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SOME BASIC CONSIDERATIONS IN THE PLANNING OF LARGE
SCALE FIELD TRIALS OF NEW ANTIMALARIAL DRUGS*

by

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The evaluation of the chemotherapeutic efficiency of an antimalarial drug today follows a standard pattern which begins in the laboratory with the isolation of the chemical compound and progresses through intensive and varied screening procedures to the stage where toxicity and therapeutic efficiency in humans are observed in a series of, usually small, clinical trials. Only at the end of this sequence of events comes the large scale trial of the drug in the field and this ultimate position cannot be too strongly emphasized. The experimental administration of a drug to a sizeable population does not constitute a rapid method of drug evaluation, nor does it in any way reduce the need for thorough prior laboratory and clinical investigation. Before a large scale field trial is contemplated sufficient general information should be available to indicate clearly the mode of action and the value of the new drug. Data such as effective dosage, rate of absorption, duration of effective blood level, mode of antiparasmodial action and the manifestations, both mild and severe, of toxicity, should be available.

It follows, therefore, that the large scale trial occupies a distinct but limited place in the systematic evaluation of any new drug - a place which can be likened to the few apical blocks which eventually complete the pyramid. In essence it represents an attempt to observe the consequences of mass drug administration in a selected population and as such the trial may reasonably be expected to

- (a) confirm drug action at a given dosage level;
- (b) indicate the acceptability of the drug to the population and in consequence provide an assessment of its value in malaria eradication campaigns;

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- (c) illustrate the value of the drug as a prophylactic;
- (d) detect, at an early stage perhaps, the existence of strains of plasmodia resistant to drug action; and
- (e) demonstrate, when combined with the requisite entomological investigations, the effect of drug administration on the malaria transmission indices of the area.

While it is conceivable that mass drug administration may be undertaken solely as a research venture it is much more likely that the principal objective will be to assess the value of the drug in question as a weapon in extensive malaria eradication campaigns. With this latter point in mind it is clear that before any large scale trial is even contemplated the new drug should be known to fulfil certain essential requirements.

- (1) It must exert no toxic effect either mild or severe which would prejudice a community against it.
- (2) It must be capable of achieving satisfactory action in a single dose.
- (3) If the drug does not exert a profound effect on the erythrocytic cycle of plasmodial development, terminating it swiftly and completely, it must be capable of being linked with some other drug which possesses such an action.

Other advantageous features could be added but the above points represent basic requirements without which, in the opinion of the author, it would be folly to undertake a large scale field trial. In short, drug administration should involve minimal dislocation of normal community life, it must not be attended by an appreciable incidence of undesirable side effects and its benefits should be patently obvious to the population.

In few branches of medicine is medical supervision spread quite as thinly as in field research, and consequently the decision on the size of the population to be studied is most important. It should be made in consultation with a

statistician and the community should be large enough to satisfy statistical requirements without being so large as to embarrass medical supervision.

As field investigations of antimalarial drugs have perforce to be made in areas of holo- or hyperendemicity, it is to be expected that the majority of inhabitants will possess some degree of immunity towards the disease. The drug dosage employed therefore must be pitched to the requirements of the least immune members and the population should contain an adequate representation of such individuals, i.e. very young children and pregnant women.

The community selected must be fully co-operative and be prepared to submit to pre-treatment examination, accept drug administration willingly and permit post-treatment examination for as long as is necessary. Much has been written on the part that intensive propaganda before and during field operations plays in enhancing co-operation, and today this point seems to be universally accepted. The propaganda campaign must however be devised to suit the particular population to be examined and in its construction the assistance of a sociologist broadly experienced in local habits and customs is invaluable.

In primitive communities, however, the most important factors contributing to success are the prestige and personality of the individuals conducting the trial. The greatest care, therefore, should be taken in ensuring that each team member who comes into direct contact with the population has a personality fitted to the task on hand. In no instance is this more important than in the appointment of the team leader.

The size of the team is determined by the size and scope of the investigations but every effort should be made to keep it as small and compact as possible. Each member must be technically competent and above all thoroughly honest and reliable. It is desirable that some, if not all, of the team should be well known to, and completely trusted by, the population; if this is not possible some well known and highly respected individual should be appointed locally to act as public relations officer. The medically qualified members of the team must be prepared to examine and treat sick individuals encountered during the investigation in addition to coping with their normal duties.

The team leader must keep fully in touch with progress at all stages of the investigation and rapprochement between him and the other team members should be complete. He should encourage the immediate notification of snags that arise no matter how unimportant these appear at first sight, and he should arrange frequent discussion groups at which general progress is reviewed and improvements debated. In addition to supervising the overall plan of campaign and assessing results, the team leader should participate to some degree in all stages of the operations. By so doing he will create his personal yardstick to measure progress and thus facilitate his recognition of incipient errors and difficulties.

The greatest problem in mass drug administration is that of ensuring drug consumption. In campaigns designed to reduce or eradicate malaria, schemes of self-administration have been employed in which supplies of the drug have been made readily available to communities but ingestion left entirely to the individual. However, in a field trial devised to assess the efficiency of a new drug so haphazard a method ought not to be employed. Indeed the only satisfactory mode of administration is where team members distribute the drug by nominal roll and observe and record ingestion. All observed side effects should be recorded immediately but the greatest care must be exercised in the questioning of individuals concerning possible toxic effects. Direct questioning should always be avoided for inherent in it is the risk of creating suspicion and apprehension of drug action.

Throughout the post-treatment observational period a close watch must be kept for the occurrence of any positive blood film. When one is detected the dosage record of the donor should be checked without delay. Should this indicate satisfactory drug ingestion, and provided vomiting did not occur shortly after ingestion - a point that should always be checked at this stage by direct questioning - the possibility of drug resistance must be considered. The indubitable diagnosis of drug resistance is beset with difficulties for it is always conceivable that persistence of parasitaemia after apparently successful drug administration may be due to drug failure rather than to an intrinsic characteristic of the parasite. Drug failure originates in some defect in the patient, perhaps in an

inability to absorb an effective quantity of the drug or in abnormal metabolism of it after absorption. The differential diagnosis can only be established by demonstrating the persistence of parasitaemia despite adequate treatment when the parasite is transferred to a new and susceptible individual either by subinoculation of blood or by the bite of a mosquito infected from the original subject. Such an investigation is not a practical possibility in the field and in the opinion of the author there exists a need for the establishment in some non-malarious region of an international centre in which "resistant" parasites detected in field campaigns could be studied with precision.

In the event of parasitaemia persisting despite the field records showing apparently successful drug administration and ingestion the patient should be contacted immediately and the drug administered for a second time at the dosage level on trial. Thick and thin blood films should be taken no less frequently than daily for a period of at least ten days. Persistence of parasitaemia or the return of parasites to the blood after an absence of a few days will confirm the suspicion of the existence of resistance or drug failure and an estimate of the degree of this abnormality should be made by observing the results of increased drug dosage. Finally, but only when drug resistance or failure is clearly proven, the infection should be eradicated by treatment with a different drug.

From the foregoing the need for an accurate records system is evident and much thought should be given to this in the early stages of the planning of field research. The system adopted must not only record all the essential information but also do so in a manner which facilitates statistical analysis of results. A most important point to ensure is the accurate identification of individual members of the population. In primitive areas villages often contain several people with the same name and it becomes necessary to record not only the name and address of the individual but also the names and addresses of the parents. Sex, estimated age and any obvious identifying characteristic should also be noted.

Finally, at all stages it must be remembered that a large scale field investigation represents an essay in public relations. Retaining in mind that it requires the good will and active participation of a community busily engaged in the turmoil of everyday life it should be approached in a spirit of humility and tolerance and undertaken with understanding and compassion.