

The Chairman. Thank you.

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

4 Dr. Lederberg. Thank you, Senator Kennedy.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1 year's budget.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

3/1 19 If there is one biological concept that has emerged in  
20 the last five years, it is the concept of receptors. We  
21 have understood that for the cells of the body to be able to  
22 function as an organism, to function as a well-regulated  
23 society, that they have to have ways of signaling one  
24 another, or providing outputs from cells that would  
25 determine what the state of the organism was and providing

1 receptors that would be responsive to those inputs.

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

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

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

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

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

10 This applies to the drugs like Somitadine--

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

12 Dr. Lederberg. Sir?

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

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

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

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

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

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

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

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

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

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

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

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

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

17       [Statement follows:].

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