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THE PRESENT STATUS AND ORIENTATION OF BASIC MALARIA RESEARCH<sup>1</sup>

I. INTRODUCTION

Since its existence, the World Health Organization has been actively engaged in promoting and coordinating research in malaria covering the fields of fundamental and applied research. These research activities were planned, reviewed and coordinated by the Division of Malaria and other Parasitic Diseases or its preceding services.

In the late fifties, the general trends in the field of malaria research were mainly related to the gradual building up and progress of malaria eradication. Earlier interest concentrated on the technical problems of application of residual insecticides, the assessment of the duration of activity of various formulations, the sorptive action of surfaces on which insecticides were sprayed and the development of technical equipment. With the advent of insecticide resistance of malaria vectors and parasite resistance to antimalarial drugs, these areas received increasing attention.

However, throughout the world, support of basic malaria research was dwindling away at a dangerous rate and, at one time the very source of new tools and approaches to malaria control was nearly dried up. Renewed awareness of the threat posed by malaria and its alarming resurgence in areas which 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.

II. RATIONALE

Like 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.

The main pillars of antimalarial operations remain to be 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 environmental structure 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 which may invalidate the use of particular approaches.

As yet the range of financially and technically feasible means and methods of interference is quite limited, compared to the potential range of intervention. Apart from the risk of becoming ineffective the means and methods at present employed for the control of malaria would appear to be quite coarse compared to potential 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.

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## III. OBJECTIVES

The primary objective of WHO sponsored research in malaria is the promotion of the better utilization of existing tools and methodologies and the development of new tools and approaches for the control of malaria, in order to enable the malarious countries of the world to curb mortality and suffering from the disease, to reduce its prevalence and eventually to eliminate it altogether. This implies a determined effort in laboratory and field research in areas such as the biology, including the in vitro cultivation of malaria parasites, chemotherapy, immunology and immunodiagnosis, epidemiology, aspects related to the 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.

## IV. WHO SPONSORED RESEARCH

While applied research, through a number of special field projects, was and still is largely financed by the Organization, fundamental research was until recently almost exclusively carried out under collaborative agreements with the institutes concerned. Here the WHO contribution often constitutes only a small fraction of the actual amounts spent in the particular research line, the bulk of financial allocations coming from the institutes' budget or other grants. It is not rare that the ratio of WHO : other input, is of the order of 1:20 or more. Thus, the slender resources of the Organization devoted to collaborative research in malaria, recently of the order of approximately US \$100 - 150 000 per year, have helped to harness substantially greater national and foundation resources to a high priority activity. This sum contains also allocations for WHO Collaborating Centres which provide technical standards and standardized biological material and reagents to a considerable number of other research institutes.

Although these research activities produced appreciable and important results it was realized that the operational and technical constraints of malaria control would require urgent solutions which could only be obtained through an acceleration and intensification of basic and field research. The same situation exists in other major tropical diseases. A WHO Special Programme for Research and Training in Tropical Diseases has therefore been established recently, whose aims are identical with the objectives mentioned in chapter II. The Special Programme puts a major emphasis on the building up and strengthening of research capability and capacity in the developing countries. In keeping with its objectives the Special Programme intends to put considerable funds at the disposal of research and institutional strengthening. In the malaria sector, the budgetary provisions for 1977 amount to US \$ 4.6 million. They are expected to reach US \$ 9.1 million in 1980.

In the area of basic research, detailed programmes were developed by Scientific Working Groups on the Chemotherapy and Immunology of Malaria which met in 1975 and 1976 respectively. The implementation of the programmes is being carried out jointly by the Steering Committees of the Scientific Working Groups, and the WHO Secretariat. Aspects of basic biological research and in vitro cultivation of malaria parasites were considered in specific workshops early in 1977.

## V. PRESENT STATE OF BASIC MALARIA RESEARCH

The following summary is restricted to research in parasite biology, chemotherapy and immunology since the aspects of epidemiology including vector bionomics are covered in other papers.

(a) Parasite biology and in vitro cultivation

Research in parasite biology is an essential prerequisite for research in immunology and chemotherapy. The *in vitro* cultivation of parasites provides material essential for biological and immunological studies, and for routine procedures such as immunodiagnostic tests. *In vitro* cultivation systems may be used for chemotherapeutic screening and studies of growth factors and metabolism.

(i) In vitro cultivation of Plasmodium spp.

Since Trager's successful establishment of the continuous culture of Plasmodium falciparum in 1976, using a continuous flow system, several laboratories have implemented studies aiming at the mass production of P. falciparum. The candle jar method yields parasite densities of up to 16%. Dialysis methods are in an early experimental stage. Production of viable gametocytes has been obtained *in vitro*. Exflagellation of *in vitro* cultivated P. falciparum microgametocytes (from continuous cultures) has been observed.

While completion of the tissue phase, from sporozoites to merozoites has been achieved in avian Plasmodia (P. fallax or P. lophurae), attempts with P. berghei and P. vivax sporozoite infections in perfused liver or in hepatic cell lines have never produced more than a small number of bodies which may represent very early tissue schizont stages.

Complete *in vitro* development from gametocytes to mature sporozoites, without change of medium and substrate has not yet been achieved. Starting from male and female gametocytes, ookinetes were regularly obtained in avian, rodent and simian plasmodia. Oocyst growth and maturation until sporozoite production were attempted in mosquito gut preparations and more successfully in mosquito cell lines. The completion of development always required several culture transfers. In P. relictum development from a 3-day oocyst to one containing mature sporozoites required only one transfer. P. gallinaceum and P. cynomolgi oocysts were more difficult to grow.

(ii) Parasite preparation and isolation, parasite preservation

Proper isolation and preparation techniques are a sine qua non for subsequent biochemical, morphological, biological and immunological studies employing parasite material of various stages of the plasmodial cycle. Modern separation and purification techniques, from Ficoll separation to column chromatography, have improved the preparation of parasite material. However, problems associated with the erythrocytic parasite's outer membrane, the separation of parasite and host material in general, and the partial destruction or denaturation of the parasite and its parts require the development of improved methods of preparation and isolation which are appropriate to the subsequent use of the parasite material.

The preservation of non-viable parasites and parasite-derived material, mostly effected at  $-70^{\circ}\text{C}$ , poses no major problems. The long-term preservation of viable parasites in form of sporozoites and parasitized erythrocytes or merozoites, using 1-step or 2-step cooling procedures and storage in liquid nitrogen is still associated with a considerable loss of infectivity and important fluctuations of reproducibility.

(iii) Strain differentiation

Major progress was recently made in the strain differentiation of rodent plasmodia after the successful implementation of cloning procedures. The differentiation is based on the establishment and the comparison of iso-enzyme patterns. With the development of the continuous culture systems it is expected that proper strain differentiation of human-pathogenic plasmodia will soon become practicable.

(iv) Host-parasite relationships

The function of erythrocyte and parasite membranes in the process of merozoite invasion are subject to intensive research which recently led to the identification of the Duffy blood group substances as a receptor involved in the invasion of P. vivax merozoites. Current studies concern the receptors for P. falciparum merozoites, while the investigation of sporozoite invasion and its cell specificity is still in the very early stages; research in this area could be accelerated were an adequate in vitro system available.

Research on the function and role of erythrocyte and parasite membranes in metabolite, antimetabolite and energy transport is expected to gather momentum after a wider introduction of in vitro cultivation systems. Recent studies of membrane structure have led to the discovery of specific proteins in infected erythrocytes which were absent in normal RBC. Moreover, the membranes of infected erythrocytes were found to be permeable to some compounds, e.g. L-glucose, which are unable to pass the membranes of normal RBC. The parasite-induced erythrocyte membrane changes also extend to an altered surface binding capacity, e.g. for lectins. These observations have particular relevance to chemotherapy, the mode of action of antimalarial drugs and immunological phenomena.

(v) Parasite metabolism

Most of the biochemical studies on the malarial parasite have been restricted to the erythrocytic stages of development since these are the only material which, at present, can be prepared in sufficient quantity for such studies.

In all Plasmodium spp. glucose is the major energy substrate of the erythrocytic stages. It is glycolytically metabolized to lactate. Investigations of the pentose-phosphate pathway showed that the parasite most probably utilizes the pathway of the host erythrocyte. The major role of the pentose-phosphate pathway is believed to be associated with membrane stabilization. It may also provide ribose for nucleic acid synthesis.

The erythrocytic stages of plasmodia are apparently incapable of synthesizing fatty acids de novo. However, they can make glycerides and phosphoglycerides from the fatty acids, nitrogenous bases, alcohols and CoA obtained from the host. The parasite derives many lipids and fatty acids from the erythrocyte membrane. In P. knowlesi biosynthesis of cholesterol was observed at the early stages of development.

The erythrocytic stages of rodent plasmodia use exogenous purines for nucleic acid synthesis, but must add the ribose and phosphate moieties to the preformed purine, using to this purpose the enzymes of the "salvage pathway" to form monophosphate from adenine or adenosine. Plasmodia do apparently not incorporate exogenous pyrimidines, although the parasite membrane may be permeable to pyrimidines. Thus, it is more likely that the parasite lacks a pyrimidine salvage pathway and synthesizes pyrimidines de novo. Studies in rodent plasmodia have proved the presence of a number of enzymes involved in the de novo synthesis of pyrimidines.

In *P. knowlesi* the majority of DNA is synthesized during growth from ring to late trophozoite stage. This positively correlates with the periodicity in the synthesis of thymidylate synthetase.

Haemoglobin is the most important source of amino acids for the growth of plasmodia which make use of proteolytic enzymes to degrade the haemoglobin within a food vacuole, liberating amino acids and forming haemozoin. Chloroquine is also concentrated into the food vacuole and may act by a specific inhibition of proteases participating in the degradation of haemoglobin.

Studies on plasmodial RNA have not yet produced conclusive results. This area is of particular interest to research on the mechanism of action of antimalarial drugs, but also to immunological research especially in relation to the synthesis of antigenic proteins and its genetic control.

Among the few co-factors proven to be essential for the development of the intra-erythrocytic development of plasmodia is PABA which is required for the synthesis of folates. The parasite, unlike its host, synthesizes folate co-factors de novo. This is also the site of chemotherapeutic action of sulfonamides, inhibiting dihydropteroate synthetase, and of pyrimethamine, inhibiting dihydrofolate reductase. The parasite is able to incorporate methionine from exogenous sources, but apparently this amino acid may also be biosynthesized, utilizing N<sup>5</sup> methyltetrahydrofolate. Pantothenate is not used directly by the parasite (*P. lophurae*) but rather in form of CoA synthesized by the host cell. None of the enzymes of CoA biosynthesis are found in the parasite, indicating a major metabolic lesion. Systematic search may yield evidence of several metabolic lesions of the mammalian plasmodia.

#### (b) Chemotherapy

Chemotherapeutic research is goal-oriented, striving at the improvement of compounds which are already in clinical use or the development of new drugs and formulations which help to overcome the problems posed by parasite resistance to the classical anti-malarials. It is realized that up to now this research was largely based on an empirical approach, but future studies on normal parasite function and metabolism, the mode of action of antimalarial compounds and structure-related activity of antimalarials may produce advances in the field of lead-directed synthesis, the design of receptor-blocking agents and lysosomotropic drugs.

#### (i) Mechanism of action

Chloroquine-sensitive strains of *P. berghei* and *P. falciparum* possess a saturable receptor site for the drug that is lost when chloroquine resistance develops. The binding site has been isolated. In *P. berghei* a second less sensitive site, probably DNA, has been found. 4-aminoquinolines, like mepacrine, cause a disruption of the digestive processes leading to acute amino acid deprivation and cytolysosome formation. These processes are associated with clumping of the haemozoin.

The mode of action of quinine is still largely unknown. Quinine may intercalate with DNA. There is some evidence that it competes, in binding, with 4-aminoquinolines.

8-aminoquinolines and several naphthoquinones, e.g. menoctone, disrupt the function of plasmodial organelles which apparently possess mitochondrial function such as the biosynthesis of ubiquinone-8.

Sulfonamides were shown to inhibit dihydropteroate synthetase, while pyrimethamine and proguanil inhibit dihydrofolate reductase. This also explains the marked synergism of both. There are several dihydrofolate reductase inhibitors the response to which varies in the different *Plasmodium* spp. Equally, a *Plasmodium* strain may be fully

susceptible to one dihydrofolate reductase inhibitor, but resistant to another.

On the whole, and especially in respect of 8-aminoquinolines, the knowledge of the mechanism of drug action is still quite limited.

(ii) Mechanisms of drug resistance

Investigations with <sup>14</sup>C-labelled chloroquine and indirect studies based on the model using chloroquine-induced haemozoin clumping in P. berghei (mouse) and P. falciparum (Lotus trivirgatus) indicate that resistance to chloroquine depends primarily on a defect in the high affinity binding sites of the resistant parasites. Chloroquine-resistant P. berghei apparently utilizes essential substrates and enzymes from the host erythrocyte to help overcome metabolic deficiencies associated with other aspects of the drug's action. Relative differences in the degree of resistance to various members of the 4-aminoquinoline group, e.g. chloroquine and amodiaquine, are not yet satisfactorily explained.

Pyrimethamine resistance has been shown to be associated with the production of a mutant-related dihydrofolate reductase that possesses a lower affinity to this inhibitor. However, exclusion of the drug from the enzyme site and increased production of dihydrofolate reductase may be contributing factors.

The exploration of the genetics of drug resistance has received new impetus with the successful introduction of cloning techniques in rodent plasmodia which may in future also be applied to in vitro culture systems with human-pathogenic plasmodia.

(iii) Drug screening

Although the interest of industry in the development of new antimalarial compounds has shown a marked decrease since the beginning of the chloroquine era, the search for new antimalarials was carried on in various centres, especially in the USA and in Europe. The most important effort was and is being made by the Walter Reed Army Institute of Research which, since the existence of its malaria drug screening programme, has tested some 250 000 compounds, several of which yielded promising results and were developed up to pre-clinical and clinical phase I/II stage. In the past this programme was mainly oriented towards testing for blood schizontocidal action. Meanwhile screening systems for extended blood schizontocidal, tissue schizontocidal and sporontocidal action have been developed with a view to expanding appropriate routine screening of pre-selected compounds.

Promising candidate compounds whose development for clinical use may be envisaged were found in the following chemical groups: 9-phenanthrenemethanols, 4-quinoline-methanols, 2,4-diamino-6-sulfur-substituted quinazolines, 4,6-diamino-1-substituted dihydrotriazines, naphthoquinones, chlorinated lincomycin derivatives and acridin compounds. Recently several new 8-aminoquinoline derivatives were found to show markedly higher antimalarial activity than the base compound.

(iv) Improvement of drug formulations

The major shortcoming of the present available prophylactic drugs is the rather short duration of effect which necessitates repeated administration at relatively short intervals. For antirelapse treatment, 8-aminoquinolines must be given daily for a fortnight. The availability of sustained-release type formulations would solve operational problems. Recent studies have shown that constant maintenance of low drug levels (in tissue and blood) may be more effective and better tolerated than the interrupted administration of high doses. Advances with slow-release devices and matrices such as micropumps and polymer techniques are expected to provide means for the improvement of drugs already in clinical use and for the utilization of compounds

which, for reasons of toxicity associated with the interrupted administration of high doses, could not yet be employed in routine antimalarial treatment or prophylaxis.

(v) New drugs

(2,8-bis-(trifluoromethyl)- $\alpha$ -(2-piperidyl)-4-quinolinemethanol (mefloquine) is the most advanced of the new candidate drugs. Mefloquine has been developed under the programme of the Walter Reed Army Institute of Research. The compound was found to be well tolerated at prophylactic doses. Weekly administration of 180 mg or fortnightly administration of 360 mg mefloquine hydrochloride in adult Thais was well tolerated. Both regimens were equivalent in chemosuppression of *P. falciparum* and *P. vivax*. Mefloquine is also effective against chloroquine-resistant *P. falciparum*. For radical treatment of falciparum malaria a single dose of 15 mg mefloquine/kg body weight appears to be adequate. Extensive clinical trials (stage I/II/III) are envisaged.

Triazine compounds were found to be quite effective in rodent and simian malaria models. In human malaria the compounds were highly potent but toxic. Different formulations and slow-release approaches may be able to improve tolerability.

Menoctone type drugs, quinazolines and some of the 9-phenanthrenemethanols hold promise. Further studies are in course.

(c) Immunology

Since it has been shown that immunization against malaria can be achieved, the main thrust of immunological research is directed towards the development of vaccines, with the essential supportive investigation of immune mechanisms and the phenomena of innate resistance. Immunodiagnostic tools have been developed whose wider utilization in surveillance and epidemiological research has so far been hampered by the scarcity of antigen.

(i) Mechanisms of malaria resistance

Innate resistance to infection with plasmodia is specific and may relate to a requirement of the parasite or to a substance of the host that is deleterious to the parasite. As in biochemical research most investigations were limited to the erythrocytic stages of the parasite since this material was more readily available. As already indicated in V (a,iv) specific surface receptors are involved in the merozoite attachment to and invasion into erythrocytes. This may explain host cell preferences, e.g. reticulocytes (*P. berghei*/mouse and rat) or the refractoriness of Duffy blood group negative human erythrocytes to *P. vivax* merozoites. Using *in vitro* models, refractoriness to merozoites was also induced through treating erythrocytes with proteolytic enzymes.

Intraerythrocytic factors such as structural changes in haemoglobin (haemoglobins S, C and E), quantitative changes in the synthesis of haemoglobin chains (thalassaemia), or G-6-PD deficiency may not be compatible with the metabolic requirements of *P. falciparum* and thus confer relative advantage to those afflicted with these genetic traits.

The by far most important aspect of malaria resistance is the specific anti-parasitic immunity conferred by malaria infection or vaccination with attenuated or non-viable parasites or parasite material. There is evidence that both cellular and humoral immunity play a role in specific antiplasmodial immunity. Thus fractions of serum, containing IgG, have conferred protection on human recipients. Protection against low inocula of *P. berghei* has been achieved in outbred rats with hyperimmune serum. Moreover, protective antibodies have been shown to block merozoite invasion of erythrocytes and to promote phagocytosis of free and intracellular parasites by macrophages.

T-cells are required to initiate mechanisms that lead to the destruction of plasmodia. Congenitally athymic mice do not recover from malaria infection unless reconstituted with syngeneic thymus cells. Spleen cells, but not cells from lymph nodes or thoracic duct, from convalescent mice or rats could confer resistance against malaria to normal, irradiated, or nude mice. Transfer experiments have so far not distinguished between T and B lymphocytes as effector cells. Helper effects of antigen-sensitive T-cells have been demonstrated using hapten-conjugated parasites.

A variety of adjuvant agents stimulate macrophages and provide considerable protection to mice against P. vinckei. Since this phenomenon is also observed in congenitally athymic mice, the macrophage stimulation seems to be effected through the product of complement activation, C3b. In the P. berghei/mouse system macrophage stimulation in the absence of the appropriate antigen is less pronounced.

The area of immune evasion in plasmodial infections still requires extensive investigations. There is evidence that malarial infections induce non-specific immunodepression.

#### (ii) Immunopathology

Immunopathological phenomena play an important role in the pathogenesis of some of the lesions associated with malaria, e.g. in glomerulonephritis (quartan malaria). Circulating antigens were observed in acute falciparum infections with high parasitaemia. After the introduction of highly sensitive radioimmunological techniques, soluble antigens were also demonstrated in infections with P. malariae. Antigen-antibody complexes were demonstrated in the glomerular capillary walls in malaria patients. Acute infections due to various parasite species produce reversible renal damage; chronic infections with P. malariae are associated with chronic progressive, irreversible renal lesions.

The complement system plays an important role in the development of immune complexes. The latter usually activate the classical pathway with the participation of early complement components (C1, C4, C2). This pathway leads to a cleavage of C3 and the activation of late complement components. Research on complement components in various simian models and human malaria have not yet provided conclusive results, mainly on account of difficulties encountered in the measurement of complement metabolism.

#### (iii) Immunodiagnosis

Several serological methods have been developed and used in laboratory and epidemiological field studies. The major obstacle against the desirable propagation of the tests was and still is the limited availability of the required antigens. As far as erythrocytic-stage derived antigens are concerned, the recently developed continuous parasite cultivation may soon provide the essential material and also promote the standardization of antigens.

The gel precipitin test is chiefly used for the detection of soluble antigens associated with the erythrocytic forms of P. falciparum. These antigens were classified into L (labile), R (resistant) and S (soluble) antigens and, within these groups, subdivided into subclasses.

Immunofluorescent antibody and passive haemagglutination tests are well established methods, whose limitations and merits have been determined quite well. Recently standardized protocols for these tests have been developed.

Radioimmune assay methods are still the most sensitive test systems which are suitable for the detection of antigens as well as antibodies in low concentrations.

Their use is restricted to a few specially equipped laboratories.

The enzyme-linked immunosorbent assay (ELISA) holds promise for wide epidemiological application as it allows quantitative estimations of specific antibodies by enzyme-labelled anti-immunoglobulin. Peroxidase and alkaline phosphatase are the usual labels. The ELISA requires only modest quantities of antigen and serum at a single dilution. It lends itself to automation and objective (machine) reading. The test is also suitable for application under field conditions. Further studies are necessary in order to optimize and standardize antigen preparation.

Various other tests, e.g. circumsporozoite precipitation, sporozoite neutralization, schizont-infected cell agglutination, opsonization, merozoite inhibition tests are used as research tools.

(iv) Immunization (vaccines)

Extensive studies in rodent malaria systems have shown that specific protective malaria immunity can be induced through the chemo-suppression of an existing malarial infection, through the immunization with non-viable parasites of erythrocytic stages (without or in conjunction with adjuvants), and through the vaccination with irradiated sporozoites.

In rhesus monkeys protective immunity against P. knowlesi was achieved through vaccination with P. knowlesi merozoites administered with Freund's complete adjuvant. Similar observations were recently made in the Aotus trivirgatus/P. falciparum system when mature schizonts were used as an antigen together with Freund's complete adjuvant.

In man complete protection against challenge with viable sporozoites of P. falciparum and P. vivax was obtained after repeated inoculation of sporozites of the same parasite species through the bite of irradiated infected mosquitos. The protection was also complete upon challenge with different parasite strains (P. falciparum).

Inoculation of blood containing gametes of P. gallinaceum in gametocyte-carrying chicken resulted in the formation of specific anti-gamete antibodies which interfered with exflagellation and consequently with zygote formation. All animals so vaccinated proved to be non-infective to the vector in spite of the presence of gametocytes. Transfer of serum containing anti-gamete antibodies to non-vaccinated, gametocyte-carrying chicken rendered the blood non-infective to the vector mosquitos. Similarly, removal of the serum and washing of the blood corpuscles of the vaccinated animals restored normal viability of the gametocytes. These experiments have successfully been repeated in the rhesus/P. knowlesi model, where Freund's Complete Adjuvant was required for obtaining results similar to those observed in the P. gallinaceum/chicken model.

VI. RESEARCH PROGRAMME, BASIC RESEARCH (MALARIA)

The following major areas of interest have been identified in the framework of WHO-assisted basic malaria research (areas of biology, chemotherapy and immunology only) in due consideration of operational needs in malaria control and in the endeavour of following leads towards innovative operational approaches:

(i) Parasite biology and in vitro cultivation

(a) In vitro cultivation of Plasmodium spp.

- Forms of the erythrocytic cycle (including production of viable gametocytes)
- Tissue forms
- Sporogonic forms

- (b) Parasite preparation and isolation
- (c) Parasite preservation
- (d) Strain differentiation
- (e) Host-parasite relationships
  - Membranes and receptors
  - Metabolite, antimetabolite and energy transport
- (f) Parasite metabolism
  - Carbohydrate transport and metabolism
  - Protein synthesis and fate
  - Lipid metabolism
  - Coenzyme biosynthesis and fate

(ii) Chemotherapy

- (a) Mechanism of action of antimalarial drugs
  - Synthesis of radiolabelled compounds
  - Nature of parasite/drug interactions
  - Drug metabolism and fate in parasite and host
  - Mechanism of drug resistance
- (b) Improvement of drugs in clinical use
  - Development of formulations permitting sustained release
  - Development of long-acting drugs
- (c) Improvement of existing and development of new drug screening procedures for
  - Blood schizontocidal action
  - Tissue schizontocidal action
  - Sporontocidal action
- (d) Development of new drugs (including pre-clinical studies)
  - Further evaluation of already identified compounds
  - Development of long-acting or sustained release formulations
  - Exploration of mixtures of new compounds
  - Design of receptor blocking agents
  - Design of lysosomotropic drugs
  - Lead-directed synthesis
  - Computer-aided structure activity analysis
- (e) Clinical studies
  - Phase I and II clinical trials
  - Phase III trials
  - Baseline assessment of drug susceptibility and monitoring of the development of drug resistance

(iii) Immunology

- (a) Malaria antigens
  - Isolation
  - Purification
  - Identification and characterization
  - Evaluation of their role with regard to:
    - Immunogenicity
    - Immune complex formation and immunopathological phenomena
    - Immunodiagnosis

- (b) Mechanisms of immunity and immune evasion
  - Cellular immunity
  - Humoral immunity
  - Immune evasion
  
- (c) Immunodiagnostic tests
  - Standardization of available immunodiagnostic tests
  - 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
  - Development of simple techniques for seroepidemiological purposes (with a view to automation)
  
- (d) Development of blood stage vaccines (including adjuvant studies)
  - Rodent malaria systems
  - Simian malaria systems
  - Aotus/P. falciparum system
  
- (e) Development of other vaccines (using rodent and simian models)
  - Sporozoite vaccine
  - Gamete vaccine
  
- (f) Vaccination against malaria in humans
  - Development of suitable vaccines (blood stage, sporozoite, gamete vaccines)
  - Vaccine safety, preservation and efficacy studies
  - Trials in small, selected groups of individuals after due approval by international, national and local regulatory authorities
  - Expanded trials and evaluation of vaccine

This summary of the basic research programme shows its major orientation towards the improvement of existing and the development of new antimalarial drugs, the development of receptor-blocking agents and vaccine(s) against malaria, including the necessary supporting studies on the biology and in vitro cultivation of the parasites. The objectives of the research programme are thus goal-oriented with a view of securing the availability of life-saving, curative and prophylactic drugs, and of developing fundamentally new and environmentally acceptable tools and approaches for the control of malaria.