of anti-idiotypes might be expected to have therapeutic value. Observations in our unit (unpublished) have shown that in certain circumstances immunosuppression does result in disappearance of the lupus anticoagulant. Furthermore, Lubbe *et al* recently reported successful pregnancies in five patients who had previously had spontaneous abortions and whose lupus anticoagulant disappeared on immunosuppressive treatment.[14]

Of even wider clinical interest is the possibility that such antibodies may react with complex brain lipids such as sphingomyelin. Clinical studies have hinted that the cerebral features of systemic lupus erythematosus may be associated with the presence of this family of antibodies. To study this possibility, the assays used to detect antilipid antibodies would need to be refined; so both clinical and research interest has been stimulated by the recent study by Harris *et al*, who have developed a sensitive solid phase radioimmunoassay for anticardiolipin antibodies some 200-400 times more sensitive than, for example, the precipitation method used in the Venereal Disease Research Laboratory test.[15] There was a strong correlation between raised titres of anticardiolipin antibodies and venous and arterial thrombosis. Of the 15 patients with the highest anticardiolipin antibody titres, six had a history of venous thrombosis and five had cerebral thrombosis without other predisposing factors. Two each had pulmonary hypertension and multiple abortions.

This simple immunoassay appears to have predictive value for thrombosis in systemic lupus erythematosus and related disorders. Harris *et al* also found high titres of anticardiolipin and antisphingomyelin antibodies in a patient with transverse myelitis and a false positive Veneral Disease Research Laboratory test result. This disease had features similar to the endemic Jamaican disease "Jamaican neuropathy"—a meningomyelitis in which similar abnormalities have been seen.[16 17]

Spreading the net even further, they reported high titre anticardiolipin antibody values in a patient with Behçet's disease—a syndrome characterised by thrombosis and features of central nervous system disease including myelopathy. The potential implications of research into antibodies such as anticardiolipin and antisphingomyelin antibodies are obvious, with clinical applications in other diseases where thrombosis or demyelination occur.

These antibodies may, of course, be epiphenomena—fellow travellers with little or no pathogenic importance. That seems unlikely. Though the results of the immunological analysis are always open to dispute and the association with neurological disease is still speculative, the clinical association with thrombotic disease appears strong.

For those of us hardened into nihilism by years of study of various autoantibodies in systemic lupus erythematosus, there is a rare sense of excitement at the implications of the associations now being reported.

GRAHAM R V HUGHES

Consultant Physician,
Hammersmith Hospital,
London W12 0HS

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Malaria vaccination: two steps forward, one backward

In the two years since the topic of malaria vaccination was last reviewed in the *BMJ*[1] important technical advances have been made in the search for antigens that can induce a protective response against the various stages of the malaria parasite. The pertinent question is whether, or to what degree, these advances bring us closer to the manufacture and practical deployment of a vaccine to protect people against this disease.

Without question multiple drug resistance in the malignant tertian parasite, *Plasmodium falciparum*, is spreading alarmingly across the eastern parts of the African continent and Madagascar. Resistance is also extending westwards across India and eastwards as far as malaria goes in the south west Pacific. The endemic areas of Latin America, too, have faced this problem for many years. Radically new antimalarial drugs are most unlikely to become available in the short term, especially for prophylaxis. Reports on mefloquine, a potent, synthetic analogue of quinine, are already throwing up hints that parasites can become resistant to it, even though the drug is still only in the stage of clinical trial. Artemisinine (Qinghaosu), the new derivative of an ancient Chinese herbal remedy, is at an early stage of its development and looks likely to lend itself only to therapeutic and not to prophylactic use. Other new drugs such as halofantrine (in a sense an analogue of mefloquine) and a new series of quinones which are the subject of patent applications by the Wellcome Foundation will need at least five more years of investigation before they could be widely applied even if they overcome all the hurdles of new drug development. No new insecticides are on the horizon that are both technically superior to DDT and economically deployable by most Third World countries. Inevitably, therefore, great hopes are being pinned on the malaria vaccines as

additional weapons to keep malaria in check and perhaps even to make substantial reductions in its levels of transmission.

Vaccine research is progressing in two main directions: firstly, the identification of protective antigens on the surfaces of three stages of malaria parasites (the sporozoites that develop in the mosquito and infect man, the merozoites that invade his red cells, and the gametocytes that, to complete the cycle, infect the mosquito); and, secondly, vaccine production by genetic engineering or synthesis of the relevant polypeptides. The emphasis has turned from the study of avian and rodent malaria to the use of simian and human parasites—*P knowlesi* in rhesus monkeys, *P falciparum* blood stages in continuous culture, and *P vivax* in cyclical transmission through squirrel monkeys (*Saimiri*). Monoclonal antibodies have opened the road to the identification and purification of antigens of all three stages. Nussenzweig and her colleagues in the United States were the first to identify a major protective antigen on the surface of rodent malaria parasites (Pb44, a polypeptide of around 44 kilodaltons); they were able to show that a monoclonal antibody against it rendered sporozoites non-infective to mice. Analogous polypeptides have now been identified in *P knowlesi*, *P falciparum*, and *P vivax*, and their analysis by peptide mapping and other techniques suggests that they may share structural features—which could lead to the eventual production of the essential antigens by gene cloning or peptide synthesis. One such clone has been reported: it expresses a sporozoite surface antigen of *P knowlesi*.[2] The great advantages of vaccination against the sporozoite stages are, firstly, that this may completely prevent an infection becoming established in the individual who is bitten by an infected mosquito, and, secondly, that sporozoites of a given *Plasmodium* species do not appear to produce antigenic variants, as may the blood stages.

Protective antigens against the blood stages of mammalian parasites have proved to be more complex than are some of the sporozoite surface antigens. For example, a 66 kilodalton polypeptide on the merozoite surface of *P knowlesi* has been identified with the aid of two monoclonal antibodies that, in turn, inhibit the invasion of erythrocytes by merozoites.[3] Further antigens have been identified of molecular sizes ranging from 230 000 down to 40 000 daltons. A vaccine against *P knowlesi* containing a 74 kilodalton antigen in Freund's adjuvant is now reported to protect monkeys challenged with heavy inocula of parasitised red cells,[4] but this in turn points up the main problem to date with merozoite vaccines: they appear to give adequate protection only if incorporated with adjuvant. So far no acceptable adjuvant has been identified for use in man with any merozoite vaccine. This is unfortunate, since several protective antigens have recently been found by Australian workers in *P falciparum*. *Escherichia coli* clones expressing these antigens have been engineered by this group, a major step that may lead to the production in Australia of a merozoite vaccine.[5]

The identification and isolation of antigens on gametocytes or gametes that will prevent these stages developing in the mosquito is much more difficult technically. An antigamete vaccine would be a major advance from an epidemiological point of view, however, since it would help interrupt the cycle of transmission in the community, whereas antisporozoite and antimerozoite vaccines would protect only those individuals who actually received them. Ideally a mixture of at least two of these vaccines would be desirable. In practical terms, however, we are far from realising even one vaccine at the moment.

The technical obstacles are, in a sense, the lesser of the problems once truly protective antigens have been identified. Here the sporozoite vaccine would seem to be several years ahead of the others. Either by genetic engineering or by peptide synthesis it should not be too difficult to produce large quantities of the antigen. Next, however, come all the practical problems of clinical trials, of production, quality control, stability, safety, duration of action, and requirements for repeated vaccination, parasite specificity and—at least in the case of a merozoite vaccine—the identification of a suitable adjuvant. This may also prove necessary when a highly purified sporozoite vaccine is subjected to critical testing.[6]

Clearly the whole development process of malaria vaccines is both lengthy and costly and the harsh commercial question is who is to foot the bill?[7 8] Conflicts of interest will need to be resolved between the potential manufacturers and the consumers—exemplified by the recent dispute between Genentech and the World Health Organisation concerning the Nussenzweig sporozoite vaccine. Such conflicts can, however, be resolved with mutual understanding and good will. Moreover, this is exactly the sort of biotechnological area which would fully merit major financing both for research and development by philanthropic foundations such as the Rockefeller and others in the United States and the King Faisal in Saudi Arabia. To underwrite malaria vaccine development would be an ideal way of utilising their wealth in a way that stands a good chance of producing, relatively rapidly, a much needed weapon to help eliminate a disease which is still one of the major obstacles to the health of man in the poorest countries of the Third World.

W PETERS

Professor of Protozoology and Head of Department,
London School of Hygiene and Tropical Medicine,
London WC1E 7HT

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