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30 years of science and technology: the example of malaria

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In 1997 we celebrate the centenary of Ross' discovery of the development of the malaria parasite in the mosquito. The next 30 or so years saw the laying down of a body of knowledge of the biology, immunology, and epidemiology of malaria that is surprisingly relevant today. The middle third of the century produced two powerful tools, chloroquine and DDT, and the belief that it would be possible at last to control malaria. In 1953 the World Health Assembly adopted a plan of eradication. There followed an extraordinary mobilisation of effort in many parts of the world and considerable initial success—but eradication was doomed to failure. The last third of Ross' century began with the field crestfallen and uncertain, fixed in a mind set that still longed to eradicate malaria even when it was clear that this was impossible. Despite this unpromising start the next 30 years saw an explosion in technology and its application to malaria research.

Parasite biology, biochemistry, and genetics

Our understanding of parasite biology has been revolutionised by a series of technological and scientific developments which include genetic crosses, in-vitro parasite culture,¹ monoclonal antibody technology and gene cloning. The first malarial gene was cloned in 1983.² The genome mapping project should yield the sequences of thousands of genes of *Plasmodium falciparum* within the next few years. Gene cloning is only the first step; understanding function is more difficult and more important. Monoclonal antibody technology combined with methods for localising targets, such as confocal microscopy, permits the study of membrane trafficking. Gene transfection and “knockout” models are also powerful tools for the rapid dissection of function. We are beginning to understand more about the interactions of merozoites and sporozoites with host cells, mechanisms of drug action and resistance,³ and antigenic variation.

Advances in parasite biochemistry have been less striking; the malaria genome project may lead to a renaissance in this area. This should give a much needed push to the development of new antimalarials, an area which is in a desperate state as the drugs in mass use are failing rapidly and the few new ones are unlikely to have an impact because of cost.

Immunology and vaccine development

30 years ago the major barriers to malaria vaccine development were insufficient parasite material and the inability to purify antigens. Parasite culture, gene cloning, and monoclonal antibody technology have changed all that and raised the possibility that subunit vaccines could be engineered or even synthesised chemically. Essentially similar approaches were

taken initially to the identification of potential vaccine antigens for all stages of the parasite. The first antimalarial vaccines to come to trial were based on repeat regions in the circumsporozoite protein. Results were disappointing but the recent protection of volunteers by a prototype vaccine based on essentially the same sequence ⁴ illustrates how progress in other fields (ie, powerful new adjuvants) may open doors. Vaccine development at first concentrated on humoral immunity but the specificity and restriction of T-cell responses—a central feature of immunology over the past 30 years—has had a major impact on thinking about preerythrocytic vaccines. An example of where this has taken us is the identification of peptides with high specificity for class I molecules associated with protection from malaria, and the targeting of corresponding sequences in the parasite genome as potential vaccine candidates.

Many of the molecules still under consideration for inclusion in vaccines were being talked about ten years ago, and the difficulty in moving forward from molecular characterisation to vaccine trials can be frustrating. It is unfortunate that so much emphasis was put on single-component vaccines. The move to multicomponent preparations began with SPf66, a synthetic peptide mixture.⁵ The latest field trials with SPf66 have been disappointing but the multicomponent approach is now established and several are under development. At first this depended on delivery systems such as modified vaccinia but DNA technology now offers the exciting possibility that vaccines could be produced in almost any laboratory in the world. Engineered avirulent vaccines may even be a future possibility.

Disappointingly, improved knowledge of parasite antigens has not led to a greater understanding of how immunity to malaria develops.

Pathophysiology and clinical management

Until recently little had been added to the classical descriptions of clinical malaria. This stagnation began to be reversed from the early 1980s with a series of studies of the pathophysiology and treatment of severe malaria in Thailand ⁶ and by reports from Africa that are building up a comprehensive picture of the spectrum of life-threatening malaria in African children.⁷ These new insights include the roles of hypoglycaemia, raised intracranial pressure, seizures, and metabolic acidosis. Most of these developments depended more on a conceptual shift than on new technology, though the refinement of physiological monitoring equipment to make them practical to use under adverse conditions has been important. Understanding of the molecular basis of pathophysiology has depended on the same technologies that have revolutionised our understanding of parasite biology and immunology. The two most important advances have been recognition of the role of cytokine ⁸ activation and an understanding of infected red cell cytoadherence.⁹ The major challenge now is to integrate the clinical picture with the molecular events.

Epidemiology

So powerful was the idea of eradication that the study of malaria as a disease that could lead to death was virtually ignored by epidemiologists for 30 years. This began to change in the mid-1980s both from the practical necessity of carrying out intervention trials with outcomes relevant to public health, and from the more basic point of view of understanding the factors that influence the development of disease. Important developments have included the exploration of the effect of endemicity on disease spectrum¹⁰ and an increased understanding of the importance of malaria on selecting human genetic polymorphisms.¹¹

At the beginning of the 1980s massive amounts of data were transcribed by hand and posted to a centre in the developed world to be transferred to computer via punch cards and analysed. Today, small hand-held computers can be used to enter data directly at the point of

collection before downloading to facilities at field stations or forwarding by electronic mail anywhere in the world. Ground positioning by satellite now permits the rapid drawing of high-resolution maps and their integration with ecological indices derived from satellite surveillance, demographic profiles, and data on human and parasite polymorphisms. The project for a high-resolution malaria map of Africa¹² could be considered the epidemiological equivalent of the malaria genome project.

Vectors

The failure of eradication in most areas highlighted how important it is to understand differences in the biology and behaviour of different anopheline vectors. The move from morphological to genetic characterisation of vectors began more than 30 years ago but recent advances include that subspeciation in the *Anopheles gambiae* complex. This new knowledge has not had much impact on control strategies. Molecular biology has opened up new areas (eg, DNA probes for speciation and, controversially, the possibilities of genetic manipulation of susceptibility to malaria¹³) The advance which does seem to have had the greatest impact on vector control did not stem from research directed at malaria or even mosquitoes: this was the synthesis of permethrin.

Where has it got us and where are we going?

The better knowledge referred to here might be expected to have transformed the world malaria situation. Instead we stand on the brink of what *Nature* has described as “catastrophe”¹⁴

The major problem is in Africa. Chloroquine resistance has been a disaster. Mortality is set to go on rising. Worse, the drug usually considered to be the only affordable alternative to chloroquine, pyrimethamine-sulphadoxine, is likely to have a short useful life. Africa is not the only difficulty. The epicentre of multidrug-resistant malaria is in South-East Asia, notably on the Thai/Myanmar border where therapeutics is only one step ahead of untreatable parasites.

There seems to be a mismatch between technical and scientific achievement on the one hand and the lack of impact on malaria on the other. Are the current research emphases in malaria misdirected? Vaccine development and mosquito genetics are high cost, high risk, long-term approaches. Might a more resolute application of existing technologies, coupled with socioeconomic development, obviate the need for them? Certainly, much more should be done in applying the tools we do have but these are holding operations, and the search for new tools must continue. The complexity of the challenge of malaria has been badly underestimated. Developing a vaccine against malaria has more in common with developing a vaccine against breast cancer than one against smallpox. The 1996 PRISM report¹⁵ provided an essential corrective in pointing out that funding of malaria is derisory compared with the scale of the problem. Malaria will not go away and what is needed now is a long-term commitment both to operational measures and to basic research, and it is vital that neither researchers nor funders lose their nerve if the scientific gains of the past 15 years are to bear fruit.

Does anyone have the vision and resolve to do what is necessary? Fortunately there are signs of change: a recent meeting of researchers, policy formers and funding bodies in Dakar gave hope that the World Bank and the major research funders are beginning to recognise the scale of the problem and of the effort necessary to address it.

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