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Introduction to Malaria Symposium

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In a history dating back 133 years, the British Pharmaceutical Conference has tended to focus on scientific and technological themes rather than disease states. The 1996 Conference represented a departure from precedent, focusing on malaria, tuberculosis and asthma in separate sessions. The symposia on tuberculosis and asthma are presented elsewhere.

The intention in designing the malaria programme was to provide an overview of the topic by acknowledged specialists as well as more detailed examination of specific issues. The first session, which was given the title "Problems with chemotherapy" (under the chairmanship of R. S. Phillips), began with an overview of drug resistance by D. C. Warhurst.

Chloroquine resistance has been traced to a "multiple drug-resistance" (mdr) gene in *Plasmodium falciparum*, with current work aimed at monitoring drug resistance in field populations. It has recently proved possible to use the polymerase chain reaction to distinguish between resistance arising in old and new infections.

W. M. Watkins gave an account of malaria in local communities in Kenya, from the coast, down to the Rift Valley and as far north as Turkana. The Global Eradication Strategy has been replaced by a policy of Malaria Control, with *P. falciparum* being the major problem, accounting for almost all the morbidity in the region: approximately two million African children die each year from malaria. Quinine remains the standard treatment for severe malaria in East Africa. Chloroquine has been the mainstay of outpatient treatment for 40 years, but resistance is now common, in which case pyrimethamine–sulphadoxine may be used. However, there is an urgent need for alternatives to this combination, with pyronaridine being one possibility.

P. V. Rollason gave the practising pharmacist's view of malaria chemotherapy in southern Africa, particularly in Zimbabwe. There are problems of diagnosis and considerable confusion over the prevalence of drug resistance in this very large geographical area. Unlike Kenya and other parts of the world, the first choice for prophylaxis is pyrimethamine–dapsone.

The first session concluded with an account by D. Walliker of the genetics of *P. falciparum* and the effect on drug resistance of, for example, the sexual phase in the life cycle. Ingestion of blood from patients with more than one genetic form of the parasite will be very likely to result in cross-mating; the ensuing recombination will produce parasites with a wide variety of responses to different drugs. In only a few cases is the mechanism of resistance understood.

The second session, under the chairmanship of D. Walliker, commenced with an overview by a clinician, P. Winstanley, who considered that the situation with malaria would be likely to deteriorate, given economic pressures, global warming and multi-drug resistance. In considering the four strategies of 1) dealing with the vector 2) preventing bites 3) chemoprophylaxis and 4) symptomatic treatment, he concluded that the latter is the most likely to remain effective in the long term: affordability is the primary requirement.

The status and prospects for malaria vaccines were reviewed by E. M. Riley, who outlined the problems associated with development of a vaccine to an organism which produces surface antigens showing allelic polymorphism and clonal variation in the antigens inserted into the erythrocyte membrane. In addition, the only reliable way to evaluate a candidate vaccine is by a full scale human trial: only one vaccine has undergone multiple field trials, with high resultant specific antibody titres but little or no protective effect.

P. Olliario summarized the newer potential targets for chemotherapy, only a few of which have been fully validated. The approach taken by the World Health Organization Steering Committee on Drugs for Malaria is to combine the efforts of university and government researchers in drug discovery and to develop potential drugs through contracts with industrial partners. A number of high priority targets have been identified, although the absence of an identified target will not be a barrier to development where there is proven efficacy.

The second session concluded with a detailed account of the acute febrile stage experienced by non-immune humans infected with *P. vivax*, presented by R. C. Carter. This febrile stage is probably related to parasite control by the host as an emergency response in the early stages of an infection and coincides with the presence of gametocyte-inactivating mediators in the plasma. The inactivation is dependent on the cytokines interleukin 2 and granulocyte–macrophage-colony stimulating factor, which suggests the possibility of T cell activation.

The third session, under the chairmanship of J. M. Midgley, concentrated on antimalarial drug design directed at a variety of targets. R. G. Ridley began by describing the identification of three proteases involved in haemoglobin degradation: several compounds appear to mediate their antimalarial activity through inhibition of two of these proteases. He went on to describe the remarkable bisquinolines, which bind to free haem, prevent its polymerization, and do not show cross resistance with chloroquine.

Continuing the haem theme, G. Edwards discussed the effect of haemin on the degradation of artemether in-vitro; haemin also potentiates the neurotoxicity of three artemisin analogues in-vitro, as measured by the effect on neurite production in two neurally-derived cell lines, probably by catalysing breakdown of the peroxide bridge.

G. H. Posner then described some elegant studies on the Fe(II) catalysed breakdown of artemisinin, leading to a detailed understanding of the mechanism of formation of, among other species, a potent alkylating epoxide. An understanding of the mechanism has allowed the design of a number of simple, symmetrical endoperoxides with substantial in-vitro antimalarial activity.

The activity of iron chelators as antimalarials both in-vivo and in-vitro led R. C. Hider to consider the design of orally active compounds based on 3-hydroxypyridin-4-ones. Such compounds are relatively non-toxic, but for high efficacy require to be targeted towards the parasite and to fail to gain access to sensitive tissues such as brain and bone marrow. While there is evidence that such selectivity is achievable, the available animal models may be inadequate; parasite biochemistry in rodents may be different from that in primates, with regard to iron transport.

Moving away from the involvement of iron, P. K. Rathod outlined several years work on the synthesis of antimalarials directed at thymidylate synthase. While direct selective inhibition is difficult, it is possible to take advantage of the requirement by the parasite for exogenous orotic acid. As a result, 5-fluoro orotate inhibits *P. falciparum* in-vitro with IC50 of 6 nM and with no distinction between chloroquine-sensitive and -resistant cells. A combination of 5-fluoro orotate and uridine increases selectivity and cures malaria in mice.

B. Kilbey was indisposed and could not present his paper on the malaria replisome as a drug target; the text is included here as a potential guide for antimalarial drug design. DNA synthesis occurs at five stages in the complex life cycle and work continues on cloning and characterizing the genes which encode the replication proteins, followed by attempts at gene expression. These studies are helping to gain information on the patterns of expression in the erythrocyte and the mechanisms which control the expression.