SPECIAL REPORT

MALARIA VACCINES IN THE FUTURE - WHAT STRATEGIES NOW?

Chev Kidson

Faculty of Tropical Medicine, Mahidol University, Bangkok 10400, Thailand.

In addition to the inherent challenge, driven by curiosity and the excitement of the chase, the quest for malaria vaccines has been made more imperative over the past two decades or so by pragmatic assessment of the odds in a disease which has been with mankind for millenia. Accelerating spread of parasite resistance to more and more drugs, with too few new molecular structures in the pipeline casts a dark shadow over the future-the *immediate* future. Coupled with insecticide resistance of vectors and the momentous cost in money and human effort absorbed by classical malaria control programs, the pressure of decreasing drug efficacy became critical in making available a relative profusion of funds over a short time period for the vaccine quest on a global scale.

The public hype that accompanied this developmental effort over the past decade led the world to believe that vaccines were almost around the corner. The complexity of the multispecies, multistage game, which has evolved into a truly multidimensional jig saw puzzle, and the inherent genetic plasticity of *Plasmodia* have made the task far more exacting than was originally anticipated. There is reason for optimism at the eventual outcome of vaccine strategies if enough players (and sponsors) stay in the game to the final period.

By the same token the time frame calls for reassessment of control strategies in the global malaria arena, in a realistic challenge to keep at bay this persistent parasite of man within economically feasible limits permitted by political realities.

This challenge was addressed in an innovative symposium hosted by the London School of Hygiene and Tropical Medicine on 14-17 April 1991, co-sponsored by the Overseas Development Administration, the Swiss Tropical Institute, the World Health Organization and the World Bank. The title, "Malaria: Waiting for the Vaccine" aptly captures the current dreaming mood of overexpectant anticipation from which we need to be awakened and put to work on more immediate re-planning.

This symposium did not come forth with any leading new ideas but it did serve the role of an oasis in the proverbial desert, providing the chance for public health operatives and academic scholars to breathe fresh air together for a few moments of history, to identify problems, to recapitulate the options and to agree that action must be taken now. This brief report aims to highlight and reflect upon some of the issues, not to act as a record, which will be published in its own right later in 1991.

A long path through history

Whatever illusions we may harbor about the special nature of our particular era of history need to be diluted by the realities of the past, since some of the dramas have been played many times before, with different costumes, different scenery, different actors but very similar themes. The fever and enlarged spleen which are characteristic of some forms of malaria infection featured in recorded Chinese archives about 5,000 years ago. Hippocrates described the clinical picture of the disease, rampant as it was for centuries around the Mediterranean. Exploitation of the Amazon rain forest, acute today, goes back to the earlier, more gentle perhaps, but equally money-oriented period when Cinchona trees yielded their quinine potions to

the waiting world: but the debate concerning the time of introduction of malaria into the Americas, pre- or post-Colombian must be left unbiased as unresolved. The wisdom of the dwellers in the tropical rainforest opened the doors for effective therapy, just as we are witnesses now to the hope that qinghaosu derivatives bring from the distant past of Chinese traditional medicine as other drugs derived from the industrial chemistry laboratories of the west pass one by one into the realms of resistant uncertainty.

Listening to the brilliant erudition of David Bradley as he recalled the contrasting perspectives of Manson (clinical, pathogenesis) and of Ross (epidemiology, control) in their singular contributions to the malaria arena, it was as if a dream revealed the parallel history of wisdom emenating from vast communities outside the direct mantle of western science whose impersonal contributions go unheralded except as potential fodder for the world of transnational industry. It is from both sides of the historical coin that wisdom for the future must be sought, a reality which sits somewhat uncomfortably with the technology-based enthusiasms of the moment.

The lesson from history is double-edged in so far as it foreshadows the future: do we go forward into the realm of unending technological expectation with its ever-changing tomorrows or do we dig more deeply into the wisdom of the past in the realization that we may have skimmed it too lightly before? In hope, seeking to circumvent despair, will we hedge our bets, trying to blend the two together? Most probably so.

The historical drama in which we are currently entwined may have some of the flavors of the chaos of present global political economics. Central planning under whatever flag is not winning unless it has a special trick card. As David Bradley spelled out so poignantly, malaria became a "WHO disease", passing from the **control** of the 1940s to the **eradication** of the 1950s and the **consolidation** of the 1960s, from the **resurgence** of the 1970s and **chaos** of the 1980s to the **hope** of the 1990s. Throughout the decades some malaria programs quietly went on, doing their thing, as if oblivious to the vicissitudes of this semantic obsession. Some vast populous provinces of China, for example, simply eliminated malaria at a time when eradication had become a bad word. They were perhaps fortunate that they had not yet been invaded by western sociologists but did what is now defined as "health behavioral research" by these concert masters: they brought health education into the daily life of every village and mobilized the human resources in those communities. While few would question the need for WHO to play the conductor's role in the grand symphony, the players in the orchestra are the control program operators at these levels where the people host the parasites and bear the disease burden. They have deep wisdom, they must have freedom to use it and they must have the appropriate resources, old or new in origin.

If there was a fault in this carefully planned symposium it was that there were many field controllers from the real world of endemic malaria present but that they had too little opportunity to voice their wisdom alongside the perceived wisdom of the scholars.

Clinical immediacy and epidemiologic programming

Children **do** die of acute malaria, in large numbers, especially in Africa. So too do migrant adult workers who abound in the malaria endemic countries of the tropical world. Severe, including cerebral malaria has had its deserved focus of attention in recent years, advances have been made in its management, we **are** moving forward in the attainment of knowledge and its practical application, as was well delineated by Kevin Marsh. Not only is there now a better chance of recovery from severe disease than in the past, but this work has opened up new ideas for further therapeutic developmental challenge in the molecular laboratories of academia and of industry.

So why do people die from malaria, where and when do they die? It is not even certain that African and Asian severe disease represents the same syndrome, as David Warrell has often pointed out in his devotion to this central clinio-pathological puzzle: why might this be so?

It is evident that part of the problem lies in the structures of societies, in logistics, in poverty, in the limits to appropriate education availability. Superimposed upon these burdens is the growing one of limited efficacy of available drugs. Even more serious is the efficacy of **affordable** drugs and whether new compounds can be made afford-

able to the people in the middle of the nightmare. Recently Vietnam, for example, made the decision to continue using chloroquine as the drug of first resort, despite widespread resistance, not because it is particularly good in these circumstances but because it is affordable and will reduce mortality and morbidity to some extent. This was a tough decision, time will tell if it was a wise one. Its reversal will depend more on international investment and trade than on public health wisdom.

Bringing the vector controllers back-to-back with the clinicians on center stage was a stroke of conference genius, as they are so often placed in separate corners. Vector control **has** made a difference in many situations, as Vinod Sharma demonstrated in India, but it requires broad-based biological activists rather than addicts to the spray can, as Chris Curtis succinctly illustrated. It is critical to realize that we have not yet explored more than a fraction of the options for biological control in any depth: whether the genetic engineers or the fish breeders will have the last say is an exciting contest. Willingness to listen to the wisdom of the village sages again comes to the fore: economics is for them a serious game of marginal survival, food fish that eat mosquito larvae make much more sense than zoological ideals. There are many examples of success with particular vectors, using fish that taste good and sell well at the market: surviving malaria with cash in hand makes more sense than satisfying academic curiosity.

Bed nets impregnated with permethrin or deltamethrin are in the midst of many trials, there are enthusiasts and there are doubters. Lou Baolin's erudite story of the Chinese experience in Hainan, Guandong, Henan, Jiangsu and Sichuan reflected once again the capacity of that oldest of civilizations to work carefully and quietly towards new goals without fanfare. There is promise and hope but the scholarly flamboyance of Pierre Carnevale reminded us that impregnated bed nets are not the last word, either in terms of efficacy or of feasibilty.

Epidemiologic programming based on technologies, simple or profound, in the final analysis is planning with people for people. Cultures, economies, geographies are not uniform, they are diverse, wondrously and distressingly so. Thus too the debates on chemoprophylaxis versus presumptive treatment need to be seen in the context of particular communities, as well as in terms of academic niceties. There clearly are some situations which justify prophylaxis but they are few: presumptive treatment is frowned upon by the diagnostic purists but deserves economic evaluation in high risk areas with very mobile populations: the miners, the foresters, the smugglers, the armies, legal and illegal, who frequent the fringes of the tropical forests the still resist the disposable chopstick trade. These people are not only at high personal risk but also contribute in no small way to broader community risk amplification.

Drugs and the resistance scenario

Anders Bjorkman gave a masterly runthrough of the therapeutic minefield which is by now so widely known in principle, Nick White added a great deal of incisive clinical icing on the cake, rightly questioning the practical value of *in vitro* drug resistance testing. Would temporary withdrawal from the market of chloroquine, for example, lead to reversal of resistance under reduced selection pressure? The positive points need to be made strongly: there is still a spectrum of useful drugs, particularly in judicious and carefully evaluated combination. There have been some promising indications that time can be bought. It would have been helpful to have brought to the dais others in that audience who have been involved in this game of drug manipulation for a long time and who bear some of the responsibility in endemic countries. Nevertheless, molecule designer imagination is running down, if not out, or is it just that too few industrial consortia see this field as fiscally unrewarding even as a loss-leader in the tropical market place?

Susan Foster surveyed that dilemma. Halofantrine costs 50 times the shelf value of chloroquine. Few in the malaria endemic world can afford chloroquine on all occasions, so who has a hope of getting halofantrine or other new drugs each time they have the ague? She raised an intriguing question: is it ethical to test drugs in a country whose population will not be able to afford to buy it when it reaches the market place? There are sociological strategies that are designed to help but it is not at all certain that they are viable in the villages where it counts.

Nice progress is being made in many laboratories on the mechanisms of malaria drug resistance.

There is no doubt that soon we will have a compendium of molecular genetically defined mutants and that these will serve to make some sense of the problem. However, we already know from the now vast data base of gene and antigen structures that Plasmodia are beautiful evolutionary models of genetic plasticity which has made them successful parasities of man since before the dawn of civilization. If this knowledge enables us to design new classes of drugs quickly enough to circumvent the looming therapeutic impasse then it will be of immense practical value in addition to its intrinsic worth. However, the traditional time frame of getting any new drugs from blue-print to market stages does not augur well for the short term.

In the overall drug story a critical component is developing an equitable basis for a continuing partnership with industry. In this the quiet diplomacy of Tore Godal, attempting to evolve a new environment for this collaboration, will be as decisive as the innovations of science.

Vaccine variables

Kamini Mendis took a broad brush sweep across the canvas of malaria vaccinology as only the master of two worlds can do. The earlier hype bred the unreal expectations and led to the pessimism. So too did the growing recognition of genetic diversity of the parasites as the gene sequence data poured forth almost daily over the past several years from laboratories all over the world. But the parasite has to do its job of surviving and multiplying, not all sequences are allowed to change at will, there are conserved sequences and they must have a role. This is one of our challenges. The T cell repertoire is another, but is T cell memory strong? Are cytotoxic T cells potential knights in shining armor that need to be targeted in order to recruit their assistance?

One of the reasons for optimism and pessimism is the array of genetic information which has emerged from the truly global effort of the first hectic years of the program. Optimism because within that information bank are some answers, pessimism because we are rather slow to read the message. But given time, support and quieter opportunity than has been possible these past few years there is reason to believe that a number of vaccines on the drawing boards will give some protection in at least some target groups.

Multistage vaccines have always been a target of the developers' ambitions and there is every reason to hold to that objective now that so many antigens of all stages have been cloned, dissected and pieces are being rebuilt into possible formats. The pace of progress to field trials is a matter of heated debate but it is perhaps crucial that some have had the courage to go ahead a bit too fast for the justifiably conservative regulation process, since it may give courage to go part way along the route of more classical vaccines: try it and see. This is not heresy, it is what has worked in the past even it is not what we would prefer to do in the present. Many vaccines from the past would not get to first trial base now but we are happy to go on using them because they work. However, subunit vaccines, synthetic or recombinant, have much greater limitations than classic attenuated vaccines made from whole organisms and this may be a major part of the problem. There are some indications that improved carrier and adjuvant technology may provide the trick if we have the right combination of antigen molecules and the patience to try enough combinations. There is a lot of encouraging work in this field.

John Playfair reminded us that we might do better by trying to tackle the pathology rather than the organism. The possibility that certain cytokines such as tumor necrosis factor might be appropriate targets is intriguing but needs more work to ensure that this approach makes things better rather than worse in terms of severe disease.

Developing a vaccine is difficult enough, trialing it in the field is more so. But it is reassuring to realize that the professionals have been thinking through this part of the challenge using what is now substantial experience with epidemiologic modelling. The complexity stems in part from the diversity of situations which exist in endemic regions, partly from the variety of possible vaccine combinations that we may be asked to try. Certainly the basic parameters are understood even if the details need filling in as we go along.

Control and the costs

Curiously the economics of control were addressed before the organization of control. It doesn't really matter, what is important is the realization that ultimately the cost and the benefit must be integral to control replanning. For too

long we have taken for granted that malaria budgets would be forthcoming whatever the cost but there is no justification for such an assumption, especially where present strategies are not reducing the malaria burden. The idealistic argument is waning in an ever more competitive world.

It was clearly stated by Anne Mills and Somkid Kaewsonthi that there are many possible targets for economic analysis that could help to rationalize control planning more effectively. These concern human and material resources, diagnostic alternatives, therapeutic options, vector control methodologies, vaccines. In the latter category development costs may have to be written off by governments or international agencies but production costs cannot be handled by such sleight of hand. Industry has to make money to prosper.

There has already been some epidemiologic modelling of vaccine field requirements, perhaps now is the time to begin putting fiscal clothing on this skeleton by way of economic modelling which encompasses the molecular and epidemiologic data bases, to build dynamic concepts of what is affordable alongside what will work? We cannot expect scientists to be constrained ahead of time by mathematical modelling of what economists believe can be allowed to work - the disciplines are still too far apart to allow this as a prospective game. But parallel evolution of a flexible kind would prepare the ground for evaluation of the options which loom ahead. Thus transmission blocking vaccines have limits as well as attractions in both epidemiologic and economic vistas, as do infectivity blocking and disease modulating vaccines. Developing the equations now will provide a framework into which each new data set can be put for assessment in what must eventually be a decision-making chess game.

Meanwhile the day-to-day realities of malaria control strategies require continuing evaluation to optimize flexibility. The paradigms identified by Awash Teklehaimanot are central to this effort. There are many types of malaria pattern and each different priorities: savannah, irrigated and non-irrigated agriculture, urban, desert fringe, forest and forest fringe, highland fringe, coastal. Across the whole spectrum is cast the shadow of population mobility, as ancient as human society but accentuated by the changing demands of economic development throughout the tropical world. Old methods were programmed for stable village communities. These are no longer the norm but are simply part of a dynamic, ever-changing series of scenarios. This will not diminish with time and the endless task of the control planners is to be able to respond to change.

Louis Miller, polymath of malaria scholarship. stressed this point in his summary address. He concentrated on the options for the investigator but the same is true for the planner, both need to be open to totally new ideas. Wisdom does not reside in ivory towers, in the white coat domains of laboratory or clinic, nor in the rice fields or the forests alone but in the synergy of minds and hands. History, distant past and more immediate past, does hold many lessons in this complex arena which make for exciting challenge to all concerned.