appearance and degree of streptomycin resistance with clinical results brought out the fact that on the whole those patients from whom highly resistant strains were isolated early did less well than those whose organisms showed lesser degrees of resistance later. Seven patients whose organisms did not develop resistance over 32 times that of H37Rv improved steadily. The figures are not large enough to correlate the clinical results, the degree of streptomycin resistance acquired by the organism, and the other relevant factors such as the type of lesion present at the beginning of treatment.

This investigation has achieved its limited object by proving that streptomycin is of value in the treatment of acute forms of pulmonary tuberculosis. Many further problems remain to be solved, however, before the indications for the use of this new remedy in pulmonary tuberculosis can be regarded as firmly established. There are already enough favourable reports to justify the use of streptomycin in the treatment of ulcerative lesions of the main bronchi at the pre-stenotic stage where these are affecting prognosis. Its value in ulcerative tuberculous lesions of the larynx, pharynx, and tongue is also well established. Patients with old and apparently stable lesions who develop, while under observation, acute spread of the disease in previously unaffected parts of the lung may be expected to respond well, since they can be treated when the lesions are at the very earliest stage. Whether or not streptomycin should be used as a routine prophylactic against extension of the disease after surgical treatment for pulmonary tuberculosis remains to be seen. It is certainly of great importance to determine, for instance, whether streptomycin should be given prophylactically to patients undergoing thoracoplasty or whether it is better reserved for the treatment of the smaller number in whom the disease actually extends after operation. The answer to this question cannot be deduced *a priori*; even if patients treated prophylactically showed better immediate results, in the long run they might be worse off, since those among them who later had a recrudescence of disease suitable for streptomycin treatment might prove to be harbouring resistant organisms and to be no longer responsive to the drug. The question of the proper use of streptomycin as an adjunct to collapse therapy, both medical and surgical, must be settled.

Streptomycin resistance is perhaps the most important problem of all. From the point of view of the individual patient the probability that the organisms will develop resistance after a relatively short period of treatment means that a course of streptomycin may be effectual only once during possibly a long and chequered illness. From the point of view of the community there is the risk that patients with unsuitable lesions ineffectively treated may disseminate streptomycin-resistant organisms, so that an increasing number of new cases of all forms of tuberculosis may in future be found to be unresponsive to streptomycin. It therefore seems in the best interests both of the individual patient and of the community that streptomycin should be used for the treatment of pulmonary tuberculosis with a proper understanding of the difficulties and dangers and only when the indications for its use are clear. Streptomycin may, of course, be outmoded in the treatment of tuberculosis by new and more potent antibiotics. Even so, the enormous amount of work done upon it will not have been wasted. Laboratory and clinical techniques which have been evolved can no doubt be applied to the problems of other antibiotics, and the Medical Research Council's controlled trial will serve as a model for future investigations of substances introduced for the treatment of pulmonary tuberculosis.

THE CONTROLLED THERAPEUTIC TRIAL

The clinical trial of a remedy is as old as medicine itself. The idea of controlled investigation and statistical analysis is recent enough to call new. With the older hit-or-miss method the patient was treated, and subsequent observation showed with what result. If the patient—or patients—died, or at least failed to get well, the results that flowed from the remedy were unequivocal. It is when the patients, or anyway some of them, recover that we are faced with the *post hoc propter hoc* dilemma. Is the result due to the remedy or to the *vis medicatrix naturae*? Until quite recent years that difficulty was principally met—when it was met at all—by comparing patients submitted to the new treatment with the patients the clinician had observed in past years. The problems of such a comparison were many. It was often not certain that the patients selected for the trial were comparable with those previously seen; those earlier patients were often not equally well documented, so that records were lacking and the comparisons necessarily crude; the numbers involved were frequently far too few to merit the confidence placed in them; and mortality from the same disease at different periods of time is affected by factors such as breeding out of highly susceptible stock, economic and social conditions, and variations in the infecting organism. With a new discovery that produces dramatic results there would rarely be any doubt about the answer, but such discoveries are rare. It is the smaller, yet often important, advances that it is difficult to substantiate—or disprove—by such rough-and-ready means. The meteoric rise and regrettably slower fall of many a form of treatment bear eloquent witness to the lack of the controlled trial in medicine. The application of such trials was gaining ground before the war and their value becoming more and more appreciated by the clinician—subject always, it must be stressed, to the fundamental ethical problem inherent in using human beings as the subject of experiment.

In developing the trial of streptomycin in the treatment of pulmonary tuberculosis, reported on page 769, the Medical Research Council's Committee was clearly relieved of this particular moral responsibility. It had allocated much of the limited streptomycin at its disposal to treating and observing two fatal forms of tuberculosis—the miliary and meningeal. It had, needless to say, a quite insufficient supply to treat all possible cases of pulmonary tuberculosis, and in this situation rightly set about planning a rigorously controlled investigation. The plan adopted is worthy of careful study in itself, quite apart from the results to which it led, for it may well serve as a model in this field.

To begin with, the Committee was clearly of a mind not to dissipate its energies—and its small supply of the drug

—in attempting to cover too wide or too ill-defined a field. It selected one type of case and defined it as rigidly as possible—acute progressive bilateral pulmonary tuberculosis of presumably recent origin, bacteriologically proved, unsuitable for collapse therapy, ages 15 to 30. In such trials it is often tempting to add little groups of patients of differing types here, there, and everywhere with the object of learning rather more. Though with a statistical design it will certainly sometimes pay to do so, very often the rather more becomes the rather less. Such a trial gives doubtful answers to the many points but no decisive answer to any. This temptation the Committee, and the clinicians co-operating with it, resisted.

Having defined the type of case it proposed to observe, the Committee next obtained the co-operation of various hospitals in carrying out the controlled trial and sought for suitable patients to place in their care. The important point here is that without some such central organization to direct the work, and without the collaboration of a number of hospitals in carrying it out, a sufficient number of patients of the same type will rarely be available. Small groups here and there will give conflicting answers. Then to ensure that the patient did conform to the features laid down the Committee set up a selection panel. This panel conceivably might have been influenced in selecting or rejecting a patient if it had known beforehand whether the patient was to be allocated to the streptomycin or to the controlled group—e.g., if alternate patients had been taken. It was relieved of any such worries by an ingenious system of sealed envelopes. Once a patient had been accepted an appropriate numbered envelope was opened, and not till then was the patient's group revealed. The allocation to "S" or "C" in this form had been made at random by the statistician. It is instructive also to see how close an equality of group characteristics this statistical method produced. For instance, 54% in the "S" group and 46% in the "C" group were in poor general condition at the start of the trial; 20 and 17 were desperately ill; 65% of "S" patients and 56% of "C" had a sedimentation rate over 50; 32 "S" and 30 "C" cases showed large or multiple cavities; in 19 of each group there was radiological evidence of segmental atelectasis. The random allocation has not only removed personal responsibility from the clinician and possible bias in his process of choosing patients, but has on the whole effectively equated the groups—fundamental, of course, to the general comparisons (the "S" group, as it happens, was slightly the poorer).

The hospitals to which these patients passed were provided beforehand with standard record forms designed specially for the trial, and examinations of the patient were required at fixed intervals. Thus uniform records were assured and any loss of essential particulars guarded against. Treatment was likewise standardized, though the clinicians in charge of the patients were naturally given freedom of action in urgent cases. To overcome any difficulties that might arise—indeed, were certain to arise in a trial of this nature—frequent meetings were held both of the clinicians and pathologists concerned, while the co-ordinator at the centre constantly visited the periphery. Clearly in this way much trouble was taken to ensure smooth running and to develop a co-ordination of methodology in every respect throughout the hospitals. Finally the monthly reports from the hospitals were assessed centrally, and thus again uniformly. In this assessment it may be noted that one of the fundamental criteria of the effect of the drug was bound to lie in the change in the radiological picture. To remove all possibility of bias the Committee had the films assessed independently by two radiologists and a clinician, each of whom had no knowledge whatever whether the film they saw related to a streptomycin or to a control case. Such a method vastly increases confidence in the results, and it is important to realize that it in no way questions the intellectual honesty of the investigator who is thus asked to work "blind." It guards not only against unconscious bias but, equally important, against any honest attempt in the assessor to allow for a possible bias.

It was by these careful means that the Committee reached its objectives—a rigorously controlled investigation, an impartial assessment of its results.

SOCIAL WELFARE AND VOLUNTARY ACTION

In his report on Social Insurance and Allied Services Sir William (now Lord) Beveridge told the Government of the day how the State could cure poverty by a comprehensive scheme of compulsory insurance. His new contribution to sociology[1] contains an account of the methods which have been used to alleviate misfortune. In effect he asks, Can the State, using all the means at its disposal, cure unhappiness? The answer is obviously No, even if we knew how to define happiness. A "good" society cannot be made without voluntary action for social advance even in what Lord Beveridge calls a Social Service State. He divides voluntary action into two categories, mutual aid and philanthropy. The best example of mutual aid is the friendly societies, which were established in order that men known to each other could pay money regularly into a common fund and draw on that fund when they were in need. But to the bulk of their 8,000,000 members in 1947 the friendly societies represented not good fellowship but a means of insurance by contract. In the first Beveridge report it was suggested that the friendly societies should be used as the agents of the Government for the distribution of State benefits to their members. Instead the marriage of 1911 between the State and the voluntary agencies has been followed by a divorce, and the State is now constructing a complete and exclusive administrative machine of its own.

Lord Beveridge gives some other examples of mutual aid societies, including the hospital contributory schemes, the growth of which he considers to have been one of the greatest successes of mutual aid in modern times. The need to provide for special expenses at death has been as widely felt as the need for security in sickness. From this grew the remarkable form of modern business known as industrial assurance. The Royal Commission which inquired into the work of friendly societies in 1871–4 did

[1] *Voluntary Action—A Report on Methods of Social Advance*, 1948. Allen and Unwin Ltd, London. Price 16s.

[2] "Report (1947) of the Committee on the Care and Treatment of the Elderly and Infirm," *British Medical Journal Supplement*, 1947, 1, 133.