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Introduction of
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New York, New York
By
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We are certainly privileged to have the opportunity of listening to a presentation by Dr. Joshua Lederberg. He comes to us as one we all know and respect as an outstanding teacher, as an outstanding research person in genetics, as one who has received the Nobel Prize in recognition for his work.

We are also going to have the privilege of listening to one who is currently providing very distinguished leadership for Rockefeller University, a university which means a great deal to us and to the life of our nation. I regard it as both an honor and a privilege to present to you at this time Dr. Lederberg.

Toward A More Perfect Union: Science and Medicine
By
Joshua Lederberg

Fellow students: I've spent the larger part of my life and all of my academic career in the pursuit of scientific knowledge. in the fields now described as molecular biology and genetics. These are the study of the functions of DNA at the very core of the cell. Throughout that time I have been very much concerned with what difference it makes.

I began that career almost 40 years ago, and for a large part of that time it was very difficult for me to give verifiable answers to the question, "Has anybody's life been saved by your research?". Indeed, has anybody's life been saved by our knowledge of the structure of DNA? I used to pursue this question somewhat obsessively. I wondered if there were faults to be found, if there were sufficient connections between the basic research enterprise and the development and application of clinical insight.

It has been only in the last few years that I've realized that we are going through a substantial revolution in our approach to these questions. There is hardly fault to be found. Rather I recognize that there has been distinct segmentation in the history of health and its relationship to science. Admitting that there is necessarily some oversimplification in any rendition of history, I would like to go through with you why I believe we are experiencing a very important and very different Third Phase today.
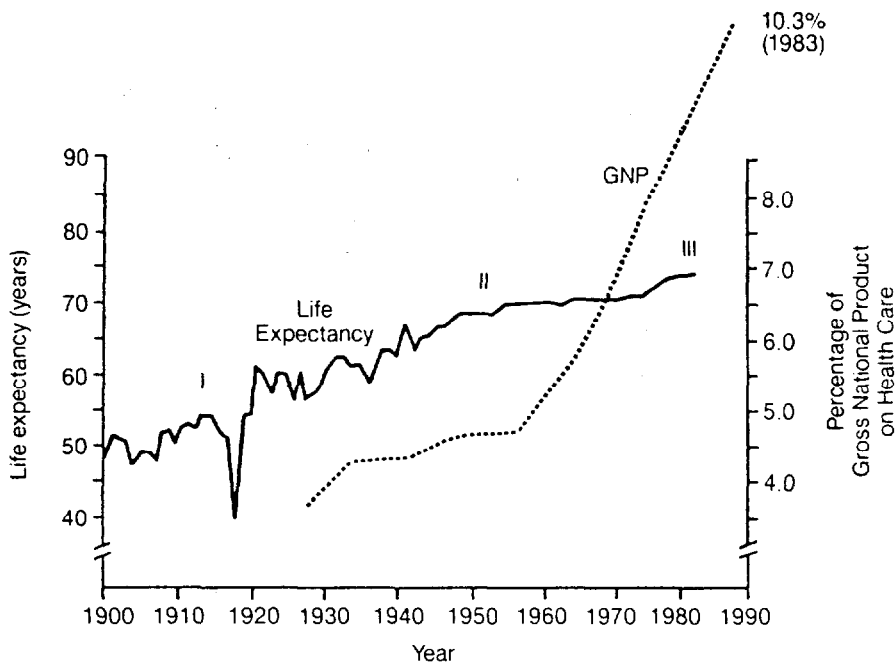
Figure 1.

Life expectancy for the United States. 1900-1981. contrasted with the proportion of the Gross National Product expended for health care. Roman numerals (I, II, III) represent major cycles of biomedical progress (see Fig. 2).

Part of my argument, and part of our mutual concern, is epitomized in a chart familiar to many of you: the improvement of life expectancy since 1900 (Fig. 1). It also shows the percentage of the Gross National Product which has been devoted to health expenditure since 1930, when the collection of those statistics began. The striking thing you can see from this chart is that there seemed to be no correlation between the very sharp increase in expenditures for health that this country has experienced since the middle fifties and the near flattening of our mortality rate until the last decade.

Let me stress that throughout this period expenditures for health research have fluctuated between a little over one percent and perhaps as much as four percent of the total health expenditure at various periods. In fact, there is no

year during that period in which the annual increment in health care expenditure did not substantially exceed the current total expenditure for health research. I wonder why there is so much fuss about justifying research expenditures that are in fact so trivial in comparison with our overall effort and investment in health.

I would also ask you to reflect how much of the improvement in these indices (it had been substantial although it did flatten out around 1960; in the last few years there has been some further improvement, particularly with regard to outcomes in coronary heart disease) — how much of that improvement in performance can be traced to improved access to health care and how much can be traced to increasing our knowledge of what to do about public health, both preventively (which I submit is the larger part) and therapeutically, using measures that have been newly discovered and applied.

What certainly has altered substantially is people's anxiety about paying for their health care, how they will survive financially, and about their encounter with the physician. (If anyone has objective statistics on the partitioning of the improvement in health during this period from the three sources I have indicated — preventive public health, augmentation of new knowledge, and improved access to medical care — I would be interested to see those numbers.)

I have tried to identify the actual ingredients in the change of both health and medical practice during the periods I had been pondering. My greatest concern is how little we know about it and how little we understand it. There certainly has been no satisfactory global partitioning of where the benefits are lodged and how they can be attributed, either to the major categories or even to some of the smaller modalities of a health-related experience.

One can look at a few specific diseases and gain better insight. At least you can have a well-reasoned argument about how much of the decline in tuberculosis could be assigned to improvements in nutrition and in the social setting of individuals suffering from the disease; how much to improvements in management — from the difficult and ponderous methods of bedrest to the application of antibiotics (admittedly at a time when the disease was already declining substantially); and how much to the social measures of segregating actives cases of tuberculosis.

Even when one does focus on a specific entity, and has some qualitative understanding of the procedures that were applied in dealing with that disease, there is still room for argument. There really has been no attempt to apply that sort of analysis to the totality of health experience to try to get a clearer idea of the precise way in which the management of disease, other than infectious disease, has altered in a significant way.

Paul Beeson has made a very useful contribution and provided at least a checklist on this point.[1] As the editor of *Cecil's Textbook of Medicine* for 30-odd years, he was well qualified to do a comparative study of the recommended management of disease, as described in the older and newer editions of this standard text. Unfortunately one can get hardly more than a qualitative snapshot of the various isolated areas in which new methods of management have been employed. No one has statistics available to show what difference

various measures have made. It is very hard to pinpoint the relative importance of particular components. I will cite several things from Beeson's account and suggest a few of my own.

The importance of antibiotics in the treatment of bacterial infection, and the importance of vaccination in the prevention of viral disease, can hardly be disputed. We take those for granted today, and one feels a little tired dredging them out over and over as justifications for the augmentation of knowledge. In fact, they have been very important and certainly have played a large role in that part of the diminution of mortality, and morbidity as well, during that time.

One thing Beeson points out is the number of totally discredited approaches that were at one time part of the medical armamentarium and which we now know did no good and may well have done harm. I will mention a couple of the "homey" examples, one being castor oil, the other, putting iodine or even mercurochrome into wounds. These are typical of the kinds of things which people, at an earlier era, thought of as medical care — and better that they hadn't! I suggest that there are practices today that, although somewhat better founded, will be viewed as no less barbaric from our future perspectives of the nature of disease.

Going beyond infectious disease, trying to get some perspective on what has been the most important change in medical management, my own vote would be fluid therapy. The use of saline infusions for individuals who may be subject to shock, to alteration in not only water balance, but also salt, pH, and specific ions, is routine. It is one of the important things for which people are kept in hospitals instead of being given ambulatory care. Again, we take this practice for granted to such a degree that it is hard for us to contemplate what a great lapse there would be if that form of therapeutic management were suddenly no longer available.

Trying to trace the scientific roots of that particular innovation in management is an interesting enterprise. It probably is one of the last of the important developments connected with Phase I of the history of medical innovation, namely, those findings which are founded on biological knowledge looking for applications. Phase II begins in real style roughly in the forties with the determination to make medicine more scientific, but with a change in the focus of problems from the relatively more tractable infectious disease to that of constitutional disease in the human. I would submit that it has been characterized by problems to which serendipitous solutions have been found, sometimes fairly empirically, and which have then provoked far more detail from the mental inquiry which has helped to build the relevant basic science.

You may guess that Phase III is a return to the reductive principles of Phase I. Whereas our problem 60-70 years ago was the invading microbe, we are beginning again to acquire a certain amount of fundamental scientific knowledge, of the human organism, looking for applications that might be useful medically. I will offer an admittedly subjective impression about the reductive influence in therapeutic practice with a few cases (Table 1).

TABLE I
Some Therapeutic Developments Calibrated by the Role of Rational (10) versus Empirical (0) Elements of Discovery

Procedure	Scale
Vaccines	9
Surgery	8
PKU nutritional therapy	8
Oral contraceptives	7
Beta blockers	7
Diuretics	3
Antibiotics	2
Antibiotics — molecular manipulations	8
Cortisone for arthritis	1
Psychotropics	0
Chlorination of water	7
Fluoridation of water	1
[A grotesque pathfinder:]	
Nerve gas as by-product of insecticide research	2
Pralidoxime antidote (not very effective)	9

The empiricism scale goes from 0 to 10 — zero for a purely serendipitous innovation that perhaps then provoked fundamental inquiry. Number ten would be the other end of the scale, which is established scientific knowledge looking for application.

Curiously or not, surgery stands very high on the scale of applications of reductive knowledge. The reductive knowledge is *anatomy*. With knowledge of body structure, it is not a great feat to imagine ways in which a reconstruction of those anatomical relationships could be beneficial. The separation of the tumor, the reconstruction of blood vessels, the repair of broken parts all fall in that category. You begin with that structural knowledge and then look for and validate the applications.

Again, this is a vastly simplified example and there is an enormous amount of physiology as well as anatomy that has to be included. But the starting point in surgery is not random surgery, which occasionally works, from which we figure we have a procedure worth following up. The procedure is rationally designed from the start. One may run into unexpected discovery, of course, but the principal point of departure is the body of prior fundamental knowledge.

Exactly the opposite can be said of the psychotropic medications — the drugs used in psychopharmacology — which have had such an impact on the practice of psychiatry. These drugs have emptied institutions as a result of their use in the management of schizophrenia and, somewhat less systematically, in the management of depression.

Without exception, the agents relevant to important medical application in those fields were originally derived from accidental observations. Sets of molecular structures that had originally been intended for other purposes or had no intention at all (as in the case of lithium) were accidentally discovered to have an impact on the behavior of an organism and then proved to be useful for the treatment of psychiatric disorders. They were iconoclastic in their application because the prevailing theory was that no medication would be effective!

On the foundation of the pharmacological efficacy of these compounds, we developed a new basic science that you might call biochemical psychiatry because there was, for the first time, evidence that chemical substances could influence mental pathology. This is hardly founded on any fundamental theory of the biochemistry of mental process, but precisely the converse. Some of our best clues to that biochemistry have come from attempts to track down the actual molecular targets of those drugs that initially were discovered entirely serendipitously.

On the empirical scale, I grade vaccines close to "1" because I submit that the germ theory of disease was the reductive foundation of most work in microbiology, virology and infectious disease. For the development of the viral vaccines, we needed contributions from people working in ancillary fields such as tissue culture, who had no original intention of contributing to the solution of viral disease. Then, we needed the convergence of that technical information with two observations: one, that diseases are caused by exogenous self-replicating agents (the germ theory of disease); and two, the observation (so deeply rooted in human history that its origin is obscure) that the survivors of an infection will be resistant to re-infection from that source — which is the reductive foundation of immunity. Together these factors provided a rational research program which could not fail.

Starting 100 years ago with Koch and the identification of specific disease agents, adding the fact of immunity, building on knowledge, looking for applications, orienting the search toward the disease believed to be of the highest priority and most amenable to scientific investigation — that was the Golden Age of Microbiology, and in some sense, of medical science, from about 1880 through 1940. That was what it took to reach the fruition of our attack on that set of problems.

The one other area in medical science in the fifties and sixties that I have been able to think of, where scientific knowledge preceded the therapeutic application, was in nutritional and nutritional-genetic disease. For example, the knowledge that phenylketonuria was a genetic disease, with a specific block in the metabolism of phenylalanine, enabled the inference that lowering phenylalanine intake might have a useful effect in controlling the disease.

There are very few others, largely because we have not had a good theory of etiological pathology over the vast range of human ailments. In phenylketonuria, when we had a notion of the genetic origin and a pinpointed view of the metabolic step in question, it was possible to think reductively and to design, from principles, an approach that might work and could then be

tested. Of course, there is still some controversy over how effective this approach is in the long run, but it is certainly the best we have in trying to deal with an established case.

The next approach after PKU, prenatal diagnosis by amniocentesis, is similar. It was designed from the prior knowledge of cell structure in chromosomal disorders and the cell's metabolic properties in enzymological defects. You weren't taking a great gamble in terms of the science needed to move from the general arena of scientific thinking to identification of particular cell types obtained by amniocentesis.

In another important area of medical intervention, contraception, the oral contraceptives probably are the most pervasive. On the empirical scale, we might say contraceptives are a mixed case. Even there, there is a certain serendipity. The notion that one might prevent true pregnancy by the use of the same hormones or simulants of the same hormones that occur normally during pregnancy, inspired the search for those agents, which could then be used for contraception. Nevertheless, the actual mode of action, critical to any particular oral contraceptive, is still a question, which has in turn inspired new investigations of the sites of action of the progestagens and estrogens. It is also necessary to look in great detail, an unfinished process, for unexpected side effects and appropriate dosages. It is surprising that people are sufficiently homogeneous that a standard dosage can be published.

In each of these examples, whether the innovation was derived from serendipitous empiricism or from prior knowledge, once it has been well started, an enormous amount of further investigation is needed to validate that therapeutic approach, to discover the appropriate range of action, the side effects, the interactions with other situations, and so forth.

I hope you understand how routine it has been since World War II to have the practical innovations, so important to medical practice, originate essentially in serendipitous observation or empirically oriented studies. For example, the organic chemist might be set to work to produce a hundred compounds in a given series without any particular clue to pharmacological activity, but as soon as one was noticed, it would be sniffed out for further perfection.

If I may use one more example, I will remind you about aspirin, a remarkable drug with very many applications, and certainly the best anti-arthritic agent available today. It has been a folk remedy. It was certainly a serendipitous discovery. It was not designed by the people who looked for it in willow bark. We uncover new modes of action of this one molecule regularly! It is a multifarious agent. There are some interesting questions raised by its paradoxical effects in relation to dosage. That its primary mode of action is on the prostaglandin system has become clear during the last decade. That hardly accounts for its analgesic effect or its antipyretic effect. There is much still to be discovered about one of our most important medications. The fact that it is not a prescription drug should not confuse you about what a potent and important chemical agent it is.

Three Major Cycles of Biomedical Progress*

I. **Infectious Disease**
fl. 1880-1940+
(Germ theory seeking
applications)

II. **Empirical Pharmacology and Physiologic Medicine**
fl. 1922-1980
(Clinical observation and accidental
discovery calibrated with science)

III. **"Molecular" Medicine**
Science fl. 1944-
Applications 1980-
(Convergence of new biology with
human physiology)

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1985 ff

Vaccines
Antibiotics

Surgery
Insulin
Fluid therapy
Cortisone
Diuretics
Psychotropics
Chemotherapy
Diagnostic instrumentation

Cimetidine
Captopril
Calcium blockers
Cyclosporin for transplant
DNA diagnosis
Recombinant DNA production
methodology

———————
Atherosclerosis
Cancer
Psychiatric disease

*Toxicology is the 'sleeper' that will set the pace of progress.

Figure 2.

I'll briefly recapitulate my view of the first two stages (Fig. 2). I think I've given you my principal argument. At the same time, of course, those same four decades after World War II were a period of very intense activity — the National Institutes of Health might have been thought of as a little schizophrenic. In fact, maybe it was even a little biased in terms of where it put most of its investment, in rather more basic lines of research. This was to balance the fact that the empiricist line of inquiry was already being pursued on a substantial scale by the industrial sector. That was where new products could very readily be found. They didn't require a lot of basic science information for their discovery. They required a lot of acute scientific analysis for their further elaboration and validation.

Why do I think things are different today? Because of the extent to which it is possible now to design, from our insights on molecular biology, our inquiry either for the diagnosis of genetic disease, or, by using similar probes, for the diagnosis of infectious disease, or for the elaboration of materials important to human physiology, or to probe the mechanism of physiological processes.

The latter I can illustrate by the fact that we are just now learning the fundamental coding of the apoproteins, which become the various lipoproteins in the blood stream and are responsible for the transport of cholesterol. A great deal has been learned about the mechanism by which cholesterol-laden lipoproteins are internalized in target cells. That is substantial justification for the view that the two major categories of plasma lipoproteins, namely the high density and low density, play a crucial role in the determination of whether cholesterol will be deposited at the periphery (where it does great

harm if it's in the walls of your coronary arteries), or if it will be scavenged from the periphery with the result of preventing atherosclerosis.

This is our most important public health problem by far, since atherosclerosis and related cardiovascular disease account for half of our overall mortality. We can now begin to describe the apportionment of synthesis of the HDL versus LDL in terms very close to the root, that is, the regulation of the expression of specific DNA sequences. Those genes have been identified, they've been mapped. We do not have specific entities as yet that can turn those genes on and off, but I have no doubt whatsoever that these will be forthcoming in the very near future.

At present, the best information that we have, I guess, is that alcohol is the most potent chemical agent that can be relied upon for some stimulation of HDL synthesis. Cigarette smoking seems to depress it. Exercise seems to augment it, as well as a handful of other pharmacological agents now being tested that were originally put into the system from essentially empirical sources. But that's going to turn around very rapidly.

In the field of cancer, the site of the lesion is an alteration of the DNA of the cell. Our ability to specify in chemical detail what the alteration of the nucleotides is, really cannot help giving us a completely new insight into its recognition, prevention, and, just conceivably, how to deal with it therapeutically. I am more discouraged about the latter than about the two former points, mostly because cancer is such a multifarious disease in which different changes in DNA in many different sites can alter the final outcome. I don't expect we're going to have one magic wand to deal with all varieties. For that reason, I'm much more optimistic about a sudden change in the health picture for atherosclerosis than for cancer.

The actual historical turning point in identifying an actual working medical application of that level of knowledge of DNA is just five years old now. Y.W. Kan demonstrated that one could characterize the gene for sickle-cell traits by looking just at the DNA[2]. It had been very frustrating up to that time to know that tests for sickle hemoglobin could identify the one out of every hundred couples in the American Black population who were at risk (one chance in four) of producing sickle-cell disease children. But unlike a variety of other genetic diseases for which antenatal diagnostic procedures had been developed, nature was playing an unkind trick here. This human gene, about which the most was known in terms of the characterization of the gene product, the change in the amino acid structure of the hemoglobin — the trick that nature was playing was to not express that gene in the fetus. The fetus has its own hemoglobin system, different from the adult's. The adult hemoglobin is turned only after birth, and that, until Kan's work, frustrated every effort to try to diagnose the disease per se antenatally. By looking at the DNA of amniocytes, it is now possible and has begun to be a practiced clinical procedure (I have no doubt it will be a routine one in the next five to ten years) to spot the defect at the level of the DNA molecule, and thereby be able to advise those couples at risk so that they can have normal children. The only advice currently available was, "Don't have children at all because one in four will be severely damaged."

The next stage would be approaches to the mitigation of the consequences of the hemoglobin S homozygosity, and there are some clues about that too. Also, there is some preliminary knowledge at the level of DNA expression of the way in which that gene can be turned on and off, namely, the use of azacytidine.

A Primer on Human DNA

- 3,000,000,000 units in a human cell (uncoiled = 2 meters)
- 10,000,000 genes possible
- Information content comparable to a full set of *Encyclopedia Britannica*
- Only about 1% active (rest 'selfish'?)
- 100,000 proteins probably make up the constituents of the human body
- About 1000 proteins have names AND can be guessed to be present in the body
- About 100 proteins have been isolated and definitely characterized in humans
- About 10 human proteins have *medical uses* today
- If DNA were scaled to width of magnetic tape, it would stretch round the world
- Until recently, DNA was the most asymmetric physical object in the universe. (Now there are commensurate optical fibers 10^7 meters long)

Figure 3.

Let me give you a kind of snapshot (it is a couple of years old now so I may want to alter these numbers) about exactly where we stand in a metric of our assault on the complexity of the human genome (Fig. 3). I use that as proxy for the robustness of our reductive understanding of what is in a human cell. Just knowing the DNA sequence of course is only the beginning of the story. We want to know how a bit of DNA is regulated, how it is expressed, what the protein looks like, how it folds up, how it functions, how that protein relates to other proteins, what enzymatic roles it plays, and so forth. But if you do not know the DNA sequence, you do not have any deep understanding of what the structural elements are within the cell.

We each contain in every cell of our body three billion units of DNA. If uncoiled, that would stretch two meters long. It is an extremely asymmetric object. That DNA is very long and very thin, and it is very nearly the most asymmetric physical object in the universe. Spiders do not spin fibers that long, relative to their width, although recently we have begun to spin glass fibers of commensurate length for transcontinental optical fiber communications. The asymmetry is enormous.

That three billion units would code for about ten million different genes, a gene meaning enough DNA to encode for some specific protein product. That

is about the information content of a full set of the *Encyclopedia Britannica,* only it is in the alphabet of the nucleotides — there are only four characters, that correspond to the bases that are strung in the DNA structure: the A, the G, the C, and the T.

There is reason to believe that most of that DNA is not functionally active, at least does not encode for protein structures. Some 99% leaves us mystified as to its function. Some people think it is just parasitic, that it is a free rider DNA that the cell does not have any way to get rid of. It is there, it replicates the same way that the active DNA does, and there is no very efficient method for removing it because there is no great selective advantage to a cell that has chopped out a piece of DNA compared to a cell that has not done so. There may be bulking requirements — I think of a lot of that DNA as being ballast. The reason to suggest that is that the human genome is divided into 23 pairs, and the two smallest ones are the ones most likely to be lost by accident during the formation of the gametes. And that says that they are already marginal with respect to their ability to stay on the spindle and be properly distributed during cell division and during gamete formation. So it may be that there are rather prosaic bulking requirements for chromosomes to behave properly, and that is why some of the redundant DNA is present, but that only one percent of it is really necessary for the specifications. That would add up to 100,000 proteins. I have not seen any serious dissent to that scale of magnitude of complexity of what it is that makes up the human organism.

Approximately a thousand of these proteins have names, in the sense that we can guess the metabolic steps that are occurring within the human organism. We know some of the structural proteins that are involved, we know the transport proteins. We do not always know them for the human organism, but we may know them for other mammals and for other species. Whether or not they have been studied in the human, we have good reason to believe that they are going to be there, enough that even without knowing, I could put a name on them. Of those thousand which have names, up to the present about 100 have been specifically isolated and categorized to the extent that we know the actual amino acid sequence. A good many of them now have been cloned and have been isolated by the procedures of recombinant DNA technology. For a variety of technical reasons it is easier to get out the sequence of a bit of DNA than it is to get out the sequence of the proteins that are coded for by that same DNA.

So we are seeing an inversion of the historical steps. It used to be starting from the protein and then looking for the gene. Now there are many laboratories that have libraries of genes, not yet all 100,000 of them specifically sorted out. If you put all those libraries together, I am sure there are 100,000 entities, of which only these few hundred or a thousand have actually been sorted out so far.

At present, about ten of them have medical uses, for example, the hemophilia-replacement proteins, insulin, growth hormone, interferon. The immunoglobulins are proteins that have enormous uses, but none of them at the present time are available in pure form; they are the convalescent serum

antibodies that may be produced against a variety of agents used for vaccination.

I submit that we are in a new stage, that we are seeing a very rapid acceleration of the application of this fundamental knowledge. If I am wrong, over a billion dollars of investment in biotechnology over the last two years is wrong as well. It has not earned a great deal of profit as yet because so many of these things are still in the pipeline for clinical investigation, and behind that, the characterization of materials that might have therapeutic uses — all the immunomodulatory proteins, of which interferon is just one example. Interleukin II is a very promising entity. And perhaps most exciting of all, the DNA probes are providing the way in which we can discover the other 99,000 proteins of which we are only dimly aware. We know that they must be present within the organism, but each one of them in such a trace amount, furnishing some nonetheless indispensable aspect of regulation of function, that they need be present only in a relatively small number of molecules. We would never find them by trying to fish out from plasma or from cell extracts these materials, but where we can find the codes for them in the DNA, they are going to be harvested in full measure.

What is all this going to mean? I will be quite surprised if we have not radically transformed our views of prevention and treatment of atherosclerosis during the next decade. All the ingredients are in place. I feel fairly confident making predictions when it is a matter of moving from a secure scientific base to the technological application. That is really as far as I am willing to go in that kind of remark. But it is all there.

We are fishing around, looking for other approaches to dealing with psychiatric disease. We have very powerful methodologies, but it is not possible at the present time to give a robust enough model of schizophrenia. One of the most powerful tools comes directly from the DNA probes. A number of people, as part of those DNA libraries I just mentioned, are collecting examples of genetic tags which are sufficiently variable from individual to individual that, like the human blood groups, they can be used to trace the transmission of particular chromosomes or particular segments of chromosomes from one generation to the other. With those tags, for the first time, it will be possible to make a useful step past Kallmann's ancient observations of the heritability of schizophrenia. With those kinds of tags, we will soon identify particulous chromosome segments that are associated with schizophrenia, and develop a nosology that will subdivide this psychiatric category according to its genetic components. That will direct our pharmacological approaches in looking for the underlying biochemistry. The use of these probes is by no means confined to making new pharmaceutical products. I think the probes for fundamental knowledge of physiological processes may, in turn, be far more important.

After heart disease, I am less confident about what problem areas will fall into place during the next decade. The immunological disorders are falling into place very rapidly, using somewhat similar methodologies. It could be five

or fifty years before we really run through all of them. But they will all be run through within a few decades of this kind of investigation.

Will this knowledge result in the reduction of health care costs? Not at all. Not because the DNA-based technologies are going to be expensive — by and large, they will not. What will happen is simply the alleviation of one misery after another that we are eager to shed — we want to be cured, we don't want to die of cancer, we don't want our loved ones to suffer from psychiatric disease, we don't want to have heart attacks — and at the present time we will do almost anything individually to deal with any one of those circumstances. And we will be able to provide large answers to many of them. But we will go on living. And we will get older.

The end result is that the nursing care of many individuals between their tenth and fifteenth decades is going to be the largest cost connected with the elaboration of health technology. There is no way around that. We can hope for improvements in the quality of living as well as in the prolongation of life, but that is a much more difficult thing to do. To keep the overall organism going in some patchwork, makeshift fashion is technically far easier, whether we are talking about today's medical care or about new patterns in medical advances.

The costs are going to be there. Health is a good to which we all aspire, to which there will always be some margin at which we are willing to make some investment. It is not the technology and it is not the system. It is our own decision about how much of our goods we are willing to put out, and more importantly, what we are willing to tolerate by way of transfer payments to others, in order to sustain this as a social good, that is going to determine the level of health costs. That is the process operating today, it will be tomorrow, it will be the day after tomorrow.

What we can hope for is a better outcome from the application of these procedures, and even that has its paradoxes in view of those fourteenth decade individuals that I mentioned before. We face some terrible dilemmas of choice in terms of discovering what we want to do and directing our energies so they bear some relationship to those wishes. In the course of doing so, we are not going to influence the overall outcome very much without also influencing microscopic choices. Taking one individual at a time, who is going to act for the social benefit by foregoing those five decades of nursing care I have described, and who is going to impose that choice on anybody else? I think that really is the root problem, which has been surrounded by all kinds of fluctuating artifacts of the details, of the system of "delivery of health care" which has been discussed at this symposium. I suggest you should think about that as a central issue.

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1. Beeson, P. B. Changes in medical therapy during the past half century. *Medicine* 1980; 59: 79-99.
2. Kan, Y. W., Dozy, A. M. Antenatal diagnosis of sickle-cell anaemia by D.N.A. analysis of amniotic-fluid cells. *Lancet* 1978; 2: 910-12.

Postscript, recorded 3/29/84
        (See also Hahnemann 10/24/83)

        Limits of Reductive Explanation

The Laplacian paradigm notwithstanding, we have to be
humble about the practical possibilities of predicting
the development, behavior, and evolution of complex
organisms from first principles.   100,000 genes and
gene products interact in the developmental pathways:
we have great challenges in understanding the structure
and function of the components one by one! We can foresee
great advances in explaining an epigenetic or pathogenetic
pathway once observed -- that clinical or natural historical
observation will help isolate the pertinent variables.
Much more difficult will be the prediction of, say, the
details of disease issuing from nucleotide changes in an
arbitrarily marked gene. The enormous complexity of these
interactions of genes with one another, and with environmental
experience may, to be sure, be made more tractable with the
development of mathematical formalisms and computer models:
indeed these are rapidly becoming indispensable even for
narrowly focussed research. In practice, for the foreseeable
future, explanation in biology will still resemble that in
history more than it does in nuclear physics. Practical
applications will emerge from accumulated knowledge looking
for uses to a much greater degree than in past decades,
but most of all from the convergence of theory with the
observation of the world as it has actually evolved.