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Mechanisms of acquired immunity and epidemiological patterns of antibody responses in malaria in man*

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This paper considers the participation of macrophages, thymus-dependent lymphocytes (T-cells), and thymus-independent lymphocytes (B-cells) in man's immune response to malaria. Although phagocytosis by macrophages is an important feature of malaria the full extent of cooperation between these cells and T- and B-cells is not known. Evidence that T-cells play an important defensive role is at present unconvincing. B-cells on the other hand function importantly in the synthesis of immunoglobulins and specific antibodies and factors possibly influencing their activity are considered. Different epidemiological patterns of malarial antibodies in sera are described and the need for the routine inclusion of reliable antibody detection tests as part of malaria survey techniques, particularly where antimalarial drug usage is frequent, is emphasized.

MECHANISMS OF IMMUNITY

Today, man's immune response to infection is regarded as closely integrated, involving different populations of cells. Antigens may first require processing by macrophages before they stimulate lymphocytes that are either thymus-dependent (T-cells) or thymus-independent (B-cells). T-cells comprise the bulk of circulating lymphocytes, are long-lived, and may function importantly in immunological memory. When stimulated by antigen they give rise to lymphoblasts, which can be cytotoxic to target cells and release soluble factors thus forming the basis for delayed hypersensitivity. These lymphoblasts do not synthesize antibody but they may cooperate in the immune response to certain antigens by stimulating B-cells to antibody production. B-cells seem to be relatively short-lived and are more restricted to lymphoid tissues. They give rise to plasma cells, which are essentially concerned with the synthesis of immunoglobulins and antibodies. The stimulus to antibody production is the recognition of antigen by cells of the B-lymphocyte line. Some antigens appear to be recognized directly, possibly with the aid of macrophages, while others may require the cooperation of T-cells. In addition to immunocompetent cells and antibodies other substances such as complement may be required to amplify the immune response.

This section briefly reviews the present knowledge of acquired malarial immunity in man in the light of these concepts.

Phagocytosis

Phagocytosis by the macrophages of the reticulo-endothelial system (RES) is a prominent feature of malaria infection in man (1). In spleen, liver, and bone marrow, and to a smaller extent in other organs, these cells have been shown to ingest intracellular and extracellular parasites, pigment, and malarial detritus. The exhaustive studies of Taliaferro and his colleagues (2) indicated that, both in avian and in simian malaria, phagocytosis of parasites in the non-immune animal was sluggish at first but increased markedly as immunity was acquired, possibly through the mediation of specific opsonizing antibodies. Splenic macrophages consistently appeared to be more active phagocytically than did those of liver or bone marrow. Since then, it has been generally assumed that phagocytic processes in man are similar.

Sheagren et al. (3) have shown that during acute malarial illness in man the blood flow through the RES slows, but despite this the phagocytic activity of the tissues of the RES, as judged by their ability to

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clear labelled microaggregated human serum, is enhanced. It may be inferred from these findings that even during acute malaria the RES remains capable of phagocytosing nonmalarial antigens and that therefore the immunosuppression in man that has been observed in association with malaria (4, 5) probably does not result from reticuloendothelial blockade.

Knowledge of the full function of the macrophage in acquired malarial immunity is lacking. Current immunological thought (6) accords this cell important roles in the degradation, processing, and retention of antigen, in collaboration with both T- and B-lymphocytes and possibly also in the maintenance of immunological memory. How these sequences are achieved in malaria is not known.

The implication of T-cells

Results from investigations in animal malaria have indicated that T-cells may function in the acquisition and maintenance of protective immunity (7–9). These studies, however, utilized techniques that are inapplicable to man and, consequently, comparable information on human malarial immunity is not available.

To date, few investigations have been made to detect a possible T-cell function in human malaria. Some have attempted to seek evidence that T-cells from persons with previous malarial experience are sensitized to malarial antigens; others have sought to find whether T-cell function in general is depressed in individuals experiencing acute clinical malaria.

Kass et al. (10) have reported the histological evidence of blastoid transformation of peripheral blood lymphocytes obtained from partially immune patients when these cells were cultivated *in vitro* for 3 days with extracts of *P. falciparum* trophozoites and gametocytes. No such results were obtained with extracts of uninfected erythrocytes from a non-immune volunteer or when peripheral lymphocytes from non-immune controls were cultured with the *P. falciparum* extracts. Blastoid transformation remained detectable for as long as 2 years after radical cure of the malaria infection.

Osunkoya et al. (11) have reported blastoid transformation of lymphocytes in unstimulated cultures of peripheral leucocytes from most of 18 children infected with *P. falciparum*. Transformation occurred irrespective of whether the cells were cultured in autologous plasma or in fetal calf serum. Substantially lower transformation scores were noted in cultures from control children with fever but no parasitaemia. Those authors considered the change to blast cells of lymphocytes from the malarious children to represent spontaneous transformation, possibly in response to stimulation by malarial antigens. The addition to some cultures of intact or homogenized parasitized erythrocytes did not further increase transformation rates, suggesting that maximum stimulation had already occurred, perhaps *in vivo*.

Studies in progress in The Gambia (Moore, personal communication) have measured labelled thymidine uptake as a measure of lymphocyte transformation in 3-day leucocyte cultures. Cells from donors with and without experience of malaria have been examined unstimulated and stimulated by malarial and control nonmalarial antigens. Malarial (*P. falciparum*) antigens were extracts of heavily infected placental blood or of infected peripheral blood cultured to parasite maturity. Human sera containing malarial S-antigens were also used. Control nonmalarial antigens comprised sera from nonmalarious individuals and extracts made from uninfected placental and peripheral blood. Culture cell donors were immune Gambian adults, Caucasians with or without previous malarial experience, and young Gambian children. The latter were investigated approximately 6 weeks after treatment for acute malaria and in some instances the malarial and nonmalarial antigens used were autologous. To date 10 adults and 15 children have been studied and no consistent pattern of results has emerged to show that malarial antigens induce specific transformation in requisitely sensitized persons.

Greenwood et al. (5) found no evidence of depressed T-cell activity, as assessed by skin sensitivity to dinitrochlorobenzene and transformation of lymphocytes in response to stimulation by the non-specific mitogen phytohaemagglutinin (PHA), in malarious, as opposed to healthy, Nigerian children. Their 2-day cell cultures employed purified lymphocytes and a constant dosage level of PHA. In contrast, Osunkoya et al. (11) found depressed responses to PHA in lymphocytes from malarious Nigerian children. These authors, however, employed 5-day leucocyte—not purified lymphocyte—cultures. Moore (personal communication) found that responses to low (0.1 μg/ml) but not to higher (1.0–10.0 μg/ml) doses of PHA were significantly lower in some Gambian children with heavy *P. falciparum* infection than in either healthy or severely malnourished, nonmalarious controls. In the Gam-

bian studies 3-day leucocyte cultures were used and a significant inverse correlation was observed between response to the low PHA dose and the proportion of granulocytes in individual cultures.

Currently, the evidence that T-cells function in human malarial immunity is not strong and the results of studies in this field are difficult to assess for two reasons—the paucity of the studies and the diversity of the techniques utilized. Some investigations involve the culture of peripheral blood leucocytes while others use purified lymphocytes; the duration of cell culture often varies substantially; sometimes cells are cultured in autologous plasma and sometimes not; differences in the purity, potency, and dosage of PHA are common; different methods of assessing lymphocyte transformation are employed; and finally there is probably great variation in the nature of the malarial antigens used to induce responses. Greater standardization of techniques will be required before studies made by different workers can be adequately assessed.

The implication of B-cells

It is not known how antigen is presented to cells of the B-line. From studies in murine malaria Greenwood et al. (12) have postulated that lymphoid cells that are not T-cells carry immune complexes to the germinal centres of lymphoid tissue and that the immunosuppression described in association with malaria (4, 5) may be the result of parasitaemia depleting these carrier cells.

Once B-cells are stimulated by malarial antigens they respond by synthesizing increased amounts of three of man's five immunoglobulins. In studies made in non-immune volunteers (13) serum concentrations of IgG, IgA, and IgM rose almost simultaneously shortly after parasitaemia became patent. The increases were greater in IgG and IgM than in IgA. In similar investigations Collins et al. (14) showed that specific antibody responses occurred in the same three immunoglobulins soon after the onset of parasitaemia. IgG antibodies persisted longest while those of IgA and IgM were more transient, sometimes almost disappearing while parasitaemia persisted.

Population studies made in The Gambia (15) have shown malarial parasitaemia to be associated with elevated levels of IgG over the first 20 years of life, but with elevated IgM levels only over the first 2 years. In association with the presence of malarial precipitins, however, serum levels of IgG and IgM were elevated at almost all ages. No consistent relationship of IgA with either parasitaemia or precipitins was found.

Prolonged exposure to malarial infection leads to greatly enhanced daily rates of synthesis and to high serum levels of IgG (16). Results from absorption studies have indicated that only a small part of the total IgG present in immune serum represents antibodies directed against the parasite (17, 18), thus implying that some proportion may be without specific malarial antibody function. However, absorption investigations tend to employ a restricted range of malarial antigens and to be particularly deficient in soluble antigens, which may represent either parasite secretions or altered components of host tissue cells (19). Furthermore it is not yet known if the plasmodia that infect man are capable of the extensive antigenic variation that *P. knowlesi* displays in the rhesus monkey or what role such variation may play in enhancing specific antibody formation.

More than 30 distinct antigens have been identified in association with the blood forms of *P. falciparum* and antibodies of corresponding specificity have been detected in sera obtained from Gambians resident in hyperendemic areas. Wilson et al. (20) have classified these antigens into three main groups—L (labile), R (resistant), and S (stable)—on the basis of their ability to withstand heating and have further divided these classes into subgroups—e.g., La^1 and La^2, Lb, R^1 and R^2, S^1 and S^2 on the basis of other factors. They have also described the physicochemical properties of some individual antigens. Recent unpublished studies by Wilson on the incorporation of labelled amino acids with *P. falciparum* parasites cultured *in vitro* suggest that L and R antigens are of plasmodial origin while antigens of the S class might represent altered components of host tissue.

Not all the antigens of *P. falciparum* are equally immunogenic to B-cells. La antigens appear to be good immunogens since antibodies to them can be demonstrated, often in high titre, in sera taken from all age groups in hyperendemic areas (21). S-antigens, although they occur frequently in the sera of heavily parasitized children, often fail to induce a detectable antibody response (19). Furthermore when responses do occur they are often weak and transient (21). R^1 antigen has been identified in all extracts of *P. falciparum* parasites examined by Wilson and his colleagues yet antibodies to it have been found in only one of thousands of immune human sera studied.

The capacity of B-cells to respond to specific malarial antigens may change markedly with age. Antibodies to S-antigens are not frequently found in sera taken from young age groups in cross-sectional studies of populations resident where malaria is hyperendemic. They can however be found commonly in sera taken from older adult age groups (21). Since young children are exposed to S-antigen stimulation to at least as great an extent as adults, the change with age in antibody prevalence may represent either a change in the sensitivity with which B-cells recognize and respond to these antigens or a marked increase in the number of responding cells.

The factors that determine the Ig class of antibodies synthesized by B-cells in response to malarial antigens are not known. Age, immunocompetence, and previous malaria experience of the host are probably important. Intrauterine stimulation by certain bacterial and viral antigens has been shown to induce premature synthesis of IgM and IgA in the fetus (22), but studies in The Gambia have failed to show that malarial infection of the placenta is associated with increased levels of either of these immunoglobulins in the sera of newborn infants (23). In early infancy, however, malaria infection leads rapidly to the synthesis of specific IgM antibodies (24). The physicochemical nature of antigen may also influence immunoglobulin selection: Nossal et al. (25) have shown that particulate bacterial antigens may induce an early IgM antibody response, whereas in the case of certain soluble antigens the earliest antibody response may be in IgG. While there is no precise information on the role of such factors in malaria it is of interest that antibodies to La antigens of *P. falciparum* are found essentially in the IgG fraction of immune human sera while those to S-antigens occur with almost equal frequency in IgG and IgM fractions.

Recently, antibodies to S-antigens have been found to possess restricted electrophoretic mobility, the majority tending to migrate in the γ_1 region (26). Different antibodies did not possess identical mobility and differences were noted in the mobility of antibodies formed by different individuals in response to the same antigen. These and other findings suggested that antibodies to individual S-antigens possibly originate from clones of B-cells. That antibodies in malaria may be synthesized by discrete subpopulations of B-cells is also implied by the observation of Curtain & Baumgarten (27) that malarial antibodies identified in the sera of Melanesians showed phenotypic restriction.

The destruction of parasites

Although studies on the passive transfer of malarial immunity (16) have provided presumptive evidence that acquired protective immunity operates mainly against either erythrocytes containing mature asexual parasites or extracellular merozoites, precisely how these parasites are destroyed is not known. Phagocytosis of intracellular and extracellular parasites, possibly with the cooperation of specific opsonizing antibodies, is probably important. Destruction of parasites by sensitized T-cells may also occur but as yet there is no evidence of the existence of such a mechanism in man. Currently, the balance of evidence favours a view that parasite destruction is mediated principally by specific IgG antibodies. Whether these antibodies are directly lethal to the parasites—e.g., destroying them by lysis—or whether they require the cooperation of a primed phagocytic system is not clear.

In the course of malaria infections complement-fixing antibodies are formed (28) and variations in the haemolytic activity of complement in human sera have been described (29). Together, these observations suggest that complement may participate in some malarial antigen–antibody reactions and perhaps play a part in parasite destruction. However, there is at present no additional evidence to support such a view, although the activation of complement in antigen–antibody complexes deposited in the kidney during *P. malariae* infections in children may be important in the pathogenesis of the nephrosis associated with quartan malaria (30).

According to some workers (31) interferon is increasingly being regarded as part of the immune response. Certainly, studies on murine malaria have shown that it may significantly affect the progress of *P. berghei* infections. Jahiel et al. (32, 33) have reported that exogenous mouse interferon and also interferon inducers administered at or soon after sporozoite inoculation appear to inhibit *P. berghei* development either during or at the end of pre-erythrocytic development, but not once erythrocytic parasitaemia is established. Interferon is thought to achieve its inhibitory effects on viral reproduction by interrupting the synthesis of viral coded protein at the ribosomal level. The explanation of its apparent effect on pre-erythrocytic forms of *P. berghei* may be that these are perhaps the forms of the parasite in which synthesis of RNA and protein is most active. Whether interferon exerts a similar action in malaria infections of man is not known.

EPIDEMIOLOGICAL PATTERNS OF ANTIBODY RESPONSES

The assessment of the endemicity of malaria in a country has often posed problems. Today the difficulties that oppose its measurement increase yearly in many developing countries because of the gradual but uneven extension of antimalarial measures, particularly the irregular and poorly supervised use of drugs as suppressive or therapeutic agents. Classically, an area of high endemicity could be identified by the concurrence of a number of clinical features. Congenital malaria was rare, and newborn infants showed a distinct resistance to infection in the early months of life; parasitaemia was prevalent and dense, often associated with clinical illness, in young children; in older children parasitaemia remained prevalent but declined in density, while in adults it became infrequent and scanty and clinical malarial illness became rare; spleen rates were high in children but declined markedly in adult life.

Today drug use may alter this clinical pattern without necessarily effecting substantial reduction in disease transmission. Its effects will be proportional to its regularity and coverage. Antimalarial drugs supplied to discrete groups, such as mothers and infants attending maternal and child welfare centres and children attending school, may profoundly affect malariometric indices in these groups but not in other sections of the community. The effects of such group-oriented drug administration may not be difficult to assess provided accurate information is available on the actual uptake of treatment. However, when drug use spreads throughout all sections of the community and is irregular and unsupervised it greatly complicates the assessment of malarial endemicity when customary indices are used.

Over the past decade many field studies have been undertaken to determine age-specific patterns of malarial antibodies in serum taken from populations living in areas of varying endemicity. Despite the lack of standardized techniques a consistent pattern has been described in association with hyperendemic malaria in many different parts of the world. Antibodies are found in high prevalence and titre in sera from newborn infants. In the early weeks of life antibodies decay and antibody-negative sera become frequent. In response to infection antibody prevalence rises rapidly, reaching 90–100% around the third year of life, and it maintains this level in older age groups. Antibody concentrations rise more slowly and peak mean titres are not discernible until adult life. Comparison of this well defined pattern with antibody profiles established for communities living in different circumstances could form a valuable basis for the assessment and classification of malarial endemicity.

A few field studies have attempted such comparisons. In The Gambia, Harverson et al. (34) found the prevalence and titre of antibodies to be very much lower in city dwellers than in children living in rural villages and considered the difference to be due to extensive antimalarial measures practised in the city. In Nigeria, Voller & Bruce-Chwatt (35) considered malaria to be holoendemic in two distinct populations on the basis of age-specific parasite rates. However, when patterns of antibody prevalence and titre were compared the results indicated that the cumulative malaria experience of one population was considerably greater than that of the other. Importantly, this study also showed that serological indices were less affected by seasonal fluctuation in malaria transmission than were the customary indices.

Draper et al. (36) have recently examined communities resident in the South Pare district of Tanzania where between 1956 and 1959 successful malaria control operations took place. Although they found the density of vectors and the theoretical inoculation rate to have returned to levels similar to those obtaining in the area before control, the age-specific parasite rates were far below those normally associated with hyperendemicity. Serological investigation revealed that the pattern of antibody prevalence was very similar to that found in hyperendemic areas, reaching 90% in children by the second year of life and 100% at older ages. Antibody titres however were considerably lower at all ages than those associated with hyperendemicity. This situation was thought to be the result of widespread therapeutic use of antimalarials, which, although curtailing the duration and magnitude of parasitaemic episodes and consequently also their immunogenicity, did not materially reduce transmission.

Draper and his colleagues (37) also investigated a community living in an area in which a chloroquinized salt campaign had been in operation for 10 years with only moderate success as judged by parasite rates. Parasitaemia was found in all age groups at rates varying from 5% to 32%.

Serological findings in this area differed markedly from those in South Pare. The prevalence of serum antibodies rose slowly from 26% in infancy to 86% in adult life while antibody titres were low in all age groups and showed no tendency to increase throughout childhood.

There is thus sufficient evidence to indicate how knowledge of antibody profiles can be utilized in conjunction with other malariometric indices to provide a fuller and better assessment of the endemicity of malaria than has hitherto been possible. It is to be hoped that future surveys will routinely include serological studies aimed at measuring the cumulative malaria experience of the population.

RÉSUMÉ

MÉCANISMES DE L'IMMUNITÉ ACQUISE ET ASPECTS ÉPIDÉMIOLOGIQUES DE LA RÉPONSE EN ANTICORPS DANS LE PALUDISME HUMAIN

Si l'on tient pour probable que des populations différentes de cellules interviennent conjointement dans la réponse immunitaire de l'homme au paludisme, on ne connaît pas encore complètement, à l'heure actuelle, les phases successives et l'importance de cette coopération. Les antigènes subissent l'action des macrophages avant d'être à même d'activer les lymphocytes, que ces derniers soient dépendants du thymus (cellules T) ou indépendants de cet organe (cellules B). Une déficience de ce processus est peut-être à l'origine de l'absence de réaction à certains antigènes non paludiques observée chez des sujets atteints de paludisme.

Il est difficile d'interpréter les résultats des recherches effectuées en vue de définir le rôle des cellules T dans la réponse immunitaire au paludisme. Ces recherches sont en effet peu nombreuses et elles ont été faites sans qu'on ait eu recours à des techniques uniformes. Pour le moment, il n'existe aucune preuve convaincante de l'importance des cellules T dans la défense de l'organisme humain contre le paludisme. De nouvelles recherches, faisant appel à des techniques plus standardisées, sont nécessaires dans ce domaine.

En revanche, le rôle des cellules B semble considérable. La parasitémie est rapidement suivie d'une hausse des taux sériques d'IgG, d'IgA et d'IgM et de l'apparition d'anticorps antipaludiques spécifiques dans chacune de ces classes d'immunoglobulines. On ignore cependant si ces anticorps spécifiques sont responsables en totalité de l'accroissement de la synthèse d'immunoglobulines. Certains antigènes paludiques sont plus immunogènes pour les cellules B que d'autres. Les facteurs qui déterminent la classe d'immunoglobulines synthétisée par les cellules B en réponse à la stimulation antigénique ne sont pas connus, mais l'âge et les antécédents immunologiques de l'hôte, ainsi que l'état physico-chimique de l'antigène, peuvent avoir une influence. Des observations donnent à penser que l'aptitude des cellules B à réagir face à certains antigènes paludiques peut varier considérablement selon l'âge de l'hôte, sans que l'on sache si ce phénomène correspond à une modification de la sensibilité des cellules B ou à une augmentation graduelle de leur nombre.

Le rôle de substances comme le complément et l'interféron dans la réponse au paludisme chez l'homme n'est pas élucidé, de même qu'on ne connaît pas avec certitude la façon dont les parasites sont détruits par les mécanismes immunitaires.

D'études sur le terrain effectuées dans des régions d'endémicité paludéenne, il ressort que dans les secteurs où l'usage des médicaments antipaludiques est répandu, mais non contrôlé, les indices paludométriques classiques, comme l'indice plasmodique selon l'âge et l'indice splénique, fournissent une sous-estimation appréciable de la prévalence de l'infection. Dans de tels cas, l'établissement de profils sérologiques au sein des collectivités, basé sur la recherche correcte des anticorps, a permis d'obtenir une évaluation plus exacte de la prévalence réelle. Les techniques sérologiques présentent donc un grand intérêt pour l'étude de l'endémicité paludéenne et leur emploi régulier dans les enquêtes sur le paludisme est recommandé.

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DISCUSSION

MCGREGOR: Decreased immunity to pregnancy must be related to parity. There may be an attenuation of immunity in the first and second para but there is much less indication of any attenuation at, say, the sixth para. IgG levels appear to fall progressively throughout pregnancy and are at their lowest in the last 10 weeks.

BRUCE-CHWATT: There is no satisfactory explanation for the comparative absence of congenital malaria, i.e., circulating parasites in the child within 24 hours of birth in the hyperendemic areas of Africa, whereas its prevalence in hypoendemic or mesoendemic zones of Algeria, Sri Lanka, and Turkey is greater. Heavily parasitized placentae undoubtedly affect the nutrition of the fetus and this contributes to the low birth weight and subsequent mortality of neonates associated with infected placentae.

MEUWISSEN: Parasites can be found at birth in the cord blood of African neonates but not in their circulating blood 24 hours after birth. This seems to indicate that the lack of congenital malaria in endemic malarious areas must be due to maternal antibody.

MCGREGOR: High IgM levels are found in neonates but this is not associated with placental infection. However, the fetus does not appear to be immunologically reactive to malaria and presumably maternal IgG neutralizes any parasites crossing the placenta.

CORRADETTI: Why is it that parasites of avian malaria may start to grow inside macrophages?

COHEN: Parasites are usually contained in a phagosome in macrophages, which fuses with the lysosomes for digestion of the parasites. Some parasites, such as *Toxoplasma*, appear to be able to arrest this fusion and so escape digestion.

BRAY: The nature of the phagosome wall, and whether lysosomes move in on the phagosome or not, are also relevant factors.

MCGREGOR: S antigen was not found in neonates or in cord blood even when this antigen was present in the maternal serum. Individuals are frequently found with circulating S antigen and no detectable antibody to it.

BRAY: The use of phytohaemagglutinin (PHA) response of lymphocytes as a measure of the efficiency or efficacy of the cell-mediated immune system is questionable. It seems to be subject to effects from various disease conditions that may exist in the population examined besides the one under study. It records only mobilization by division rather than any effector system, such as the production of lymphocyte activation products. Furthermore, the response is to a mitogen, whereas a specific antigen might elicit a different response. Effective mobilization in any case could be stimulated by some other antigen-mediated process rather than through the physiological response elicited by PHA. Various serum factors are known to suppress PHA responses. On the whole, an effector response measure, such as cytotoxicity, which could conceivably be carried out by means of cultured cells from a small amount of blood, is preferable.

COHEN: The PHA response is not a very appropriate test in this field.

BRAY: A seroepidemiological survey should be made in a seasonal vivax zone for a couple of years to study further the possible relationships between immunity and relapse.

AMBROISE-THOMAS: There is no drop in antibody prior to relapse in vivax malaria, either in the field or in induced malaria. However, we do not know if the antibody we are looking at is protective.

MCGREGOR: It is essential to be able to identify protective antibody so that the antigens can be successfully investigated by a technique such as gel diffusion.

BRUCE-CHWATT: Should not low age groups be protected against malaria?

MICHEL: We assessed the percentage of antibody carriers in relation to splenomegaly and parasite levels during a longitudinal chemotherapy study of infants. In the control group, the percentage of precipitating antibody carriers was closely related to the rainfall indices following their seasonal variations. In the group receiving chemoprophylaxis, there was no marked fall in the percentage of antibody carriers until 6 months after the commencement of treatment.

KAMEL: Prophylaxis is of value to a whole community in a hypoendemic vivax malaria area; even if there is a 6-week break in chemotherapy, the levels of parasitaemia are still low when treatment is renewed.

AMBROISE-THOMAS: Chemoprophylaxis will reduce IFA titres and precipitins, but as we do not know which are the protecting antibodies we cannot ascribe any significance to this. Children protected by chemoprophylaxis may still be able to develop immunity.