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The orientation of immunological research in relation to the global antimalaria programme

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Immunological research on malaria has produced a wealth of information on the relationship between Plasmodium *and the vertebrate host, introducing new serological tools into epidemiological methodology and experimentally proving the possibility of protecting vertebrates against malaria, thus moving vaccination from the realm of pure hypothesis to the level of feasibility.*

The alarming malaria situation in the world is reason enough to expand immunological research further to improve diagnostic and epidemiological tools and to develop methods for the protection of man against malaria. The programme of the Scientific Working Group on the Immunology of Malaria, UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases, complies with these objectives.

A projection of potential effects of malaria vaccines on the malaria situation shows considerable promise in areas with relatively low basic reproduction rates; in areas with high basic reproduction rates they would need to complement other malaria control measures and may ultimately add the critical momentum required to render adequate malaria control feasible in tropical Africa.

The UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases established the Scientific Working Group on the Immunology of Malaria in 1976, at a time when complacency about the malaria situation had started to be replaced by growing concern. In view of the severely limited means available for the control of malaria and the constraints on their use in areas where they are most needed, it was concluded that research was required to find better and more widely applicable approaches in order to overcome the existing stalemate. While large sectors of the Special Programme's activities cover traditional and innovative approaches in the classical areas of tropical disease control—such as chemotherapy and the control of vectors and animal hosts—it was realized that immunological research would be conducive to expanding the perspectives of diagnosis, surveillance, and epidemiological evaluation, and could lead to the development of an entirely new outlook in the field of immune protection.

That these approaches are no longer at the level of mere speculation was demonstrated by successful protection against falciparum and vivax malaria in man following immunization through sporozoites conveyed by the bites of irradiated mosquitos and by experimental proof of immune protection after inoculation of nonviable blood-stage parasites or material derived from these forms in rodent and simian models. However, it was clear that knowledge of the mechanism of immunity against malaria, of the parasite antigens, and of the host/parasite relationships involved is still too scanty to allow the production of a sufficiently safe and effective vaccine.

PROGRAMME OF THE SCIENTIFIC WORKING GROUP

For these reasons the Scientific Working Group on the Immunology of Malaria has drawn up a research programme, which includes the following areas:

1. Malarial antigens
   - (*a*) Isolation
   - (*b*) Purification
   - (*c*) Identification and characterization
   - (*d*) Evaluation of their role with regard to:
     - (i) immunogenicity
     - (ii) immune complex formation and immunopathological phenomena
     - (iii) immunodiagnosis
2. Mechanisms of immunity and immune evasion
   - (*a*) Cellular immunity
   - (*b*) Humoral immunity
   - (*c*) Immune evasion
3. Development of blood-stage vaccines (including adjuvant studies)
   - (*a*) Rodent malaria systems

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(*b*) Simian malaria systems
(*c*) *Aotus/Plasmodium falciparum*
4. Development of other vaccines (using rodent and simian models)
   (*a*) Sporozoite vaccine
   (*b*) Gamete vaccine
5. Vaccination against malaria in humans
   (*a*) Development of suitable vaccines (blood-stage, sporozoite, gamete vaccines)
   (*b*) Vaccine safety, preservation, and efficacy studies
   (*c*) Trials in small selected groups of individuals after due approval by international, national, and local regulatory authorities
   (*d*) Expanded trials and evaluation of vaccine.

In addition, the development of immunodiagnostic tests is to be promoted with the objectives of (*a*) improving and standardizing available tests, (*b*) developing new ones as tools for research on immune mechanisms and for measuring protective immunity, and (*c*) providing simple techniques for seroepidemiological purposes.

In the two years between the establishment of the Scientific Working Group and this Workshop on the Immunology of Malaria, we have witnessed a vigorous implementation of major sections of the research programme. Recent developments in the *in vitro* cultivation of the blood stages of *P. falciparum* and the renaissance of interest on the part of major funding agencies have helped to accelerate and intensify research in malaria immunology.

This Workshop provides an opportunity to review and, it is hoped, to confirm the premises on which the Scientific Working Group's programme is based. It may also be timely to examine critically this programme's eventual practical contributions to malaria control in order to keep its principal goals in sight and to maintain a realistic outlook. This will entail an examination of the present malaria situation and the constraints on malaria control in the world, together with a critical projection of potential and apparently achievable results.

DEGENERATION OF THE MALARIA SITUATION

The two decades following the end of the Second World War were marked by a highly successful antimalaria effort in the majority of the world's malarious areas with the exception of tropical Africa, where the application of malaria control measures remained rudimentary.

The success was based largely on the regular and systematic use of residual insecticides, such as DDT, for the control of the anopheline vector of malaria, and on the administration of antimalarial drugs, especially 4-aminoquinolines and 8-aminoquinolines for the radical treatment of malaria, i.e., the elimination of the parasite. These operations required high technical precision, skilful administration, an adequate budget, timely release of funds, sound logistics and, last but not least, considerable flexibility in order to cope quickly and efficiently with unexpected epidemiological developments. The antimalaria programme was usually entrusted to a specialized service, since ordinary government services and administrative machinery would not have been able to meet the above-mentioned requirements.

Several technical obstacles to malaria control and eradication became evident in the fifties and sixties: some of them resulted from the type of antimalaria measure used, e.g., vector resistance to insecticides or drug resistance of parasites; others, such as exophilic behaviour of vectors and factors related to human ecology, had always existed but had not been sufficiently recognized.

Even so, with the necessary degree of operational flexibility and precision, and with adequate funding, many of the programmes continued to gain substantial ground in spite of technical problems.

During the mid-sixties several countries relaxed their antimalaria measures under the impression that the small residual number of malaria cases would not merit a sustained effort and that the final elimination of the disease could very well be undertaken by the general health services. Consequently, financial allocations for antimalaria measures were sharply reduced, malaria services were often "integrated" with the general health services, epidemiological surveillance was scaled down or phased out, and operational flexibility was lost. In addition, bilateral and international assistance to antimalaria programmes was substantially reduced or totally terminated at the time. As a result, malaria has made a major resurgence in several areas of the world, particularly in Asia. Although the signs of these developments were recognizable in the late sixties, little could be done to stop this development in the face of general inertia and administrative rigidity.

Thus, in the late seventies, the malaria situation is considerably worse than it was a decade earlier. While there was no substantial change in tropical Africa, where malaria generally remained hyper- or holoendemic, malaria has invaded large areas from which it had previously been eliminated, especially in India, Pakistan, and Sri Lanka.

Meanwhile technical problems, such as vector resistance to insecticides and parasite resistance to antimalarials, have acquired considerable operational importance. The application of alternative control methods is expensive, but generally feasible if the number of malaria foci and their extent are limited.

Controlling a massive resurgence of malaria in problem areas, however, may easily push a government to the limits of financial capability.

In the poorest countries of the world, malaria continues to be a serious impediment to health and socio-economic development. In most of these, the reasonably priced means and methods at present available are clearly not adequate to achieve a major impact on the malaria situation. Moreover, further important increases in the cost of equipment and materials during the past years and months have placed even the simplest, palliative control measures outside the reach of many governments.

The malaria situation in tropical Africa provides striking evidence that effective malaria control—and even more so eradication—requires a multipronged approach. This will have to be supported by new techniques designed to improve the chemotherapeutic attack on, or protection against, the parasite, by the introduction of new concepts and methods of vector control and by developing immunization of man against malaria.

The experience of the past few years has confirmed the need for research in the above-mentioned fields and thus the continued validity of the Scientific Working Group's concept.

PROSPECTS FOR IMMUNOLOGICAL RESEARCH

This leads to the question of the contributions that immunological research might make on a short-, medium-, and long-term basis.

Immunodiagnostic tests have proved to be valuable tools for surveillance and epidemiological evaluation. Although the routinely available systems, such as immunofluorescent and passive haemagglutination tests and the enzyme-linked immunosorbent assay (ELISA), do not apparently reflect protective immunity, they are relatively reliable in detecting present or past contact between parasite and vertebrate host. There is room for improving and standardizing these techniques and for explaining their application. Problems of producing the essential antigens are being overcome through the increasing availability of parasite material from culture. In addition, immunodiagnostic tests need to be developed as tools for research on immune mechanisms and immunization as well as for monitoring protective immunity in communities exposed to endemic malaria and, eventually, in persons vaccinated against malaria. This area of short- and medium-term research will be specifically reviewed in a meeting of the Scientific Working Group on the Immunology of Malaria in June 1979.[a]

This Workshop is to give an account of the present status of research oriented towards the immunization of man against malaria, including the essential supportive discipline of production and purification of parasite material and the isolation, purification, identification, and characterization of antigens.

It would be useful at this stage to give some thought to the potential impact of vaccines against malaria. Unlike viral and bacterial pathogens, malarial parasites have many different developmental forms with stage-specific antigenic patterns. Experiments undertaken with vaccines prepared from merozoites (the asexual blood stage), gametes, and sporozoites allow projections of a potential impact on various essential sites of the parasite's life cycle.

Vaccines would introduce a new concept in malaria control. This may be visualized most simply by regarding the major elements of natural malaria transmission, which Macdonald (*1*) has summarized in the formula of the basic reproduction rate

$$Z_o = \frac{m\,a^2\,b\,p^n}{-r\log_e p}$$

where Z_o (the basic reproduction rate) denotes the number of cases resulting from the seed case in a non-immune, i.e., fully susceptible, population, m the density of vector mosquitos, a their daily number of bites on man, b the proportion of mosquitos with gland infections having viable sporozoites, p the probability of mosquito survival through one day, n the number of days required for sporogony, and r the proportion of infected persons who revert to the uninfected state in one day.

The values of m, a, p, n and $-\log_e p$ are given by the bionomics of the vector and the environmental conditions. Vector control measures are used to modify m, p and $-\log_e p$; in some cases they may also have an impact on a.

It is well known that immunity has a major bearing on the parameters b and r and thus on the value of Z_o. While b is, so far, outside the reach of antimalaria measures, a modification of r can be achieved through radical and gametocytocidal treatment.

Under conditions of stable malaria of high endemicity, an equilibrium is reached through the combined effects of immunity and saturation of the reservoir. In this case the reproduction rate can be expressed as

$$Z_o = \frac{p^n}{p^n - L_s}$$

L denoting the limiting value of the proportion of persons infected when equilibrium is reached and s the proportion of mosquitos with sporozoites in their salivary glands (*1*).

Disregarding the factors of immunity and reservoir

[a] Editor's note: a short report of this meeting will be published in a future issue of the *Bulletin*.

saturation in the first formula, one may arrive in tropical Africa at basic reproduction rates of 500 and more. Technically feasible modifications of m, p and r may not suffice for reducing Z_o to a value below 1.0, i.e., the critical limit of achieving the gradual disappearance of malaria. The availability of vaccine(s) may bring the much desired additional impact. Therefore it would be useful to consider the potential approaches against *P. falciparum*.

TYPES OF VACCINE

Sporozoite vaccine

This would have a causal prophylactic effect as it should prevent infection altogether. Sterile immunity might be expected to develop once an existing blood infection has ended naturally or as a result of treatment. Unlike vaccines directed against blood schizogony, a suboptimal sporozoite vaccine would confer no benefit on persons who develop only incomplete antisporozoite immunity. The impact on the epidemiological situation would depend essentially on the degree of efficacy of the vaccine and on the rate of vaccination coverage. In the basic reproduction rate this could be reflected by modifying a^2 into $a_1 \times a_2$, where a_1 expresses the daily number of bites on potentially infective man, and a_2 the daily number of bites on protected man. In the absence of new infections in protected persons, a_1 will eventually assume the value of a_2. Under these conditions the effective protection of 80% of the population by sporozoite vaccine would reduce the basic reproduction rate to 1/25 of its original value if protection affected all age-groups alike. In practice, the reduction would be somewhat less, since there would certainly be a delay in covering infants and other newcomers to the community.

Gamete vaccine

This vaccine would interfere with sporogony and thus reduce the quantum of transmission as a function of the effectively vaccinated population and possibly also of the degree of efficacy of immunization. Since the vaccine does not modify the susceptibility of man to infection, the expression of its impact on the basic reproduction rate will necessitate replacing a^2 by $a_1 \times a_2$. In this case, a_1 denotes the daily number of bites on man without an effective level of antigamete antibodies, and a_2 the daily number of bites on protected man. The effective vaccination of 80% of the population by antigamete vaccine would reduce the basic reproduction rate to $\frac{1}{5}$ of its original value if one presumes equal efficacy in all age-groups.

Vaccines directed at blood schizogony

Vaccines directed against merozoites and asexual blood schizogony forms offer a rather wide range of possibilities, from a mere reduction in blood schizogony to sterile immunity. While vaccines that reduce but do not eliminate blood schizogony may be highly effective in curbing mortality and clinical morbidity from malaria, they are not expected to have a major impact on the malaria reservoir level unless they also shorten the duration of infection, thus increasing the value of r. In the case of induction of full immunity against merozoites and asexual blood stages, one would expect a similar influence on the basic reproduction rate to that described for sporozoite vaccine, with the proviso that these vaccines would not exclude infection but only prevent blood schizogony and gametocytogony.

From these somewhat simplistic considerations, it is evident that vaccines against falciparum malaria would not by themselves be able to reduce the malaria reservoir in the majority of tropical African areas unless they were fully effective and were given at a very high coverage. For instance, some 96% of the population would need to have full, active protection through sporozoite or merozoite vaccines in order to reduce the basic reproduction rate of 500 to a level of just under 1.0. In practice, this is not feasible under the local conditions, the more so as it would require the earliest possible protection of infants.

However, vaccines could be a very useful tool in combination with other means of malaria control, even under less exacting conditions of population coverage and of occasional lack of efficacy in some individuals. Much, of course, will also depend on the target groups that are to be protected.

APPLICATIONS OF VACCINES

When considering the issue of vaccine development, several important questions need to be answered, such as the impact of vaccines on persons harbouring malaria parasites at the time of vaccination, the relationship between parasite-induced immunosuppression and the natural development of immunity, and the immunocompetence of infants and young children and its relation to vaccine effect. Infants and young children are epidemiologically significant groups, since they normally represent the major gametocyte reservoir in areas of high malaria endemicity.

Attention should also be given to the eventual consequences of suppressing one parasite species and leaving another one relatively untouched. Such a situation could result in tropical Africa, where *P. malariae*

would probably take a leading role if *P. falciparum* were suppressed, a phenomenon that is well known to occur in several areas of Africa during the dry season when the transmission of *P. falciparum* is low or temporarily interrupted. A massive vaccine-induced reduction of the transmission of *P. falciparum* might manifest itself in a similar way with as yet unknown immunopathological implications.

Sooner or later we shall be confronted with the question of whether it is justified to limit vaccine development to one species. Admittedly, *P. falciparum* causes a killing disease and is the most frequent human malaria parasite. Moreover, material for research and vaccine production is more accessible from this parasite than from other species. However, *P. vivax* may deserve increasing attention in the future. This species has a considerable socioeconomic impact, especially in Asia and the Americas, where the basic reproduction rates are generally only a fraction of those observed in tropical Africa and where vaccines might revolutionize malaria control which, as a result of vector resistance to insecticides, has in many areas reached the limits of technical and financial feasibility.

At this stage it may seem premature to address the issue of the ethical aspects of vaccine trials. However, the need to define basic epidemiological and clinical parameters in the preparation of such trials may soon be pressing and much valuable time and precision would be lost were the discussion of this subject postponed. Only an initial dialogue is possible at present, but it should help to strengthen the liaison between field workers and laboratory investigators, which will be indispensable in such an endeavour.

RÉSUMÉ

ORIENTATION DE LA RECHERCHE IMMUNOLOGIQUE AUX FINS DU PROGRAMME MONDIAL DE LUTTE CONTRE LE PALUDISME

Les recherches sur l'immunologie du paludisme ont permis d'amasser une vaste somme de renseignements sur les relations entre *Plasmodium* et son hôte vertébré, qui ont servi de base à l'application de nouveaux moyens d'investigation sérologique. Les résultats obtenus expérimentalement ont confirmé la possibilité de protéger les vertébrés contre le paludisme, et la vaccination est ainsi en voie de perdre son caractère d'objectif théorique pour entrer dans le domaine des réalités.

Le tableau alarmant que présente le paludisme dans le monde justifie amplement l'élargissement et l'intensification des recherches immunologiques. Le programme du groupe de travail scientifique de l'immunologie du paludisme, créé dans le cadre du programme spécial de recherche et de formation concernant les maladies tropicales PNUD/Banque mondiale/OMS, a défini deux grands objectifs: le développement et l'amélioration des techniques diagnostiques et épidémiologiques, et la mise au point de moyens applicables sur une grande échelle pour protéger l'homme contre le paludisme, notamment de vaccins. La réalisation de ce programme s'appuie nécessairement sur l'étude des antigènes parasitaires et celle des mécanismes immunitaires et de leur mise en échec. Elle suppose également l'essai sur des modèles animaux (rongeurs et primates) de diverses approches à la vaccination faisant appel à un matériau antigénique d'origine variable—mérozoïtes, parasites des stades asexués érythrocytaires, gamètes et sporozoïtes—avec ou sans adjuvant.

On n'a pas jusqu'ici évalué de manière précise l'impact que pourrait avoir la disponibilité de vaccins sur le tableau du paludisme. Cette démarche est pourtant nécessaire pour mettre la vaccination à sa juste place parmi les autres moyens possibles d'endiguer le paludisme et pour éviter tout optimisme exagéré. La formule de Macdonald pour le calcul du taux de base de reproduction a été utilisée pour apprécier l'impact éventuel de différents vaccins antipaludiques. Certains pourraient permettre d'agir sur la mortalité et la morbidité dues au paludisme sans modifier essentiellement le niveau de la transmission. Ces vaccins ne constitueraient donc qu'un palliatif, sans effets sur le plan épidémiologique. D'autres, qui rendraient totalement inactifs certains stades du parasite ou détermineraient l'apparition d'une immunité stérilisante, constitueraient des outils précieux, dont l'efficacité serait maximale lorsque prévaut un taux de base de reproduction peu élevé; dans les régions où ce taux est élevé, comme l'Afrique tropicale, la vaccination ne pourrait sans doute à elle seule influencer de manière significative la situation épidémiologique, mais elle pourrait, si d'autres mesures sont prises parallèlement, renforcer suffisamment l'effet de celles-ci pour entraîner une réduction notable de la prévalence de l'infection et son élimination éventuelle. La protection contre *P. falciparum* figure naturellement au premier plan des travaux visant à la mise au point de vaccins. Il semble cependant qu'il serait justifié de vouer tout autant d'attention à la protection contre le paludisme à vivax, étant donné les aspects socioéconomiques très importants de ce fléau dans certaines parties du monde.

REFERENCES

1. MACDONALD, G. *The epidemiology and control of malaria,* London, Oxford University Press, 1957.