GENETICS RESEARCH

WITNESSES

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Mr. FLOOD. Our next witness is Dr. Joshua Lederberg, Nobel prize winner of medicine in 1958, Department of Genetics, Stanford University School of Medicine, Stanford, Calif.

You have with you Dr. John Herndon.

Dr. LEDERBERG. Yes, sir.

Mr. FLOOD. He is the medical director of the National Cystic Fibrosis Research Foundation in New York City.

STATEMENT OF DR. JOSHUA LEDERBERG

Doctor, I see that you have a statement. How do you wish to proceed?

Dr. LEDERBERG. I think my statement has some material in it, not just dry numbers. On the other hand, I was so impressed by the syncretic dialogue that just preceded I would be very happy to proceed in that fashion.

Mr. FLOOD. Suppose we insert your statement in the record and then you can comment on it.

Dr. LEDERBERG. All right.

(The statement follows:)

STATEMENT OF DR. JOSHUA LEDERBERG

I am grateful for the opportunity to bring before you today some matters of great and urgent importance to the physical and mental well-being of people not only in America but throughout the world.

I have come here at the request of the National Cystic Fibrosis Research Foundation. It is their responsibility, as a voluntary health organization dealing with a major disease problem, to bring such matters as these to the attention of the public and the Congress. I hasten to emphasize, however, that I am not going to limit my remarks to cystic fibrosis. I shall be dealing with the broad range of conditions of man which are either wholly or partly genetic, or hereditary, in nature. I would therefore appreciate it if I might submit a statement by Dr. John Herndon, vice president for medical affairs, dealing exclusively with cystic fibrosis.

In the course of my remarks on matters relating to the growing problem of genetic disease, I shall establish the basis for the following recommendations, which I shall present in greater detail later on:

First, I propose that genetics research—which is just beginning to pay off substantially in the field of medicine—be given the continuity it now lacks by creating a "Task Force in Genetics" in the scientific community of the country with a panel of coordination within the National Institutes of Health. This inter-Institute panel representing all 10 Institutes would serve as a clearing house for information concerning all on-going research in genetics and related areas. In this way, the panel could develop a picture of where this important field of research stands today and where it is going, which would greatly facilitate the most efficient planning and funding of future research.

Second, I propose a special allocation of funds for genetics research over and above the NIH budget. This would support the creation of the task force in genetics and initiate a purposeful national program by wiping out the backlog of genetics research grant proposals which have been approved as meritorious but have not yet been funded.

I am fully aware that these proposals come at a time of tight money. I am also aware of your intent to support additional biomedical research as our economy permits it. I will argue today that, in a time of skyrocketing medical costs, our economy cannot afford not to increase its investment in this vital area of genetics research and development.

We are witnessing today the beginning of a third major stage in the evolution of medicine. The development of the scientific art of healing began centuries ago, based upon the discipline of anatomy, which concerns the structure of the body and its organs. The second stage of medicine's evolution was based upon the function of the body's organs, a discipline we call physiology.

The new stage also involves functions, but at the level of individual cells and cell components which determine the fundamental properties of organic matter that we identify collectively as life. In this new biochemical-genetic stage of medicine's evolution, we are not so much interested in what fundamental functions take place in the life processes as in how they do, how they are regulated naturally and how they might be influenced medically.

Medicine's new evolutionary stage comes at a propitious moment. Antibiotics are at hand to cure bacterial infections and there is the early promise of broad-spectrum drugs against viral infections. Research in biochemical genetics and molecular biology represents the next wave. It is just beginning to provide the knowledge and technology to deal with a category of diseases which are, at present, incurable and are assuming a growing proportion of our medical budget and our health services and facilities. I am referring to human genetic disease.

Today, at least 25 percent of all hospital beds and of all institutional places for the handicapped in this country are occupied by persons suffering some degree of genetic disease, and an estimated two out of every 1,000 persons—not counting relatives of the genetically ill—spend full time caring for them. Some authorities expect the percentage of the Nation's health burden attributable to genetic causes to increase rapidly; this would happen as our control of other forms of disease and our ability to deal with genetic diseases both increase.

Although it seems hard to believe, the majority of practicing physicians in this country are totally unaware that a genetic disease problem of such magnitude even exists. Needless to say, under the circumstances, there is no coordinated program for dealing with it.

I took my estimate of the size of the problem from studies conducted outside this country but which are believed to reflect reliably the situation here. The reason no accurate assessment of the genetic disease problem has yet been made in the United States is that many of the conditions we now classify as wholly or partly genetic were, until recently, consigned to a diffuse, "wastebasket" category of afflictions including the metabolic, degenerative, functional, chronic, or idio-

phathic disorders. Only quite recently have many forms of mental retardation and such widespread metabolic disorders as cystic fibrosis been identified as clinically distinct genetic diseases.

There has been little hope up to now for coming to grips with the genetic disease problem because of its immense complexity and our lack of appropriate knowledge and medical technology. What I am here to tell you today is that developments in the fields of molecular biology and biochemical genetics—within the past few years and months—now, for the first time, give us reason to expect that we shall soon be able to treat effectively and perhaps even cure many of these disorders. Indeed, I shall cite some instances where this has already been done.

Before I do, however, let me note parenthetically one aspect of the swift pace of development in molecular biology which all of us would do well to keep in mind. This concerns the sometimes unexpectedy rapid translation of the basic research findings into practical medical therapeutics.

For example, you are all familiar with the genetic code, the so-called dictionary of the language of life, according to which chemical instructions are written in the molecular structure of the genetic material for determining the form and function of all living things.

Well, less than 9 years ago, we did not know for certain that such a thing as the genetic code even existed. Then the classic codebreaking experiments in late 1961 by Dr. Nirenberg and Dr. Matthaei at the NIH, workers all over the world began trying to complete the decipherment. After 4 years, this effort encountered technical obstacles that seemed sumountable only by means of tedious chemical techniques that have not been developed yet. Then, in just 1 year, the application of intelligence and ingenuity overcame those obstacles, and the entire genetic code was spelled out. That was in the spring of 1966.

Now, this was a magnificent feat—truly a monument to man's intellect and resolve. Yet, strangely enough, the full detail of the culmination of this work, the complete decipherment of the code was hardly reported, if at all, in the public press!

The main reason was probably that the initial codebreaking achievement was seen as the key—hence more dramatic—event. Also there seemed little likelihood that the knowledge of the code could ever be put to use in the practical way that would affect the lives of newspaper and magazine readers and television viewers.

Now, however, I can tell you that—quite unexpectedly—scientists at the National Heart and Lung Institute of the NIH are hoping soon to apply the knowledge of the code—and particularly, the chemistry that was developed in the course of deciphering it—for the first time to the treatment of human disease: a fatal blood disease of children, called *beta thalassemia*. Other insights into genetic disease have led to even more tangible advances in the treatment of another blood disease, *sickle cell anemia*.

My point in all of this is that the grandest predictions made for the fields of molecular biology and biochemical genetics have had a way of being bettered by reality in less than the allotted time. I can see no reason why this remarkable record cannot be improved upon—even more to the benefit of humanity—if the moment were seized and given guidance, say, by developing a strategy for progress in the new biochemical-genetic medicine.

I shall try now to explain the basis for my conviction that the time has come to focus a coordinated effort on genetics research. The aim will be to identify problems whose solutions promise rapid practical utility for the new genetic medicine and to spot areas of investigation that must be developed now to provide the basic underpinning for overall growth of the field in the future.

Tremendous progress has been made in the identification of the hereditary human diseases. The number of these conditions recognized has been multiplying for the past several years, as witness the annual growth in the thickness of Dr. Victor McKusick's catalogue of genetically distinct human disorders—now numbering over 2,000. This work has aided greatly in defining the dimensions of the genetic disease problem and also in pointing the way to the development of effective diagnostic and therepeutic techniques for managing these disorders.

For instance, understanding the genetic basis for many of these diseases is enabling physicians to detect carriers, or probable carriers, of the traits and, hence, to counsel prospective parents on their chances of having defective children. In addition, there is an explosive growth in the prenatal diagnosis of genetic defects. With a technique known as amniocentesis, fetal cells are removed from the amniotic fluid inside the womb and tested in the laboratory for sus-

pected genetic defects. If a defect is detected, therapy may be instituted even before birth, and the defect's harmful effects thereby prevented from ever becoming expressed. Or the diagnosis may provide medical justification for interrupting the pregnancy and in that way, also, prevent a genetic tragedy.

To give you an idea of the extent of the genetic disease problem in the perinatal period, it is estimated that more than 40 percent of all deaths in the pediatric service of any large, general-care hospital can be attributed to diseases that have a genetic basis of some sort. The possibility of substantially reducing this toll is at hand now with the application of newly available techniques for identifying carriers, diagnosing the fetus and, in some instances, in utero treatment.

For example, research supported by the National Institute of General Medical Sciences has, in the past few months, produced a comparatively simple—but ingenious—blood test that potentially can screen for 30 or 40 different genetic anomalies involving enzyme defects. In addition, diagnostic tests for the detection of 21 hereditary neurological disorders in the fetus are now available, and carriers of the gene for each of six of these cruel diseases can be picked up, and related tests and genetic counseling be provided.

It is our hope, gentlemen, that one day we may actually be able to correct the genetic defect itself at the level of the gene or in some early stage of the gene's expression. A year ago I could not have come before you and predicted the kind of progress that has been made in regard to the gene. Scientists have reported the isolation of genes from living cells, and just last week a small gene was synthesized with chemicals from bottles off the laboratory shelf. These and other developments have cleared the way for administration of genes to cells, tissues, organs, and to individual patients for medical treatment.

Meanwhile, the techniques one can envision for introducing genetic material into living systems are already in routine use at a fairly simple level in laboratories throughout the world. Such material can be injected directly into cells, or it can be attached to certain viruses which are used to infect cells (a modified form of vaccination). Then there are procedures for fusing healthy cells with sick cells and for growing defective cells in the presence of genotherapeutic agents, rectifying defects so that "cured" cells might be reimplanted in the patient.

Daily we come closer to the command of skills and capacities that a few years ago would have been considered almost magical. At the present time, Dr. James Cleaver of the University of California in San Francisco is preparing to explore the feasibility of treating the disease called xeroderma pigmentosum by infecting its victims, who lack an essential enzyme, with a virus known to posses it.

I would now like to return to the proposals I made at the outset of this statement for the consideration of this committee and the Congress.

The first concerns the creation of a genetics task force consisting of the country's most eminent and competent scientists in this area of investigation for the coordination of a national effort in genetics and genetics-related research to capitalize most effectively on each promising breakthrough.

This task force would be backed up by a panel of coordination in genetics-related research representing the 10 National Institutes of Health and the NIMH, responsible through its own chairman to the overall direction of NIH. It would thus be responsive to the genetics needs of each of the Institutes but independent of them in making its decision. It would also enjoy liaison with the NSF, AEC, Children's Bureau, and OEO which also have important interests in genetics research.

The panel would serve as a clearinghouse for communications concerning all genetics research in progress or under consideration. Thus, relevant research projects in genetics within one Institute would be made known to all the others. It could begin to fill in the picture of where this complex field stands today and where it is going. It might be possible, for example, to construct a graphic representation of the field, on which selected 'horizons" of advance in knowledge and technology would be assigned velocities corresponding to their speed and direction of movement. Such a dynamic scoreboard for genetics research would change from time to time in response to new developments. This sort of visual aid could be valuable to the panel in communicating its recommendations and particularly in enabling it to spot likely breakthroughs or courses of convergence among different lines of research. In this way, it should be possible to anticipate important advances and effect the conditions for their realization.

My second proposal concerns the appropriation of funds, over and above the normal NIH budget, which would bring the task force in genetics into existence

and would wipe out the backlog of unfunded grants in genetics and genetics-related research.

I propose then, that a separate and additional fund of $10 million be appropriated for fiscal year 1971 to support genetics research projects, many of them growing out of breakthroughs such as I have described. The actual disbursement of this sum would be determined by the Director of the NIH on the basis of the panel's recommendations.

My purpose in urging that the $10 million be in additional funds is to provide for accomplishment of our goals without penalty to other important areas of health research.

In conclusion, I should like to recall to your attention the fact that we are, indeed, on the threshold of a new era in medical science. We can expect not only to improve man's physical and metnal well-being, but probably to improve man, himself, in a qualitative way. To foster our own perfection humanely and unselfishly—and safely—will require new knowledge and technical abilities of the sort I have discussed with you today.

In this connection, I would like also to leave with you a paper I presented last year at a Nobel symposium entitled "Orthobiosis: The Perfection of Man," in which I set forth my views in this overall concept.

The method proposed here today may not be the only one, but I believe it is both the safest and the most direct way for man to perfect himself—a supreme goal that now appears to be within our grasp. Thank you.

DR. LEDERBERG: ADDENDUM TO TESTIMONY BEFORE HOUSE APPROPRIATIONS SUBCOMMITTEE

As an afterword to the statement you have just heard, gentlemen, I should like to leave you with a thought expressed just this week by my eminent colleague, Dr. Har Gobind Khorana. Dr. Khorana, the first man to synthesize a gens, was interviewed by Victor Cohn of the Washington Post. Asked why he and others of this country's molecular biologists employ so many assistants from abroad, he replied: "There has been a dearth here for some years of organic chemists also trained in biology. This has been quite a barrier."

In an effort to counteract this, Dr. Khorana said "the National Institute of General Medical Sciences began making general chemistry a major program. But with recent fund cuts," he went on, "the situation is again much worse. NIGMS is now one of the hardest hit parts of NIH."

The main import of Dr. Khorana's remarks was contained in a warning that the United States is in imminent danger of losing its leadership in unraveling the biology of life. My purpose now is to underscore this warning.

Thank you.

Dr. LEDERBERG. If I may make some introductory remarks.

Mr. FLOOD. Dr. Herndon, you can do the same thing. Sound off any time you wish in the course of the hearing.

Dr. LEDERBERG. May I also introduce for the record a statement by Dr. Herndon and some additional material?

Mr. FLOOD. We will do that.

(The statement and additional material follows.)

CONTINUED STATEMENT OF DR. JOSHUA LEDERBERG

Dr. LEDERBERG. Thank you.

Dr. DeBakey spoke so eloquently about the general situation of the medical schools and in particular of their research programs that I find I can hardly improve on it. I echo and resonate every word that he said with great feeling and I think he may be better informed than I am about the details of the dollars and cents figures as they have an impact on schools.

Mr. FLOOD. You received the Nobel Prize in 1958 in medicine.

Dr. LEDERBERG. The formal designation is "physiology or medicine." My own work has been in the basic aspects of genetics, a field that is now called molecular genetics.

Mr. FLOOD. As you gather, we were concerned about the idea of this condition of the artery, insofar as it affects the heart, being transmittable. Could you develop that?

Dr. LEDERBERG. Well, Dr. DeBakey's point about that, I think, does dramatize what is the central point of my presentation; that is, that there are a great many diseases that we do not ordinarily think of as "genetic disease" but where there is an important genetic component.

Mr. FLOOD. Does the Law of Mendel apply or is it just transmitted one generation after the other?

Dr. LEDERBERG. I am confident that we will find Mendelian laws apply when we can dissect the many factors interwoven in the situa-

tion. These are so numerous we are often not able to trace them out one at a time.

Mr. FLOOD. Would the gene of transmission be male or female or both?

Dr. LEDERBERG. It is very difficult to predict; the information we have at the present time about the genetics of cardiovascular disease is very vague, but I do not know of specific information on transmission through male or female. It would be transmitted through either parent, although, as you know, males are more susceptible. (Whether this is a biological difference or a cultural one is uncertain.) The outlook I had on Dr. DeBakey's testimony was, as a surgeon he treats the end product in an advanced stage of a process that began at the time of birth or perhaps even earlier. We must proceed to the unraveling of the factors that distinguish why this baby will develop cardiovascular disease and this one not.

Mr. FLOOD. Concerned with prophylaxis?

Dr. LEDERBERG. Prophylaxis is always the most efficient choice when we can develop the means to achieve it. The sort of research program I would have in mind would require studies of cells and tissue culture derived from different individuals in accordance with their family background, correlating the cells' biochemical behavior with eventual cardiovascular disease in the subjects or their families. We don't know which cells are the most critical.

Mr. FLOOD. Do you deal with the fetus at all?

Dr. LEDERBERG. It may be desirable at some stage to do investigations on fetal cells. This is easy to do now; and for research purposes it would be done without harming the fetus in any way. There has been the most extraordinary development of the technique of amniocentesis, which is the sampling of fluid. This is the sampling of the aminocsac from the fetus. The fetus sheds some cells into that fluid. A needle is inserted into it, and outside—a perfectly safe procedure. This is a bit like taking blood samples. These cultures are examined in the laboratory.

At the present time we don't know well enough what to look for in respect to what will lead to cardiovascular disease, which gives little specific indication for examining the fetus at the present stage. The day may come when we look at people's cells and applying therapy before or soon after birth as a way of preventing heart disease at the age of 60. That is a very reasonable proposition.

Mr. FLOOD. What is the earliest stage in which you have been able to identify the fact that the arterial condition as a fact can be transmitted?

Dr. LEDERBERG. I believe there have been findings——

Mr. FLOOD. What is the earliest year?

Dr. LEDERBERG. I believe there were findings of 16- and 18-year-olds with remarkable signs of arterial failure. Dr. DeBakey can speak more knowledgeably about it than I can. The genetic basis of this is known only to the extent that the disease runs in families.

I should remark I am not a physician. My end of the game is exactly the opposite from Dr. DeBakey's. I am a basic scientist interested in fundamental genetics. I am nevertheless passionately concerned about their application to human problems. I am not knowledgeable about the clinical aspects of cardiovascular disease but acquainted with the

literature in it. All we know at the present time is that the disease runs in families and in such a manner as to strongly suggest genetic factors are involved.

Mr. FLOOD. I wouldn't want to restrict your testimony this morning to the heart just simply because Dr. DeBakey preceded you. You are here to testify about the field of genetics.

Dr. LEDERBERG. That is right.

Mr. FLOOD. I don't want to restrict you by my questions.

Dr. LEDERBERG. It is not really a restriction because the genetic aspect of cardiovascular disease is one of the most pointed illustrations that could be made of my central theme. The main point I want to make is that we can collect statistics on all the disease to which man is heir and make an estimate of the genetic components in them and add them up, but we come to the astonishing result that at least 25 percent of our total problem of health, medical care, hospital care, is on a genetic basis.

Mr. FLOOD. What do you mean by genetic?

Dr. LEDERBERG. "Genetic" refers to those factors transmitted through the germ cells, factors that we inherit from our parents through biological transmission.

Mr. FLOOD. Do you have a geographical or racial problem, color, geography?

Dr. LEDERBERG. Certainly there are differences among peoples, depending on where they live. These are sometimes sharply defined enough to be called races. Different races do have different patterns of disease and that is one of the lines of evidence that we are dealing with in genetics.

Mr. FLOOD. Inherent and peculiar to a race?

Dr. LEDERBERG. Yes, sir. I will give you one of the most significant examples, that is, sickle cell anemia, which is almost completely confined to blacks. It is an adaptive condition in Africa. It has positive merit in Africa for it conveys resistance to malaria. The child who has one dose of this gene suffers few ill effects of it, but in Africa it is an advantage where malaria has been endemic. A certain fraction of children receive two doses of this gene and then have a serious blood disease with this gene. Approximately as many as a tenth of the Negroes in the United States carry this factor. We do not know the total impact of this on their health. Another example is a disease, which is essentially "Tay-Sachs disease" which is confined to Jews. It is a very serious though rare condition and affects only a small minority of people within that racial group.

Mr. FLOOD. What is the nature of that disease?

Dr. LEDERBERG. It has recently been discovered to be an enzyme defect that can be detected in fetal cells taken by aminocentesis. The effect represents an accumulation of abnormal materials in cells of the central nervous system to prevent their normal function.

The other main point that my testimony addresses is related to the need to develop exactly this kind of perspective over a wide range of diseases. Physicians are now accustomed to specializing in heart disease, diabetes or psychiatric disease, they are classified according to either the age at which the disease manifests itself or according to the organic system in which a disease appears——

Mr. FLOOD. Are you suggesting that in your studies as a geneticist, and being aware and having been able to identify specific transmitted disease, that you are examining the possibility of removing this inherent danger? Can you do something medically, surgically, or any other way to prevent this known transmission? You know now that Mr. A and Mrs. B have this condition. Are you interested in preventing that transmission, examining that possibility? It that beyond the rule of reason or what?

Dr. LEDERBERG. No, it is not beyond the rule of reason but there are very great difficulties in it today. I think in the ultimate event we will have approaches that can prevent the actual transmission of damaged genes from generation to generation. That is almost the last thing that we will be able to do in the control of genetic diseases.

Mr. FLOOD. Would you say to Mr. and Mrs. A, if they have a child and this child is now 16 years of age, "We can now tell you that this condition exists in either or both of you and if you have another child it undoubtedly will have the same condition"? Are you concerned about that?

Dr. LEDERBERG. Very much concerned about that, although that particular eventuality does not happen very often. The statistics are usually such that we cannot tell a couple that a child will undoubtedly have a disease but only a certain probability of having it. Only in very unusual circumstances would all the children be bound to have a disease that was carried by one or both parents.

Mr. FLOOD. Then it does not follow that all their children will inevitably have this disease?

Dr. LEDERBERG. That would almost never be true. The usual circumstances for many diseases, for example, would be one-fourth of the children might be expected to have it. That would be the case in cystic fibrosis, where the usual circumstance is that both parents are healthy. One parent in 25 is a carrier of the gene and one in——

Mr. FLOOD. You make Mr. Mendel look like an amateur, don't you?

Dr. LEDERBERG. No, sir. He was the professional who founded the game. We follow his rules exactly. You see, it would be quite remarkable to find that all the children would show the disease. This makes the problem more perplexing because the parents who know they are carriers of genetic disease have the difficult problem of facing a substantial, but less than total, risk. Should they proceed or not proceed to have a child? In many circumstances where a disease is very serious, even a chance of one in four is more than they can bear. However, here is where——

Mr. FLOOD. I know that, but do you feel called upon or have any burden, you and your allied doctors in medicine, to advise them and inform them?

Dr. LEDERBERG. Certainly so! In fact, genetic counseling at the present time is a very active program in many medical centers. They can offer special expertise for the counseling of parents to understand the nature of the problem that they confront and to give them sound advice with respect to what the outcome of pregnancy might be.

I would like to say that an even more positive alternative has come about lately. Although many people may have moral or religious objections that must be respected, there is a choice that must be made by an individual family counseling with their own physician.

With amniocentesis it is often possible to find out whether a fetus will belong to the 1 in 4 to be stricken or the 3 in 4 that will get by.

In many circumstances now, a couple knowing they were in severe risk, have started a pregnancy and have had it monitored by examining fetal cells. They have then chosen an abortion if they found that the child was doomed to be damaged and have continued if it were not. This has a very positive side. This obviously has a negative aspect to it, but it also has a very positive side. It is not a very satisfactory solution to the problem but it does permit a mother carrying certain genetic diseases to undertake a pregnancy with confidence that she can bear a healthy child! If her first pregnancy does not do it she can try again. This has happened again and again. I believe this is a remarkable achievement, knowing that not everyone will agree with respect to this approach. I would stress it is, of course, not a good long-term answer; but it is a stopgap that can be provided on the basis of present knowledge in a number of diseases.

I do have some remarks I would like to bring to your attention, particular recommendations that I have to offer in my prepared testimony. I might just as well read them. These are in the record.

It refers, first of all, to the fact that we need a way of coordinating our present knowledge of the impact of genetic factors on disease in a way that has never been collected up to the present time. I made a very rough estimate, say 25 percent of our medical problem can be traced to genetic factors. That is undoubtedly a conservative figure but it is one I could easily defend. That number is bound to increase as testimony to the very power of medicine. Medicine takes care of infectious disease, for example, and eventually there will be very little left but accidents and inborn errors for medicine to deal with.

Mr. FLOOD. Is that an alarming figure?

Dr. LEDERBERG. Well, it is paradoxical. It is alarming in the sense that we are not facing up to this aspect of our medical problem. I think that you will not find that our health research budgets deal with genetic issues as if they had this much to do with our medical problems.

I think that you will find physicians are compartmentalized in their thinking about this, and to that extent it is alarming. To a certain extent it is encouraging. It is testimony to the ability of medicine to have taken care of a wide variety of other situations, external factors that result in disease. We are left with the internal ones, which is what the genetic factors are. We must not stop but continue to deal with the inherent limitations to healthy life we are born with. That is what the genetic factors are.

Why should we tolerate that a considerable fraction of us will suffer from diabetes though it may only appear in advanced age and neglected in most of our lives because we don't know enough to realize it was bound to happen to us? Or schizophrenia or a large number of other diseases, some of them not as common individually but in the aggregate affecting most of us?

Mr. FLOOD. Schizophrenia is transmitted?

Dr. LEDERBERG. There is a strong genetic factor in schizophrenia. It is not obviously the total story, but from some of the best studies which have been done by Professor Kety at Harvard looking at the Scandinavian population—who keep better records that we do—they find

twins separated at birth show a high incidence of concurrence in psychiatric disease. These twins have random environment but the fact they have the same genes means they have similar outcomes in many cases.

We know nothing about the way in which this pattern is developed. A child born with a certain set of genes interacts in a complicated way with his environment to create this mental disturbance. It is by no means inevitable that a child with that genetic pattern will come down with the disease. But until we know much more about it we have no way of ameliorating the environment. We need to learn what factors in the environment are crucial for those circumstances where one twin has become schizophrenic and the other not, which is the most hopeful aspect of it.

Many people have a fatalistic attitude about genetic disease which is totally inappropriate. It is a little like saying we are doomed to blindness because many of us will have eyes that are myopic. We have learned how to make spectacles and live very happily with them. They are a nuisance but not a basic impediment to our function. If we knew exactly where to go with our treatment and our specifications, many other diseases that we are very frightened of today will appear no more alarming and require treatment no more difficult than putting on spectacles to take care of our vision.

I want to get at this issue of genetic fatalism because it is partly responsible for a refusal to come to grips with some of the problems of genetic disease. I suggest that public policy understanding of this matter is grossly deficient.

It is another way of looking at the spectrum of disease, and I am not contradicting any of the things that Dr. DeBakey was advocating. I do not think we have adequate respect for genetic problems and I think this is one reason why basic research in this area which I speak to has been so seriously undercut. There is a grossly deficient understanding of the intense relevance of things like the development of the genetic code and the structure of DNA and so on.

We know the recession and the depression that science in general and health research in particular has been under in the past years. In dealing with that I must also say, dealing specifically with this backlog of unfunded good health research applications, and there is at least $10 million worth of important research which is approved; good scientific research which is simply unfunded. It may be much more than that that would go in under the heading of genetics, but is scattered among the various institutes, and without the deliberation of the task force that I am advocating it would be hard to say what that volume is.

Now, I know you get similar applications from other specialties and other disciplines, and I am suggesting only that genetics has not been understood as a significant factor. The task force I propose would serve as a clearinghouse for communications concerning genetic research in progress or in consideration. It would allow for better communications between the institutes in this particular area. It would help fill in the picture of where the field stands today, where the gaps are, and we could find the most appropriate horizons where it would be possible to facilitate the movements from basic research into more applied directions.

I think, to give you one example, there is a lot of work going on the biology of viruses, virus diseases; but there has been relatively little thought to the way in which viruses could be used to repair genetic damage.

That represents a confrontation of two seemingly unrelated fields. Yet we can foresee the development of agents that would resemble vaccines except that they are there to repair genetic defects rather than to provoke immunity and prevent other virus infections. This is one of the most promising approaches that the theoretician is able to propose today.

May I return to a point that you made earlier about being able to intervene in the transmission of defective genes from one generation to another? This is a subject that has seriously loaded overtones to many people. They are afraid of those aspects of genetic research that might lead to what is called genetic engineering. By this is usually meant the idea that the State might decide what the characteristics of an individual ought to be, that it might program what a human being ought to be like and so forth.

I can't deny that there is a certain validity to those kinds of concerns, although they may be many dozens or even hundreds of years off. But these concerns should follow exactly the same pattern as our concerns about education. The most appropriate way to look at the problem of "biological engineering" is to think of education as being a kind of "psychological engineering." It has an exact counterpart in our responsibilities for trying to decide what is the optimum kind of life that you can help to bring about, the kind of opportunity that you can offer to a child for him to work within the framework of our society. As in education, we have the tension between individual decisions and the needs of the community. We have been able to work it out to a reasonable degree in the one field. We don't know all that we would like to know about optimum patterns of education.

We don't know all that we would like to know about optimum patterns of biological health and welfare of a child. But if one looks at the problem from that point of view, many of the fears that have been expressed about genetic engineering will be seen to be quite specious. There is no more reason to be afraid of massive intrusion of the power of the State with respect to biological engineering than there is reason to be afraid that it will dominate the thought processes and the information fed to the individual. This is, of course, to say that in a nondemocratic society there is serious concern for any kind of totalitarian manipulations. If you have mind control through the operation of a fascistic state you could also have genetic control. But if we in a democratic society we have developed reasonable rules to provide for the tension between the individual and the community, they should certainly be able to provide just as well in the biological sphere as they do in the educational and communicational.

However, these developments are a very long way off? I think we have so many more proximate things to do in the application of genetic knowledge. The most important is the working out of developmental pathways: understanding just what the genes are that are involved in heart disease or diabetes or schizophrenia, factoring them out one by one, being able to anticipate what the heritage of a par-

ticular child is, and learning what are the therapeutic measures or the prophylactic measures, that will prevent the manifestation of the disease later in life. Obviously the earlier you can know about it, the earlier you can do something for the child and the greater the likelihood that you will be able to provide a form of therapy that is the least intrusive. Think what a serious intrusion a heart transplant is—if we could erase the need for it with better preventive knowledge we would all be happier. But this requires an enormous expansion in our present knowledge. We only know enough to know how little we know about it. We can frame the questions but we don't know the answers yet.

I would like to also bring to your attention another item in the record, a quotation from Professor Khorana who is at the University of Wisconsin, and who has been responsible for a number of the most extraordinary developments in the field of molecular genetics. As you know he was recently awarded the Nobel Prize for his work in this field. Last week he announced the successful synthesis of a portion of DNA that corresponds exactly to the structure of a small gene. This is an extraordinary feat of laboratory engineering, of the assembly of units obtained as chemicals off the shelf, so that they correspond exactly to the structure of the gene that was isolated from a living cell. This is comparable in its significance to the chemical synthesis of a protein which was accomplished just a couple of years ago and will have, I think, many more long term implications.

In response to a question of why he has had so many assistants from abroad in his laboratories, he has pointed out that there has been a dearth for some years of organic chemists also trained in biology which has been quite a barrier. The National Institute of General Medical Science started some years ago to make genetic chemistry major programs. With recent fund cuts the situation is again much worse and it is indeed true that NIGMS is now one of the hardest hit parts of NIH. He warned that the United States is in imminent danger in losing its leadership in unraveling——

Mr. FLOOD. Are you suggesting that it is important to pursue the study of the artificial manufacture of a cell?

Dr. LEDERBERG. Certainly the artificial manufacture of components of cells. I am not sure whether it will ever be worth the effort to assemble a whole cell from all of its parts. Once you know the principle of how to go about it, the actual job of doing it may be relatively unimportant because there after all are lots of cells around. You can take cells already in being and do experiments by interchanging parts and so forth. When a scientist speaks of "wanting to make a cell" what he really means is that he wants to understand how it is put together. You also want to understand the difference in the structure of a cell which is functioning normally from one which is diseased.

Mr. FLOOD. Yes, but of course when you find out all that, and you have all the many, many, many components of the cell, the next step, of course, like night follows day, will be you people will want to make them by the millions.

Dr. LEDERBERG. That is a little bit like saying that a teacher wants to make a child's mind. I will revert to my previous analogy. We need educational research in order to know how to teach, in order to know what the learning consists of, in order to learn how best to serve the

needs of the children in the community. That doesn't make you want to make a child's mind, not in the sense that I think is behind your statement. But if you think we should not do it, you can pass a law. You know, I really don't see any abuse so imminent on the horizon that there is any requirement for this kind of legislation. I think the time may come when some form of social control of genetic technology may be very desirable. I don't think we know enough now to say what an appropriate form of legislation would be. Exactly what would you legislate against at this stage of the game? That day may come but I think in a democratic society we have all of the resources we need to keep these matters under very tight control. How can it run away?

Mr. FLOOD. Just so we know.

Dr. LEDERBERG. Well, I think it is very important that scientists give the utmost ventilation to their findings and certainly we work very hard to try to convey the meaning of our works to the public every day. We are not keeping any secrets! We are not Dr. Frankensteins locked up in an inaccessible laboratory secretly plotting something that we will thrust on the world. Exactly to the contrary.

Mr. FLOOD. I think the way all elements of the news media in the last 10 years have devoted space and time to these things we are talking about is extraordinary.

Dr. LEDERBERG. We strive for public understanding and public participation in these decisions, and that is obviously one of the major purposes of our meeting today, to assist in that ventilation. Problems will come. There is no doubt about it. I think they are not as pressing as the problems of war and of peace, and of poverty, providing for a proper distribution of the goods of the earth. They will come and we will be able to meet them, but progress has always got problems connected with it. I don't think we need be afraid of that.

Mr. FLOOD. No, I think they have removed that image of the medieval soothsayer in some tower, and so on, in recent years.

Dr. LEDERBERG. Mr. Flood, I am most grateful for your attention to my principal remarks. I would be happy to answer any further questions. If not, I do have another general comment or two on some things that Dr. DeBakey brought out. He mentioned the interrelationship of teaching and research, may I point out that whatever capability we have had for the past 15 years for the education of medical students is a byproduct of the institutions that have been built on Federal research funds. I think medical schools have been careful enough about their bookkeeping,—with some prodding from the gentlemen of Congress—about a careful allocation of costs to different functions. It is still undeniable that if we did not have the institution of the medical school which research funds have built up, we would not have the framework in which the medical education that we have been able to offer would be possible.

Medical education has been funded, you might say, as an incremental cost on top of the institution which has mainly been funded from research sources.

Today there are many pressures for redirection of the funds of the medical schools and the pressures are undeniable and their virtues are undeniable. We need more physicians and we need to provide for health services on a much larger scale than we have in the past. We are also told in order to do this we must cut back on research. If there were a

calculated transfer of budgetary support from the research side to the training side, I could not argue very strongly against that. I am not sure it would end up changing very much what we are already doing. It would help specifically to amplify the direction of teaching that we do, but we would be able to do our job.

What in fact has happened is that we have been cut back de facto very severely in our research budgets and sometimes the excuse is given that we need the money in order to turn out many more doctors. But the funds have disappeared in the gap; we have never gotten the money to turn out doctors and that is the source of the bind we are in, and I must address this to you as a very, very serious problem. We have no way of solving it. We have no other resources in order to deal with it. If the delivery of health services is to become a dominant theme of the social function of the medical school in the future, and if the Congress is to be the voice of the people in this respect, then it must transmit the resources in order to accomplish those functions, but we have been the subject of a certain amount of double dealing on this question.

Mr. FLOOD. Mr. Hull?

Mr. HULL. No questions.

Mr. FLOOD. Mr. Casey?

Mr. CASEY. Doctor, this is a fascinating subject. As I understand it, right now you think that possibly it is only in the dim future that you could change the genes, is that correct, to overcome the one-fourth of the maladies that you say are attributable to genes.

Dr. LEDERBERG. I think not only in the near future but in the recent past we have been able to compensate for those difficulties, and sometimes very, very effectively. I used the spectacle as the analog of that, in a more domestic vein.

Mr. CASEY. That is corrective devices but I am talking about an actual change in the gene.

Dr. LEDERBERG. Without changing the gene itself, I mean. For example, there is a very serious disease that you well know called Phenylketonuria. It is a very rare one. It has been the subject of a level of investigation out of proportion to its statistical incidence, but it is a prototype of a lot of kinds of metabolic disease.

times very, very effectively. I used the spectacle as the analog of that, his diet can be adjusted so that he can develop in a perfectly normal and happy fashion. Without that detection, and that in turn depends on knowledge of the metabolic changes that are involved in that disease, if he had been exposed to the customary diet of the usual infant, his mother's milk, for example, he would be intoxicated by it and his brain would be damaged by it. You could argue it is a semantic question whether he was really damaged by his genes or damaged by the ordinary environment for those particular genes which it turns out to be rather toxic.

Diabetes is at least partially ameliorated, although it is a genetic disease, by providing insulin. One can provide a number of other similar examples that don't change the gene, but where we have learned enough to influence the deleterious pathway so that the deleterious gene no longer harms the child.

I do see as the next step being able not so much to change the genes where they are defective; but to add missing "information" to the

genetic complement that is in the individual. There are experiments going on today that bear on that question very strongly. These depend on the selection, as I mentioned earlier, of viruses that are able to have very specific characteristics, viruses used as vaccines for genetic therapy instead of infectious-disease immunity.

Mr. FLOOD. You have friendly viruses in your arsenal?

Dr. LEDERBERG. Yes indeed.

Mr. FLOOD. How do you use them?

Dr. LEDERBERG. The specific example that is being studied at this very moment would be the Shope virus which is known to cause warts on rabbits, the Shope pathologic virus, and as far as is known it is absolutely harmless in man.

I think before it is applied on a very large scale that matter would have to be gone into very much more carefully again, but there is good evidence that many people in contact with rabbits or doing laboratory work with the virus have in fact been infected with it, with no clinical signs whatsoever. All that is known is they have developed antibodies to it or have certain other changes which does not impair them in any way. It is not a disease in the usual sense of the term. This virus however, among other things adds to the pattern of enzymes in those cells that it infects and it adds an enzyme that happens to be effective in a very rare disease, a lack of the enzyme arginase. Dr. Stanfield Rogers at the Oak Ridge Laboratory pursued several years of laboratory work on this enzyme before anyone knew there was a corresponding disease countered. Recently he saw published reports of the first occurrence of this particular disease and he has been in touch with their physician to arrange for some experiments with the Shope virus as a genetic vaccine.

There are many friendly viruses. All of the live virus vaccines are friendly; the Sabin polio virus, the new measles vaccine are good examples of these. They do something analogous to what Dr. Rogers is doing. They introduce genetic information, here we call it the vaccine, of the virus itself into the body in order to provoke a specific biological response. When we do a vaccination we want to provoke the development of specific antibodies. The new dimension that is being brought up here is to introduce a virus that will provoke the development of new enzymes that were genetically defective or missing in that particular individual. This doesn't change the genes. The transmission of this characteristic will be unaltered in future generations, but an individual who for example had Tay-Sachs disease could be helped if we could find a virus that could restore the missing enzyme in his own body cells.

As a general principle, if you find some enzyme missing in fetal cells, it should be possible to treat a fetus with the appropriate virus by an intrafetal vaccination and allow him to develop in a perfectly normal fashion.

Mr. CASEY. You hear once in a while, or read, something of a particular drug or chemical that will change the genes. Is that actually what happens?

Dr. LEDERBERG. Yes, but it is changing the gene in a way as if you fired a shotgun into a complicated machine—you change some of the cogs in that machine. There are many environmental agents capable of

causing genetic damage and they represent an aspect of this entire problem which is indeed very, very serious.

Mr. CASEY. If it can be changed to the detriment of the next generation they could possibly be changed for the better, could they not?

Dr. LEDERBERG. If we knew how to change radiation at an ultramicroscopic level so it could be pointed like a rifle instead of like a shotgun that in principle would be correct. We are some years away from that in man. It will be possible someday.

Mr. CASEY. Your genetic counseling is primarily done now with people after they are married, isn't it?

Dr. LEDERBERG. That is correct, although sometimes a couple will present themselves who are thinking of getting married, believe that they may have the same disease in their families and want to know what the prospects for their children would be. The advice that is often passed on to them is that this is not so much a consideration about marriage; but it is consideration about their having children. If they do face that risk, they might be better advised to adopt rather than having their own children for their own peace of mind and welfare as well as that of the community.

Mr. CASEY. You know they do a lot of advertising now about computer dates, where they feed into the computer the likes and dislikes and interests, and then come up with matched couples. Could you foresee that for genetics also?

Dr. LEDERBERG. Well, I have heard it talked about. I think the dating computer is mainly an excuse for people to meet one another in an age that has bypassed church socials and promenades. It is not the first thing in my agenda. You see preventing those mismatches in this sense doesn't really do anything to the frequency of the gene. It just delays the occurrence of defective children. The gene is still going to be there if they marry somebody else.

Mr. CASEY. I was thinking in the reverse, of someone who wants to produce superchildren, superintelligent children, gifted children, and so forth.

Dr. LEDERBERG. I am not sure the computer can do very much better than you could with your own commonsense. If you want smart children be smart yourself, have a smart wife and have enough money so send them to college. I don't want to completely shut off such considerations, but we know so little at this stage of the game about exceeding the norm; the things that we are able to deal with are the defects, where an individual is defective or damaged in some particular respect and we can say, okay, there is some disease related to that. Let's find out what is wrong and maybe we can try and repair it. Of course we are all diseased with respect to some hypothetical ideal, but we know so little about it, or to put it a little differently, we are all defective in so many different ways simultaneously that I don't see any promising approach there, by the things I am talking about.

Mr. CASEY. Some years back I recall reading, and I don't know whether it is fact or a reporter's fiction, of an artificial pregnancy in which the woman—and of course she never knew the father—with the consent of her husband picked the type of male she wanted for the father of her child. Does that actually happen?

Dr. LEDERBERG. I believe there have been a few examples of that.

In fact there are many, many examples of this, where the husband is sterile, where a couple still wants a child. This is something about which the law is monstrously defective, because the children of such a marriage are subject to all kinds of legal risks, as are the couple and so on. You can imagine the complications that might arise if any party to that arrangement ever changed his mind, who has the rights to what in relation to whom. The law really should be changed in order to accommodate that.

Mr. CASEY. I think the laws are more explicit on cattle than on humans.

Dr. LEDERBERG. I think they are. The State of Oklahoma, I believe, has pioneered in this respect. It is the one State that allows that a child the product of an artificial insemination by consent of the two parents is in all respects subject to all of the legal prerogatives of a natural born child, which I think is the only way this can possibly be dealt with. Otherwise, there are enormous ambiguities. Artificial insemination is a humane procedure in the circumstances that I mentioned, where the couple is unable to conceive by their own device, so to speak. It does allow a woman who chooses it the opportunity of the experience of a pregnancy while remaining within the marriage, and many women have adopted it. I have seen some estimates that perhaps as many as 100,000 children have already been born in the United States by this route.

Mr. CASEY. Do you make a study or is there any need or reason to make a study of how this genetic concept matches up?

Dr. LEDERBERG. Well, it is not really a genetic concept. There has been very little effort in these cases to choose the biological father with respect to any particular characteristics except to be or try to be sure he is reasonably healthy. You have exactly the same considerations that a couple has in adopting a child. They don't want one who is obviously ill, but that is about as far as we could go at the present time anyhow. Perhaps in the future a woman will be more demanding about the biological characteristics of a donor for such an insemination. I will say also that there have been very vehement proposals by some geneticists (very few, I should say agree with them on this point) to do this in a more systematic way, that is to encourage the selection of particular males as donors, even to put their sperm into frozen storage so that they can be banked over long periods of time.

My main reaction to that is that it is at least premature and it may be very undesirable not because of its main effect but because of all kinds of side effects. Consider, for example, the problem of advertising the characteristics of a particular male as against some others, and you can't evade those kinds of issues, if this is ever to be done on any very large scale.

Where there is already an indication for artificial insemination from another doner, certainly as much attention as our present knowledge allows should be paid to avoiding genetic disease on the part of such a donor. I think this is already understood by those gynecologists who perform these procedures, but it represents an area where we don't know very much.

On the other hand, it would as a matter of social policy be preposterous to bear very much more strongly on those conceptions than

we do on the millions of conceptions that arise naturally out of marriage. I don't see any issue of social policy to justify the demand that there be any extraordinarily higher criteria for genetic quality of artificial inseminations. And I prefer that reproductive questions be kept as far as possible a matter of private choice unless there are compelling social claims at stake and a solid basis of knowledge on which to legislate.

Mr. CASEY. Where does your research money come from?

Dr. LEDERBERG. Almost entirely from the National Institutes of Health.

Mr. CASEY. Which institutes?

Dr. LEDERBERG. The AID, Infectious Diseases and Allergy, at the present time, although I did a good part of my work on the molecular biology of bacteria under the aegis of the National Cancer Institute.

Mr. FLOOD. How much money did they give you last year?

Dr. LEDERBERG. About $48,000. That is after a 15 percent cut which was negotiated and subsequently changed several times. I have had an essentially stable budget for the last 9 years.

May I add that these are the funds that determine what tools I have to work with. Of course I am chagrined to be hindered in the exploration of my own ideas. But this is not as serious as the frustrations faced by younger investigators who have not established a reputation. Their "stable budget" is likely to be zero.

Mr. CASEY. Thank you, Mr. Chairman.

Mr. FLOOD. Thank you, Doctor.

Dr. LEDERBERG. Thank you, sir.

WEDNESDAY, JUNE 10, 1970.