AUSTRALIAN AND NEW ZEALAND ASSOCIATION

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SYDNEY UNIVERSITY

SOCIAL AND ETHICAL IMPLICATIONS OF ANTI-VIRAL THERAPY AND VACCINES FOR PATIENTS WITH AIDS

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AIDS DRUGS, VACCINES AND THE LAW - LESSONS FROM THE UNITED STATES EXPERIENCE

The Hon Justice M D Kirby CMG*

URGENT PROBLEMS: URGENT SOLUTIONS

Every day, in the United States, as in most of the countries of Western Europe, Latin America, Central Africa and Australasia, patients are diagnosed as infected by the HIV virus. In the United States, the figure currently runs at an average of 35 Americans every day who receive this grim news. Based on the current level of infection, officials at the Centers for Disease Control in Georgia, USA, expect that there will be 324,000 cases so diagnosed in that country by the end of 1991. By that time, the virus is expected to have killed nearly 180,000 people in the United States alone[1].

The toll in the rest of the world is constantly mounting. The latest report from the World Health Organisation (WHO) in Geneva gives more than 88,000 cases of AIDS reported from around the world. 57,575 had been reported from the United States of America, 1,426 from Britain and 813 from Australia. The WHO sources estimated that the actual number of cases presenting around the world is probably twice as high[2]. Quite possibly it is very considerably more.

Add to these facts the further fact that the virus attacks mostly young and usually productive people in the prime of life and with, typically, considerable economic contribution to make, and some glimmer will be had of the dimension of the growing human and economic implications of this challenging disease.

One of the Justices of the High Court of Australia (Justice Windeyer) once said that law marches with medicine, but "in the rear and limping a little"[3]. Already, we are beginning to see in the courts of many countries, and in legislatures, the development of legal responses to the implications for individuals and societies of the AIDS virus. It is not the purpose of this contribution to review the cases or to survey the legislation. My objective is to examine some only of the possible legal implications of anti-viral therapy and possible future vaccines for patients with AIDS.

Not a great deal has been written on this subject in Australia. But in any case, the important developments in both spheres are likely to occur, in the first instance at least, in the United States of America. This is because that country is at present the epicentre of the epidemic. Furthermore, it has belatedly embarked upon a massive research program to develop therapies and vaccines. If that research, with the urgent motivation provided by the growing toll of dead and infected, is to succeed, it is probable (looking at the matter realistically) that it will succeed first in the United States. I do not discount the importance of local experimentation and fundamental research everywhere. Nor do I overlook the possibility that a remarkable breakthrough in

anti-viral therapy or AIDS vaccines could occur anywhere. By serendipity and lateral thinking, the remarkable instrument of the human mind could just as easily stumble over the key to pharmaceutical solutions to the AIDS dilemma in Australia as in the United States. But the major thrusts of the research effort is likely, in the foreseeable future, to remain primarily in the United States and secondly in France and Britain. Furthermore, unless approved in the United States, it seems unlikely that anti-viral therapies or vaccines developed elsewhere will secure a sufficiently rigorous and rapid clinical trial to gain universal acceptance. It is in this sense that the United States of America presents the most important gateway to the development of effective anti-viral therapies and vaccines which are of importance to patients with AIDS in every land.

This said, it is necessary to acknowledge a number of special problems which face the manufactures of therapeutic substances and vaccines in the United States. The prize of developing effective drugs or a safe and effective vaccine is a potential market of huge dimensions, great profits, world acclaim, honours and a Nobel Prize or two[4]. But the obstacle race which must be run in the United States is a very considerable one.

For example, in the field of vaccine manufacture, two chief theories have been propounded by the law of that country to deal with the possible mishaps which can occur in the manufacture of a vaccine. The first is the proof of negligence on the part of the manufacturer and whether it was at fault by the standards of what could reasonably be expected. The second is "strict liability". The first focuses on the conduct of the

manufacturer and whether it was at fault. The second attends to the characteristic of the product, ie whether there was a defect in its manufacture design or the warning attached to it which was given to the medical profession and potential users.

In the United States, there have been a number of recent cases which have been rather discouraging to drug manufacturers and to vaccine manufacturers in particular. Evidence has been called in cases of alleged vaccine injury and juries have been faced with deciding whether the approved vaccine was safer than some other available product. For example, in a recent case, a jury in Kansas awarded $10 million in damages to a patient in a case involving use of the Sabin Oral Polio vaccine. Apparently the jury accepted that the vaccine had been defectively designed because it was "less safe" than the competing Salk vaccine. The judgment was ultimately reversed by the Supreme Court of Kansas. But the judges of the appellate court divided 4 to 3[5]. This shows the uncertain position of vaccine manufacturers and the risky operation they conduct in the legal environment of the United States.

The result of litigation of this order in the United States is that vaccine manufacturers have been described as a "dying breed"[6]. Having regard to the risks of litigation and the gauntlet of approval by the Food and Drug Administration (FDA) in the United States, the estimated cost of getting a vaccine from first design to market is between $50 million and $75 million in the United States. The lack of a sure, guaranteed market for the eventual product and concern about potential liability if defects later emerge (as occurred with

the drug Thalydomide) show why vaccine and drug manufacturers are operating in a relatively risky legal milieu.

LEGISLATIVE INTERVENTION

A series of cases in the United States have involved the polio vaccine. It is, of course, one of the vaccines most beneficial to public health this century. However, in Reyes v Wyeth Laboratories[7], the Fifth Circuit of the United States Court of Appeals upheld the strict liability standard as applicable to the vaccine manufacturer. The court concluded that a Sabin-like oral live polio vaccine was an "unavoidably dangerous product". It implied that a design defect allegation might not be proved but focused its attention on the suggested defects in the warnings given concerning the use of the vaccine and the availability of possibly safer alternatives.

The implications of this decision were soon felt. In 1976, the United States faced a major swine 'flu epidemic. The Centers for Disease Control recommended a national immunisation program. Congress appropriated funds to pay for it. However, the drug manufacturers and their insurers refused to go ahead without legislative protection against liability of the kind which had been established in the case involving polio vaccines. Ultimately the congress passed legislation designed to make the United States itself liable for damages, should cases arise from swine 'flu mass inoculation[8]. However, the United States Government reserved the right to bring an action against a vaccine manufacturer whose proved negligence had resulted in an award of damages.

The fears of the drug companies were quickly realised. A number of the 45 million people who were vaccinated developed an impairment of the central nervous system which appeared to have been caused or accelerated by the swine 'flu vaccine. Ultimately, the United States paid out nearly $80 million in claims. It is not disclosed whether the government sued the manufacturers for negligence.

The very large verdicts that may be recovered in the United States themselves present an important cost factor in the development of vaccines and therapeutic drugs for that market. Because, as I have said, that market is often the gateway to markets elsewhere, what occurs in the United States is of immediate relevance to Australia[9].

In 1985 the First District Court of Appeals in California opened the way for the future development of an AIDS vaccine and its use in the United States without some of the problems which have occurred with the earlier polio vaccines. The Court refused to follow the strict liability principle in a polio vaccine case[10]. The Court held that, if a trial court determined that a product was "unavoidably dangerous" but that the social benefits nevertheless outweighed the risks, the plaintiff would only be able to recover from the manufacturer on the basis of proved negligence in the basic design defect of the vaccine.

Subsequently the legislature of California adopted this principle in the Health and Safety Code of that State. It created an AIDS Vaccine Victims Compensation Fund and guaranteed purchase by the State of California of 500,000 units of a future AIDS vaccine at up to $20 per dose. A precondition

is that the vaccine should be FDA approved. The United States Congress has yet to pass legislation similar to that enacted in California.

THE SENSE OF URGENCY

Because of the already high and growing toll of dead and infected, impatience has been expressed in many quarters in the United States concerning the very slow procedures ordinarily required for the approval by the FDA of the use of vaccines and drugs for humans. The FDA points to its care as one of the principal reasons why the United States was spared the Thalydomide disaster which befell other countries, including Australia. Those countries had not imposed quite the same rigorous and lengthy tests before sanctioning the general use of the drug.

Now, however, concern is expressed that there is simply not sufficient time to indulge the lengthy procedures usual in the FDA in respect of AIDS. Moreover, what is at stake is not morning sickness in pregnant women but a virus which is potentially lethal and presently incurable.

The result of this impatience and growing sense of urgency, and even desperation, has been a number of developments which deserve to be noted.

* The first is the growth of a subculture of "guerilla clinics" for the sale of therapies which have not yet been officially approved. In San Francisco there is a whole network of self treatment centres catering for a growing circle of anxious patients. One of the experimental drugs being trialled in Israel is developed by Ethigen Corporation (formerly Praxis Pharmaceuticals

Inc) of Beverly Hills, California. This is AL-721. The product could not be trialled in the United States because the company's insurer stated that it was not convinced that the informed consent necessary for litigation-proof use on United States patients warranted the risks of using the experimental therapy in that country. The result has been the growth of self help manufacture of substitutes for AL-721 or its smuggled importation from Mexico or other countries where the rigorous FDA standards are not required. Even home-made versions of the therapy are being distributed. These include the use of a product derived from egg yolks which is apparently the principal source of AL-721's active ingredient[11].

* Secondly, the California legislature, under the pressure of the very large number of AIDS cases in that State began in mid 1987 to explore the possibility of State testing and approval of AIDS therapies. It would be necessary that such treatments and drugs did not enter into interstate commerce as, if they did, they would be caught up by Federal regulation and the necessity of FDA approval. The California Attorney General, John Van De Kamp asserted that the federal authorities had not acted as expeditiously as possible and that the State plan "would try to accelerate the process"[12].

* Thirdly, in late May 1987, the Reagan Administration issued new regulations permitting access to some experimental drugs by people already dying of AIDS and a few other "immediately life threatening diseases". This

move came partly in response to criticism of the FDA's regulatory assistance which can sometimes involve up to nine years of testing before a drug is approved. There is now a growing acceptance that the size and urgency of the problem outweighs the protective mechanisms which limit the distribution of even partly promising medications for the seriously ill. The FDA Commissioner retains the authority to deny requests for the use of experimental drugs outside clinical trials. Furthermore, the FDA itself emphasised that it would not tolerate exaggerated or fraudulent claims by drug manufacturers, pandering to the fear of patients and their friends already faced with the terrors of a deadly virus.

* Despite the changes in the regulations, in June 1987, the National Gay Rights Advocates filed a suit in the United States District Court in Washington DC against the FDA Commissioner and the National Institutes of Health. They brought the action as a class action on behalf of all persons infected by the AIDS virus[13]. The suit charges that the defendants accelerated consideration and approval of AZT whilst ignoring or delaying consideration of other "promising drugs" including AL-721, DNCB and Virazole. The relief sought is an injunction requiring the defendants to adopt and implement rules ensuring public disclosure of the process for choosing drugs for testing and the reasons for those drugs being selected and requiring the FDA to remove the clinical hold on the other drugs for those who are beginning to display early symptoms of worsening health. This legal battle is, so far as I am aware, continuing.

CONCLUSIONS: THE NEW NUCLEAR CLOUD

Realisation of the size of the problem and the urgency of solutions together with pressure from the growing circle of young and otherwise vigorous and productive people afflicted, and their families and friends, has begun to produce results in the United States. An estimated 1.4 million Americans are already infected with the HIV virus. Although it is not yet known how many will proceed to AIDS, it is suspected that at least a third and possibly more will become ill and require treatment. The problem with the one drug which is being used extensively, AZT, is that it is extremely costly and frequently has severe side effects. Furthermore it does not eliminate the virus from the body. The general belief of scientists seems to be that, like cancer, AIDS will most likely be controlled by a combination of agents. This requires a continual mix of therapies, many of which will have serious side effects and thus render manufacturers and distributors liable to legal proceedings which may themselves prove an inhibition to the energies of manufacturers and their insurers.

In the United States, the way ahead seems to be signalled by legislation such as the National Childhood Vaccine Injury Act[14]. This statute, which was opposed by the Reagan Administration, creates a federal compensation system for reactions and lasting injuries associated with any of seven vaccines used for childhood diseases. Under the Act, claims can be brought in a Federal Court and a special Master is then appointed to hear the case and decide whether the reaction was caused by the vaccine. If so, the Master decides the amount of the award with a $250,000 limit placed upon general damages for

pain and suffering. No inquiry is made into the negligence of the manufacturer. No punitive damages are allowed. Only after the Master's findings are reviewed by a District Judge does the person injured have the option of rejecting the decision and bringing a suit in a State court in negligence against the manufacturer. In such proceedings, the drug company cannot be held liable for the warning supplied with the vaccine if it meets FDA requirements. Nor can it be subject to punitive damages if FDA rules were followed.

There have been various criticisms of the statute[15]. So far it has not been funded. However, it does seem to point the way ahead in respect of the proper legislative response to possible future AIDS vaccines and drugs in the United States. Moreover, it provides a possible precedent for us to consider in Australia. We face an urgent and rapidly escalating problem of global dimension. The epicentre of the problem, and the likely centre of the principal experiments towards the solutions, is the United States of America. Just as it was the First Amendment of the United States Constitution which effectively guaranteed the liberalisation throughout the world of censorship laws by the international spread of United States films, books and magazines, so the United States legal system controlling drugs and vaccines profoundly affects the rights of others who are outside its network. This is just the latest example.

If the legal system of the United States imposes undue restrictions on the experiments and clinical trials with the multitude of interacting therapeutic agents for treating AIDS, the discovery of useful therapies may be seriously delayed.

They may be delayed in reaching a principal target audience profoundly and urgently affected by the AIDS virus. That delay will have ripple effects throughout the world, including Australia. Similarly with vaccines. If the principles of early decisions on the polio vaccine, established by the Federal courts in the United States are followed, the inhibitions against the mass trial of vaccines in the United States may be such as to force such trials to take place elsewhere. Already this is happening to some extent with the trial by Dr Daniel Zagury of the University of Paris being held in Zaire using a vaccinia - AIDS vaccine.

The way ahead in the United States is already signalled. This has occurred as a result of the realisation that the equation has shifted because of the size and urgency of the AIDS epidemic and the very high fatality of those diagnosed as suffering from AIDS. In such circumstances, the patient is still entitled to the best of medical treatment and protection against unnecessary side effects. But desperate situations require urgent and even risky solutions. This must be recognised by legal regulation and by court decisions as much as by the community of patients and their families. At last this message is being appreciated in the United States. FDA regulations are being changed. Greater flexibility is being introduced. Court decisions are also looking realistically at the overall "social benefits" which may outweigh the inescapable individual risks.

A golden thread must run through all medical treatment whether by vaccines or anti-viral therapies whether for AIDS or otherwise. This is the need for informed consent by the

patient unless the law specifically excuses it. Where there is risk, the extent of that risk must be fully and candidly explained to the patient. It is for the patient - not the medical practitioner or the family - to take the ultimate risks affecting the life of the patient. The same obligation of candour and informed consent is required in the case of clinical trials. Generally, in the terribly serious predicament of AIDS, informed consent will be given. Deciding whether to give a risky vaccine to low risk groups or to continue a futile or promising trial present very serious ethical problems which fall outside the scope of this paper.

Faced by this most serious challenge to public health, law makers, judges, scientists, drug and vaccine manufacturers and indeed the whole community must show a marked flexibility of mind. At stake is nothing less than the lives of millions of young people who face a world made suddenly different by a peril which may prove just as serious as the events of Hiroshima. The youth of this century have lived for forty years under the nuclear cloud. Now they live under the AIDS cloud. The immediate need is for community education to prevent the unnecessary spread of this virus. But to reinforce such community education - notoriously problematical as our experience with tobacco and other drugs demonstrates - we need anti-viral therapies and vaccines. It will be vital that the law responds flexibly to that need, not only in the United States but in Australia as well.

FOOTNOTES

* President of the Court of Appeal, Sydney. Trustee of the AIDS Trust of Australia. The opinions stated are personal views only.

1. Kay Bishop, "Desperate Lives, Unknown Risks" in California Lawyer, 1987, 45. Cf W K Mariner and R C Gallo, "Getting to Market: The Scientific and Legal Climate for Developing an AIDS Vaccine" in Law Medicine and Health Care, Vol 15, No 1, Sum 1987 pp 17-26.

2. "World AIDS Cases Rise" in Washington Post Health Report 3 May 1988, 13.

3. Windeyer J in Mount Isa Mines Ltd v Pusey (1970) 125 CLR 383, 395.

4. "The AIDS Race" in Washington Post Health Report, 3 May 1988, 14-15.

5. Johnson v American Cyanamid Company 239 Kan 279; 718 P 2d 1318 (1986).

6. B Franklin, "Legal AIDS - Vaccine Manufacturers Seek Limit on Potential Liability".

7. 498 F 2d 1264 (1974). See also Toner v Lederle Laboratories, 732 P 2d 297 (1987).

8. 42 USC 2476.

9. Bishop, 111.

10. Kearl v Lederle Laboratories 172 Ca 3d 812 (1985). The Court criticised the "rather routine and mechanical fashion" in which courts had found vaccines "unavoidably unsafe". See Mariner and Gallo, 21.

11. Bishop, 46.

12. Quoted Bishop, 48.

13. National Gay Rights Advocates v Department of HHS referred to in Bishop, 48.

14. 1986 PubL 99, 660.

15. Bishop, 112.