

## EDITORIAL

### AIDS VACCINES: MONEY GAMES AND ELUSIVE STRATEGIES

HIV/AIDS arguably is the most insidious plague of current times. This field has had more research money thrown at it in a short time than any other disease group in history: we are entitled, then, to question the outcome globally in terms of cost effectiveness. The difficulty in so doing lies with uncertainties of both the science and the economics. Both public and private sectors have been heavily involved, which adds to the complexity concerning the battlefield on which this catastrophic global epidemic is being played out.

Controversy has permeated the early history of the science of this controversial disease, particularly the initial discovery of its causation. An inside view on this debate has been recorded in a personal memoir-cum-perspective by Luc Montagnier (2000), the discoverer of the causative virus, HIV. The famed NIH/Pasteur agreement to share royalties from HIV diagnostic tests did not resolve the enmity aroused by the suspected piracy by super-power science strategy. This record identifies the foibles beyond the science in a game that is poignant and deadly serious. This game bears reflection, for in an era of technology dominance and globalization catch-cries there are some simple tenets that tend to be forgotten.

A recent monograph by science journalist Jon Cohen (2001) helps to define the battlefield in both historical and prospective terms. The scenario is multifaceted, to say the least. If we reflect on history we should have learned to expect periodic epidemics of one infectious disease or another, but perhaps we do not like to linger in the past enough for that. Part of the problem, however, lies with perspective of the raconteur: what is periodic from the vantage point of the richer North is often insidious from the viewpoint of the poorer South.

Thus western history focuses on the first cases of AIDS in American homosexual men and for a considerable period the disease was thought to be restricted thereto. Haiti became a convenient scapegoat as a presumed entry point to the United States, stigmatized for a long period but later cleared of prime culpability, without the fanfare that accompanied the initial accusation, of course. Only later was it recognized that AIDS cases were occurring in a number of countries, particularly in Africa, that the pattern of transmission elsewhere was more often by the heterosexual route, while a common thread was transmission by needle sharing by intravenous drug users (IDU). The Asian explosion came somewhat later, following the pathway from IDU to heterosexual transmission.

A major part of the current problem is that the vast majority of HIV positive and clinical AIDS cases world-wide reside in countries in Africa and Asia, in populations that, by and large, are too poor to afford the potential hi-tech solutions which are beginning to appear on the horizon by way of anti-HIV vaccines and drugs. Thus vaccine development objectives over the past two decades have focused on constructs that might target HIV strains prevalent in the North and thus would, if successful, be of rather restricted applicability globally, given the array of virus variants that exists world-wide. This focus results in large measure from the cost structure of the enterprise, which in turn depends on the complexity of the chemistry and immunology involved, and from the complexity of clinical trials.

Historically over these two decades much of the basic research funding has been in the US public sector, mostly under theegis of the National Institutes of Health (NIH), distri-

buted over many academic institutions. From small beginnings this public funding has mushroomed greatly in recent times due to astute political lobbying by HIV/AIDS activists as well as scientists and in part due to the expansion of congressional allocations generally to NIH. But over this period there has also been very substantial activity in the private corporate sector, primarily in the US and to an extent in Europe. Naturally the corporate sector targets potential profit and thus affected or at-risk populations in the North with ability to pay, individually or at the community level.

It is noteworthy that many of the companies working in the field have been small biotechnology firms, closely allied with academia (Cohen, 2001). Over time large corporations have joined the fray, in some cases through takeovers of the biotech firms or by close collaboration. This helps to share the financial risks but when from time to time a major corporation closes down a program the downside effect can be disastrous in terms of scientific endeavor. Then there is the role of the US Food and Drug Administration (FDA) which must approve vaccine constructs for US clinical trials. Through political channels the FDA is not entirely impervious to lobbying, despite their historically good record in application of high standards to vaccines and drugs. Thus there are well-documented examples of pressure to race ahead to trials of scientifically dubious vaccine constructs, and of mis-interpretation of the results of animal experiments, in the race to get to the clinical phase.

There is another aspect of animal experiments in the HIV/AIDS field. Chimpanzees can be infected with HIV but do not develop clinical AIDS. Chimpanzee trials are very expensive, so that statistically significant trials are rarely if ever concluded satisfactorily, thus leading to guesswork with a high "fudge factor". Ethically it is hard to justify the use of the chimpanzee model anyway, given their supposedly protected status as endangered ape species and their close genetic relationship to

the human species of apes. Nevertheless such pseudotrials go on and on producing statistically useless and biologically dubious data. The simian immunodeficiency virus (SIV) in certain species of monkeys does provide some parallels to HIV infection in man, but it is a limited model, with its own ethical problems. Models of course especially occupy the attention of the would-be commercial vaccine developers, since FDA approval of new vaccines normally requires animal testing prior to human trials.

But the scientific debate has focused heavily at the molecular level. It is natural that in the currently sophisticated molecular age vaccine constructs should aim to target virus envelope protein epitopes, particularly popular being the HIV surface protein gp120. Critical parts of this molecule exhibit great amino acid sequence diversity. As expected, these epitopes are critical to the binding of HIV to the T-cell (CD4) receptors and thus are logical vaccine targets. They are also logical targets of antigenic variation and thus of adverse selection by vaccines directed thereto. These considerations led to advocacy of whole killed virus vaccines analogous to the polio vaccine developed by Jonas Salk. Indeed Salk himself devoted much energy to promoting this approach up until his death in 1995. The possibility of live attenuated vaccines, analogous to the Sabin polio vaccine, has also been raised but naturally the thought triggers considerable fear of potential disease causation, as indeed has occurred with the global polio campaign that uses this class of vaccine.

From the viewpoint of safety and cost genetically engineered HIV vaccines are clearly attractive, particularly in the light of continuing advances in adjuvant technology, but the high rate of viral genetic change cast a long shadow. As the global epidemic rages the vaccine game goes on, as it surely must. While the concentration of interest and effort has been skewed towards the North, it is in some ways fortunate that the disease is global, despite the large numbers of victims in poorer nations. At least there will be a chance of a spill-over

effect of any technical advances from the North to the South if resources can be found for applications. Indeed, a number of clinical trials have been instigated in Thailand and elsewhere in Asia/Africa, however, these trials have mostly been designed in the US or Europe and thus are not fully collaborative in all respects as they should be. Scientific colonialism has no place in this context: many issues, including ethical considerations, exhibit variation in geographic and cultural context.

Even assuming that partly effective vaccines can be developed against the major HIV strains, that most of the financial burden can be borne by the North and that some or all of these vaccines are active in the African/Asian context, the possibility of sustainable vaccination programs in countries of the South would currently seem to be remote. Even where public health infrastructure is soundly based, the long-term costs are likely to be insurmountable. A glimpse of the reality can be gained already from the situation regarding anti-HIV drugs produced by transnational pharmaceutical giants. These drugs (reverse transcriptase inhibitors, protease inhibitors) cost a patient as much as US\$10,000 per year in the North. They inhibit but do not eliminate virus, so require life time administration for symptomatic relief. Cessation of drug administration leads to AIDS relapse. Indian drug companies have led the challenge to the transnationals, offering to sell generic compounds at US\$350 per year to South Africa in the context of a court challenge by a consortium of transnational corporations in that country. This is a critical test case, for in a very real sense the future of HIV/AIDS globally lies with a win against the corporations.

A win might further throw open the much broader issue of differential drug pricing generally in North and South, by way of eventual challenge to the TRIPS agreement of the World Trade Organization (WTO). This agreement currently protects the profit motive of the transnational giants against the needs of the

global poor. However, for the moment, even at US\$350 per head anti-AIDS drugs would be out of the reach of most of the poor populations of the world, many of which budget < US\$10 per capita per year on all health care activities.

The resources crisis underlines all considerations of the health care shortfall. Transient aid is no answer, since it brings forth no contribution to sustainability. In certain respect the HIV/AIDS calamity highlights the need to re-invent global public health strategy (Garrett, 2000): it epitomises the global nature and/or potential of communicable diseases and the long-term futility of local solutions, given the vast population mobility within and between countries and regions. In retrospect the fortune made available from Northern public and private coffers for the frustrating vaccine search might well have been better distributed globally for more immediate constraint of virus dissemination using traditional public health strategems. However, over twenty years that money has been spent and some of it has helped to open up the knowledge base essential for further action. It is hoped that the next phase of contemporary history will witness greater wisdom, with much wider, more equitable participation from the South in the science itself, in application strategy design and in the requisite long-term economic planning.

Chev Kidson

## REFERENCES

- Cohen J. Shots in the dark: The wayward search for an AIDS vaccine. New York: WW Norton & Company, 2001.
- Garrett L. Betrayal of trust: The collapse of global public health. New York: Hyperion, 2000.
- Montagnier L. Virus. New York: WW Norton & Company, 2000.