Resistance among Malaria Vectors

Twenty years ago there were high hopes of the total elimination of malaria when the World Health Organization accepted the challenge of global eradication. In view of some gloomy later events it is as well to remember the positive achievements of this attempt. Mainly owing to house spraying with DDT nearly three-quarters of the 1,800 million people living in potentially malarious areas are now partially or completely protected from the disease. A world incidence of 300 million, with at least 3 million deaths, has been reduced to about 50 million with under 1 million deaths.

Yet this is still far short of the successful reduction of other fatal vector-borne diseases. Cases of yellow fever and plague have been brought down to a few thousand and of typhus to 10 to 20 thousand. None is responsible for more than a few hundred deaths annually. Unfortunately the residual refractory endemic malarious area is vastly larger than similar foci of other vector-borne diseases. Further progress presents intractable difficulties, one of the most important being the growing incidence of strains of anophelines resistant to insecticides. The present situation has been recently reviewed by a member of the W.H.O. staff.[1] At present two malaria vectors are resistant to DDT alone, nine to dieldrin alone, and 17 to both organochlorine groups. Fortunately, when resistance occurs in a particular vector, it seldom extends throughout its entire geographical range. Moreover, though resistance to dieldrin builds up rapidly, resistance to DDT grows slowly and does not always destroy its value for malaria control.

Extensive basic research on the nature of resistance did much to improve our understanding of the trouble but did not disclose a cure. So in 1960 the W.H.O. initiated an empirical search for alternative insecticides in a scheme involving investigators in four continents. After some 10 years of operation, however, this produced no radically new insecticides, though it did select the most suitable of existing organophosphorous and carbamate compounds. Despite their greater cost these will have to replace the organochlorines where resistance renders the latter ineffective.

But several vectors have already become resistant to these newer compounds, among them *Anopheles albimanus* in Central America. It is quite possible that similar forms of resistance will develop in other species. Certainly vigilance is imperative. The detection of resistance in mosquitoes to organophosphorous and carbamate insecticides presents special problems. When only organochlorines were concerned the W.H.O. standardized test for resistance used papers impregnated with DDT or dieldrin, both of which had excellent storage life. Base-line data were obtained with a range of concentrations and a standard one-hour exposure. This procedure is not feasible with the variety of new compounds, since it is impossible to select a single compound as an infallible indicator of resistance in the others. Furthermore, the W.H.O. could not supply a full range of concentrations for all the possible new insecticides, especially as their shelf life is uncertain but shorter than that of organochlorines. To meet this difficulty it was suggested that resistance should be detected on the basis of exposure time rather than concentration, thus greatly reducing the numbers of papers to be provided. This tentative decision, made in 1970, has been validated by subsequent research on the technique.

A further point discussed in Dr. Pal's paper is the difficulty of early detection of resistance in the field. Despite the long history of the emergence of resistant strains it seems that many field workers are still rather hazy about the implications of monitoring tests for resistance. As a result, various rule-of-thumb criteria of doubtful significance have been adopted. This paper therefore attempts to explain the statistical basis of monitoring tests in simple, unequivocal terms.

The problems of insecticide resistance have been with us for a quarter of a century and are likely to continue indefinitely. It would, indeed, be good to think that entirely different control methods can soon replace insecticides, but there is little hope of this in the foreseeable future. Moreover, even some new techniques are not immune to resistance. For example, it is depressing to find that insects can become resistant to harmful applications of their own hormones (or mimics), which is contrary to all expectations.

[1] Pal, R., *Journal of Tropical Medicine and Hygiene*, 1974, 77, 28.

Anoxic-ischaemic Brain Injury

Cerebrovascular disease is responsible for more admissions to hospital than any other neurological disorder, the great majority of patients having cerebral infarcts. Morbidity and mortality rates are high.

In addition to arterial disease cardiac arrest is increasingly common as a cause of widespread cerebral ischaemia. Rational treatment must depend on a clear understanding of the mechanisms underlying anoxic-ischaemic brain damage. Experimental results are difficult to interpret, so that a number of controversial views have emerged.

In June 1973 a symposium devoted to the threshold and mechanisms of anoxic-ischaemic brain injury was held in New York and the proceedings have recently been published. Plum[1] succinctly stated the initial problem: "What duration of anoxia or ischaemia defines the watershed between recovery of the tissue and extensive permanent injury?". This leads into the further questions of what factors determine the selective vulnerability of different parts of the brain, and what can be done to increase the chances of restoring neuronal function. No satisfactory answers are forthcoming.

The common clinical impression is that consciousness is lost after about 6 seconds of total arrest of cerebral circulation, and permanent damage is produced within 5 to 8 minutes. Severe bilateral brain damage in animals has usually been found after about 15 minutes of substantial ischaemia[2] or hypoxia,[3] but this view has been challenged by Hossman and Kleihues.[4] They report that a degree of recovery in metabolic and electrical activity of the brain can occur after 1 hour of total ischaemia—a claim in conflict with conventional views. Neurologists disturbed by the prospect of a radical reappraisal of orthodox ideas will be reassured to find Brierley and colleagues[3] arguing that the unexpected findings of Hossman and Kleihues can be explained in terms of incomplete experimental ischaemia. More evidence is needed in this difficult problem.

The regions of the brain most vulnerable to hypoxia are the cerebral cortex, the hippocampus, the amygdaloid nucleus, the cerebellar cortex, and the brain stem. A different pattern of damage is found when blood flow is reduced by sudden, severe reduction of the cerebral perfusion pressure with a sustained