A Changing Concept of Health Care

During the past two decades there has been an incredible revolution in our understanding of the scientific basis of life, particularly in molecular biology and genetics. This has been paralleled by a revolution in technology, particularly in the space and military fields. The combination of these two seems to us to open the door for vastly improved possibilities of health care.

The revolution in our understanding of life processes has occurred so quietly and so rapidly that many individuals, even in the field of medicine, are unaware of the extent of our new knowledge. Nevertheless, during the next two decades this knowledge which is coming out of the research laboratories will inevitably bring about changes in health care of such a magnitude that they will modify all of our lives and indeed our social institutions —our philosophies, laws, and politics—as well as the practice of medicine.

It is significant that Caltech students, some of the brightest young people in America, see this future perhaps more clearly than their elders and are turning in steadily increasing numbers toward subjects related to scientific medicine.

The changes in medical practice that are certain to occur over the next two decades will result from the cooperative efforts of geneticists, molecular biologists, chemists, physicists, engineers, and physicians. They will be put into practice most rapidly by those physicians whose training is heavily biased toward scientific medicine. Undoubtedly, we will see the application of many of the resources developed in our space and military research programs turned toward such health-care problems, since it is exactly this type of high technology that will bridge the gap between research and application in scientific medicine.

Many of us believe that there is an exciting opportunity for Caltech and the Jet Propulsion Laboratory, together with local medical institutions, to play a major role—indeed a leading role—in bringing about these developments.

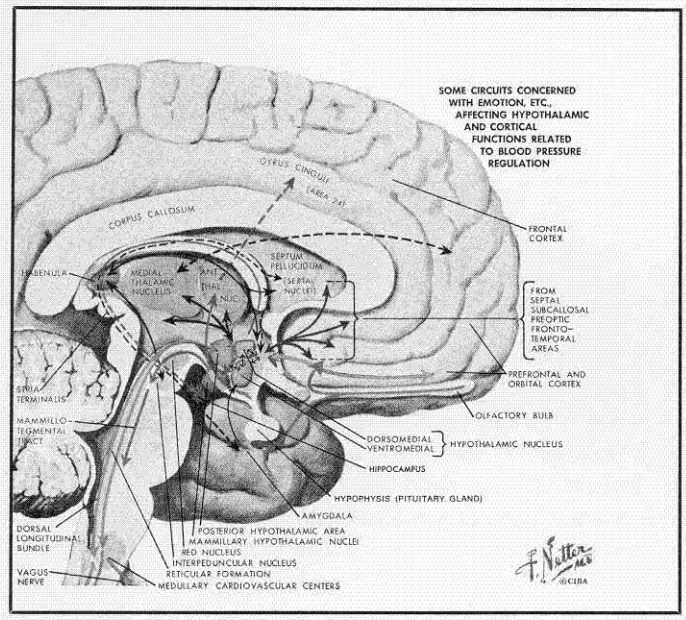
Caltech and JPL are in a unique position. On the one hand we have a long-established and internationally recognized leadership in genetics and molecular biology, and on the other hand internationally recognized expertise in the most advanced level of modern engineering. Thus between us we have almost all of the key ingredients required to lead the way: geneticists, molecular biologists, chemists, physicists, engineers, and space-age technologists. Furthermore, we have the most gifted student body in the world, with, as I have already pointed out, an ever-increasing number of them turning their attention to the very problems we are discussing. Moreover, as a result of agreements between NASA and Caltech, we have the promise of facilities at Caltech's Jet Propulsion Laboratory together with some of the world's most advanced instrumentation—much of which is directly relevant to our needs.

I say we have almost all of the requirements. In my view, we lack a small but vitally important "critical mass" of medical experts, specifically trained and experienced in the new scientific medicine. But, for now, I simply want to give you a feeling of how these views have come about —and the best way I know of to do this is to get very personal, and share with you some of my own experiences over the past two decades—the time in which these revolutionary advances in biological knowledge have occurred, and also the time in which I have been involved both academically and personally in biology and medicine.

In the early 1950's I was an undergraduate at Reed College. Reed, like Caltech, has an excellent student body and encourages undergraduate research programs. I was inspired to undertake one such project, but found it impossible. Both the reason for my interest and the reason for my frustration are, I believe, significant.

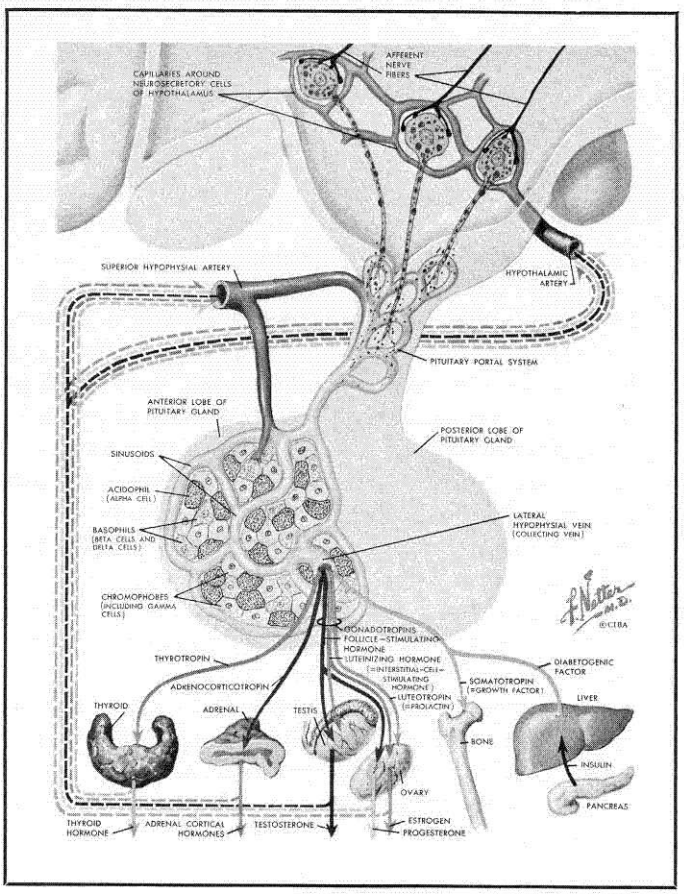
Some time earlier, when my grandmother was in her late 40's, she had developed a goiter, and a thyroid operation was necessary. This problem is rare nowadays since we have learned the importance of iodine and include it in our salt. Unfortunately, the surgeon also removed her parathyroid glands. The results over the next ten years were shocking. She rapidly developed many of the symptoms of advanced aging—poor vision and hearing, hardening of the arteries, premature senility, and finally death from coronary artery disease while she was still in her 50's. In less than ten years she had progressed through a 40-year cycle of aging.

My curiosity was quite naturally aroused, and I was motivated to learn more about the parathyroid hormone and its role in control of vital life processes. But my



The brain (above) is not only the center of our conscious thought processes, it is also the control center for our emotions and sexuality, for the programming of our growth and aging processes, and for all of our biochemical activities. The hypophysis, or pituitary gland, is a very small but vitally important lobe just below the hypothalamic region.

The pituitary gland and hypothalamus are shown in a schematic enlargement below. When the proper signals are received by the hypothalamus, small groups of specialized neurons release factors into an extraordinary circulatory system which disperses the control molecules throughout the anterior pituitary. Each of the different types of "releasing factors" reacts with a particular class of cells. In response, the pituitary excretes the appropriate one of the numerous pituitary hormones, thus regulating the various organ systems illustrated across the bottom of the drawing.



by William J. Dreyer

The new knowledge coming out of basic research laboratories will result in changes in health care of such magnitude that they will modify all of our lives and indeed our social institutions—our philosophies, laws, and politics—as well as the practice of medicine

studies into the matter showed me rather quickly that my search was futile. That is, it was impossible to approach such a problem as this scientifically at that time. There was no real knowledge of the role of the parathyroid glands. Although the concept of hormones existed, there was no knowledge of the chemical structure of the particular hormone associated with the parathyroid and certainly no knowledge about its connection with the process of aging. One could not obtain the hormone itself. There was no simple or effective assay nor any solid scientific theory of its mode of action—or of the activity of any hormone, for that matter. Now we have a large part of this knowledge. Today we know the exact chemical structure of the parathyroid hormone and many others. We know how to synthesize them, or at least their active portions. We know how to assay for them in a simple way, using antibodies. Furthermore, we have a preliminary understanding of their role in the central control systems which program all of our critical life processes.

This system operates through the brain. The brain is the control center of our thoughts, our feelings, and our attitudes. It controls our muscular activity and our biochemical activity. When the proper signals are received in a particular part of the lower portions of the brain, small groups of cells (which you might think of as microsyringes) introduce active factors into a complicated and very special circulatory system through which they are dispatched to the pituitary gland. In response to a particular factor, the pituitary excretes the appropriate one

William Dreyer

of the numerous pituitary hormones. These hormones play a major role in the function, growth, and aging of the body. For example, growth hormone—which determines our size—is excreted by the pituitary under the control action of one portion of the central nervous system. Of course, there is a feedback mechanism from the body back to the brain which provides information to this control system as to when to turn on or turn off the controlling chemicals. The details of all this control circuitry are certainly not completely understood yet. But compared to our knowledge of 20 years ago, the information now at our command represents, as I keep emphasizing, a revolution.

Many people have regular chemical tests of their urine and blood—usually as part of an annual physical checkup. And such tests generally include one for sugar in the urine—an indicator of hormone function. But have you ever had assays performed on any of your vital hormones? Very few people have ever had such a checkup.

Let me reiterate the present situation. We now understand the role of hormones in the central controls of bodily functions. Specialized research laboratories can assay for many of these hormones. We know that we could manufacture them artificially and inject them into the individuals who need them. And yet, in standard medical practice, such diagnosis and therapy are rare. Why? The answer is this: At present, both the assay procedures and the syntheses are complex and expensive laboratory procedures. They need not be so. With the application of the technology that has been developed in space and military research and development over the last two decades, automatic assay and synthesis equipment could be designed and marketed so as to make hormone therapy as accessible and as inexpensive as antibiotics.

Furthermore, if such automatic assay and synthesis equipment were readily available, it would immediately result in still more research into the role of hormones in a variety of major health problems such as premature aging, heart disease, and the control of our mental and emotional well-being.

So much for hormones. Let me go on with the second personal experience which came about just as I was starting graduate studies in biochemistry at the University of Washington Medical School. I was married by then to my wife, Mary, and our first daughter, Brynn, was on the way. A physical examination revealed that I was the victim of cancer. I had a chance of about one in ten of living one year. I was subjected to the only therapies available, radical surgery and radiation treatment. The inevitable secondary effect of the radiation therapy kept me sick for three months. But, as you see, I was one of the lucky 10 percent who beat the odds.

But that was more than a decade ago, and what has happened in the meantime? Now we are able to identify cancer cells from a specimen of body tissue or fluid, and, in a manner of speaking "paint them red" for identification, using specialized techniques involving antibodies. Furthermore, we know that the immune system of the body is set up to attack cancer cells. Our immune system recognizes them as foreign. Some researchers believe that 9 out of 10 cancer cells (which occur throughout our body) are destroyed by our own immune systems. Some put the figure as high as 99 out of 100. But every now and then a cancer cell manages to coat itself with a layer of protein (thought to be a malfunctioning type of antibody) which protects it. It disguises itself so that the rest of the immune system fails to recognize it as a foreign body, and a tumor develops.

This new knowledge of the role of immunochemistry

in the development of cancer opens up a new diagnostic procedure; we can detect cancer cells. We can also assay body fluids for those particular antibodies and antibody cells that are produced to fight cancer cells. If these are present, then we know that the individual in question has cancer cells in his body. If these antibodies disappear over an appropriate time period after surgery, we will have increased confidence that all of the cancer has been removed.

Here again, as in the case of hormones, such assays are complicated and expensive laboratory procedures, but here again they need not be. With the help of modern technology, such procedures can be made as automatic and as inexpensive as those now used for routine clinical laboratory testing of glucose or any of the other substances picked up in your annual physical checkup. Scientists at Caltech and at JPL are already at work on a joint program aimed at developing just such a system. Rational therapies are also being designed by the cooperating scientists and engineers.

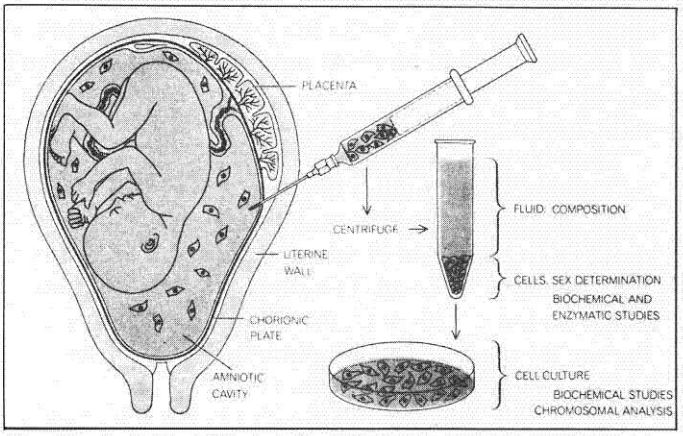
The third personal example has to do with my best friend in graduate school, Murray Thelin. Murray happened to be a victim of a genetic disease, hemophilia. This is the disease, well known in royal families, which causes severe bleeding problems from even minor injuries. He was a gifted young man and, not surprisingly, took up the study of blood-clotting control mechanisms. Unfortunately again, the needed factor was not available; its structure was not known, and its role in the control process was completely obscure. Nothing much could be done, and the odds against Murray were very great indeed —he died of a brain hemorrhage. Today we can isolate the factor; we understand much of the elaborate control circuit in which it plays a role, and there are several possible approaches to the control of this genetic disease in the future.

It is now known that to a considerable extent both hormone problems and cancer development represent aspects of this much broader problem—the problem of genetics. Every cell in our body, and all the organs constructed from these cells are, fundamentally, under the control of the genetic information stored in the nucleus of those cells. When something goes wrong with that genetic information, then abnormality and disease usually result. It is now believed that all types of cancer cells are genetically altered—sometimes by viruses, or by certain chemicals, or even by cosmic radiation. In some types of cancer the error in genetic information is known to be congenital.

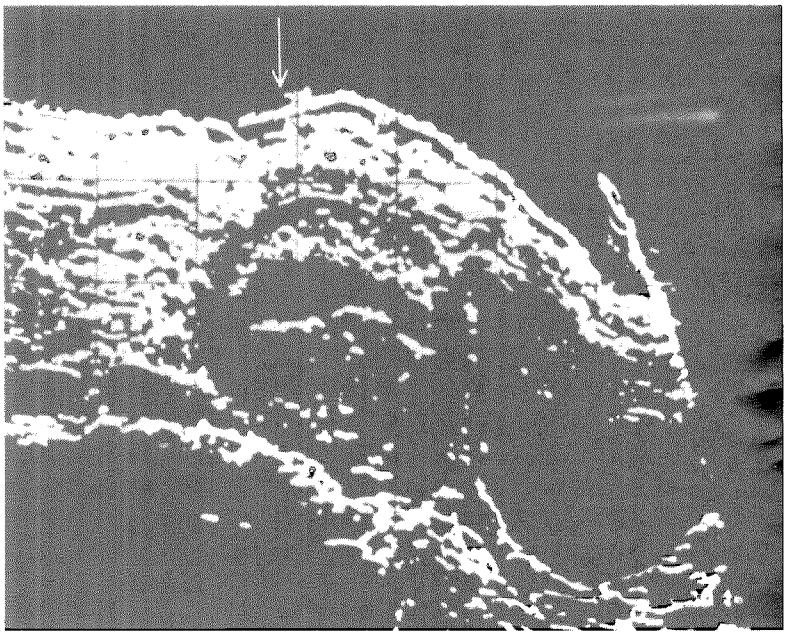
Well over a thousand other congenital genetic diseases have now been identified, including sickle cell anemia, cystic fibrosis, and mongolism. Undoubtedly, some of you have within your own families, or families very near to you, examples of such tragic problems, and know well the heartache that results. For in fact there is, as yet at least, little that can be done when a genetic malfunction is present.

But modern genetic knowledge combined with modern technology opens up a path to prevention, if not cure. It is now possible to sample the cells released by a fetus in its very first months after conception and to determine whether certain genetic defects are present. It is possible to do this early enough so that the option of a therapeutic abortion may be offered to the parents if the results show the inevitability of a deformed child.

In order to carry out this procedure it is necessary first to obtain a sample of the amniotic fluid—that is, the fluid that surrounds the growing fetus—by puncturing



New biochemical and genetic knowledge has made it possible to detect serious hereditary diseases early in pregnancy. Medical research scientists accomplish this by removing a sample of fluid surrounding the fetus—a process known as amniocentesis. The loose cells contained in the fluid can be cultured and their chromosomes analyzed. Hundreds of biochemicals can also be monitored for evidence of a serious genetic malfunction.



This sonogram was made by ultrasonic scanning of the abdomen of a pregnant woman. With this technique the fetus can be viewed within the uterus without the harmful effects of x-rays, and it aids physicians in locating the placenta before performing amniocentesis. Engineers at JPL are working on a new ultrasound system that could produce greatly improved images of the growing fetus.

through the wall of the uterus. Of course, this must be done in such a manner that the fetūs itself is not injured. Even at this step, modern technology comes into play. Ultrasound techniques permit a physician to view the position of the fetus within the uterus in a method that avoids the potential harmful effects of x-rays while at the same time visualizing soft tissue structure normally invisible to x-rays. Ultrasound techniques, which have reached an advanced state of development in military applications, are in their infancy in this medical application; an expert is required to interpret an ultrasound image and be sure that the needle he inserts would indeed be safely located. It is of interest to point out that engineers at JPL are working on an improved ultrasound system that will produce x-ray type images that a doctor can immediately recognize. It is possible that this work will lead to an improved viewing system for examing the fetus and for the placement of the needle.

Space photography systems are very appropriate for yet another related project which is under way at JPL. New optical systems are being used to permit a physician to view and photograph a fetus. This is possible using optics inside of a long needle less than 2 mm in diameter. In this way the fluid-sampling process could be monitored visually while, at the same time, the fetus could be photographed and examined for serious birth defects.

There is also another approach (though in all fairness I must point out that this is in the stage of exploration and thus highly speculative) that may permit fetal cells to be sorted out of the blood of the mother without having to puncture the uterus at all. This possibility arises because a tiny fraction of cells from the fetus work their way through the placenta and into the bloodstream of the mother, where they can be detected.

What can be done with fetal cells and amniotic fluid after they are obtained? One procedure already in practice is called karyotyping. This is an examination of the chromosomes of the cell, the carriers of the genetic code. Once a few cells have been obtained from the amniotic fluid, they can be cultured and their chromosomes examined. It is possible to make a map of these chromosomes, actually arrange them in a definite order, and compare them with those that are typical for a normal human being. Normally, there are 23 pairs of chromosomes in any human cell. Their length and their appearance under the microscope permit them to be numbered and arranged in a chart called a karyotype. It is important to note that in Down's Syndrome (mongolism) there is an extra chromosome number 21. So if amniocentesis is performed on an expectant mother, and a karyotype is made and an extra number 21 chromosome is found, then it is absolutely certain that the child would be born a mongoloid.

As you can imagine, obtaining the amniotic fluid, culturing the cells, taking microphotographs of chromosome displays, and finally arranging these chromosomes into an understandable chart is a laborious process—and consequently expensive. One can hardly "cost account" the human aspects of this disease, the emotional trauma which inevitably occurs in a family upon the birth of a mongoloid child and the other problems, but let me say a word about the economics. It has been estimated that the cost for the support of the mongoloid children born this year in the United States will be one billion dollars! (This estimate assumes a cost of $250,000 for the lifetime institutional care of each severely retarded child.) Furthermore, statistical data are adequate to show that if every expectant mother of the age of 40 or older (a high-risk group) could be examined by the process of

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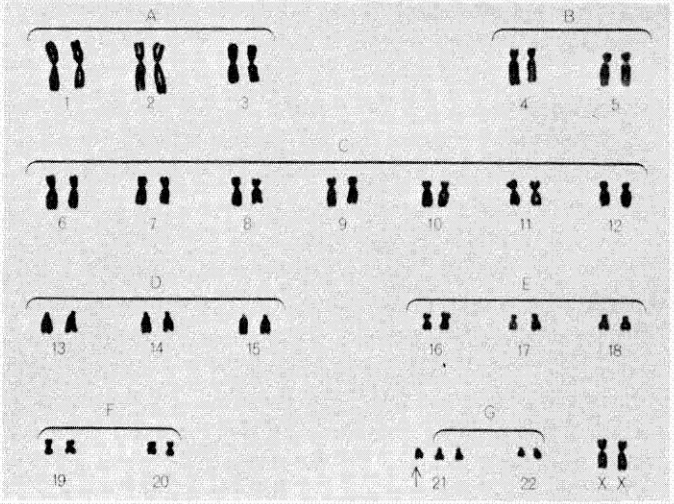
amniocentesis and karyotyping (with subsequent termination of pregnancy if indicated), the annual birth rate of mongoloids would be cut in half.

As for the emotional cost, do you know any families who have produced a mongoloid child? To speak personally once more, I have a close relative whose wife spent six months in intensive psychotherapy after the birth of a mongoloid child, because of the intense guilt she felt over this genetic accident.

Today, amniocentesis and karyotyping are expensive and laborious processes. But here again, they need not be. The Jet Propulsion Laboratory has already developed a prototype device for automatic karyotyping in which the computer automatically searches over a microscopic slide after an operator has scored several convenient arrays of chromosomes. The computer then automatically arranges them into a chart suitable for a doctor's interpretation. The cell-culturing step could also be automated, and the procedure of obtaining the fluid might be made more safe and certain with the help of the new ultrasound techniques. All of this, the result of modern aerospace technology applied to medicine, means that in a few years karyotyping can be a routine examination procedure available at reasonable cost whenever the physician feels it is indicated.

Indeed, it may be indicated in a variety of situations.



Chromosomal analysis of cells obtained by amniocentesis can be used to detect hundreds of severe genetic defects. This karyotype shows that the fetus is a female (two X chromosomes) and that she will be seriously mentally retarded (mongoloid) as a result of the extra No. 21 chromosome.

Mongolism is only one genetic problem that can be detected by amniocentesis. Let me emphasize these points. First, more than 1,600 genetic diseases have already been identified, many of which we know can be detected by amniocentesis. Many of them are quite rare, but all together they represent enormous human suffering and enormous cost to society.

Second, we already know how to determine the presence of such congenital defects via amniocentesis in ample time to permit a healthy termination of pregnancy. We are steadily learning how to make still more tests, how to do the present testing in a safer manner, and perhaps even how to sort fetal cells from samples of the mother's blood without ever having to puncture the uterus at all.

Third, these procedures and these tests are still in a laboratory stage, and can be carried out only with the help of expensive equipment and highly trained experts. However, modern technology is already at hand which can automate, simplify, and greatly reduce the expense of all these procedures.

Caltech and JPL have for more than a year been holding committee meetings on the question of how to push forward our efforts in this area—how to combine the scientific leadership of Caltech with the engineering expertise of JPL in the service of health care and research.

A Changing Concept of Health Care . . . *continued*

Very early in the committee meetings I suggested the possibility of some sort of workshop meeting which would bring outside medical experts together with a few people from Caltech and JPL to discuss these problems. By a procedure which I am sure you are all familiar with, it was suggested that I take on the task and, specifically, locate some funding sources to defray the inevitable costs of such a meeting.

This was accomplished with the help of Dr. Milton Wexler and his California Chapter of the Committee to Combat Huntington's Disease, a foundation whose aim is to find either a prevention or a cure for a very tragic neurogenetic disease—Huntington's Chorea. The representatives from Caltech at this workshop included the chairmen of the divisions of biology and engineering—Robert Sinsheimer and Francis Clauser—as well as William Corcoran from chemical engineering and John Baldeschwieler, the newly appointed chairman of the chemistry division. Leroy Hood, a campus immunologist and cancer specialist, was present as were Norman Horowitz and Richard Russell, both outstanding scientists in the field of genetics. William Pickering, the director of the Jet Propulsion Laboratory, was present along with some of the other JPL people who have the largest amount of responsibility for JPL's program in medical technology—Frank Goddard, Al Hibbs, and Robert Mackin. We had about a dozen experts from government, medical schools, and outstanding biology and biochemistry departments of other universities.

We found that there was great interest in this subject, as indicated by the fact that of all the outside experts we invited to attend this workshop not one refused the invitation and almost all were able to attend.

I have no intention of reviewing the three days of discussion or of speaking for all present, but the consensus of the group was strong on some points. For instance, we agreed that over the next two decades we will witness a revolution almost impossible to imagine in the practice of medical science, as new biological and chemical knowledge and new skills in high technology and engineering are brought to bear on health care. Furthermore, as we ourselves believed—and our visitors agreed—Caltech and JPL together have almost all the key components to lead the way in this revolution. The component that is missing is medical leadership—a critical mass of outstanding experts in scientific medicine who could communicate with our molecular biologists, geneticists, and engineers; who could help teach our students who are already excited about these new fields of interest; and who could work with us to make sure that the application of our scientific and engineering knowledge is pointed in the correct direction.

Caltech and JPL together have almost all the key components to lead the way in the coming revolution in health care

As to how many such individuals are needed, numbers ranging from one to twenty were suggested, together with a variety of implementation plans. Nothing attracts a great scientist more than other great scientists; that is to say, outstanding men and women seek an environment in which there are others equally able and who work in closely related fields. I believe it is for this reason that the consensus at the workshop seemed to suggest—as a minimum starting position—that we should attempt to find three outstanding specialists in molecular and genetic disease, place them on our staff at the earliest possible time, and provide them with the facilities and technical support which they would require.

How this might be accomplished we do not yet know. But that it can be accomplished seems amply demonstrated by the enthusiasm of our guests at the workshop—individuals of the same caliber as those whom we would seek. That it needs to be accomplished, by us, here and now, I hope I have convinced you. □