An Impending World Cup: Man vs. Virus

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Divining the future can be a precarious exercise under the best of circumstances and, in this era of exponential change, perhaps an exercise in futility. But tonight I would like to take a brief look at some aspects of the future as we endeavor to anticipate virological scenarios of the new millenium. In doing so, it is important to reflect on a not so distant past when a mixture of complacency and perhaps hubris served us ill and this we should not forget.

For ~~recent~~ part history, I have arbitrarily selected a 40 year time bracket in part because it spans most of my professional life and so is an era to which I can most readily relate. Interestingly, (however, it was almost 40 years ago that Sir Macfarlane Burnet wrote (1962): **SLIDE 1** "...one can think of the middle of the twentieth century as the end of one of the most important social revolutions in history, the virtual elimination of the infectious diseases as a significant factor in social life." It was a view that was surprisingly widely shared. The United States Surgeon General effectively subscribed to this belief in indicating to our public health community that it was time to move on from studies and programs dealing with the infectious diseases to deal now with the predominant causes of death -- cancer and heart disease. With this perspective on the virological world, who would have forecast 40 years ago that there would be in 1999, a Congress such as this, dealing specifically with virology, a topic that ~~not so long ago~~ was ~~thought to be of~~ once a fading concern. Today, it attracts to Sydney upwards of 2000 persons from across the world.

You will recall that it was just 50 years ago that Enders, Robbins and Weller demonstrated the use of tissue cell culture for the growth of viruses. **SLIDE 2** Inactivated

polio vaccine, developed and introduced with unprecedented speed, soon reduced dramatically the numbers of polio cases. Four decades ago, a more promising live polio vaccine was on the immediate horizon. Measles vaccine would soon be introduced and the likelihood of many more viral and bacterial vaccines seemed certain. New and improved antibiotics were being introduced annually with dramatic success. Antiviral drugs were in development. Global malaria eradication, launched in 1955, was recording astonishing early successes in a number of countries and there was talk of embarking on other eradication campaigns. The heady pace of progress suggested, indeed, that with only modestly optimistic extrapolation, one could envisage for the future, a virtually disease free state, at least in our industrialized societies.

It was a time when a young Public Health Service Officer at ~~the U.S.~~ CDC Communicable Disease Center, having only recently been ~~both stimulated and~~ challenged by his first forays into infectious disease epidemiology, took the advice of the Surgeon General and reluctantly bade farewell to his new but fading field. He enrolled at Johns Hopkins University in an effort to retread as a chronic disease epidemiologist. The effort failed. ~~It seemed to him that so much of the practice of chronic disease epidemiology lay in trying to make sense of batteries of answers to thousands of questions. Inevitably, it seemed, the most salient questions were the ones that had not been asked at the beginning of the study.~~ I retreated to the field of infectious disease epidemiology albeit with little optimism that there was sufficient to keep very many like myself employed over the course of a career.

I would remind you also that forty years ago, smallpox eradication was considered an improbable dream; the Australian Society for Microbiology was just being founded; and, Burnet ~~was~~ had yet to receive the Nobel Prize. Travel was then a far more daunting challenge as I discovered during a 1960s trip to the Philippines to investigate the beginnings of pandemic el Tor cholera. It provided me my first introduction to

Australia -- my return itinerary from Manila being on propeller driven aircraft with stops at Port Moresby, Sydney, Fiji, Hawaii, Los Angeles and Chicago. It consumed the best part of 4 days.

Eradication and Vaccination

With victory over the infectious diseases proclaimed, if not ~~decided~~ achieved, medicine in the industrialized world of the 1960s and 70s turned to the evolving technologies of curative medicine -- organ transplantation, cardiovascular surgery, chemotherapy and the like. A public health infrastructure whose original purpose and continuing concern were the infectious diseases began to crumble; in hospitals, departments of microbiology contracted; and many infectious disease training programs were terminated.

There were two developments, however, which for the infectious disease epidemiologist, helped to illuminate the darker days of the 60s and 70s -- the launching of a program for smallpox eradication and the development of population-wide vaccination programs. Both provided important lessons to the future.

Smallpox eradication was launched in 1967, although by the narrowest of margins. At that time, continuing introductions of smallpox into Europe and other countries ~~engendered fear and concern and resulted in~~ were so frequent that virtually all nations ~~sponsoring~~ sponsored ~~continuing~~ on-going national vaccination programs. Australia and New Zealand, protected by distance and ~~strict~~ quarantine measures, were virtually the only exceptions. In the developing countries, smallpox remained a continuing serious problem only partially controlled by inadequate supplies of often sub-potent vaccine.

In 1966, it was proposed at the World Health Assembly that $2.4 million be appropriated annually for a global program. Many objected on the grounds that eradication was an untenable proposition. The eminent virologist, Rene Dubos, spoke for many in asserting that the intricate adaptive relationships between man and microorganisms that had evolved over time, made eradication of any species an unlikely

proposition. **SLIDE 3** As he said " eradication programs will eventually become a curiosity item on library shelves, just as have all social utopias". Indeed, at that time, malaria eradication was floundering -- the fourth in a failed series of international eradication campaigns which had included hookworm, yaws and yellow fever. In addition to those who considered the program technically impossible, there was a bloc of countries who were opposed to a larger WHO budget for any purpose. After a rancorous debate, smallpox eradication was eventually endorsed by the Assembly but by the margin of only two votes.

The Director General of WHO was convinced that the program could only fail and serve to discredit the Organization. Although the Soviet Union had been the original advocate for smallpox eradication, later joined by the United States, the Director General faulted the United States in particular and asked that an American direct the program. As he said, When the program failed, he wanted it to be apparent to all that the U.S. shared the onus of blame. It was, for me, not an auspicious beginning.

However, the saga of the succeeding decade was a gratifying one. **SLIDE 4** The time elapsed between the launch of the global program in 1967 and the occurrence of the last case was just over 10 years -- 130 months, to be precise. A disease that had claimed over 10 million victims and 2 million deaths during the first year of the program was history. For the World Health Organization, for many developing country health ministries, it provided a new measure of confidence to undertake other public health programs. And for me personally, it had been a welcome opportunity to work closely with Frank Fenner who served throughout as the program's principal adviser.

Unquestionably, one of the most important new health initiatives was a global program to assure that children throughout the world received vaccines against polio, measles, diphtheria, pertussis, tetanus and tuberculosis. **SLIDE 5** We conceived it as an extension of the smallpox program and so it was dubbed the "Expanded Program on

improperly stored; reuse of non-sterile equipment was common; and seldom were those attending clinics for other purposes offered vaccine. A well-managed mass campaign offered many advantages and a number of countries carried such campaigns a step further. They began the practice of staging national vaccination days twice each year. On such days, all children of a certain age were offered vaccination. Both China and India, for example, are now vaccinating some 100 million children on each national day twice each year.

Clearly, disease control using a vaccine that can be administered on a populatio n-wide basis and on a planned schedule is inevitably simpler, logistically more practicable and almost always far less expensive than any disease control program which must rely on a therapeutic drug, ~~such~~ as is the case with tuberculosis, and malaria. Accordingly, as we look to future disease control efforts, it would seem only logical to give special priority to developing strong public-private sector programs of vaccine research, development and production. A host of new developments promise a new era of disease control --including recombinant vectors, DNA vaccines, antigens expressed in such as bananas and potatoes and a new generation of adjuvants. Surely, in all of this are answers to the three greatest challenges of the third world -- HIV, malaria and tuberculosis --and potentially for new and emerging agents as they may threaten.

Disease surveillance played an extremely vital role both in the smallpox and polio campaigns and there is now general agreement that priority should be given to developing such systems for selected other diseases throughout the world. Surveillance consists simply of a system with a professionally staffed office ~~for~~ which regularly and promptly receiv~~ing~~ reports of disease, usually from health centers and hospitals; the epidemiological analysis of this information; the broad dissemination of such information; and the implementation of necessary studies and control measures.

Immunization." It was launched in 1974 at a time when less than 5% of children in the developing world were receiving these vaccines, even the newest of which had been widely available in the industrialized world for more than a decade. Major support to that effort was provided by UNICEF, Rotary International, many bilateral agencies, the development banks and others. Much of the leadership and creativity was provided by young health professionals who had acquired experience and training in the smallpox campaign. By 1990, 80% of the children were receiving these vaccines; a global polio eradication campaign had been launched; and by 1991, the Western Hemisphere had become free of polio. Other areas soon followed, including Europe, many countries of Asia and countries in northern and southern Africa. Now, other vaccines are beginning to be added to national programs including those for hepatitis B, rubella, yellow fever and hemophilus influenzae. Recently, the William Gates Foundation contributed $100 million for a new initiative designed to facilitate the introduction of new vaccines into third world settings.

Vaccination and Surveillance

Two important lessons deriving from these programs have special significance as we look to future combat with the microbial world. **Slide 6** First, is the remarkable power and simplicity of vaccination and, second, is the importance of surveillance in quickly identifying and in monitoring disease problems.

We discovered during the smallpox campaign that vaccination was readily accepted virtually everywhere and with coverage levels of 90% or greater. This was far better than had ~~been~~ expected. Key to these efforts was active support and participation by community leaders as well as national officials and the provision of vaccination at convenient sites and times. It became clear that if vaccination were offered only through hospitals and primary health centers, coverage of greater than 60% was ~~unusual~~. Moreover, vaccines in hospital and health center settings were often found to be

We are unimaginably ignorant of disease occurrence throughout the third world. Data from many countries are regularly published citing the incidence of various diseases but few appreciate that most of the data consists only of fragmentary reports, estimates based on small samples or simply guesses. The smallpox campaign provided many startling examples to illustrate this despite the fact that smallpox is a disease that can readily be diagnosed and that all countries, by treaty, were obliged to report cases to WHO. For example, we were to discover at the beginning of the program that the 100 000 cases officially being reported annually actually represented more than 10 million cases as we were later to determine through special surveys. The Ethiopian government recorded each year only 200-700 cases and was convinced that smallpox was not a problem warranting a special program. During the first year of Ethiopia's surveillance program, more than 26 000 cases were found and it was estimated that the actual number was probably closer to 200 000.

Surveillance systems are even more critical today for dealing in a timely manner with new and emergent diseases which now have a greater capacity than ever for rapid and widespread dissemination..

New and Emerging Infections

The success of smallpox eradication and subsequently the Expanded Program on Immunization helped to sustain a flickering interest in infectious diseases, at least in the industrialized world, but well into the 1980s, a complacency prevailed that any serious microbial challenge to health in the industrialized world could be readily handled.

In June 1981, a cloud appeared on the horizon. **SLIDE 7** That month, the first cases of AIDS were discovered and by February 1983, the first 1000 cases had been identified. In April 1984, the then United States Secretary of Health, Education and Welfare announced that the human immunodeficiency virus had been identified. She said, "Today's discovery represents the triumph of science over a dreadful disease" and,

predicted that a vaccine would be ready for testing within two years. Fifteen years later, and with research expenditures exceeding US$2 000 million per year, the first phase III vaccine field trials are only beginning, albeit more with hope than confidence that they will be successful. There are a number of drugs that, at enormous cost are able to suppress virus proliferation for months to a few years but the drugs are so costly as to be inaccessible to more than 95 % of the world's victims of AIDS.

In 1989, a more humble group of scientists met in Washington to explore the uncomfortable question as to what prospects were for other serious epidemics -- that is, new or emergent diseases. One especially disturbing speculation was raised, specifically what if HIV had possessed a capacity for transmission by aerosol, as influenza, for example. The implications were profound. Given that the average time from initial infection to AIDS is on the order of ten years, those first cases of AIDS in June 1981 might well have been the first symptomatic victims of a massive pandemic which, by the time of detection, might well have already infected much of the world's population.

Other new diseases, such as canine parvovirus, dramatized the rapidity with which even a new enteric organism could spread in a world where intercontinental traffic has burgeoned. Less than two years elapsed between its emergence in dogs and its spread through the world.

Another new disease, however, variant Creutzfeld-Jakob disease echoed, in part the AIDS scenario of potentially widespread dissemination of a viral agent before being recognized. As you know, variant Creutzfeld-Jakob disease first emerged in 1995. This was approximately 15 years after the first bovine cases are thought to have occurred and when humans might have first become infected. **SLIDE 8** As with AIDS, Creutzfeld-Jakob disease and bovine spongioform encephalitis have protracted incubation periods

and thus, by the time the first cases were identified, more than 500 000 cattle are believed to have entered the food chain. To date, however, human cases number 41. Undoubtedly, there will be more although the epidemic curve now looks less ominous than it did two years ago..

There is every reason now to postulate that we will see many more new and emergent infections than in the past. **SLIDE 9** Growing, densely populated, poorly sanitated tropical urban areas housing a nutritionally marginal population, provide a fertile environment for organisms to become fully adapted to man. The many additional inoculations administered in hospitals or by special inocculators in such as Africa and Asia, often with non-sterile equipment, offer new opportunities for blood borne organisms such as ebola, marburg and lassa fever. The industrialization and internationalization of our food supply provides myriad new opportunities for widespread disease transmission.

Our ability to detect new entities at the earliest possible time and an ability to respond in a timely way, very possibly with vaccines, will depend heavily on an alert surveillance network of public health and clinical specialists backed up by competent laboratory support. This is ~~needed~~ a critical necessity world-wide.

The Deliberate Release of Organisms

It is now clear, however, that there is yet another dimension to the challenge in the coming millenium and that is the threat of a human-engineered release of biological agents. Until very recently I shared the view of many that this was a very unlikely although potentially catastrophic event. In part, our confidence had derived from the knowledge that acquiring, propagating and effectively disseminating especially virulent organisms was a complex task requiring substantial expertise in several technical areas. Moreover, time, money and facilities to permit experimentation would be required to produce such materials in quantities sufficient to cause serious problems.

Offensive biological weapons programs in the West terminated in the early 1970s as most countries became party to the Biological and Toxin Weapons Convention and, so far as was known, the capacity to develop such weapons in any other country, ~~especially those thought to be engaging in terrorist activities~~ was thought to be limited. Thus, it seemed that there were no known laboratories where advances in contemporary biotechnology were being applied to the development of bioweapons

The ~~1992~~ defection to the U.S. in 1992 of Dr. Ken Alibek, deputy director of the Soviet bioweapons program, brought staggering news. There had been concerns that the Soviet Union might be experimenting with biological weapons, but none imagined the scope of that effort. In his recently published book, *Biohazard,* Alibek describes a sophisticated enterprise comprised of more than 60 000 persons and 200 laboratories. Industrial scale methods were perfected for producing smallpox, anthrax, plague and ~~[illegible]~~ other organisms in multi-ton quantities. Through genetic manipulation, antibiotic-resistant strains of anthrax and plague were developed and experimental studies proceeded to produce recombinants of Marburg and smallpox viruses. In brief, a vast industrial enterprise solved all manner of technological problems and scientifically advanced the state of the art. With the present stringent economic conditions in Russia, with many senior laboratory personnel leaving the bioweapons facilities for unknown locations, new weapons are potentially now available to all manner of groups, be they such as the Aum Shinrikyo, the bin Lauden group, Hamass or whomever. Terrorists seeking to inflict vast numbers of casualties now have at hand weapons that are inexpensive, readily transportable, undetectable until long after release and capable of causing more havoc than either chemical or nuclear weapons. **SLIDE 10** Everyone agree that the most serious agent of them all is smallpox.

Thus, the new millenium brings a heightened challenge of new and emergent organisms better able to spread than ever before and large crowded population

agglomerations where they can incubate. We must anticipate as well the possibility of a deliberate release of organisms, perhaps bioengineered, a "dark side" to the biomedical revolution.

The best defense for all of this is a strong public health and medical infrastructure coupled with strong microbiological research and development programs. However, whatever measures are taken, our view today must be Despite the progress which has been made in recent years, today's view of our microbiological future is rightly more guarded than it was 40 years ago. A sobering quotation from Dr. Josh Lederberg provides a contrasting bookend to Burnet's proclamation of victory.

SLIDE 11 As he wrote: "...we have too many illusions that we can govern....the microbes that remain our competitors of last resort for dominion of the planet." Appropriately, Lederberg speaks of survival, not of victory.

We need to detect and define problems at the earliest possible time and to take needed counter-measures