

The relevance of research to the global antimalaria programme

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Malaria is part of a biological system that encompasses various *Plasmodium* species, their vertebrate and arthropod hosts, and the hosts' physical environment. In human malaria the range of *Plasmodium* species is restricted to *P. falciparum*, *P. vivax*, *P. ovale*, and *P. malariae*, and that of the arthropod hosts to *Anopheles* spp. While *P. falciparum* has received most attention on account of its often peracute and fatal clinical course, it would be wrong to neglect malaria caused by the other *Plasmodium* spp.; *P. vivax* is responsible for much suffering and temporary disability, especially in Asia; the pathogenetic role of *P. malariae*, frequently found in Africa south of the Sahara, has not yet been elucidated and we may well be facing the "tip of an iceberg", with the real bulk of the problem still hidden.

As with any other biological system, malaria and its transmission lend themselves to interference in practically every part or phase of the system, given the appropriate means. In the past, such means were found empirically; but at the start of this century when a large part of the malaria parasite's life cycle had been elucidated, a more systematic approach began to be employed. So far the range of financially and technically feasible means and methods of interference is quite limited, compared with the potential range of intervention. The means and methods at present employed for the control of malaria would appear to be rather unrefined compared with possible future approaches which may provide more effective and environmentally more acceptable weapons against the disease, as, for instance through subtle modifications of cellular receptivity to parasite invasion.

The main pillars of antimalarial operations are still vector control using residual insecticides and antilarval measures, chemotherapy, and chemoprophylaxis. The choice of the appropriate tools depends on the objective of the antimalarial operations, the epidemiological situation, the environmen-

tal characteristics of the area, the available resources, in terms of funds, personnel, and logistics, and, last but not least, the presence of technical problems such as insecticide resistance or exophilic habits of malaria vectors, parasite resistance to drugs, and population movements or habits that may invalidate the use of particular approaches.

The objectives of the worldwide effort against malaria, in order of priority and simplicity, are:

1. the reduction and elimination of mortality caused by malaria;
2. the reduction of suffering from malaria;
3. the reduction of malaria prevalence in endemic areas;
4. the complete elimination of malaria.

While the first two objectives can be attained with the currently available means (especially chemotherapeutic agents), entailing relatively modest financial efforts and simple logistics, only achievement of the fourth objective will once and forever rid mankind of the threat of malaria.

On the other hand, the advent of chloroquine resistance in *P. falciparum* in East Asia and South America clearly emphasizes the need for new means and approaches to replace those which are becoming ineffective due to the adaptability of the parasite and vector.

In view of this precarious situation of malaria control and of the heavy impact of the disease on the health of populations in developing countries of the tropics, malaria holds a prominent place in the WHO/UNDP Special Programme for Research and Training in Tropical Diseases. The primary aim of this Programme is to promote the better utilization of existing tools and methods and the development of new tools and approaches for the control of tropical diseases. In malaria control this implies a determined effort in laboratory and field research in areas such as the biology and *in vitro* cultivation of malaria parasites, chemotherapy, immunology and immunodiagnosis, epidemiology, all aspects related to the

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malaria vector and malaria control operations. Such research will demand an increasingly multidisciplinary approach and will often acquire a transdisease character, especially in the fields of basic biology and epidemiology. The research effort will have to involve the developing countries to a far greater extent than in the past in order to enable them to build up their own research capacity for dealing with their health priorities, among which malaria and other parasitic diseases usually take a prominent place.

The Special Programme for Research and Training in Tropical Diseases is still quite young. Most of the initial activities have been devoted to the planning of research, the implementation of which is about to gather momentum as a result of improved funding. In particular, Scientific Working Groups on the Chemotherapy and the Immunology of Malaria, which met in November 1975 and July 1976 respectively, have taken stock of the actual status of basic malaria research and have developed programmes, whose implementation is being pursued jointly by the Steering Committees of the Scientific Working Groups and the WHO Secretariat.

The research programmes include the following major areas of interest:

1. Parasite biology and *in vitro* cultivation
 - (a) *In vitro* cultivation of *Plasmodium* spp.
 - (i) Forms of the erythrocytic cycle (including production of viable gametocytes)
 - (ii) Tissue forms
 - (iii) Sporogonic forms
 - (b) Parasite preparation and isolation
 - (c) Parasite preservation
 - (d) Strain differentiation
 - (e) Host-parasite relationships
 - (i) Membranes and receptors
 - (ii) Metabolite, antimetabolite, and energy transport
 - (f) Parasite metabolism
 - (i) Carbohydrate transport and metabolism
 - (ii) Protein synthesis and fate
 - (iii) Lipid metabolism
 - (iv) Coenzyme biosynthesis and fate
2. Chemotherapy
 - (a) Mechanism of action of antimalarial drugs
 - (i) Synthesis of radiolabelled compounds
 - (ii) Nature of parasite-drug interactions
 - (iii) Drug metabolism and fate in parasite and host
 - (iv) Mechanism of drug resistance
 - (b) Improvement of drugs in clinical use
 - (i) Development of formulations permitting sustained release
 - (ii) Development of long-acting drugs
 - (c) Improvement of existing and development of new drug screening procedures for:
 - (i) Blood schizontocidal action
 - (ii) Tissue schizontocidal action
 - (iii) Sporontocidal action
 - (d) Development of new drugs (including pre-clinical studies)
 - (i) Further evaluation of already identified compounds
 - (ii) Development of long-acting or sustained release formulations
 - (iii) Exploration of mixtures of new compounds
 - (iv) Design of receptor blocking agents
 - (v) Design of lysosomotropic drugs
 - (vi) Lead-directed synthesis
 - (vii) Computer-aided structure-activity analysis
 - (e) Clinical studies
 - (i) Phase I and Phase II clinical trials
 - (ii) Phase III trials
 - (iii) Baseline assessment of drug susceptibility and monitoring of the development of drug resistance
3. Immunology
 - (a) Malarial antigens
 - (i) Isolation
 - (ii) Purification
 - (iii) Identification and characterization
 - (iv) Evaluation of their role with regard to:
 - immunogenicity
 - immune complex formation and immunopathological phenomena
 - immunodiagnosis
 - (b) Mechanisms of immunity and immune evasion
 - (i) Cellular immunity
 - (ii) Humoral immunity
 - (iii) Immune evasion
 - (c) Immunodiagnostic tests
 - (i) Standardization of available immunodiagnostic tests
 - (ii) Improvement of existing or development of new test systems to:
 - detect low blood levels of malarial antibodies/antigens
 - assess the level of protective immunity
 - determine antigenic variation
 - detect immunopathological reactions

- (iii) Development of simple techniques for sero-epidemiological purposes (with a view to automation)
- (d) Development of blood stage vaccines (including adjuvant studies)
 - (i) Rodent malaria systems
 - (ii) Simian malaria systems
 - (iii) *Aotus/P. falciparum* system
- (e) Development of other vaccines (using rodent and simian models)
 - (i) Sporozoite vaccine
 - (ii) Gamete vaccine
- (f) Vaccination against malaria in humans
 - (i) Development of suitable vaccines (blood stage, sporozoite, gamete vaccines)
 - (ii) Vaccine safety, preservation, and efficacy studies
 - (iii) Trials in small selected groups of individuals after due approval by international, national, and local regulatory authorities
 - (iv) Expanded trials and evaluation of vaccine.

The above summary of the basic research programme shows it to be predominantly oriented towards the improvement of existing and the development of new antimalarial drugs, on the one hand, and towards the development of receptor-blocking agents and vaccines against malaria, including the necessary supporting studies on the biology and *in vitro* cultivation of the parasites, on the other hand. The objectives of the research programme are thus goal-oriented with a view to securing the availability of life-saving, curative, and prophylactic drugs, and to developing fundamentally new and environmentally acceptable tools and approaches for the control of malaria.

While basic research is required to provide better and new tools, field research plays a major role in evaluating them and in optimizing their use. Field research, moreover, permits us to gain insight into the natural history, i.e., the epidemiology, of malaria and to assess the impact of antimalarial measures on the host-parasite relationship. A few of the aims of

current or prospective field research projects are mentioned below:

1. to improve and maintain the usefulness of existing tools;
2. to search for environmentally acceptable means of vector control, such as predators and pathogens;
3. to assess the susceptibility of anopheline species to infection with *P. falciparum* (with due consideration of insecticide resistant anophelines and drug resistant strains of *P. falciparum*);
4. to make a global assessment of the drug susceptibility status of *P. falciparum*;
5. to evaluate the impact of drug prophylaxis on the immune status of communities and individuals in malaria endemic areas;
6. to evaluate the potential of community participation in antimalarial operations, especially chemoprophylaxis;
7. to evaluate the use of immunodiagnostic techniques in epidemiological assessment with a view to improving the present methods.

From these few examples it can be seen that field and basic research are closely interrelated. It should be mentioned that, as a result of the neglect suffered by basic malaria research in the past decades, the very source of new tools and approaches had, at one time, nearly dried up, a laudable exception being the drug development programme under the auspices of the Walter Reed Institute of Research.

Renewed awareness of the threat posed by malaria and its alarming resurgence in areas that had been freed from the disease, together with recognition of the increasingly difficult technical problems confronting malaria control have brought about a new interest in malaria research. It will be the role of the Workshops on the Biology and the *In Vitro* Cultivation of Malaria Parasites to provide an up-to-date review of the status of research in these fields and to identify areas in which efforts and progress are most needed to further the expansion and acceleration of chemotherapeutic and immunological research.