CONTROLLED CLINICAL TRIALS

C.I.O.M.S. SEMINAR IN VIENNA

[FROM A SPECIAL CORRESPONDENT]

At the end of last month the Council for the International Organizations of Medical Sciences (C.I.O.M.S.) sponsored a seminar in Vienna on "Controlled Clinical Trials," at which a British team of 17 medical scientists played the leading role. The seminar was attended by specially chosen representatives (clinicians, statisticians, laboratory workers) from most European countries, including Poland and Czechoslovakia but not the U.S.S.R., and by medical staff from British and Continental pharmaceutical companies, making altogether over 100 participants.

The main objective of the seminar was to discuss with Continental colleagues the ethics, methodology, and applications of this experimental approach to therapeutics.

Aims and Ethics

After short speeches of welcome from Professor J. MAISIN (C.I.O.M.S.), Professor K. FELLINGER (Council of Hygiene, Vienna), and representatives of the Ministry of Social Welfare, Unesco, and W.H.O., the scientific proceedings were opened by the chairman, Professor A. BRADFORD HILL, F.R.S. (London), with an introductory paper on aims and ethics. After a drug had passed the laboratory trials of safety and pharmacological efficacy, the physician had to test its clinical worth on sick patients. If it was quickly seen that the drug had a life-saving effect on diseases with a very high case fatality, as happened with penicillin in subacute bacterial endocarditis and streptomycin in tuberculous meningitis, a control group was not necessary; but it was still desirable to find out the optimum dosage, etc., of the drug in order to obtain the best therapeutic results. Where the new treatment was less likely to have a dramatic effect, the controlled trial allowed the physician to make his comparisons more precise, informative, and convincing. The trial must be designed to answer a specific question, and, as a preliminary, it called for careful definition of the type of patient concerned and of the criteria by which recovery, or improvement, was assessed: objective measurements and subjective judgments of progress were both desirable. Sometimes a defined, uniform treatment for all patients might be called for; at other times the clinicians would need freedom to vary the treatment according to the patients' responses; both methods were possible in the controlled trial. There was no golden rule about the ethics of controlled trials, except that whenever a therapeutic trial was thought desirable each case should be examined on its own merits.

Professor L. J. WITTS (Oxford) continued on the same theme. While the consent of the patient to be included in a therapeutic trial was regarded as essential, it was often in fact unnecessary. It should always be obtained if an orthodox remedy was being withheld or if there was an element of risk. Very often it was more important to obtain the approval of the family doctor and the nursing staff. A clinical trial should bring some benefit to society not otherwise obtainable; in other words, as much as possible must be learned about the new drug by animal experiment before it was tested in man. There must also be avoidance of unnecessary suffering.

Professor Witts favoured the "double blind" trial, in which a dummy tablet for the control group was used so that neither doctor nor patient knew who was getting the drug under test. In any controlled trial there must always be permission to withdraw a patient if the doctor became worried about his condition or for other valid reasons. Even so, the "double blind" trial might create a conflict of loyalties between the search for truth and the welfare of the individual patient; but in society both doctors and patients have duties as well as rights.

Comparability and Assessment

Dr. P. ARMITAGE (London), in discussing the construction of comparable groups, pointed out the fallacies of comparing treated and control groups at different times or in different hospitals. Some system of random allocation avoided bias, and entry into the trial must be recorded before the patient was allocated to one or other groups by random numbers or other acceptable procedure. Exclusion from a trial might be necessary for several valid reasons, but such exclusions should occur equally in the different groups. If this were not possible, it might be advisable in the analysis to consider the whole group for whom the treatment was intended rather than the small group on whom it was performed.

Dr. C. M. FLETCHER (London) discussed criteria for diagnosis and assessment in clinical trials. Assessment might be predominantly subjective, as were answers to questions about symptoms, observations of clinical signs, or the interpretation of radiological or histological appearances. If observations could be graded in a semi-quantitative manner, they became more objective, but both subjective and objective measurements were liable to observer error or lack of repeatability. Tests should provide good discrimination between normal and abnormal, and they should be simple to perform, so that they were readily available to others who might want to repeat them.

Treatment of Colds and Sore Throats

These opening papers on aims and principles in controlled clinical trials led on to their application, first to acute infections, of which the common cold and sore throat were chosen as examples, and then to chronic infections such as pulmonary tuberculosis and rheumatoid arthritis. Dr. J. KNOWELDEN (London) reviewed the 10-year-old trial of an antihistaminic drug which had been claimed to abort the common cold. He showed that in a large trial with 1,500 patients the rate of amelioration and cure, as judged on subjective criteria, was the same in those given the drug and in the controls given lactose tablets.

Professor R. CRUICKSHANK (Edinburgh) described a trial of penicillin in the treatment of sore throat among military recruits. Since sore throat was a clinical syndrome and not a specific infection, laboratory control of aetiology was essential. The progress of the patients suffering from streptococcal sore throat (about two-thirds of the total), of whom half were given a 4-day course of penicillin injections while both groups received aspirin gargles, was assessed subjectively and objectively. There was a more obvious difference in favour of the penicillin-treated group on the objective measurements (temperature and leucocyte counts) compared with the subjective criteria (complaint of local pain, inflammation in the throat). The bacteriological data showed that, while the penicillin temporarily reduced the infecting streptococci, at the follow-up three weeks later streptococcal carriers were as frequent in the treated as in the control groups.

Chemotherapy of Tuberculosis

The session on chronic infections was opened by Dr. IAN SUTHERLAND (London), who described the methods used in the designs and measurements of the M.R.C. controlled trials in the chemotherapy of pulmonary tuberculosis. In the first trial, only 100 young adult patients suffering from progressive bilateral pulmonary tuberculosis were needed to demonstrate the efficacy of streptomycin. Larger numbers were wanted when two or more effective drugs were being compared, and for this purpose several co-operating hospitals with central co-ordination were necessary.

This story was continued by Dr. J. G. SCADDING (London), who dealt with some of the clinical aspects of the M.R.C. trials in pulmonary tuberculosis. These had the merit of being linked in sequence, a system which obviated the need for an untreated control group. The co-operative trial with clinicians and bacteriologists from several or many hospitals taking part had both ethical and scientific advantages and tended to raise medical standards in the collaborating

centres. It was essential that the protocol be discussed by those taking part in the trial before it was started, and there must be a conscience clause to allow the physician to alter treatment if he felt this was essential for the patient's well-being.

Professor J. CROFTON (Edinburgh) discussed first some points in radiological assessment and gave as illustrations three recent trials in Scotland: (1) a comparison of chemotherapy in ambulant and bed-rest patients with mild pulmonary tuberculosis; (2) a trial of "prophylactic chemotherapy" in patients with pulmonary tuberculosis of doubtful activity; and (3) a comparison of chemotherapy plus prednisolone with chemotherapy alone for patients with severe pulmonary tuberculosis.

Rheumatoid Arthritis

The evaluation of therapy in rheumatoid arthritis presented many difficulties, said Professor J. H. KELLGREN (Manchester), since it was a chronic, phasic disease, characterized by unpredictable remissions and exacerbations, while the degree of articular crippling might depend on many different factors. Again, the aetiology and pathogenesis of rheumatoid arthritis were obscure, although the discovery of the specific serum macroglobulin might provide an answer to the problem of definition. In the meantime, diagnosis and assessment of progress were based on such subjective and objective criteria as the degree of crippling, E.S.R., *x*-ray appearances, and the presence of the rheumatoid serum factor (found in at least 80% of the more severe cases).

Professor E. G. L. BYWATERS (London) then dealt with some of the problems in a long-term trial of different drugs in rheumatoid arthritis, and presented results obtained in comparative trials of aspirin and cortisone. In the discussion, Professor MORTENSEN (Copenhagen) claimed it was impossible to have a "double blind" trial where aspirin and cortisone were being compared because of the effects of the latter drug (moon face, etc.), but Dr. R. DOLL assured him that doctors would diagnose "mooning" in patients on aspirin—an example of observer error.

Newer Designs of Trial

"Other designs in clinical trials" was the theme of the next session. Dr. D. D. REID (London) discussed the pros and cons of the serial testing of different drugs on the same patient. This "within-patients" procedure might be appropriate where the expected clinical response was temporary alleviation of symptoms or where variation in the response of the same patient over a period of time might be appreciably less than the variability in response between different patients at one point in time.

Dr. DOLL (London) discussed the multi-factorial type of trial, whereby several therapies could be currently assessed with considerable economy in patients and time. The simplest method was to divide the patients into three or more groups, to treat one as a control group and to give different treatments to each of the others. The same control group would then serve for comparison with two or more treatment groups and the total number of patients required was reduced. The number could be reduced still further if, of the eight possible combinations of three treatments, each treatment was given or withheld in combination with each of the others. If each of these combinations was given to an equal number of patients, it was also possible to discover whether any of the specific treatments had had an adjuvant effect on any of the others.

The sequential method of analysis in a clinical trial was described by Dr. ARMITAGE (London). Again, there was saving of patients and time, since the trial could be stopped when the sequential analysis had shown significant results. This method was particularly suitable if the response to treatment was apparent early, as in acute diseases, or in the temporary amelioration of symptoms in chronic diseases. The sequential method could also be applied when the patient served as his own control.

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To-day's Drugs

With the help of expert contributors we publish below notes on a selection of drugs in current use.

Detigon (Farbenfabriken Bayer (Levmedic)).—This is a new antitussive drug which was discovered by screening a large series of chemical compounds. It is 3-dimethylamino-1-phenyl-1-o-chlorphenyl-propan-l-ol, and is not closely related to any other drugs. Its mode of action has not been fully investigated, but it is said to be as active as codeine in suppressing the cough reflex in dogs. The makers claim that the action of detigon does not last as long as that of codeine, and that it can be given repeatedly without development of tolerance. It is said not to depress respiration, or cause nausea, constipation, or mental depression. It acts as a local anaesthetic, and does not inhibit secretion of mucus.

Very few clinical reports have yet been published, but the evidence so far is that it is an effective drug, palatable and free from the disadvantages of codeine. It is supplied in drop bottles containing 10 ml., and the dose suggested for adults is 15–20 drops, in water or beverages, three or four times a day. The dose suggested for infants is 5 drops, and for children an intermediate dose according to age.

N.H.S. basic price: 10 ml., 3s. 3d.

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Cancer and Coronary Thrombosis

The last two subjects chosen as illustrations, cancer and coronary thrombosis, presented more difficulties than some of the infectious diseases. Dr. RALSTON PATERSON (Manchester) pointed out that practically all knowledge of the efficacy of cancer treatment was based on comparative statistics of survival rates, although a more controlled scientific approach to the assessment of results was becoming apparent. Cancer was a disease where the first choice of treatment might be a life-and-death decision.

A controlled therapeutic trial of an unusual kind was described by Mr. HEDLEY ATKINS (London). The trial he described was undertaken to determine whether adrenalectomy with oophorectomy or hypophysectomy was the more effective treatment for advanced breast cancer. Survival rate was not a suitable means for assessment, and so the "mean clinical value" (M.C.V.) of the particular therapies was used as the criterion. This measurement was applicable to disease with many manifestations, such as malignancy with secondary metastases. Lesions in skin, bone, etc., were each given a positive mark if showing signs of regression and vice versa, so that an M.C.V. of 12 indicated general improvement and a zero mark indicated deterioration. The progress could be charted or scattergrams prepared to indicate the patient's condition at any point.

If the first illustration of the controlled clinical trial (on the common cold) in this seminar was 10 years old, the last was piping hot, for it was concerned with the report in the then current number of the *British Medical Journal* on the long-term effects of anticoagulant administration after myocardial infarction.* The organization of the trial was described by Dr. D. D. REID and the results reviewed by Sir GEORGE PICKERING (Oxford); the reader is referred to the full text. Professor WARBURG (Copenhagen) and Dr. BORCHGREVINK (Oslo) each described experiences in controlled trials of anticoagulants which had given results similar to those obtained in the British trial.

In the final session, the theme was "Problems in Organization." There were three opening papers: (*a*) on the organization of controlled clinical trials, by Dr. P. D'ARCY HART (London); (*b*) on the design of records and follow-up, by Dr. SUTHERLAND; and (*c*) on the analysis and presentation of results, by Dr. KNOWELDEN.

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