

Health, Science, and Wealth



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The International Longevity Center–USA (ILC–USA) is a not-for-profit, nonpartisan research, education, and policy organization whose mission is to help individuals and societies address longevity and population aging in positive and productive ways, and highlight older people’s productivity and contributions to their families and society as a whole.

The organization is part of a multinational research and education consortium, which includes centers in the United States, Japan, Great Britain, France, the Dominican Republic, the Netherlands, India, South Africa, and Argentina. These centers work both autonomously and collaboratively to study how greater life expectancy and increased proportions of older people impact nations around the world.

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Introduction

Robert N. Butler, M.D.

When I arrived at the National Institutes of Health in 1955, I became involved in studies relating to various aspects of aging. I worked in the Laboratory of Clinical Science under the guidance of Seymour Kety, who was one of the great founding figures in neuroscience.

My first project was a prototypic longitudinal study of healthy older people who lived in the community, because, believe it or not, up to that time most studies of older persons were conducted in chronic disease populations. Physicians at the time had no way to determine, for example, if an older person's hemoglobin count was normal based on his age.

My second area of study was the dementias. Between 1955 and 1966, my colleagues and I were doing cerebral physiological measurements on institutionalized senile patients who lived in hospital back wards and also on healthy older persons who lived in the community. Out of this study we concluded that what the public called "senility," and what in those days was called "senile psychosis," was not inevitable with age. In fact, these hospitalized people had either Alzheimer's disease or multi-infarct dementia, which means repeated small strokes. At the same time, their counterparts in the community remained vigorous and mentally sound into old age.

By 1975, a variety of studies showed that about half of the more than 1 million people who were in nursing homes in the United States at the time had Alzheimer's. That same year I became the founding director of the National Institute on Aging. Given the large numbers of Americans with this tragic disease, I decided that Alzheimer's must be made a major national research priority. Furthermore, I believed that we had to make

Alzheimer's disease a household name in order to attract both private and public funding.

In the twentieth century there were two notable concurrent events: the growth in numbers of vigorous, healthy, robust older people and the growth of older persons who suffered from myriad very significant neurological conditions, including Parkinson's, Lou Gehrig's disease, and Alzheimer's, as well as problems of hearing, vision, and mobility.

The NIH named the 1990s the "decade of the brain" because of new funding efforts to address a variety of neurological conditions. But I submit that a decade is not long enough for anything as complex as the brain, and the central nervous system requires much more major investment from all of us.

I thought it would be terrific to get together two of my absolutely favorite people, both winners of the Nobel Prize, both supported by the NIA, and both of whom, I am proud to say, are on the board of the ILC. Dr. Robert Fogel developed a wonderfully interesting concept called technophysio evolution that helps explain the nongenetic but biological evolution of longevity. And like Bob Fogel, Dr. Stanley Prusiner is a very brave person, looking at old ideas with a fresh eye. Stan actually took on the dogma that you must have DNA in order to self-assemble or replicate. He discovered the prion—the proteinaceous infectious particle that most of you are familiar with in the context of mad cow disease.

This evening each of these brilliant scholars will speak. Afterward they will engage in an exchange of ideas, and then I will open the discussion to the audience.

Robert Fogel

Nobel Laureate 1993 in Economic Sciences

The period between 1800 and 1950 was a remarkable era for the now-developed countries. In 1800, barely 5 percent of the population of Western Europe and North America was urban, the nations being primarily poor agricultural economies. Life expectancy at birth in the emerging cities was so low that their growth was due mainly to immigration from rural areas or from abroad rather than from natural increase.

As the cities grew, health problems intensified and mortality rates soared. Waste disposal problems outran the ability of authorities to provide pure water and uncontaminated foods. Although scientists and engineers struggled with the problems, solutions did not come quickly. Not only did many false theories have to be disproved, but implementing correct theories was expensive. It required an educated public, more commodious housing, new methods of water purification and delivery, and expensive new technologies that made it possible to cleanse the air of the haze of pulverized horse manure that enveloped cities and provided a rich diet for the dense population of flies. The main new technology that solved the horse problem was, of course, the automobile, which, now that memories of past problems have faded, has been transformed from savior to villain.

Severe and persistent inequality was another problem of urbanization. In the nineteenth and early twentieth centuries, mortality rates varied greatly by district in the large cities. In the worst districts of large American cities, infant death rates averaged about 50 percent in 1890 and 1900. In the best wards the infant death rate was about 8 percent. However, these disparities

declined rapidly during the early decades of the twentieth century. What we now decry as severe differences in infant mortality rates by socioeconomic class in the rich nations are a tiny fraction of what they were a century ago, although it is appropriate and urgent that we seek to eliminate the remaining differences.

Death rates were exceedingly high among the poor during the early nineteenth century, not only in the cities but in the countryside as well. In countries such as Britain and France in the late eighteenth century, food production was so inadequate that the bottom 20 percent of the population was excluded from productive activity. And the next 20 percent had enough energy for only a few hours of light work. Moreover, the majority of those in the active labor force were so stunted and wasted that their capacity for work and the duration of their active working life were quite limited by modern standards. It has been estimated that half of the English growth rate in per capita income between 1790 and 1980 was due to an improvement in nutrition and in human physiology made possible by better nutrition.

Although I am mainly interested in forecasting, I begin with this brief history because forecasting involves history. Forecasting is an extrapolation of past trends into the future. There are, however, many different ways of extrapolating. Which of these many possible forecasts an investigator favors depends upon his or her theories of future economic growth and improvement in health and longevity. I am optimistic about the cost of global economic growth over the next generation or two. The foundation for that optimism is the remarkable

economic growth since the late 1970s in countries in east and south Asia that together represent a population much larger than Europe and the United States put together. These countries, which are growing at three or four times the long-term rates of Europe and America, are likely to overtake the Western nations in total income by 2020 and may equal them in per capita income by 2040. The two largest Asian countries—China and India, which together represent 40 percent of the world’s population—have both been growing quite rapidly since 1980.

The development of the Chinese economy over the past three decades has been particularly impressive—its real per capita income increased at an average annual rate of nearly 8 percent, exceeding the best rates of such previous long-term pacemakers as Japan, Korea, and Singapore. Several factors suggest that China will continue to grow at high rates for at least another generation. One is the very heavy investment China is making in education, not only extending primary and secondary education to almost all of the school-age population, but also its dramatic effort to extend tertiary education. Between 1998 and 2003, students enrolled in four-year colleges increased from 3.4 million to 9 million. There has been a similar increase in college education in India. It is estimated that in the current academic year China will produce 3.3 million college graduates, India 3.1 million, and the United States 1.3 million.

There are two other reasons why China, India, and other high-performing Asian economies are likely to continue to grow at high rates. These countries have large shares of their labor force in agriculture, where labor productivity is low compared to labor productivity in industry and services. Hence about one-third of their projected growth rates can be obtained by shifting labor from agriculture into the sectors with much higher value added per worker. Finally, because these countries are not yet at the global frontier of

technology in any of the three major sectors of the economy, they do not have to advance the global frontier of technology to raise labor productivity within each sector. They can do so by adopting the existing global technology to their own specific conditions. I estimate the long-term growth of the United States to be in excess of its average during the twentieth century, which was about 3.3 percent per annum in GDP or about 2.8 percent in GDP per capita. I expect the U.S. rate of growth to increase because technological change is accelerating.

The scenario for Western Europe is not quite so bright. The fertility rate of the European Union is below reproduction, and the median age will exceed 50 years by 2040. This means that the dependency rate for persons outside of the labor force and divided by persons economically active will rise sharply, doubling in about a generation. Advances in technology will offset much of this rise in the dependency rate or ratio. Nevertheless the European Union will decline economically relative to the United States and the newly industrializing countries of Asia and also of Latin America. Rapid technological change is confined to a tiny fraction of the 200,000 years since the origin of our species.

For most of its existence, *Homo sapiens* lived in small, far-flung hunting-and-gathering communities that teetered on the edge of extinction. It was not until 9,000 years ago that humankind discovered agriculture, which broke the tight constraint on the food supply. However, it took 4,000 years after this discovery for agriculture to supersede hunting and gathering as the main source of food, 5,000 years for the first cities to emerge, 6,000 years to develop writing, and 7,000 years to invent mathematics. Despite these advances, which permitted a more rapid increase in the population than in the past, it was not until 1700 that humans obtained a degree of control over their environment so significant that it set

them apart not only from all other species but also from all previous generations of *Homo sapiens*.

During the past three centuries a remarkable synergism has emerged between technological and physiological improvements, producing a form of human evolution that is biological but not genetic, rapid, culturally transmitted, and not necessarily stable. Dora Costa, who is an economist and biodemographer at MIT, and I, called this process, which is ongoing in both developed and developing countries, *technophysio evolution*. Because of technophysio evolution, human beings have been able to increase their average body size by 50 percent, to increase their average longevity by more than 100 percent and to improve greatly the robustness and capacity of vital organ systems. One aspect of technophysio evolution is the substantial delay in the onset of chronic diseases during the course of the twentieth century. American men ages 60 to 64 in 1994 were two and a half times more likely to be free of chronic diseases than their counterparts a century earlier. Among those who turned age 65 between 1983 and 1992, such chronic diseases as arthritis, heart disease, and respiratory disease began 9 to 17 years later than those who turned age 65 between 1895 and 1910. What is the outlook for the current generation of college students? One leading biodemographer recently estimated they had a 50-50 chance of living to 100. That is a considerably longer life expectancy than is projected by the U.S. Census Bureau, the United Nations, OECD, and other national and international agencies. These official agencies believe that the increase in life expectancy during the twenty-first century will be less than half of what it was in the twentieth century. The same sort of pessimism prevailed at the start of the twentieth century. No authority in 1900 had the slightest inkling that life expectancy at the end of the century would be over 75. Indeed there has been a persistent tendency of authorities to underestimate the potential for increases in longevity.

Many experts today argue that the longevity gains of the twentieth century cannot be replicated because the main cause of death today is from chronic diseases at all ages and not from infectious diseases that were the main killers in the past. However, as already noted, the onset of chronic diseases has been delayed by one to two decades, depending upon the condition. And further delays are likely because those born after 1950 were healthier during their developmental ages than their parents. Moreover the decline in age-specific disabilities among older persons has accelerated in recent years.

Between 1984 and 2000, the rate of decline in age-specific disabilities among Medicare enrollees increased by 50 percent. I expect the decline in chronic conditions and disabilities to continue partly because of the continuing improvement in human physiology and partly because globally we have the economic resources and the inclination to invest heavily in health improvements. In OECD countries, the long-term income elasticity of the demand for health care is about 1.5. Income elasticity is the economist's jargon. What it says with respect to health care is that for every 1 percent increase in income, health care expenditures will increase by 1.5 percent. As for food, for every 1 percent increase in income, food expenditures will increase by only .002 percent. And this elasticity appears to be even higher in China and in other newly industrializing countries, which implies that if economic growth continues at past rates the share of GDP expended on health care could double to 30 percent in the United States' case by 2030 or 2035.

Will such a vast expansion of expenditures on health care pay off? There are reasons to be optimistic here also. Not only has the onset of disabilities been delayed a decade or so, but disabilities once they appear are milder and easier to treat. Technophysio evolution appears to be making us better candidates for evolving medical interventions. Moreover, the outlook for new

and more effective technologies to deal with chronic disabilities is very promising, not only in drug therapies but also in the marriage of biology and microchip technology.

Some people worry about the high cost of health care, which accounts currently for 16 percent of our gross national product. This share, as I mentioned, is likely to double. Can we afford such a large health bill? The answer is yes, because food, clothing, and shelter used to account for 80 percent of household expenditures but now accounts for less than a third, and in another generation will probably fall to a sixth of household

expenditures. Health care expenditures are mostly driven by consumer demand. For every 1 percent increase in income, consumers increase their expenditures on food and clothing by a fraction of 1 percent, but, as I already indicated, they increase their health care expenditures by 1.5 percent. Health care is not a burden. It is a leading sector of the U.S. economy in the twenty-first century, just as railroads were in the nineteenth century, and automobiles and durables—consumer durables based on electricity—were in the first half of the twentieth century. Health care is the economic engine that will drive the entire economy forward during the twenty-first century.

Stanley Prusiner

Nobel Laureate 1997 in Physiology or Medicine

I want to talk about the neurodegenerative diseases, which include Alzheimer's and Parkinson's, ALS or Lou Gehrig's disease, the fronto-temporal dementias typified by Pick's disease, the prion diseases, and then one example of a degenerative disease—Huntington's disease.

6 There are 4 to 5 million people in the United States currently with Alzheimer's disease for whom we can make the diagnosis. We can't say, except retrospectively, how many people have mild cognitive impairment that will eventually progress to Alzheimer's disease. Parkinson's disease afflicts about a million people. These are age-dependent diseases. If you're 60 years old, you have a one in 10,000 possibility of getting Alzheimer's disease; it goes up to about one in 1,000 by age 70, and to one in three by age 85. One in three is a horrible statistic. To avoid being killed by heart disease or cancer and make it to age 85 and then have your chances be one in three is pretty horrible. Dr. Fogel mentioned China, and there is a very interesting statistic from the UN report on population in China. It's estimated that in China in 25 years—2030—there will be 100 million people who are over the age of 80, because there is now an explosive increase in longevity among the Chinese people. So when there are 100 million people over the age of 80, there will be 35 million people in China with Alzheimer's disease and Parkinson's disease. That's equal to the entire population of California, which right now is 34 million. So imagine if everyone in California were demented. I realize people in New York at the Harvard Club think we're all crazy, but imagine if we weren't just crazy but also demented.

What causes these diseases? They are caused by protein-processing defects. It's a huge advance just being able to answer that question. When I began working in this area in the mid-1970s we had no idea what caused any of these diseases. And that's been the big achievement of the last three decades. We now know that all of these diseases are protein-processing diseases. There are different proteins in different diseases. So what is a protein? A protein is a long chain of amino acids. In order for a protein to become an action molecule, like an enzyme, and make a chemical reaction go faster, this long chain has to fold up into a little globular ball. And that is how proteins work. What we've learned is that very often in these diseases the proteins, instead of ending up as a ball, end up as a kind of hammer; then they can't be degraded, and they accumulate in the brain and destroy it.

My own work began in 1974 with a patient who had what I thought was a rare, uninteresting neurologic disease called Creutzfeldt-Jakob disease. It was described in 1920, and we now believe that the patient that Creutzfeldt described did not have the disease. But Jakob described five patients, and, in retrospect, we believe that three of them had the disease. It was one of these diseases in a wastebasket, and it was the first one to kind of edge its way toward the wastebasket, and maybe begin to go over the top before we ever knew that proteins were involved. It was transmitted to apes and monkeys by two scientists working at the NIH—Carleton Gajdusek and Joe Gibbs in 1968. And this transmission study made everyone believe that the disease was caused by a slow-acting virus, a virus like HIV, which could infect, be quiescent for years, and then erupt and kill the animal or human. But in 1982,

after working on this for eight years, it became clear to me that it was unlikely to be a virus, so I called it a “prion.” I am interested in the basic biology of prions. There are parallel studies going on all over the planet on prions, on Alzheimer’s, on Parkinson’s, and the basic biology of these diseases.

Along with the cause of the disease is the need to develop a blood test. I’m not sure how many people are currently doing this, but a lot of people have tried, particularly in Alzheimer’s disease. We need objective evidence that someone will get Alzheimer’s disease in five years or three years or two years before they manifest the problems with their memory. We need the same thing in prions, and we need the same thing in Parkinson’s disease. Why? We need it because at the same time, we need to develop effective drugs that will stop these proteins from being misprocessed, and we need to give the drugs before people have manifested symptoms, because by the time they are symptomatic their brains have half fallen apart, and we don’t know how to put them back together. We dream about stem cells, but each one of these stem cells is going to have to turn into a neuron, and each neuron will have to make thousands of proper connections. It’s going to be a long time until we—not me, but the future generations of biologists—figure out how to make that happen.

In the short term, I would argue the next 50 years, we need effective drugs that stop this protein from misprocessing, because we know what the causes of these diseases are, and we need to diagnose people long before they develop symptoms. When was the last time that an effective drug for any of these diseases was brought to the marketplace? It was 1967, at Brookhaven Laboratory on Long Island, by the neurologist George

Cotzias, who developed L-dopa for Parkinson’s disease. All the other drugs that are advertised very heavily and make lots of money for drug companies don’t do anything important. They might stimulate a patient to temporarily be a little more active, but that’s not important in the bigger scheme of things.

Contrast this with cancer and heart disease. Every week, every month, every year there are major new advances, and economically some company’s worth increases big time when people with colon cancer live three weeks longer. Now that’s important because each advance creates another movement toward a cure. Right now, 80 percent of all childhood cancers are cured. That’s incredible. That wasn’t true 50 years ago, it wasn’t true 30 years ago. I’m jealous of what’s happening in cancer biology and cardiovascular biology.

I hate to say it, because I’m sitting next to an economist, but economics is the key. The NIH budget is about \$30 billion a year. Some 40 percent of that is spent on cancer. I believe one-thirtieth is spent on dementia research. And there is not much philanthropy. Every time I pick up the newspaper and I read about Gates and Buffet, my heart grows heavy. It sinks. I feel like the world is caving in on my head, and I say to myself, “Oh, if one of these guys would just want to move back the frontiers of dementia it would be incredible.” And the biotech industry and the drug industry—they have a problem with these diseases because there are no copycat drugs out there, so they can’t get into it and have a short-term strategy. They have to have a long research horizon, and they don’t like that because economically it doesn’t help them. So my plea is for more research, for more focus on these diseases.

Discussion

Dr. Butler: *Given the reality that there has been so little progress in the world of neurodegenerative diseases, how do you think about the prospects of the continuing capabilities of people, given technophysio evolution?*

Dr. Fogel: One reason that these neurodegenerative diseases are more important is that we have more people living to an age when neurodegeneration is going to be a principal problem. In a way, all the other advances have made it possible for us to start tackling this new frontier. Given the rate at which the population is aging, I think there will be increasing incentive for drug companies and for Congress to allocate money to these areas. If I were in this area of research I wouldn't be satisfied with that answer because I would want the money now. But from a long-term point of view, I don't have any doubt that both the private and the public sectors will get oriented to this thing.

Dr. Butler: *Stan—you've heard Bob Fogel say that without longevity we wouldn't have as many of these neurodegenerative diseases, which of course is true. Do you see an aging factor in the matter of protein misprocessing?*

Dr. Prusiner: I don't really know how to think about this. My simplistic view is that there are lots of mistakes made, and if you live long enough, these mistakes catch up with you. That's a stochastic view of how this all happens. Remember that two-thirds of the people who reach 85 are not demented. They do really well, so there is something different about this one-third of the population. Why are these all age-dependent diseases? Why are they all caused by protein-processing problems? These are the kind of things we

need to understand, and we don't. We don't understand this common thread that underlies all of these diseases, and the mechanisms in each disease are quite different. In the prion disease, the whole protein is taking on a new shape. We know that it can take on one of thousands of shapes, which we didn't know until very recently. In Alzheimer's disease, we know that a small piece of a protein is cut out and that piece of protein accumulates in the plaques. But, in fact, we think that the plaque is just a wastebasket; it's a reservoir, a way of taking care of most of this small peptide of 42 amino acids, and it's the peptides that are not in the plaque that are doing the damage to the brain. So it's different in each of these diseases. In Alzheimer's disease this peptide seems to be at the surface, and it also seems to be in the extracellular space. In Parkinson's disease, the protein accumulates in the very interior of the neurons, in what are called Lewy bodies. There is a common form that mimics Alzheimer's disease in many ways called Lewy body dementia. The same protein is accumulating in the *substantia nigra* and causing all these movement problems with Parkinson's disease, or it can exist throughout the brain in many different neurons and you can lose your intellect. So I'm not sure that's a very good answer to your question. The real answer is—I don't know.

Dr. Butler: *What is your own sense—I mean, you emphasize the pharmaceutical industry, but in many ways basic science has to precede that, and undifferentiated research has been the hallmark of the NIH. And then you move from undifferentiated research in the most ideal sense—as young scientists used to think that way—to the point that it might move toward expediting drug development.*

Dr. Prusiner: I think that the NIH now is beginning to think that the economics at the first level for drug development is not very favorable to these companies. They just feel too much pressure to make money and spend as little as possible. So there's a big movement to set up large drug-screening centers around the United States, paid for by the NIH. The problem is not the screening, it's not the robotics, it's not the chemical compounds and these immense libraries—we now have on the planet about 3 million different compounds we can test. The big problem is the drug targets. So in order to have effective screening, you need to have wonderful targets. And targets come out of basic research—they don't just fall out of thin air. The discoveries in basic research have to be modified and remodified until they can function as a target in a screening system where you can screen 10,000 compounds a week by robotics. It's very complicated. And I'm not sure it's as simple as, "Okay, we'll fill up the basic science reservoir and then it will kind of spill over, and the drug companies will take it as it spills over and they'll find the magic drugs." It's a little bit easier for instance with cancer because you can take cancer cells and grow them in little tiny wells, and you can do incredible screening that way. There you have really almost the whole disease in many respects, along with all the wonderful genetics that can be done now. In most cancers you can get the tissue out of people because the surgeons are very active, and removing the tumor is a positive therapeutic. We don't do anything about removing pieces of the brain because we compromise the function of people, so we don't have access to this tissue. We have to be much more inventive, much more—I don't know the right word—all-knowing, clever. We have to be very clever about how we construct these screens.

Dr. Butler: *Since we have a public audience, a few doctors, standing back now and thinking of the Human Genome Project and its work and the step from genomics to proteomics—was that a useful investment?*

Dr. Prusiner: Oh, I think that was a great investment, really a great investment, because we now know that so many of these diseases can be modified by genetics. Now we—meaning Allen D. Roses and his colleagues—didn't find out about apolipoprotein E3 through the Human Genome Project. But it's an example of what's going to come. What we're talking about is that the age of onset of Alzheimer's disease can be predicted depending upon what is called the allele. There are three different types of this apolipoprotein E that we have in many tissues, including in our brains: There's a really bad form, and you get Alzheimer's disease in your sixties; an intermediate form, and it happens in your seventies; and a good form, and it happens in your eighties—if you are one of the one in three who is unlucky enough to get the disease.

Audience Query: *I have a true layman's question. Isn't there a way to extract from the brain, without damage, a sample protein that can be used for the screening you're talking about?*

Dr. Prusiner: Well, not from a human brain. We don't take tissue from people's brains and experiment on it. We sometimes do brain biopsies, but that's very rare and that's when we think that there may be a therapy for a disease. So let's say that we're really confused and we can't decide whether it's Creutzfeldt-Jakob disease, Alzheimer's disease, fronto-temporal dementia, or a herpes infection in the brain. Then we might do a biopsy because if we can establish that it's a herpes infection, we can treat it with acyclovir. That's the only time we do biopsies on people. Now we have many, many clever models for these diseases in genetically engineered mice, so this is a huge advance. But one of the big problems is that only in the prion diseases do we have perfect animal models. And that's not because I'm more clever than other people or that other people working in prion diseases are more clever. It's because animals get prion diseases like mad cow disease, so we have in these genetically engineered mice perfect

models of a human prion disease, perfect models of a bovine prion disease. But in Alzheimer's disease, yes, we have models that recapitulate many aspects of Alzheimer's disease, but we have no perfect model, and the mouse is really only the second level of screening. The primary level of screening for effective drugs—effective compounds that turn into drugs—has to be in little wells. So we have to have cells that are getting sick, getting Alzheimer's disease, and we have to have other wells where we can have pure proteins and see what's binding under different conditions. These are the kinds of screens we can do, but lacking these perfect models is really problematic in these diseases. Let's say that we know the proteins in Alzheimer's disease, and we come up with what we think is a blockbuster drug, and we've done all kinds of chemical studies. So we've optimized this drug, and we've done this optimization through how it binds to the Alzheimer's peptide of 42 amino acids. Now we want to know where to go, what to do. Well, the next thing people want to do is to go into genetically engineered mice, but the problem is we don't know which one of these models is the best, and none of them is perfect, and what do we do with this information? So one of the next things that happens is we end up going into people. We end up with these large numbers of clinical trials, and they tend not to be extremely well constructed because we have all kinds of problems with these drugs. I mean, we do all the toxicity studies that the FDA requires and that they should require, but then we really don't quite know how to give these drugs because we don't have a really great animal system on which we can make all these explorations and do this enormous matrix the size of this room of all the conditions. So that's what we're up against.

***Audience query:** There's a lot of discussion about the role of the growth of Asia and the international economies, yet when we talk about drug development it is very U.S.-centric—the NIH, etc. And I was just kind of curious to get your view. Are we going to get*

leadership from companies, governments, etc., outside the United States over the next 10 to 20 years?

Particularly in the context of some of those countries having more tolerant views of stem cell research, and some of them have a lot fewer lawyers than we do in the United States. What do you think happens?

Dr. Fogel: So far they haven't. So far the Chinese are working off of American and Western European technology, and one of the contributions we make is that an awful lot of Western science is given away free to the rest of the world. I'm not talking about proprietary medicine. There are no companies currently on the horizon in China that are likely to challenge America in pharmaceuticals. Whether or not they will develop in the future I don't know. It's probably not a good strategy for the Chinese to try to get into that area because they can buy these drugs here, and they have a comparative advantage in other fields.

What about in India?

Dr. Fogel: I don't know enough about India. I don't know enough about their pharmaceutical industry. They certainly have some outstanding medicine.

***Audience Query:** If health care is the driver of that economic growth in the next 10 or 20 years, when are you saying they are not going to be the source of that? What does that say about some of your prior comments, you know, economic leadership?*

Dr. Fogel: China is getting rich by duplicating existing old technology in the United States. One of the main driving forces of the economy in China is the automobile. That's not a new technology, even though we tweak it a little every year. They are doing a lot with cell phones. But they're basically replicating models developed in the West. You can get a Motorola telephone in China—you can get a Buick in Shanghai at about half the price that you can buy it in Detroit. And two years ago I was driving around in it and I thought

it felt like a Mercedes. It was a better car than the Detroit Buick. So those are the things that they are accelerating in. Whether they're going to do something with stem cell research because they don't have the political hurdles that we have I don't know. There has been some talk of it, but do you know what's happening by way of investment in that area?

Dr. Prusiner: I don't know. I was in China in June, but I don't really have a perspective of stem cell research in China. I mean, I think that we are going to see stem cell research just blossom in this country, and it will—it's going to grow and grow and grow. At some point the court challenges to, for instance, the California \$3 billion bond issue will be overturned and that will explode and then the whole thing will take off. Or it will happen in another state. I think it's going to happen here. It's also happening in Europe. Despite the decline in Europe, there's a lot of stem cell research there. So I think it's going to go on all over the world, but I agree with Dr. Fogel that at the moment China is in this copying mode. And probably that's what they have to be in.

Audience Query: Stem cell research—I just wonder what you thought if we had use of government-sponsored stem cell research in this country, would that accelerate the chance of having a final cure for Alzheimer's or Parkinson's or any of the others?

Dr. Prusiner: I think that we need to push stem cell research. The potential is enormous. And we don't know when a cure is going to come. One thing about science is that you can never predict. You can get all these wonderful sages of science sitting around a table, and you ask them what the future holds, and they all—their faces all go blank because they don't know. Nobody knows. I can sit here and tell you that it will be 50 years before we know how to make all the connections that are going to be necessary to even deal with Parkinson's disease. But you know, next month

somebody could publish a paper that melts the tip of the iceberg, and the whole thing just dissolves, and five years from now we've cured the disease. If you look at today's paper there's a very interesting, well-written article by Denise Grady on diabetes and stem cells. There have been trials—I think everybody agrees that the most likely disease to be conquered first by stem cells is diabetes—and unfortunately these trials have been very disappointing with juvenile diabetics, but we could in a year read something totally different.

Audience Query: The one concern that I have about, for example, China and the world in general is water. The distribution of water. The amount of fresh water. The elevation of the seas, global warming. And I wonder if first, Bob, you would comment about any concerns you have about limitations on this technophysio evolution that global warming and its consequences might have. And, Stan, for you, although I'm a neurologist and work on Alzheimer's disease, I endorse a lot of what you were saying, but 10 million children die a year of preventable diseases—and so we have another responsibility at the other end of the life span. There's evidence, for example, that lead, which we've known for years damages children's brains, may even in animals promote later deposition of amyloids. So in the midst of a genetic revolution there is also the potential consequence that we are doing harm to all of ourselves, including our children, due to an increasing number of environmental toxins. My question to you both is how in a world in which our environment, I think it is fair to say, is becoming increasingly altered, that tempers if at all your optimism about the future?

Dr. Fogel: Well, we've always had problems—we can look at every decade of the nineteenth and twentieth centuries and run into problems that seem to imperil society but we have found the solutions to them. In the case of water, it's not an issue of do we have enough water. It's that the cost of getting good water may rise, so that the share of expenditure on water in total

expenditures may go up. But we can desalinate the ocean or parts of it. No country has tried to do that, including countries that have more severe problems with water than we do, because there are cheaper solutions to it. So as an economist, I think the only issue is will we get technologies fast enough that keep the price of water low, almost free—except if you have a luxurious taste and like to buy Evian.

Dr. Butler: *Stan, do you want to add something?*

Dr. Prusiner: I view this a little differently. I think that, yes, the environment is critical, and, yes, we need to take care of the environment, and we need to deal with all these issues of toxins. But this is a political issue, not a scientific issue. We have identified a large number of these toxins. Second thing that's not a scientific issue, except in China, is birth control. The population of the planet is already too high in many places, and we need to do something about this. There is a wonderful book that Dr. Fogel published a couple of years ago now, and he shows a graph of the world's population going like this—if we end up with 12 billion people on this planet, which is one more doubling, I think we are in big, big trouble. And that to me is at the root of so much of this. Now that's the other end of the problem. The end I have been focusing on tonight of course is in older people. But at the other end it seems to me that the very basic issue is birth control. It's not childhood diseases, it's not toxins—it's birth control. And the rest of this will solve itself.

Audience Query: *You talk about one day there will be a blood test to diagnose these diseases when we reach our eighties, but isn't there some predictive qualities in DNA? I have read, for example, in women who may have a tendency to have breast cancer that you can have a test. Are there no tests with DNA now where you can see who is going to have Parkinson's or Alzheimer's or what have you? Does that not exist yet in a blood test?*

Dr. Prusiner: About 10 percent of people with Alzheimer's, Parkinson's, ALS, the fronto-temporal dementias, and prion diseases have a familial disorder, so in those cases, yes, DNA is terrific. But DNA won't tell us at what age to treat these people. Only in Huntington's disease do we think we can predict relatively accurately, within a decade, when somebody is going to have the onset of the disease. And that is because with Huntington's disease you have what are called expanded glutamine repeats, and the longer the repeat the earlier you get the disease; the smaller the expansion, the later you get the disease. Huntington's disease is always a genetic disease. So we're talking about a different issue there. It really comes back to the same issue—that this is a protein-processing problem, and so in these diseases we have to be looking at the misprocessed form of the protein. DNA doesn't help us with Alzheimer's, Parkinson's, ALS, the fronto-temporal dementias, the prion diseases. In 90 percent of cases, these are not genetic, and when we do the sequencing of the genes that are involved, what we find is that they are all wild type or normal, meaning there's no change, there's no mutation.

Audience Query: *So we are overwhelmed—all of these things that are going to descend on us. Is there any prevention rather than a cure, which is a wonderful idea?*

Dr. Prusiner: So if this were *Wall Street Week*, it would be what is the tip for the best stock, right? And he would be giving that, even though he doesn't believe in the financial markets for himself, and now you want me to give you the tip about which vitamins to take to prevent your brain from dementing, and the answer is that none of that garbage does anything except make the people who make it a lot of money.

Audience Query: There's a red wine cure?

Dr. Prusiner: Yes, they fed some mice red wine and that was two days ago and published a report that the Alzheimer's model in these mice did better if they drank red wine. Was there a control? I didn't see the paper. White wine?

Audience Query: We talked briefly before the dinner today, and you said in your presentation before all of us that to really tackle these issues you have to be clever. You can't go into a brain, take a bunch of tissue, you can't check for their DNA. I'm assuming you are being clever, and so I was hoping you could tell us what you are doing when you can't do these things. What's the alternative?

Dr. Prusiner: You can take DNA. You can take blood—white blood cells have DNA. You can take scrapings from the mouth, so, yes, you can get the DNA. You can study the DNA, so the prion diseases are a little easier than Alzheimer's or Parkinson's or Pick's. We've been able actually to make synthetic prions in the test tube, and we are using that as one screen for drugs to either prevent the prions from forming in the test tube or making them fall apart. Then we have cultured cells, and they're infected with prions, so we can study either the accelerated clearance of those prions or the prevention of new prions from being formed. The third way we can study this, after it passes these two sets of tests, is to go into these perfectly genetically engineered mice because as I said prion diseases are also animal diseases. So in Alzheimer's and Parkinson's and ALS we have to be more clever. And we have to figure out parallels to what I have just said, but we have no perfect cell model for Alzheimer's—we don't even have a perfect mouse for Alzheimer's. There has been a lot of screening using the various proteins of each one of these diseases, in different forms, but to date we haven't been able to find the right effective drug so we can take that instead of the vitamins.

Audience Query : I was wondering what you think is more likely to come along first, a treatment that could possibly reverse some of the damage in a patient who already has Alzheimer's or a vaccine or some such that might prevent Alzheimer's from developing—which, if either, one of those is even possible, and what are the biggest challenges for both approaches?

Dr. Prusiner: I think that the drug that will prevent the progression of Alzheimer's will show up first. And we may be able to administer the drug to asymptomatic people if we have the right test. It may be that we don't have the test but they have some small memory deficit that brings them to the physician and identifies them as a candidate for the drug. I think that's the most likely first line of therapy that will be developed. Restoring brain function is extraordinarily difficult. That's going to require something like stem cells to replace those neurons that have died off. It may be that some of the deficits can be reversed because the cells are still there. They're malfunctioning because of the misprocessed protein that is accumulating—it gets cleared out, and some of the functions of the cells are restored. That's a possibility.

Audience Query: If you're looking for something that can prevent the progression of the disease, particularly in asymptomatic patients, and if you don't have good animal models, or perfect animal models, how do you design a clinical trial that would be practical?

Dr. Prusiner: Well, you don't do it that way. What you do in these clinical trials is you take patients with Alzheimer's disease and you measure its progression. Can you stop the progression? In the first approximation, you take people generally who are severely demented and you give them these drugs—that's how most of these Alzheimer's trials work—one drug or a combination of two, and you see whether they progress. That would be the first clue that the drug was working, when they didn't progress, and then you

would use this drug on less symptomatic people, earlier-stage people, and just go backward. You couldn't use it on asymptomatic people until you had a test.

Audience Query: *We got this beautiful report from the ILC about shortgeivity and how some populations in the world are experiencing decreasing life expectancy, and I want to ask Dr. Fogel and also you what you think about the pessimistic speculation that the obesity epidemic in the United States leading to great increase in diabetes might actually shorten life span, at least for some significant segment of the population here in the United States.*

Dr. Fogel: I think that the obesity epidemic is going to increase chronic diseases, including diabetes for some people, but that's only one of the tendencies at work. Most of the tendencies are things that are alleviating chronic diseases or putting off the age of onset. There has been a lot of discussion on this issue, so it's not an issue that's just discovered. I think the weight of the evidence is that although obesity is a thing that's interfering with further improvements, it's not strong enough to overwhelm the other positive developments that are under way. You know, there's also a literal uncertainty about what the ideal body mass index is. When people speak of weight they use the body mass index, which standardizes for size. The original thought was that the BMI that would minimize health problems was between 20 and 25. There is now some evidence that what is called overweight may actually be healthier than the lower BMIs, so in my own work, in the bodies of data that I've been looking at, the ideal BMI varies with stature. If you're a 6 foot 3 inch male, the ideal BMI is about 22, and if you're 5 foot 6, the ideal BMI is 126, so it looks like lean body mass may be the underlying factor.

Audience Query: *What would you project in terms of the impact of obesity and diabetes on the rate of Alzheimer's disease and some of the other neurodegenerative disorders?*

Dr. Prusiner: I don't have a clue. I really don't. I'm not being facetious—I really don't know. There are things called vascular dementias, and some of the same risk factors for coronary artery disease are involved in those. Vascular dementias are fairly common in older people. I don't really know of any profound interactions of body mass and Parkinson's disease and Alzheimer's disease. I don't think we have any clear data that they are connected.

Audience Query: *We in geriatrics really decry the small amount of money that's spent on research, basic research, clinical research, etc. Do either of you or both of you think that money and dollars will make a big difference? If we were able to allocate the same amount of money that we allocate to heart disease research, breast cancer research, and cancer research to looking at neurodegenerative diseases, do you think that alone, or in combination with getting a lot of people into the area, given the other barriers such as not having access to tissue per se, would make a huge difference?*

Dr. Prusiner: From my point of view, the answer is absolutely. There's no better example of this than AIDS. You put a ton of money into AIDS, you get a huge number of people working in AIDS, and you end up with some pretty spectacular therapies in a pretty short time for a disease that is really quite complicated and a virus that is not immune yet to a vaccine—we don't know how to produce one because the virus is always changing its colors. You know, it's all about money. You put a lot of money into an area for a long time and you see the migration of established scientists, which means the migration of their students, their students see careers for themselves, and their students go into this area. It's all about the number of people in the area. It's like book sales. Ten percent of the people will make 90 percent of the discoveries. But if you don't have this huge base, you can't predict who this 10 percent is. Because they can't predict, they can't

self-select. So many people go into science, and they want to be successful, everybody does, and they start out all excited, and not very many have good luck. You need a reasonable brain and lots of good luck. And you can't decide who in advance is going to make these discoveries. So it's all about money—all economics.

Dr. Butler: I just would like to say a few words to wrap up this wonderful evening. In 1975, when I became founding director of the National Institute on Aging, I began to look at the issue of Alzheimer's disease. I personally counted the number of grants that were devoted to that condition. Twelve. They averaged \$60,000 each—a little over \$700,000. And that, by the way, included all aspects of brain aging, not just Alzheimer's disease. Since that time, although we still do not have a solution to Alzheimer's disease, we know so much more about the underlying pathology than ever.

But notwithstanding these advances, and despite President George Bush's designation of the years 1990–2000 as the decade of the brain, funding for brain research has lagged behind research on other organs. I continue to believe that there is some kind of

conspiracy against the brain. My sense is that this is as good a time as any to speak up and say that a decade of the brain isn't nearly long enough. It is time for a century of the brain, and even that might not be enough. And as you all know, nothing happens without funds. But consider this: When budgets are tight and situations are considered difficult, if not impossible, which is the situation some would argue exists today, historically our country has reached beyond itself to create institutions of enduring benefit to its citizens. Take for example the Cancer Institute, which was created in 1936 in the depths of the Great Depression. Just imagine—it was in the middle of the Depression, when a number of senators, among them the legendary Claude Pepper, argued that we should be doing something about cancer. We need to devote new and fresh resources, because if we are going to live longer we certainly want to have quality of life. Tonight's speakers, at least from my point of view, helped spell out both the history, as Bob Fogel described it, beginning with the 1800s, and the possibilities for the future role of scientific discovery that Stan Prusiner brought graphically to us as we begin to better understand the role of proteins in health and disease.

About the Authors

Robert William Fogel, Ph.D., is the Charles R. Walgreen Distinguished Service Professor of American Institutions at the Graduate School of Business at the University of Chicago, the director of the Center for Population Economics at the University of Chicago, and a research associate at the National Bureau for Economic Research. In 1993, he received the Nobel Prize in Economic Sciences (with Douglass C. North). His current research interests include the study of early life indicators of health in older ages and the developing economies of Asia.

Stanley B. Prusiner, M.D., is director of the Institute for Neurodegenerative Diseases and professor of neurology and biochemistry at the University of California, San Francisco, where he has worked since 1972. From 1969–72, he served in the U.S. Public Health Service at the National Institutes of Health. Dr. Prusiner is editor of 12 books and author of more than 350 research articles. He was awarded the Nobel Prize in Physiology or Medicine in 1997 for his groundbreaking discovery of a new class of disease-causing agents called prions, the infectious proteins responsible for bovine spongiform encephalopathy (mad cow disease) and its human equivalent, Creutzfeldt-Jakob disease.

The Age Boom Academy is an intensive weeklong seminar designed to deepen journalists' understanding of the unprecedented increase in average life expectancy known as the longevity revolution. Funded by a grant from The New York Times Company Foundation and conducted by the International Longevity Center-USA, Academy sessions are based at the ILC-USA's headquarters in New York City. More than 100 journalists from a variety of major national media outlets have attended the Academy since it began in 2000.

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