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EDITORIALS

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Therapeutic Trials in Leprosy
The Importance of Ethical and Nonmedical Considerations

The rapidity of medical discovery has awakened the postwar world to the urgent need for constant informed examination of the ethical and moral aspects of new procedures, new investigations, new drugs. Potent chemical compounds with novel actions or with possibly delayed teratogenic or carcinogenic propensities, new methods of investigation of bodily functions (normal or apparently disturbed) and new surgical technics of increasing range and daring, all call for wisdom as well as knowledge, for moral integrity as well as technologic competence.

On most counts, it is gratifying to observe the continually increasing scientific interest shown in leprosy by workers in related branches of medicine and natural science in general. Much good will come from the cooperation of the pioneers in the utilization of modern investigational technics, and from their tackling of the yet unsolved problems of leprosy. Fruitful interchange of ideas, and stimulating criticism between peers, will push the frontiers of knowledge a little further forward.

Of recent years, the growing concern of the general public and the medical profession that the individual patient, the person, should not be forgotten or overlooked in the impersonal quest for knowledge, has become increasingly vocal. The Hippocratic oath has provided the ethical basis of good medical practice for close on two and a half millenia, but more explicit and definite principles are now being adumbrated. The Nuremburg Code of 19 August 1947 has been followed by the Declaration of Helsinki, promulgated by the World Medical Association in 1964, and the International Code of Medical Ethics, which is embodied in the Declaration of Geneva. The International Covenant on Civil and Political Rights, adopted by the United Nations in 1966, makes explicit reference to the rights of the individual and the integrity of his person.

The (British) Medical Research Council has issued a statement that sets out clearly its own principles regarding responsibility in investigations on human subjects, principles that are incumbent on scientific workers in any branch who are employed by or who receive grants from the Council. And the British Ministry of Health has recently circulated to all hospital authorities a code

of ethics to be observed in all medical research on human beings.

In October 1967, the Council of the International Organizations of Medical Sciences convened a Round Table in Paris (at which the International Leprosy Association was represented by its Secretary-Treasurer) to consider the topic "Biomedical science and the dilemma of human experimentation."[1]

In the case of the disease that directly concerns the readers of this JOURNAL, we do well to remind ourselves of the solemn promise that "the health of the patient will be my first consideration" (Declaration of Geneva), coupled with the salutary injunction that "an inescapable responsibility rests with the doctor concerned for determining what investigations are, or are not, proposed to a particular patient or volunteer." It is conceded that "the doctor can combine clinical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that clinical research is justified by its therapeutic value for the patient" (Declaration of Helsinki). The promotion of the good and welfare of the individual patient is thus the primary consideration in the giving (or withholding) of any treatment, new or old, in the conduct of therapeutic trials, in investigations necessary to clinical assessment, and in the application of preventive measures. The mutual trust involved in the doctor-patient relation does indeed imply on the one hand the doctor's obligation to act conscientiously in the best interests of his patient, and, on the other, a readiness on the part of the patient, to be guided by the enlightened judgement and advice of his doctor.

Certain difficulties, not insurmountable, confront those engaged in drug trials in some countries. Informed and written consent to participation in a trial is usually impossible to obtain, if idealistic criteria are to be observed. Nevertheless, since intelligent agreement with the purposes of the trial may be beyond the capacity of illiterate peasants, the responsibility of the investigator is not thereby revoked. Much will depend upon "the knowledge, experience and especially the integrity of the investigator."[2]

The choice of patients for a therapeutic trial exemplifies difficulties of another order. The volunteers may show too much enthusiasm or too little. They may dissimulate regarding such matters as the history of the disease or previous treatment. The over-anxious, the mentally unstable, the incipient psychopath may abscond early, and so vitiate a trial. The impatient may obtain clandestine supplies of drugs, in an attempt to accelerate clinical amelioration. The hypochondriac may become weepily depressed if the Bacterial Index fails to fall. Family worries, social tensions, conjugal infidelity, lawsuits regarding land and crops and marital matters may all have their repercussions on trials. Hence, the overriding need to enlist the cooperation of the welfare services in investigating the background and personality of potential participants in therapeutic trials. Psychologic screening is at least as important as clinical assessment.

Public relations, too, are most important. Unless the channels of intelligible communication between doctor and patient are kept open, some breakdown is inevitable. The average patient wants to get better of his leprosy, and may not be interested in the morphology or concentration of the bacilli. Nor will he accept with equanimity the persistence of neuropathic ulceration when assured that the Bacterial Index is decreasing. He needs to know what is being done for him, why it is being done, and what the doctor hopes for.

Ideally, it is suggested, the assessor should have no contact with the trial patients between examinations,[3] but in practice this desideratum may not be attainable, and the scientifically orientated physician who can combine clinical research

[1] [C.I.O.M.S.] Biodmedical science and the dilemma of human experimentation. Round Table Conference, Paris, 7 October 1968, pp. 1-123.

[2] BROWNE, S. G. C.I.O.M.S. Round Table Conference, Paris, 7 October 1967, p. 121.

[3] WATERS, M. F. R., REES, R. J. W. and SUTHERLAND, I. Chemotherapeutic trials in leprosy. 5. A study of methods used in clinical trials in lepromatous leprosy. Internat. J. Leprosy **35** (1967) 311-335.

with professional care is the field worker responsible for much leprosy research today.

Whether, too, as some suggest, such research should be confined to a few large and well-equipped centers[4] may be debatable. For investigations, it is incontestable that first-class laboratory facilities are necessary, but for others, the adequate may be less than the ideal. The well-being of the individual patient must be—and must be seen to be—paramount in all laboratory investigations. The frequency and sites of skin smears, for instance, must be related to the necessities of patient investigation and control of therapy. In some centers, the taking of material from the mucosa covering the nasal septum has deservedly fallen into disrepute because of the ungentle and inconsiderate technic employed. Similarly, the subjection of a patient to overfrequent minor operations, as for removal of tissue for histologic or other examination, may forfeit his goodwill and continued cooperation. The patient must be "fully informed" regarding the necessity for the examination (which presupposes that his medical attendant has been fully and conscientiously convinced of its necessity), and give his "informed consent" to the operation or investigation. Sometimes, it is feared, research workers may take too much for granted, and even show more concern for the investigation than for the welfare of the individual patient (Browne, 1967). Where, however, it cannot be honestly advanced that the investigation suggested is for the immediate or ultimate benefit of the individual patient, an explanation—as full and as intelligible as possible—that the results expected are for the good of mankind in general and cannot be obtained by any other method, should be offered in the hope of enlisting a completely voluntary participation in the investigation.

In leprosy, mutual trust and confidence between doctor and patient has to be maintained beyond the limited periods of days or weeks that are the rule in less protracted diseases or therapeutic trials. Generally speaking, the doctor has to "live with" his patients; he has to see them through episodes of acute exacerbation during the slow progress to recovery. This personal involvement has its dangers—both for the doctor and the patient—and may impair the scientific detachment necessary in the evaluation of a drug as well as color the patient's subjective opinion of his clinical condition. Hence the need for objective and measurable criteria that can be impersonally and dispassionately assessed, such as the Morphologic and Bacterial Indexes and the histologic examination of typical tissues.

Another practical aspect of this problem concerns keeping patients waiting for treatment, or withholding specific treatment, or the giving of placebos. Suitable patients may not be forthcoming in sufficient numbers at any one time, and it is possible that seasonal variations at the time of intake may vitiate the results, since the activity of leprosy lesions in the skin may vary with condition of external temperature and humidity. Persisting with a treatment that is proving not to be efficacious is ethically unjustifiable, and the sooner the discovery is made, and the treatment abandoned, the better. In such a disease as leprosy, the giving of placebos is to be deprecated. The teratogenic tragedy of thalidomide could have been averted if scientific analysis of the first eight examples of associated congenital deformity in infants had been made.

In the matter of trials of new drugs, participating patients should be "fully informed," which includes information concerning the expected limitations of therapy; i.e., patients should not be led to expect too much, such as the cure of neuropathic ulceration by a putative mycobactericidal drug. Nor should the risk of possible deleterious side-effects be hidden from participants when a new treatment is offered. It goes without saying that the investigator has satisfied himself concerning these questions of toxicity, full animal testing, etc., before embarking on the trial. Thus, the question "Does this treatment do harm?" must be continually before the investigator's mind, and also the associated question

[4] Florkin, M. C.I.O.M.S. Round Table Conference, Paris, 7 October 1967, 9-13 (p. 13).

"How soon can I discover if it does?" Statistically valid data may confirm or refute early clinical impressions.

Good public relations may be fostered if the investigator can communicate directly with his patients in their own language. The more he knows of local customs and beliefs about leprosy, the better; he may be saved from committing *faux pas*, and may learn much, for instance, regarding the existence of a black market in drugs, previous treatment of patients, sale of tablets that have been secreted under the tongue or even regurgitated after swallowing, etc.

In some countries, good public relations between investigatory medical teams and the public have been endangered by reason of the lack of correlation between such teams, and also by the apparent lack of human concern on the part of the investigators. Simple villagers complain of visitors who descend on them in successive waves to take blood or skin snips or to examine them piecemeal, showing no consideration for them as human beings or for their sicknesses. In surveys for leprosy, and in mobile or static treatment schemes for leprosy patients, it is important to provide facilities for treating minor intercurrent diseases.

These are some of the ethical and nonmedical factors that may make or mar not only a therapeutic trial, but also the reputation of the investigator and the good name of an institution, to say nothing of the cause that the scientist and the humanitarian alike have at heart, viz., the dispassionate investigation of leprosy and the cure of the individual sufferer.

—S. G. Browne