VIRUSES: THE NEXT PLAGUE

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Pleasure to participate in this colloquium and to visit this remarkable center. Topics in biology and medicine, understandably, are uncommon in your colloquia, but today I would hope to describe why the problems of new and emerging viruses are a concern of more pressing relevance to all of us - in fact, I will argue that our own destiny rests upon our ability to cope with these viruses, and I will offer suggestions as to some first steps which need to be taken.

Just nine years ago, the first few cases of an unusual new disease among homosexuals were first described. At first, the illnesses (now known as AIDS) were thought to be toxic in origin, possibly related to amyl nitrite inhalation. The summer of 1982, however, brought new reports of similar cases among Haitians, none of whom were homosexuals, and soon thereafter, the discovery of cases in hemophiliacs. The search for an infectious agent began, and two years later, in 1984, Luc Montagnier (Paris) and Bob Gallo (NIH) announced that they had isolated a highly unusual virus, now called the human immune deficiency virus. Immediately the indomitable Margaret Heckler, then Secretary of HHS, announced that, with a virus in hand, we would have a vaccine in a year's time.

Six years have passed. There is no vaccine - at best, there is cautious optimism that a vaccine <u>might</u> be available by the end

of the century. A costly drug, AZT, is in widespread use in the industrialized countries, but both cost and the lack of delivery systems preclude its use in most of the rest of the world. Meanwhile, the virus continues to spread.

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- Bear in mind that ~ 50% of infected die within ten years and best evidence - all eventually will die of the disease.
- Conservative estimates (WHO) that 20,000,000 will be infected a decade from now. (Recent data from Asia show much more rapid spread than thought - ? 50% higher)

In Africa and Asia heterosexual spread appears to be the dominant means of transmission, and health education campaigns appear to be having little impact. (vignette - Zambia) In East Africa today, half or more of all hospital beds are occupied by AIDS patients, and in urban areas 30% of all women coming to delivery are infected. The impact of this disease - economically and socially - has scarcely begun to be perceived. Large sums of money have been expended for research, and many of our very best scientists are working tirelessly on both drugs and vaccine. Despite this, we stand almost helpless.

Our experience with AIDS has been sobering - indeed humbling and has generated discussion re: other viruses. Josh Lederberg, Nobel laureate and recent President of Rockefeller University expressed best our concerns when he said: "Our only real competition for domination of the planet remains the viruses" and, he added, "The survival of humanity is not preordained."

Where did this virus come from?

The origin must be speculative and politically very sensitive, but a reasonable scenario suggests the tropical rain forest of Central Africa.

- Similar virus to SIV - not a fatal disease.
- Work of smallpox research teams in rain forests of Zaire.
  - + Villages of 30 - 50
  - + Principal source of protein - monkey (WWF - note)
  - + Slaughtering of monkeys
- Very possibly a long-standing infection with periodic spread to man but no continuing spread.
- 1950's development of Zaire - roads, hospitals and clinics (and needles and syringes) Forest <---> city.
- 1960's independence/revolution/UN forces
- Report of Eecles - 1964.
- Haiti was apparently earliest and most highly infected site in Americas. Why?
- Finally ----> the sexual revolution (both homosexual and all the rest). Haiti - principal resort for homosexuals.

Not the first new virus or newly discovered virus disease to come on the scene (as I shall note) but its appearance ended a long period of misplaced confidence and complacency re: our ability to diagnose and control the infectious diseases.

How complacent we had become is epitomized in a speech given at Hopkins fully 20 years ago by the Surgeon General. He assured his audience that in this country we had effectively probed most

frontiers of knowledge in the infectious disease field, that the remaining problems in this country were marginal and that attention should now turn to the chronic diseases. It is evident now, as it should have been then, that mutation and change are facts of nature, that the world is increasingly interrelated and that human health and survival will be challenged ad infinitum, by new and mutant microbes with unpredictable consequences to human health.

Among the microorganisms, those of greatest concern are the viruses. Why? Microorganisms, much as bacteria, yeasts, parasites and the like, however small and simple, are cells. They contain DNA as the repository of their genetic information. They have their own machinery to produce energy and to synthesize nucleic acid, protein, carbohydrate and lipids. And they multiply by binary fission. Various chemical compounds - antibiotics - can interfere with their metabolism and reproduction and thus cause their destruction. Thus, we moved from sulfas to penicillin to a whole array of antibiotic products. Viruses, on the other hand, are not cells. They are metabolically inert and can only multiply in the cells of the host they parasitize. They are completely dependant upon their cellular hosts for the machinery of protein synthesis and energy production. Some viruses persist in cells by the integration of their DNA with that of the host cell. In brief, the essence of a virus is its fundamental entanglement with the genetic machinery of its host. Attempts to destroy viruses without destroying the cells they inhabit is a formidable challenge. Not surprisingly, we have developed very few antiviral drugs.

The virus's potential for mischief is further heightened by certain other unique properties. Viruses are of two types, either DNA or RNA, and many of the greatest concern are the RNA viruses which includes HIV. These RNA viruses are uniformly small and their genetic material usually codes less than a dozen proteins. They replicate rapidly and, in doing so, occasional mutations occur. Now most plant and animal cells have a so-called "proofreading" mechanism which protects the genetic material from becoming riddled with mutational changes but <u>not</u> the RNA viruses. Approximately once in every 10,000 replications one of the nucleotides is incorrectly copied and replication is rapid. To translate this into concrete terms, one of the RNA viruses was found to have changed 15% of its nucleotides in just three months. However, even comparatively few changes can result in major changes in the character of the virus. An illustration is that of parvovirus infection in dogs - a disease which causes severe diarrhea and inhibits production of white blood cells. The disease, a new one in dogs, emerged in 1978 and within a year had swept across the world. Millions died before a vaccine could be developed and effectively employed. (Note that mutant viruses may travel far more quickly than AIDS has done.) The parvovirus is related to a similar virus in cats, and when the two were compared, they differed in their DNA by less than 1%. Even limited numbers of mutations, if they are the right ones, can have profound consequences.

There is another interesting example of the destructive force of a virus epidemic among mammals - albeit, this time a DNA virus - myxomatosis - which in 1950 was deliberately released in Australia to control the rabbit population. Wild European rabbits had been introduced into Australia by settlers and, with few natural predators, they gradually spread across the country. Grazing land was progressively destroyed, and despite heroic efforts involving thousands of miles of fencing, destruction of rabbit burrows and poisoning, the rabbits could not be contained. In Latin America, a virus had been discovered which caused only small tumors and few deaths in South American wild rabbits but, in Australian and European rabbits it caused extensive tumors and death, usually within five to six days. The virus is transmitted by mosquitoes and flies. In July 1950, rabbits were infected and released at a test site in the Murray Valley in Australia. It appeared briefly to die out when suddenly, at the end of the year, the disease emerged and spread rapidly across the whole of southern Australia in a matter of a few months. Within this stretch of land, the rabbit die off was all but complete in the affected areas. What few remained were killed by the few natural predators available. Not all areas were infected and so rabbits persisted and the disease continued to reoccur and become endemic.

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It has been shown that the rabbits themselves gradually became more resistant and natural selection of virus strains tended to favor those which infected the animals but did not kill them - thus

providing a longer period during which the virus could be transmitted. Thus, both rabbits and viruses were changing under the pressures of this lethal agent. The point, however, is that a new virus can do inestimable damage before adaptation occurs, and note, even after 13 years, more than half the strains killed 70% or more of animals.

Interestingly, in U.S. history, there is a parallel in man - with smallpox virus. Smallpox in Europe in the 1700's and 1800's usually resulted in case fatality rates of about 20% and, eventually, effectively everyone contracted the disease. Without question, it was the most widely prevalent lethal disease - and the most feared. Among North American Indians, however, it behaved more like myxomatosis among Australian rabbits. Records abound of decimation - literally - of whole Indian tribes - of death rates of 90% and, indeed, extinction of some tribes. That settlers had such minimal difficulties in displacing the Indians in North America had less to do either with Indian passivity or settler generosity than it did with smallpox. However, adaptation to a new virus through natural selection takes far longer in humans than in rabbit populations.

Another illustration of the lethal potential of a virus mutation is provided, of course, by the global pandemic of Swine influenza, which occurred in two waves, each of roughly 10 weeks in autumn of 1918 and the spring of 1919. An estimated 20 to 30 million persons died - including in the U.S., 548,000 (11 times the number of U.S. troops killed in WW I). These were not only the

very young and very old - approximately one-third of the cases were young adults. Most died rapidly, within 48 - 72 hours of a hemorrhagic pneumonia. Contrary to common belief, today's antibiotics could have been of little value. One can debate the wisdom of what was done when Swine flu was isolated in a military barracks in New Jersey in the spring of 1976 and when it was found that some 200 soldiers had been infected. This was the first known outbreak of the Swine strain since it had come and vanished 60 years before. And there was added cause for concern. Based on past experience, a late spring introduction of a new influenza virus strain presaged an early autumn epidemic. The time required to adapt the strain to eggs (on which the virus was grown) and to gear up for production is a matter of months, not weeks, and as it turned out, if a major Swine flu epidemic had occurred, as feared, in the early autumn, we would have been seriously short of vaccine despite the heroic efforts made by the producers. Parenthetically and from the perspective of one who at that time was acting director for viral diseases for WHO, the political problems had there been an epidemic would have been explosive, albeit curiously, none appear to have reflected on this. A major lethal epidemic of Swine influenza would immediately have generated a tremendous clamor for vaccine, and with the only available vaccine supply in the U.S., accusations of discrimination against third world countries would have resulted in a political nightmare of recrimination. A new and lethal virus, like it or not, inevitably soon becomes an international problem with all that implies.

I hope I have made the point that new or emerging viruses are not a new phenomenon. They represent a real and present threat and, as we have seen with AIDS as well as during the threatened Swine flu empdemic, we are not well prepared to deal with these problems.

The potential for a new virus to gain a foothold and to multiply is increasingly enhanced by continuing population growth and by urbanization. Third world cities are growing logarithmically; housing is seriously deficient; crowding is unprecedented; sanitary facilities are lacking; and the flow of people to and from remote and rural areas is constant and increasingly facilitated by better transport. The problems potential in this new scenario are well-illustrated by a new entity called dengue hemorrhagic fever. Dengue is one of the RNA viruses transmitted by the aedes mosquito, which breeds best in standing water (pots, cans, old tires) in and around houses. There are few separate dengue virus subtypes. The first infection normally produces typical symptoms of high fever, a mild rash and aching pains - hence, its name "breakbone fever." Subsequent infections with other types, however, may result in hemorrhage, collapse and, sometimes, death. With increasing urbanization and increasing problems of sanitation, dengue epidemics progressively spread across Asia after WW II and occurred with greater frequency. In their wake, came increasing numbers of cases and deaths due to DHF. Until the late 1970's, dengue was seldom seen in the Americas. Aedes aegypti control programs had kept the vector at low levels,

but with increasing populations, control measures began to break down, and dengue returned with large and increasingly frequent epidemics in the Caribbean and, soon, epidemics in Central and South America. The first epidemic of DHF occurred in Cuba in 1981 - 116,000 persons were hospitalized in a three month period. There were 24,000 cases of hemorrhagic disease and 158 deaths. In 1986, more than 100,000 cases were reported from Rio de Janeiro. Last year, 94 cases of dengue were reported among returned travellers in 30 states. And Venezuela last year reported more than 3,000 severe cases with 74 deaths.

For the U.S. it is only a matter of time until outbreaks also occur. Aedes aegypti breeds throughout the southern U.S. and, in August 1985, a newly introduced Asian vector, Aedes albopictus, called the "Asian tiger mosquito" was discovered in Texas. A vigorous search turned up mosquitoes in 12 states including Illinois, Indiana and Ohio. All are partially resistant to organophosphate insecticides. The presence of the vector adds another dimension in that it breeds in more northerly latitudes and breeds in standing water far apart from homes. It is far more difficult to control.

During the 1970's and 1980's, other viruses have emerged - from the rain forest areas have come frequently fatal hemorrhagic virus diseases caused by Marburg, Ebola and Lassa fever. Monkey pox virus infections which clinically resemble smallpox but caused by a different but related virus have been found to occur sporadically in African rain forests and to result in death rates