The Chairman. Thank you.

Josh Lederberg, we are delighted to have you back here before our Committee. We have always welcomed your comments. We look forward to them today.

Dr. Lederberg. Thank you, Senator Kennedy.

The Chairman. I want to recognize Senator Harkin who is a new member of our Committee who has joined us now here at the hearing. We are delighted to have Senator Harkin. He has always demonstrated great interest in health care in the past, particularly health care in the rural areas and agricultural communities of this country. He has always been helpful.

Dr. Lederberg. I am very privileged to have an opportunity to respond to your leadership and that of your Committee in undertaking a very statesman-like overview of our overall problems in health.

As you have indicated, there are three main pillars to support our health goals: access to care, prevention and research. It is my task to say something about the research part of that.

If you had three or four hours, I would enjoy an opportunity to tell you some of the highlights of the wonderful and exciting advances in medical science over the last decade that really are starting to bear fruit. A lot of were signing a lot of promissory notes over the last

couple of decades about what the new insights into the biochemistry of the cell and the area that we called molecular biology were going to do for us. Those promissory notes are being paid off.

Every day in the press we see accounts of new diagnostic or new therapeutic procedures, of new materials coming out of biotechnology, of very exciting new insights about every aspect of human physiology and of human health. I just do not have time to go into that kind of detail at this point.

I would like to say that health research is informed by a sense of strategy. It is not always as clearly articulated as one might like. We have a multi-dimensional matrix of concerns that guide the allocation of resources and the time and attention that individual investigators will be providing for the various kinds of problems.

We have already had some review of the public health challenge, and we have objective statistics on the elements of mortality and morbidity that tell us where some of our priorities are. Heart disease is our major killer, but cancer comes next to that. And those killer diseases do, as they should, occupy a very substantial part of our concern and our research efforts.

We cannot confine ourselves to those killers. There are many other ills that do not have such high mortality,

but make life so miserable as to be hardly worth living. The deterioration of joints, body tissues that seem to go along with aging, the deterioration of mental functions, loss of capability, those are things that have to be attended to as well.

We have enormous human misery that comes out of psychiatric and behavioral disorders: schizophrenia, depression of various varieties. We have an epidemic today of anorexia and bulimia, particularly among the young women. And we have all the problems of substance abuse that have been mentioned very eloquently before. Those all require close attention to the fundamental knowledge that is needed to find amelioration.

We have problems with the newborn. We have the major anomalies, the major birth defects that are all too prevalent, and we have a universe of ignorance about the very subtle impact of prenatal damage, the disease during pregnancy, the effects of nutrition and of toxins, and even the circumstances of delivery, whether our children are born with all of the potential that they deserve.

Besides the outlook that is given us by the public health challenge, we also have to know about the scientific opportunity. It would be very gratifying if we could respond to these challenges one by one, know exactly what it is that we need to learn and what we need to do in order to

respond to each of these conditions. The fact is we are still too ignorant to know how to proceed along those lines.

If we are to pursue the problems of psychiatric disorder, it is not enough to look at the behavior of schizophrenic patients or to try chemicals at random to see which are going to improve their behavior. We have to understand the fundamentals of how the brain is organized, how the neuronal system works, and we are often very much guessing in the dark and playing very long hunches in trying to understand exactly what it is that goes wrong in particular manifestations of disease.

To do all of these things, we need new analytical approaches that can tell us what it is that is going on within the cell, at the boundary of the synapses between nerves and other elements of biochemical analysis.

Then, of course, we have limited resources, limited not only in funds from year to year but in the larger institutional framework in which research is to be done. We have limitations of facilities. We have the need to sustain those institutions that have dedicated themselves to all the problems connected with health. And above all, we have to have those skilled and educated people who need to be trained and need to be motivated and need to be sustained so that they can devote their career to these problems. And those resources cannot be turned on and off with a given

year's budget.

And then, finally, we have to recognize that all of this research operates within certain inevitable, necessary restraints. Some diseases are going to be solved much more slowly than otherwise, simply because they are rooted deep within the human organism, and we have limited opportunity of access to them.

Alzheimer's disease is a very tough nut to crack because we simply do not have a way to take biopsies of the human brain at different stages of the development of the disease in order to look closely at what is going on in a given patient. And we do not have an animal model.

When animal models are available, we are under increasing constraints. They come about concern for animal welfare, those concerns that I share. Of course, in order to deal with them, we also have to have the funds to provide the facilities, and those are not always available in the same measure as the complaints about the way in which animals are being dealt with for experimental purposes.

Then I would like to turn to some of the elements of scientific opportunity, and I would like to stress what has become the mainstream of biomedical research in the last several decades, which happens also to have been the center of my own career which is in the area of molecular biology. That is perhaps a slightly less formidable phrase than to

talk about deoxyribonucleic acid, but I think even that needs a little bit of explanation.

What we have found during that interval is that the basic blueprints of the cell can now be understood in very accurate chemical terms. The chemical involved is the deoxyribonucleic acid, DNA. We have learned the code; we have learned the way in which the messages of the blueprint are stored within the cell, how they are replicated as the cells divide, how they are expressed in instructing the cell to produce various kinds of proteins.

This, in turn, has spawned a new biotechnology, and this is what we are reading about in the papers every day: the production of powerful physiological agents not otherwise available. We have on the market today a pituitary growth hormone, tissue plasminogen activator, which is a very exciting approach to dealing with blood clots. We have the interferons and the interleukins which are under trial with various kinds of immunological disorders, virus infections and for cancer, and the enzymes. And many new vaccines which could not have been feasibly produced by any other means are coming available through the new biotechnology.

We have had something approaching a national emergency in the health field in the last few years with the emergence and alarming spread of the disease AIDS. Five years ago, we

were not even sure what it was. In a remarkably short time, with the mobilization of resources that the basic research for preceding decades alone has enabled--we have been able to discover that this is a virus disease, learned a great deal about the nature of that virus, to learn a little bit greatly constrained by fundamental knowledge of exactly how it impairs gene function.

Unfortunately, most of the news we get is bad news, but at least it is accurate in terms of what it is that we have to face as a challenge in dealing with this virus.

Fifteen years ago, had this emerged at that time, we would have been substantially helpless in even comprehending the nature of the challenge. We would not have had the basic tools for laboratory investigation to allow the isolation of the virus, its characterization, what its effect is on various kinds of cells. I know you are having separate hearings on that particular subject, so I will not elaborate.

An important set of the DNA in the cell has to do with the inborne potentiality within cells to become cancerous. These bits of DNA that are related to cancer are called oncogenes. We have come to recognize that oncogenes can be brought into the cell, can be activated by becoming part of viral agents that can be transmitted from organism to organism. But the more important function of oncogenes in

research today is the understand that they give us of cancers that are not of viral origin but are of endogenous origin, where oncogene, related bits of DNA, in the normal cell can be activated either by chemical irritants that come from outside or by physiological changes or by radiation, and then take over and result in the non-regulation of these cells where they can become cancerous and a threat to the overall organism.

We have seen the isolation of a couple of dozen of these specialized bits of DNA that provide the potential for cancer. They have really given us our first substantial clue as to what cancer really is. And from the tracing of the pathway from the change of the DNA of ultimate origin of cancer to the nature of the change of the gene products within the cell really is our most substantial hope of trying to find fundamental therapies and a fundamental understanding of what is needed for the prevention of cancer.

3/1 If there is one biological concept that has emerged in the last five years, it is the concept of receptors. We have understood that for the cells of the body to be able to function as an organism, to function as a well-regulated society, that they have to have ways of signaling one another, or providing outputs from cells that would determine what the state of the organism was and providing

receptors that would be responsive to those inputs.

Receptors used to be a rather vague philosophical concept. They have become very, very material. Receptors are proteins that are responsive to specific chemical signals, that have very definite chemical structure. There are probably dozens, if not hundreds, of different kinds of receptors on different cells of the body, and we are now starting to isolate them. We can actually isolate them as chemical entities only because of the availability of the techniques of molecular biology, the biotechnology mentioned a little while ago.

Receptors have to do with everything in well-ordered bodily functions, whether it is blood pressure or the rate at which cholesterol is taken up, or whether the growth of cells is involved in cancer, or the stimulation of the immune system, or the transmission of the nerve impulse from one cell to another, or the state of activation within the brain, or how viruses infect cells.

The isolation of receptors has probably had the most immediate impact on the way we think about pharmacological intervention and, in a very practical way, in the development of a whole slew of new drugs. Ten years ago, if you had asked me about the realities of new pharmaceutical development, I would have said, well, the future is going to bring about some change, but if you actually look at the

list of what is in the Pharmacopoeia, the new entries of that year, they were all produced by hit-and-miss methods, by the very old-fashioned techniques of trial and error.

Just within this last decade, the weight of progress, the advantage has shifted just in the other direction, and every important new drug that has come out in the last five years has come out from an understanding of receptors and looking for specific agents that can either inhibit them or stimulate them.

This applies to the drugs like Somitadine--

The Chairman. Can I just on that point, Doctor?

Dr. Lederberg. Sir?

The Chairman. Does that argue for more targeted research or less, or does it relate to that or not? If you are getting most of the breakthroughs as a result of just the broadest kind of basic research, and now that you are talking about the changes in terms of the biomedical research, does that say anything to whether there ought to be a greater kind of targeting or not? I am just interested in what you think.

Dr. Lederberg. Well, we have an opportunity to target that simply did not exist awhile ago. So that if there is a given investigator or pharmaceutical laboratory that wants to go after drugs that are related to lowering blood pressure, well, we have at least some inkling of what

systems in the body have to be influenced in order to be able to have that done.

The Chairman. That has changed significantly, has it not, in the period of the last ten years?

Dr. Lederberg. It has changed dramatically in this last decade, and it is working. You do not have to instruct people to target if the opportunity exists to solve a real live problem out there. Our whole system is geared up to try to maximize that opportunity.

The pharmaceutical industry has primary responsibility for that. Its work rests on what comes out of the basic research laboratories, but there really is no problem of knowledge transfer or technology transfer. They are eager to find every opportunity to exploit these kinds of opportunities.

Well, besides these developments in receptors, the notion has emerged that we can now count--what is the fundamental complexity of the human cell> There are three billion units of DNA in every cell of your and my body. If you stretch that out, it would be two meters long. The DNA is so thin and so tightly coiled up that that string of two meters' length, as high as you and I are, gets wound up into a little body that is less than a thousandth of an inch in diameter. But therein is the fundamental information of what it is that allows us to be human.

About 99 percent of that DNA, fortunately for research purposes, is probably essentially inactive, as ballast or some structural material. So the essential component of that total DNA is only about 30 million units long. That will encode for about a hundred thousand different gene products. In order to know the architecture of the human cell, we will have to know about a hundred thousand different building blocks. At the present time, about 300 or perhaps 500 of them have been characterized to some degree. So we have got a long, long way to go in order to fulfill that objective.

It has been suggested that we go after mapping the entire human genome and just get on with it and move from that 500 to that hundred thousand, move from the one million nucleic acid units that have been so far described and get the whole three billion of them and so forth.

As an overall objective, I would subscribe to it. I think we might do better to organize our work so that we focus on those building blocks, on those elements that are the most immediate biological and medical and physiological importance. And then as we do that, we develop improved instrumentation. We can accomplish that task more efficiently, and the end result will be that full map of the entire genome. But some parts of the genome count for much greater importance than others, and I think that is where

some of the targeting that you were talking about a moment ago would come in very, very appropriately.

There are many other important innovations in biomedical research. We have all read about the monoclonal antibodies that have given us new reagents of just extraordinary specificity and sensitivity. And these can be used for development of diagnostic procedures that were unthinkable some while ago. The protection of our blood supply depends on immunological reagents designed along these lines that can detect the AIDS virus. And we are seeing the development of similar reagents for the diagnosis of abnormalities like cancer and like high risk with respect to a variety of other diseases.

I think perhaps this would be a point to conclude with because I could go on almost indefinitely. And I think you very much.

[Statement follows:].