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Pointers

Tumour-specific Antibodies : Over 80% of patients with mildly disseminated melanoma had autoantibodies, these tending to disappear as dissemination progressed. There were two types, one specific for each tumour, the other for all melanoma cells (p. 547). Leader at p. 543.

Age and Ventilatory Capacity : Re-examination after 4 years showed a decline in the ventilatory capacity of 50-year-old Swedish men, smokers experiencing a greater decline than non-smokers (p. 553).

Exercise-induced Asthma : Investigation of three patients showed a " striking metabolic acidosis," which is thought to have triggered the broncho-constriction (p. 556).

Vitamin B_{12} Deficiency : Only two patients with pernicious anaemia found in 1,004 consecutive admissions to mental hospital over the age of 50 (p. 559).

Gastroenteritis in Maternity Hospital : Outbreak due to *Salmonella virchow* probably caused by carrier infecting her infant (p. 561).

Slow-release Fluphenazine : Severe depression may complicate treatment of schizophrenics by slow-release fluphenazine, and emphasizes need for careful psychiatric supervision (p. 564).

Diabetic Retinopathy : In newly diagnosed diabetics under 40 years of age the incidence of retinopathy was 1·5% (p. 567).

Short Reports : Changes in regional cerebral blood flow during migraine (p. 569). Abdominal tuberculosis in child in Britain (p. 570). Paraplegia after repeated cardiac arrest (p. 572). Rupture of choledochus cyst in pregnancy (p. 573).

Osteoarthritis : Refresher course article on its management (p. 575).

Trimethoprim : Clinical applications (p. 578).

Community Nurses : Advantages and disadvantages of attachment schemes for health visitors and district nurses. Thorough briefing is important (p. 584).

Samuel Warneford : Eccentric benefactor of medicine (p. 587).

Personal View : Dr. A. Paton (p. 591).

Correspondence : Letters on hospitals for the subnormal, 1969 *Medical Directory*, hospital letters, London medical schools, dispensing doctors, aged doctors, and the district hospital concept (pp. 592–599).

Motoring : Crosswise engines (p. 602).

Laboratory Reports : Salmonella infections (p. 603).

Medical Charities : See *Supplement*, p. 107.

Armed Forces : Letter from Secretary on doctors' pay (*Supplement*, p. 108).

Immunology of Malaria

Circumstantial evidence gathered slowly during the past 50 years has suggested that after malarial infection in man there is a changed response to a second attack. Furthermore, populations living in malarious areas and exposed to frequent infections acquire a degree of resistance to the disease.

By the 1930's the probable role of humoral and cellular factors of immunity to malaria had already been well defined,[1 2] but the full impact of new trends in immunology on many problems of the host-parasite relationship in plasmodial infections has become obvious only in the last decade. This new interest in the field was heralded by a symposium of the British Society for Immunology[3] and by a report of a W.H.O. Expert Committee.[4] Other scientific meetings devoted largely or wholly to immunology of malaria followed in quick succession.[5–9] Among various reviews of the subject three are of particular interest.[10–12]

Immunity to malaria in man is a state of relative resistance to the plasmodial infection or to the adverse effects of it. A degree of natural genetic immunity, at least to certain species of malaria parasites, may exist in some human groups (thus some Negro populations are resistant to *Plasmodium vivax*). Certain genetic characters also confer partial resistance to malarial infection or to its effects. This has been shown for the haemoglobin S gene carried in its heterozygous form in persons with the sickle cell trait and has been postulated in the carriers of glucose-6 phosphate dehydrogenase deficiency.

The mechanism of malaria immunity is similar to that operating against any infection, but there is evidence that it is related mainly to the erythrocytic cycle of development of the plasmodium and not to the tissue phase. Moreover, the level of the immune response depends on the reproductive potential of the infecting species of the parasite. Both humoral and cellular factors are concerned and they are closely integrated. The cellular aspect of malaria immunity is still little understood, though phagocytosis has been recognized as one of the mechanisms for the destruction of plasmodia since the pioneer observations by Laveran, Metchnikov, and Golgi over 80 years ago. The population of immunologically competent cells of the reticulo-endothelial system in the spleen and other organs responds to the antigenic stimulus by an increase in the number of specifically active lymphocytes, by increasing the phagocytic action of localized or circulating macrophages, and by the production of specific antibodies. The humoral response to the protozoan organism undergoing a number of developmental phases comprises several specific antibodies, but only a small proportion of them is protective.

There has been for many years a need for a serological test for the diagnosis of malaria and for assessment of radical cure. In the past complement fixation and agglutination tests have been evaluated with uncertain success. More recently several tests have been introduced in experimental and field studies on malaria, and three of them are of particu-

lar interest and promise. Immunofluorescence techniques made available for the first time a test in which the whole intracellular parasite constituted an antigen. This test has been widely used for demonstration of antibody in individuals and in communities exposed to endemic malaria.[13] The gel precipitation method has much to offer in the study of immunity to malaria because of the high specificity of the reaction between the antigenic determinant and its corresponding antibody. Thirdly, an indirect micro-haemagglutination test using an antigen prepared from the simian *P. knowlesi* has been introduced, and it may be of value for large scale application.[14]

The relationship between the various immunoglobulins and malarial immunity has received a great deal of attention. In individual infections IgM appears first and later IgG increases. In African populations exposed to endemic malaria the mean titres for IgG and IgM are high and increase with age. The level of IgM tends to rise at an earlier age than other immunoglobulins, while IgG levels are at near peak by the age of 5. The transient presence of IgG in African newborn children represents most probably the antibody transmitted from the immune mother across the placenta, which protects the baby during the first few months from severe infection. Much remains to be known about "congenital malaria" and about the type of passive immunity operating during the pregnancy and the neonatal period.[15] Experimental transfer of antibodies using immunoglobulin fractions from immune adults has been successful in severe malaria in children, though the results in laboratory infections of monkeys have not been consistent.

As yet there has been no satisfactory method of distinguishing between protective and non-protective malarial antibodies, but a recent study[16] provided an experimental model using an *in vitro* culture of *P. knowlesi*. In this system the immune serum inhibited parasite multiplication, which could be measured by the rate of incorporation of radioactively labelled leucine into the protein of the plasmodia. The nature of malaria antibodies was studied by gel filtration and chromatography, and the results showed that most of the antibody was composed of IgG though some of it belonged to the IgM group of immunoglobulins.[17]

The antigenic analysis of plasmodia has made much progress during the past few years, thanks to new techniques such as immunoelectrophoresis. These studies have shown a true "mosaic of antigens," with plasmodial fractions of various degrees of solubility and enzymatic composition. They have also indicated the complexity of the immune response in highly endemic regions. Soluble antigens of protein nature were found in sera of children and parturient mothers who had had attacks of malaria, and some of these antigens were immunochemically similar to antigens present in placentas infected with *P. falciparum*.[18] It appears that certain groups of such soluble "exo-antigens" may have haemolytic and immunogenic properties and may be responsible for the renal lesions which complicate some types of malaria.[19]

The possibility of autoimmunity in malaria has been raised in an attempt to explain the finding of a degree of anaemia far greater than would be expected from an observed number of parasites in the blood. Immunopathological processes due to autoantibodies may also be responsible for the nephrotic syndrome and other effects of repeated malaria infections so common in tropical areas.

The presence of antigenic variations in the parasites has been studied in simian malaria and may occur in human relapsing infection. Immunoglobulins from hyperimmune West African adults protect against falciparum infections in children from East Africa, which suggests that antigenic variants do not interfere with the production of a wider spectrum of antibodies, but the effect of antigenic variations on the specificity of protective immune response is largely unknown.

The possibility of developing a "malaria vaccine" from strains of plasmodia suitably inactivated and yet capable of stimulating an immune response has exercised the minds of research workers for the past 30 years. In order to prepare such a vaccine malaria parasites (blood forms or sporozoites) have been processed by incubation in immune serum, by exposure to various chemicals, drugs, or ionizing radiation, by passage through new hosts, and by culture *in vitro*. Interesting results have been obtained in avian, rodent, and even simian malaria since the challenging infection was generally shorter and milder. However, a high degree of fully protective immunity was not demonstrated, and most of these vaccines had a limited range of specificity.

During the past few years the combined efforts of malariologists and immunologists have provided a wealth of new knowledge on the host-parasite relationship in malaria. This scientific advance, which was triggered off by the appearance of resistance of plasmodia to antimalarial drugs, commands admiration, though only a small portion of it has been or could be applied to practical issues. The theoretical possibility of a malaria vaccine remains a desirable and justified goal, especially as new sources of suitable antigens grown *in vitro* or obtained from monkeys have become available. Nevertheless, the problems of the amount of antigen, its specificity, and the range of its protective action against the infection are formidable. It appears that chemotherapy and chemoprophylaxis of malaria remain for the time being our most reliable weapons.

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