Health Crises—Their Effects on Science and Technology

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DR. PRINCE: Ladies and gentlemen of The Proprietary Association, Mr. Chairman, Dr. Tempio, and friends and future friends of Gibraltar Laboratories: Thank you very much. And good morning. I have been asked to share with you my views on health crises and their effects on science and technology.

When I was asked to talk about health crises and their effects on science and technology the first thing that occurred to me was the current AIDS crisis, because it threatens to spread throughout the heterosexual community and at present there is no cure.

I believe, however, listening to the remarks today, that I will add as part of my introductory remarks that I firmly believe that in order to successfully meet the health challenges of the present and future we must fully learn from our past experiences. And in my opinion there is a great parallel that exists with respect to influenza A virus. I'd like to begin on that note.

Influenza has caused the most severe health crises known to man. Looking solely at the effects of influenza pandemics in the United States, beginning right around 1918 influenza A virus caused 500,000 deaths. And there has been a history of repeated episodes with comparable devastation throughout the world.

And looking strictly at the impact on the United States, we see that during the period of time from 1918 to approximately 1956 there was a great reduction in the number of lives lost due to influenza A. Approximately 88,000 lives were lost or attributed to influenza A infection in 1956–1957; in 1967 to 1968 there were approximately 8,000 deaths.

And then most recently in 1975 or 1976, I forget the exact year, there was a great deal of alarm with respect to swine flu, and there was a rapid mobilization of efforts to vaccinate the elderly and other people who were thought to be at particular risk. And perhaps because of those mobilization efforts the effect was that only a handful, if any, deaths were attributed to that particular virus.

So in terms of my point about thinking of the AIDS crisis today and remembering from the past, I think it's instructive to identify what factors are responsible for the decline in the death rate attributed to the influenza A virus in the United States.

Well, some may say it's because the virus is less virulent than it once was. And one can't discount that, but I don't think one needs to accept that as the entire truth or the entire answer to the question. For certain the other part of the explanation would be that around World War II and from then on there was the control of

secondary infection because antibiotics became available and people no longer died of complications of influenza.

And that continued to occur for a while and then I guess a plateau was reached in terms of the development of new synthetic antibiotics, with today's effort more or less meeting the challenge of new resistant strains of organisms.

But the parallel in terms of AIDS, is that, like influenza infection, what people are dying from is not AIDS itself but the complicating secondary infections.

And so what comes immediately to our attention is the fact that while the United States and the world have been very successful in the development of agents to treat bacterial infection and other agents such as fungi and Protozoa, there has been scarce success in the area of virology.

And I was asked to talk a little bit about what might be the spin-offs that will occur because of this AIDS epidemic, and I think that it will focus our energies in a productive way to come up with some antiviral agents to complement the few that are already in existence.

To point out the kinds of trends, not to give you absolute numbers because these numbers have increased, we see the rate is increasing throughout the world, as reported by the World Health Organization.

And what about the psychological impact that the fear of AIDS is having on the world in the context of when does one feel confident that there is no chance that they have been infected with the virus? We can see here that 90 percent of the individuals who do develop AIDS develop it within a period of 96 months relative to the time of first infection. And some people are now saying that in order to get 90 percent or 100 percent certainty you have to extend the incubation period to as long as ten years. So that's a very long time to have to deal with that kind of psychological worry and it puts added emphasis on impending strategies designed to prevent infection.

And what has been the approach of the world and what will be the approach of the world? In the area of science in general and in particular we'll talk about virology, it's unfortunately, in my opinion, been mostly a reactive approach. It hasn't been an anticipatory type of approach for whatever reason; and that further, part of the picture in dealing with drug development are the nationalistic tendencies and independent approaches taken by various research entities within the private sector. This approach carries with it understandable profit motives which can limit the full exchange of information and as such will reduce and possibly slow the advancement of knowledge that might lead to therapies or cures or improvements in the situation.

In terms of the average lay person's involvement and what they are able to bring to this situation, there's always been a history, and this remains the case, of great cooperation by the public to do what's asked of them to the best of their ability.

What are the possible outcomes of this HIV-1 crisis? Starting from the most optimistic and perhaps leading down to the most pessimistic:

One: There will be a cure to AIDS. And if someone wanted to pin me down today and say, "Well, where do you stand on this, Prince, of choices one to four?" I would say I think there will be a cure to AIDS. I don't know when, but I think it will be relatively rapid with respect to the history of influenza.

A second possibility, perhaps not as globally attractive a solution, will be that there will be the prevention of new cases. And this is something that the average person is very much able to take part in. Because there's not much risk of getting AIDS unless one happens to be in a certain risk group (homosexuals, I.V. drug users, Haitians, hemophiliacs, those receiving blood transfusions, and possibly occupational exposure to HIV contaminated blood).

Certainly attention to sexual practices I think is the most important area of education that needs to be passed on to our children and ourselves, because sexual transmission of AIDS into the heterosexual community I think is the Number 1 area of concern at present.

Thus, one can, through their own behavior and educational techniques, largely guard against becoming infected by being monogamous and by using condoms.

Casual contact with AIDS patients is acceptable; there is no reason to think that if you're in the room, say in this room someone has the virus, that you're going to pick it up from them. It can't be spread through casual contact.

For example, twins born, one with AIDS, one without AIDS, reared together by the same mother in the same bedroom, sharing baby bottles, etcetera, the one twin who was born with the disease has not given it to the one who didn't have the disease. And that's been eight years.

So there's really not much worry about picking it up from someone who is infected, or at least I don't know about that happening.

The third possibility is the improved chances of survival for those who are infected by treating the symptoms or, more than that, by slowing this progress of the disease. And in this category I would place the agent AZT from Burroughs Wellcome.

And then, number four, the most pessimistic view being that there will be no cure and no vaccine. And my opinion is that vaccination is even a more challenging area than the development of a therapeutic agent.

What's going on now? The approaches taken have been to treat the symptoms, to look into areas of vaccination, and to look into the area of therapeutics.

And now some thoughts on health care into the 21st century. I'm about to talk to you about approaches that are going on right now and that will continue into the 21st century. These mark a new era of modern medicine and perhaps a golden age of modern medicine, as was touched on earlier this morning. These are approaches that have at their heart molecular biology, and I'll start at the top.

Taking advantage of our knowledge of the AIDS virus, it is different from all living things in that it violates the central dogma. It takes RNA to DNA rather DNA to RNA to protein. It does that because it carries with it an enzyme known as reverse transcriptase. And therefore we have a target. We know that we can develop an agent that will wipe out or arrest that enzymatic activity without toxic

fects on a person, because that activity is not part of our human genome or ochemical makeup. And there are other enzymatic activities that are important id intimately associated with the AIDS virus that have no counterpart in man.

And so then these are sophisticated approaches that are being followed, and, I ink, with some success, as we'll go into later. Since the virus can't replicate self, it can't spread, and it will eventually be controlled.

So from mechanisms of molecular biology, learning how RNA is taken to DNA, is information will ultimately allow for experiments that will permit application that knowledge to prevent the spread of the virus.

Nucleotide analogs also fit into this category because it's a strategy intended to event replication of the virus. This is not a new area, it has been around from e '50s; indeed, AZT was discovered many years prior to it being thought of as agent to treat AIDS patients. It works by leading to the production of a "fraud-ent" HIV-1 DNA. The incorporation of it into the viral genome causes mutation id death of the infected cell.

Cytidine analogs and other analogs that carry with them poisons, such as a radio-g or a halogen group, something that would cause a mutation, are approaches at are well known and are being pursued with some success.

And this is actually the basis to a large degree of certain anti-chemotherapeutic gents because the replication of cancer DNA is so much more rapid than the plication of our normal DNA that you feed the rapidly growing cancer DNA the id analogs and it winds up being destroyed in part because of that.

Another very powerful and 21st century approach to modern medicine will be mpetitive inhibitors to, in this case, the CD-4 receptor site.

By being able to pinpoint where a virus attaches and therefore by preventing ral attachment by use of competitive inhibitors, virus infection will be prevented.

I think in terms of therapy we will have a combination of this partial listing of ve things, so there is hope.

If we tend to think of an approach that will not allow the CD-4 receptor site to t as a receptor site but at the same time will allow for the productive workings that immune cell and not be toxic, this is again a theoretical approach.

In my opinion maybe the most exciting and novel and advanced approach of iem all would be what I call the surgical removal of HIV-1 DNA, which is only ecoming possible because of the work done in the '50s by Watson and Crick, who ught us what the genomic material was and how it was composed; and Frederick anger, who taught us how to sequence DNA.

Through the discovery of restriction enzymes and through ongoing efforts to equence the human genome, we will in theory know where precisely the bad DNA . And then through very precise application of restriction analysis or via laser, or mething that maybe has not yet been discovered, we will just clip out that bad NA and re-anneal the "healthy" DNA.

This has applications well beyond AIDS infection. It might be also appropriate think of it for certain genetic defects such as the eye cancer, retinoblastoma,

perhaps muscular dystrophy, and other genetic defects where we have the knowledge of where the bad portion of the genome is.

This approach, I think, will be the first of even more sophisticated approaches that will follow which would later, even after removal, allow us to replace a proper functioning sequence to do what's not being done, and that would be gene therapy.

Well, I spoke of a reactive approach. I can illustrate that by showing in 1985 there were zero known antiviral agents or immunomodulatory agents to treat the AIDS virus. And then in 1986 or thereabouts there was one. And in 1987 I've counted 140 that I think have reached FDA's Phase II status. And I will project for 1988—and my numbers are about one year behind because of the information lag, I would project there'd be about 210.

You may recognize some of these from your companies. Some of these agents are available, have been available for other purposes and would fall into the category of the OTC. Some of them are being sold initially as food additives because of the length of time it takes to get regulatory approval to sell them as AIDS drugs. And that's happening because of pressures to bring something to the market but not wanting to mislead anyone about it. Some you will recognize as old and just being thought of as possibly being applied to HIV, e.g., interleukin.

Learning from the past, Watson and Crick won the Nobel Prize for the discovery of the molecular structure of DNA. And the AIDS virus was discovered by the French and U. S. scientists, to a large part because of Anton van Leeuwenhoek's single-lens microscope that was discovered in 1677.

The single-lens microscope of Anton van Leeuwenhoek allowed Dr. Robert Gallo and the French to recognize these electron photomicrographs made with its most sophisticated offspring, the electron microscope. These types of electron photomicrographs were the first conclusive evidence of AIDS—and at that time it wasn't certain whether AIDS was a transmissible biological agent. These photomicrographs alerted the scientists that they were looking at a retrovirus and that began to focus their inquiry and allowed them to make rapid progress thereafter.

This is a diagrammatic representation of the AIDS virus showing the reverse transcriptase as a purple sphere. The virus depends on it for its life. And because of that, and it knows its not available in the host that it infects, it carries it with its genome, represented here in black. The genome is surrounded by a protein coat, and these outer structures are used to detect HIV-1. The P-24 protein is what is commonly used in the laboratory to identify whether or not the AIDS virus is present in blood.

Antigen detection (P-24) is looking for the actual virus (if systemically present) and is what we use to detect the virus when we're looking at new therapeutics or disinfectants that are meant to destroy the virus. We look for that viral P-24 protein.

There are other HIV-1 proteins that have enzymatic activity such as a translocating factor and regulators that are just becoming understood. These are candidates for new chemotherapeutic agents which would target those specific viral activities. Again there are no known counterparts to these types of activities in man and so

therefore it would be a very attractive specific and theoretically nontoxic avenue to aggressively look into.

These are the immune cells that become infected with the AIDS virus. They grow in large spheres. And we're looking down at a field of cells, and so the focus changes from the top to the bottom. You can see they grow in groups and clusters. An individual cell is about four red dots, if you will, in diameter—unless they're infected with the AIDS virus.

You can see that they swell 10 to 30 times the size of a normal virus. These are not yet as big as ultimately they can become—with the merging of cells into one huge infected cell.

In conclusion, there are certain products that we saw earlier, approximately 143 immunomodulatory or antiviral agents that are currently being investigated as possible treatments to AIDS. Some of these agents employ the most modern thinking in terms of their mechanisms of action. That's a very hopeful thing. Some of them take advantage of the classical knowledge that we have from past experience and try to apply them to the AIDS virus. And that's also a very hopeful thing.

What's on the market now that's being used to assess the progress of these new technologies?

New technologies that were invented for the AIDS virus by DuPont and many other commercial companies offer detection systems—Abbott, DuPont, Coulter, others; not plugging one of them over the other—where they allow you to very rapidly in the laboratory—I refer to P-24—see how much virus is present in the blood or in the Petri dish; very powerful, quantitative, rapid, and relatively inexpensive ways of assessing whether or not the virus is spreading or not or reducing in number. DNA probes, in situ hybridization, IFA are also powerful secondary detection systems that confirm diagnosis and confirm laboratory test results on the presence of the virus.

In conclusion, the AIDS virus is a health crisis that affects us all today. It is a formidable challenge that deserves our attention and planning. I think with proper funding and, not relying upon reactive approaches but thinking with foresight to HIV-2 and Herpes 6 and HTLV-3, etcetera, a great deal of relatively rapid progress can be made in the area of antiviral medicine.

I'm struck by the remarks earlier about the FDA and I think that America and the world needs to put proper emphasis in terms of funding and support to federal agencies so as to allow them to fulfill their statutory objectives and encourage quality people to enter into those fields.

I have just learned two days ago or thereabouts that a Ph.D. scientist trained in molecular biology approached the FDA in West Orange, New Jersey, about a career to become an investigator and was told the starting salary was $13,000 per year. Maybe it could be $16,000 if they considered the Ph.D. years as part of the experience. So there has to be more support and allow the agencies to pay more money to attract the young people and the quality people that they need to do the

I am hopeful about the outcome. I don't think we'll ever approach the 500,000 deaths in one year that happened in 1910 or thereabouts from influenza. But the most direct and immediate thing that we can all do is educate ourselves and educate our loved ones and children and family and friends about what the risks of catching the virus are and to practice preventive medicine.