New look at malaria

World Health Organisation (WHO) reports on current malaria problems leave no room for complacency.1–3 Up to mid-1975 there was “little net improvement in the operational and epidemiological situation.” Existing gains had been consolidated in some areas, but there was general deterioration in many others, sometimes with explosive resurgence of the disease, as in the Khmer Republic and South Vietnam and especially in India, Pakistan, and El Salvador. In Africa malaria remains today the major endemic disease and about a million children under the age of 4 die from it every year.

When eradication programmes began malaria was endemic in 148 countries. By the end of 1974 it had been officially declared eradicated in 37 of these, but about 1136 million people were still exposed to it, of whom nearly 800 million lived in areas in the “maintenance” phase of eradication. At the start of the eradication campaign, based on interruption of transmission with residual insecticides, the expectation was that the disease could be defeated in 10 years. Now, 20 years later, the position is one of stagnation, and the number of areas in which specific antimalaria measures have been applied since 1969 has remained practically unchanged.

The stagnation has been caused by both logistic and biological hazards. These have included wars and other political disturbances, inadequate financing of the projects, lack of local governmental co-operation, inadequacy of general health coverage, shortages of insecticides, rising costs of operations, and difficulties of terrain. There has also been widening resistance of vectors to insecticides and of parasites to drugs.

In 1974 the report of the 16th Expert Committee on Malaria4 emphasised the need for new insecticides and drugs, a new approach to the training of malariologists, the re-introduction of the techniques of control—distinguish from eradication—and more local biological and operational research, which should be better co-ordinated under the new proposals of WHO for the organisation of such work. Research into malarial immunology is a case in point, where emphasis should be given to the development of attenuated parasites and antigens as vaccines for the production of protective immunity.5 6

The malaria parasite stimulates the production of protective antibodies, which operate on the erythrocyte parasite at the stage of merozoite liberation, preventing the invasion of fresh erythrocytes. That merozoites might have a central role in the induction of protective immunity has been shown in simian malaria, in which they induce specific immunity greater and broader than that achieved by repeated therapeutically controlled infection. These results indicate the possible preparation of human vaccines against Plasmodium falciparum parasites. In rodent malaria irradiated sporozoites can also produce protection against lethal parasites. This effect is less apparent in primate malaria, but in a single human study resistance to homologous and heterologous strains of P falciparum was achieved in this way in some but not all volunteers. Clearly there is a need for research. The difficulty is the production of adequate supplies of P falciparum merozoites, whose harvest is dependent on the culture of the parasites in vitro. Even greater problems lie in the production of sporozoites in bulk. Furthermore, some doubt the value of a vaccine for malaria, though it might be useful in mass control if it could induce immunity lasting long enough to break the transmission cycle.

Among the many factors leading to the current stagnation the former attitude of WHO cannot go without comment. As Fraser Brockington7 has said, “there was more emotion than reason in the malaria eradication scheme, which at the outset won approval in the Assembly over smallpox for immediate action.” He also voiced a widely held view that the idea of eradication mesmerised WHO for too long, to the detriment of other activities: “Had a substantial fraction of the enormous sum spent on malaria been expended in establishing permanent public health services the world might be a healthier place today.”

It is easy to criticise WHO for its total commitment to eradication, which hindsight shows was probably unwise. Nevertheless, it is to the organisation’s credit that it has been prepared to change its approach so radically and so quickly. Moreover, the limited advantages which have accrued from the attempt at quick eradication may possibly have been greater than those which might have come from alternative techniques. Objective examination of eradication programmes by WHO has shown that time-limited operations are not universally feasible and that a much revised strategy for the future attack on malaria is needed. Eradication is the ultimate goal, but progress will be more gradual and the old techniques of control will need to be reintroduced. The new strategy will demand reoriented training and research programmes as local circumstances change through socioeconomic development.

What happens in Africa over the next few years should show whether the love affair between WHO and eradication has seriously delayed the disappearance of the disease. If this
proves to be the case, there is all the more reason for getting on with the operational and research work now being planned, and especially for new ideas. Malaria must be defeated if the standards of health and living in the endemic areas are to be raised permanently. Its disappearance will not only help the endemic areas but will solve the malaria export-import problem, which at the moment menaces the rest of the world, since it will combat the evil at its source. The objective attitude of WHO to malaria problems and the proposals coming from it are encouraging. It looks as if the signpost is at last pointing the right way.

1 World Health Organisation Chronicles, 1975, 28, 474.

## Multiple sclerosis

The recently published article by Dean and his colleagues (10 April, p 861) brings to the forefront once again the hypothesis that multiple sclerosis (MS) may be caused by a virus infection. They compared the epidemiological picture of MS with that of adult paralytic poliomyelitis before the Salk and Sabine vaccines were introduced and suggested that immunity to the agent responsible for MS normally developed in childhood in the low risk zones and persisted when the person moved to an area where MS was highly prevalent. Their suggestion is that the virus agent of MS is endemic in the low risk zone, thus confirming early immunity to an adult disease. If this is the case, then persons coming from a zone where the agent is not endemic (Dean’s high risk zone) to an area where it is endemic (Dean’s low risk zone) should be considerably at risk of contracting MS as an adult. There are no figures yet to confirm or refute this possibility.

The concept that MS is caused by a virus has been debated for many years, and the weight of evidence is accumulating that a virus-like agent, virus or viruses in the plural, may play some part in the pathogenesis of the disease. The virus concept does not invalidate the theory that autoimmune processes are concerned in the breakdown of the myelin sheaths. Viruses may alter cell membrane antigenicity in such a way that the body’s allergic mechanisms do not recognise the altered cells as “self.” If, therefore, virus has entered or is attached to the cell membrane of the cells—oligodendrocytes—which produce myelin in the central nervous system, these cells may be damaged sufficiently by an immunological response for the myelin to break down. This will lead to the release of protein fractions which, even under normal conditions, the body does not tolerate well, thus further stimulating the antomyelin reaction.

In support of the virus concept electronmicroscopic studies have shown three types of “virus-like” particles in either biopsy or necropsy specimens.1–3 Perhaps the most important findings have been those reporting tubular structures resembling myxovirus nucleocapsids in association with serological studies implicating measles virus, itself a myxovirus. Serological studies have also played their part. In 1962 Adams and Imagawa4 reported that the titre of measles antibody was higher in patients with MS than in a control series. Twenty out of 22 subsequent studies in the US and Europe have confirmed this finding in serum or cerebrospinal fluid, or both. Nevertheless, measles virus has not been the only virus to which higher antibody titres occur in MS. Rises in antibody titre to herpes simplex, varicella, mumps, influenza C, or parainfluenza 3 viruses have also been reported.5 Cell culture studies from the brains of two patients dying of MS had paramyxovirus-like particles within the cells seen under the electronmicroscope. Serological tests suggested that para-influenza virus might be implicated in these cases, as infectivity for CV-1 cells could be neutralised by antisera against this virus.6 Yet all these findings suggesting a connection between MS and various viruses must be considered in the light of work by Rogers et al11 which showed that in animals a variety of viruses can be isolated from brain material where no virus was expected or illness was apparent. Such facts make the interpretation of the potential viral aetiology of MS so difficult.

More recent work12 has shown that MS material inoculated into mice either intracerebrally or intraperitoneally produced a persistent granulocytopenia but no other change. Serum from these affected mice transmitted the granulocytopenia from one mouse to another with extensive replication, the agent being of virus size—25–50 nm. More recently the same workers13 infected a transformed cell line of mouse fibroblasts with MS material. After the first subculture there was a reduction in cell yield by a hundredfold or more compared with the controls and the cell-free lysate from the 18th passage produced a granulocytopenia when inoculated into mice. Success was claimed with specimens of brain, spleen, serum, CSF, kidney, and lymph node and taken from patients with MS at every stage of the disease. No positive results were obtained with other materials. Recently another group of laboratory workers14,15 has succeeded in producing a granulocytopenia from MS material not only in mice but also in rats, hamsters, and guinea pigs. Considerable further interest has been aroused because they have found that sera, from some patients with MS and from a few of the close relatives of these patients, neutralise the agent which produces the granulocytopenia, suggesting that they have mounted an immune response. They have also shown—and this is important in relation to the paper by Dean and his colleagues—that serum samples from people indigenous to East Africa (where the incidence of MS is very low) have significant neutralising antibody to this granulocytopenic agent.

Materials from animals with scrapie cause granulocytopenia in mice,16 but no neutralising antibody has ever been detected against this slow virus agent—discovered by the veterinarians and recognised as a forerunner of the whole human “slow virus” research programme. It is particularly this research that has shown how important is the genetic constitution of the host to infection with slow virus agents. Various animals and strains of the same animal may respond in many different ways ranging from resistant to susceptible; the pathogenicity of the infection varies with the strain of the agent used. Since the recognition of the specificity of human leucocyte antigens it is now becoming clear in relation to the pathogenesis of various human diseases, including multiple sclerosis, that some people and families are likely to be more susceptible than others.

The evidence strongly suggests that an infective agent of viral size is in some way concerned in MS. Most viruses can