihistamine compound with an inert substance. Since the measure of the effects of the drug would inevitably lie in the subjective impressions of the patients, this form of control was essential and no trial could have been usefully instituted without it. Having made it clear to the patients that they would not all get the drug our own consciences were clear.

Indeed, in this connexion I believe a useful question to ask oneself is to what extent is an exact control essential? The answer certainly is not that one of the group must *always* be a mirror-image of the other. The ethical problem may sometimes, I believe, be met in realizing that and in not making the best the enemy of the good. As I described earlier, the M.R.C. Committee did not regard it as at all needful to mimic the injections of streptomycin in its early trial in pulmonary tuberculosis. Many such occasions will arise in this field of controlled trials.

In this setting the doctor will also wish to consider the doctor/patient relationship. Harm may be done if the public comes to believe that doctors are constantly using them as guinea-pigs. In exhibiting new treatments they are, it is my belief, doing that willy-nilly, but the public does not realize it. But they need not go out of their way to make it obvious by an *unnecessary* use of dummy pills. On the other hand, I do not myself believe the argument that it is never ethical knowingly to use a placebo in a controlled trial. Though they may not always be doing so knowingly, doctors are surely using placebos every day in exhibiting drugs of which they do not know the value, and many of which will disappear in the course of time.

6. Is it Proper for the Doctor Not to Know the Treatment being Administered to His Patient?

The so-called "double-blind" procedure in a controlled trial requires that neither patient nor doctor should know the nature of the treatment being given in the individual case. By such means it is hoped that unbiased subjective impressions and judgments of the course of the illness can be obtained. Sometimes one can escape the issue merely by taking a little thought and trouble. There can be no ethical objection to one doctor treating the patient and another, without knowledge of the treatment, making the assessments.

Thus in many trials of drugs in the treatment of pulmonary tuberculosis the *x*-ray evidence has been assessed by independent experts who had nothing to do with the treatment of the patients and were never in the individual case informed of its nature. Similarly, in a trial of an alleged active agent in rheumatoid arthritis one doctor injected the concoction (or its control) into the patient and knew the nature of the injection. Another doctor assessed the relief of pain, stiffness, etc., and did not know the nature of the injection. However, there are occasions when it is difficult to use such methods and when, therefore, it is needful to consider whether the doctor in charge of the patient can himself be kept in ignorance of the treatment.

If a trial of this nature is set up, it is axiomatic, of course, that the code can be broken at any moment if the doctor thinks necessary. The question, therefore, is rather whether it is proper for the doctor ever to start that way and to endeavour to maintain his ignorance. The issue, I suggest, turns as usual upon what may conceivably happen to the detriment of the patient if the doctor does not know the treatment. That is what calls for reflection in the special circumstances of each trial.

The answer may be that *nothing whatever* is likely to happen to the detriment of the patient—and this, I believe, was the case in our trial of a short course of an antihistamine for the common cold. On the other hand, it may be that some harm could occur, particularly in a trial of long duration, through, for example, the doctor failing to adjust the dose of a drug finely enough to meet the individual patient's needs. In such a situation it would seem that the double-blind procedure could not be used at all.

It is, however, in terms such as these applicable to the specific disease and its treatment that the answer to the question must be sought.

Conclusion

It is my experience that these six questions will cover the main ethical problems of a controlled clinical trial, and it is to them that the answers in every variety of circumstances must be pursued. One thing, however, I would in conclusion make very clear. In this lecture I have been concerned *entirely* with controlled trials, and the philosophy and arguments that I have put forward apply only to such trials. I have not concerned myself with a quite different problem, what one may perhaps term exploratory observations—for example, cardiac catheterization, liver biopsy, and the like. Such observations, I would believe, may call for a different approach, and, indeed, one of the problems that the profession will have to face in the proposals of the World Medical Association is the inclusion within one

and the same code of such diverse pursuits as controlled trials and exploratory observations.

I admit, as I said earlier, that it may appear impertinent for an unqualified camp follower to air such views, and particularly in this environment. There are just two things I would add in extenuation, and I hope that they may prove to be the only really categorical assertions of which I have been guilty in this lecture. The first is that from my associations with doctors in controlled trials I have learned that the better the statistician understands the doctor/patient relationship and the doctor's very real and unique ethical problem the better can he help to devise a trial that may be less than ideal experimentally but yet likely to be of some, and perhaps considerable, value to medicine.

Secondly, and still more important, I have learned that though the statistician may himself never see a patient—though indeed like Tristram Shandy's Uncle Toby he may live his life in doubt which is the right and which the wrong end of a woman—nevertheless, he cannot sit in an armchair, remote and Olympian, comfortably divesting himself of all ethical responsibility. As a partner in a combined endeavour a full share of that responsibility will always lie with him. He must endeavour to acquire the ethical perception and code of honour that is second nature of those qualified in medicine. And above all he must learn to blend the objectivity and humanity that this lecture commemorates.

REFERENCES

Brit. med. J., 1948, **2**, 791.
Cheever, D. W. (1861). *Boston med. surg. J.*, **63**, 449.
Fraser, P. K., Hatch, L.A., and Hughes, K. E. A. (1962). *Lancet*, **1**, 614.
Hill, A. Bradford, Marshall, J., and Shaw, D. A. (1960). *Quart. J. Med.*, **29**, 597.
—— —— —— *Brit. med. J.*, **2**, 1003.
McCance, R. A. (1951). *Proc. roy. Soc. Med.*, **44**, 189.
MacMillan, Lord (1937). *Law and Other Things*. Cambridge Univ. Press.
Medical Research Council Streptomycin in Tuberculosis Trials Committee (1948). *Brit. med. J.*, **2**, 769.
Pickering, G. W. (1949). *Proc. roy. Soc. Med.*, **42**, 229.
Thulbourne, T., and Young, M. H. (1962). *Lancet*, **2**, 907.
World Medical Association (1962). *Brit. med. J.*, **2**, 1119.

PREGNANCY DIAGNOSIS BY A ONE-STAGE PASSIVE HAEMAGGLUTINATION INHIBITION METHOD

BY

A. J. FULTHORPE, M.B., D.T.M.&H. **J. A. C. PARKE, B.Sc., Ph.D.**
Wellcome Research Laboratories (Biological Division), Beckenham, Kent

J. E. TOVEY, M.D.
Senior Registrar, Lewisham Group Laboratory, London

J. C. MONCKTON
Southern Group Laboratory, Hither Green, London

There have been several reports on the detection and assay of human chorionic gonadotrophin (H.C.G.) by immunological methods. Brody and Carlström (1960) immunized rabbits with a purified preparation of H.C.G. and used the immune serum in a complement-fixation test for the presence of hormone in the urine of pregnant women. McKean (1960) demonstrated the feasibility of using a precipitin test with rabbit antiserum to detect H.C.G. in urine samples. A passive haemagglutination inhibition method for the same purpose was developed by Wide and Gemzell (1960), and was shown to be qualitatively accurate.

These observations were commented on by Butt, Crooke, and Cunningham (1961), who suggested that there was some lack of immunological specificity between H.C.G. and pituitary gonadotrophin (luteinizing hormone), and that the results of such *in vitro* tests should be accepted with reserve. Midgley, Pierce, and Weigle (1961) prepared rabbit antisera, using commercial preparations of H.C.G., and demonstrated that, although such antisera contained antibodies to antigens in normal human urine and normal human sera, it was possible to use such sera to demonstrate the presence of H.C.G. in serum and urine.

This communication deals with a one-stage haemagglutination inhibition system which has been developed and used to detect the presence of H.C.G. in urine in pregnancy, and with quantitative tests which have been carried out to assay the H.C.G. content of urine and of dried commercial preparations of hormone.

Materials and Methods

Reagents

Borate Succinic Acid Buffer, 0.05 M, pH 7.5.—Sodium borate ($Na_2B_4O_7.10H_2O$) solution was prepared containing 95.5 g. of sodium borate and 37.5 g. of sodium chloride in 5 l. of distilled water. Succinic acid—$(CH_2COOH)_2$—solution was prepared containing 23.6 g. of succinic acid and 30 g. of sodium chloride in 4 l. of distilled water. Equal volumes of the two reagents were mixed and the *p*H was adjusted to 7.5 with a small volume of the sodium borate solution.

E.D.T.A. Buffer pH 8.4.—Disodium dihydrogen ethylene diamine tetracetate 17 g./l. in distilled water was adjusted to *p*H 8.4 with 2N sodium hydroxide.

Borate Boric Acid Buffer pH 8.2–8.3.—This was prepared from a mixture of 3 g. of sodium borate, 4.4 g. of boric acid (H_3BO_3), and 7.6 g. of sodium chloride made up to 1 l. with distilled water.

Rabbit Antisera

Miscellaneous rabbits of about 2 kg. weight were injected with 1,500 units of H.C.G. (Leo) in 0.5 ml. of saline mixed and homogenized with an equal volume of complete Freund adjuvant (Difco). The mixtures were injected intramuscularly in the flank ; the injections were repeated after 28 days, and the animals bled and serum separated 10 to 14 days later. The titres of the serum obtained by this method with H.C.G.-sensitized cell suspensions were usually 1/2,000–1/5,000.

Preparation of H.C.G.-sensitized Erythrocytes

Satisfactory preparations of sensitized preserved sheep erythrocytes have been made by two methods: (*a*) a modification of Ling's (1961) method and (*b*) an original method. The change to the second method was dictated by a desire to obtain a more stable product which was simpler to prepare.

Method 1.—Fresh sheep cells were washed three times in 20 volumes of saline and made up as a 1% suspension