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NOTES ON THE CLINICAL TESTING OF DRUGS IN THE TROPICS

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The principles of clinical assessment of drugs in tropical climates do not differ, or at least should not differ, from those governing the testing of drugs in temperate climates.

These principles may be summarized as:-

1. The avoidance of bias by (a) suitable sampling procedures to ensure that the characteristics of the sample and the population coincide, or, alternatively, to ensure a known probability that any divergence lies within given limits;
(b) random allocation of patients to treatment groups. This is usually obtained by simple random sampling or by some form of stratified sampling (disproportionate allocation).
2. The comparison of treatment groups to discover any major difference in any characteristics thought relevant to the problem.
3. The use of objective methods of measurements whenever possible, and an appreciation of (a) their errors and their confidence limits;
(b) their limitations.
4. The use of control groups treated with a reference drug for comparative purposes.
5. The use of statistical analytical techniques as aids to judgement.

Naturally clinical investigators must be provided with full information on a new drug as an essential prerequisite before human trials are contemplated. Such information would encompass the composition of the compound, its chemical and physical properties, methods of estimation in biological fluids, the results of pharmacological and tolerance studies in normal and infected animals, evidence of activity in as many species of animals as possible and acute, subacute and chronic toxicity data. Studies in normal humans and detailed methodology of initial investigations are also required.

In the tropics, clinical pharmacology may be carried out against a background of multiple variables which have no equivalent in temperate climes and which may introduce modifications in methodology. Such variables may be broadly grouped as technical and administrative.

Among the technical variables are the factors of aetiology and pathology of diseases peculiar to the tropics, and the applicability and acceptability of drugs. A large and ever-growing proportion of the world's population inhabit the tropics and sub-tropics. The majority of such peoples live at subsistence level, in countries where the food supplies are often dependent on natural climatic cycles, and they lack the advantages of the advanced public health systems of the temperate countries. Different emphasis is thus placed on aetiological factors in disease. Bacterial, protozoal, helminthic and viral infections play a wholly disproportionate part in local disease patterns, due simply, in many instances to inadequate sanitation or to a complete lack of sanitation. Degenerative disease, as seen in Europe and America naturally exists but is rarely obtrusive in the face of the common parasitic infections.

Host factors are different from those in temperate climates and must be considered in clinical drug testing. A background of protein-calorie imbalance in childhood, and malnutrition with associated avitaminosis in adult life, may exist. Multiple protozoal and helminthic infections abound, probably the commonest in Africa being malaria, bilharziasis and hookworm. These produce their own pathological sequelae and resultant organ or system dysfunction may be potent factors in altering responses to drugs given for yet other conditions. Inherited abnormalities of haemoglobin or of red cell enzymes are sufficiently common, in many areas, to alert physicians to the possibility of haemolytic episodes during drug treatment. There may be variation of parasitic strain or species response to the same therapeutic drug, a phenomenon well recognized in malaria, bilharziasis and trypanosomiasis, and inexplicable on grounds of dosage variation.

Immune mechanisms developed after repeated infection, or present in association with continuing infection, may modify drug response so that results obtained in the same infections in temperate climates may not be directly extrapolated to conditions and populations in the tropics.

Some of these variables may prove helpful to the clinical pharmacologist. The high prevalence of the common parasitic diseases and the use of objective methodology in the assessment of their response to drugs often leads to a

clear cut decision on the activity or lack of activity in a new drug. Large numbers of patients are available and a variety of dosage regimes can be explored. It should be noted however that although large numbers are more likely to give statistical safety, they are not absolutely necessary for the initial assessment of patient and parasite response if evaluation is careful and good objective tests are available.

In tropical medicine there is much less testing for minor changes in duration, minor improvements in cure rates or symptomatology. This is due to the fact that drugs, once shown to be active, tend to be used for mass treatment, often administered by semi-skilled personnel under sub-optimal conditions. Hence, probably the most desirable property after activity, in an active drug for tropical use, is safety. Perhaps the striking outcome of the happy union of activity and safety was the eradication of yaws by penicillin.

During clinical trials the applicability of any particular therapeutic substance from the individual to the community must always be considered, for in many tropical countries, economic advancement is largely dependent on increased agricultural productivity, itself dependent on a community in which endemic diseases associated with invertebrate vectors are controlled.

Acceptance of a drug by local populations is interdependent on some of the factors mentioned and is also related to local community patterns of behaviour, even when overwhelming evidence of drug efficacy may be present. Poverty and apathy and the influence of religion or politics may all produce difficulties for the clinical pharmacologist attempting to enlarge small group findings to larger scale trials. Efforts to break transmission by chemotherapy administration on a mass basis in diseases such as filariasis, where a large proportion of the human microfilarial reservoir is virtually symptom free may fail because of the scarcely definable influence of some of these factors.

To add to these difficulties consideration must be given to the various diverse administrative problems involved, e.g. the sheer magnitude of the task of dealing with highly prevalent endemic diseases; the difficulties of acquiring financial aid for pharmacotherapeutic research from health

administrations already overburdened with routine demands for maintenance of existing health services; the added load of man's interference with local ecology and spread of disease; as in irrigation systems (actually designed to remove another adverse factor, poor agricultural productivity); the shortage of experienced personnel with the wide variety of parasiticidal agents. A perusal of any standard work on tropical medicine will reveal commonly used therapeutic agents such as the 4-aminoquinolines, the 8-aminoquinolines, emetine, the antimonials, the organic arsenicals, various anthelmintics, tetrachloroethylene, hexylresorcinol, diethylamine, piperazine, diethylcarbamazine, suramin, etc., hardly drugs familiar to practitioners in temperate climes yet all possessing their own toxic properties and all in common use in the tropics.

Dissatisfaction with methods of assessment of endemic diseases has, however, led to intensification and diversification of effort, in which field the World Health Organization has played a leading role, and its efforts in the fields of malaria, tuberculosis and parasitic diseases are good examples of what may be achieved. The collection and exchange of data by WHO, surveys by its consultants, the formation of advisory teams, expert technical committees or scientific groups, and its periodical reviews of progress have contributed greatly in the containment of endemic and epidemic diseases of the tropics.

There had been, and there remains, a great need for standardized approaches to the problems of drug testing on parasite species and strains from different geographical areas. Here WHO has provided a lead in the formation of specialized units dealing solely with one of the major endemic diseases. At present confined to only a few of the parasitic problems of the tropics, the logical extension of such an approach would be the formation of centres to deal with the principles of clinical pharmacology in tropical countries on an international or governmental basis. Their locality must obviously be in areas of endemicity since their function would be the eventual control of endemic and epidemic diseases. To such centres may be added field teams of experienced investigators who would be responsible for the extension of trials into the larger mass of the population. The centres

themselves would be responsible for basic research, initially detailed trials to any desired level of intricacy and co-operation in multicentre investigations. Their value would depend on the use of standardized methodology, the most pressing need.