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The Future of Biomedical Research and Education

The Rockefeller University

THE FUTURE OF BIOMEDICAL RESEARCH AND EDUCATION

Four Talks on the Occasion of the Installation of Dr. Joshua Lederberg as President of The Rockefeller University

OCTOBER 16, 1978

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Foreword

On October 16, 1978, Joshua Lederberg was installed as president of The Rockefeller University. A Nobel laureate and a major contributor to modern genetics, Dr. Lederberg succeeded Frederick Seitz, the distinguished physicist who served as president for 10 years and under whose leadership The Rockefeller University Council was founded.

As part of the installation activities, the Council sponsored a colloquium on the outlook for biomedical research and education from the vantage points of the University and its two nearest institutional neighbors—Memorial-Sloan Kettering Cancer Center and Cornell University Medical College. The three speakers not only provided unique insights based on their individual involvement in the scientific pursuit, but also voiced concerns shared by the institutions they represent. Some of the major themes emerging from the colloquium were explored, eloquently and trenchantly, by Dr. Lederberg in his installation address.

We are indebted to the generosity of The Carl and Lily Pforzheimer Foundation that makes it possible to present these four statements to the wider audience they deserve.

JAMES A. LINEN III
Chairman, The Rockefeller University Council

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The Capitalism of Curiosity

GERALD M. EDELMAN

Vincent Astor Professor, The Rockefeller University

Perhaps I should begin by admitting that it is not my habit to attend parties of the Jet Set. However, it was once my pleasant fate to attend a soirée at which I met Andy Warhol, the artist. He told me, after learning that I did scientific research, that he was very interested in science. Indeed, he said that he received loads of scientific journals, none of which he was able to understand. He found that regrettable and then, after some chitchat, he said shyly, "Do you mind if I ask you a question?" "Please, go ahead," I replied. He looked up penetratingly and said, "Why does science take so long?"

I tried to answer this question by drawing analogies to some of his paintings of famous movie stars, but didn't get very far. What I tried to explain was that a scientist cannot be satisfied only with a beautiful image or idea, but must be able to make sure that the idea corresponds to some state in the outside world—a rather more difficult enterprise than simply imagining beautiful theories. Finally, I tried to discuss some of the artistic beginnings of science, because I think that, in their initial moments, art and science are very similar.

I'm afraid I didn't succeed very well in these explanations. I hope to do somewhat better today by trying to express some thoughts on both the psychology and the economics of basic research, using my field—immunology—as an extended metaphor. In particular, I want to draw your attention to an idea that lies at the center of immunology, both because it has staggering implications in its own right and because it offers fertile suggestions for the subject of my talk today.

My main purpose is to make two general observations. The first is that basic research is necessarily an inefficient process. It is not subject to ordinary rules of management and stewardship. Instead, it develops

rich and unpredictable stores of facts and ideas that comprise a kind of research capital, which can be spent later for such practical ends as the cure of disease. But, like all other capital, most of it can't be spent before it is accumulated. Many people think that the line from curiosity to application is a straight one; I do not agree. The fact is that research capitalism or the capitalism of curiosity follows a quirky and difficult route, in no way subject to the ordinary rules of economics.

My second observation is concerned with real capitalism as it bears upon the funding of scientific research. There are certain features of this funding that no sane capitalist would tolerate in his business. In the latter part of this talk, I will explore that assertion, but for now let me just state that there is an important link between the capitalism of ideas and that of material resources. This link is most indirect, however, and to make it effective requires a tolerant and wise view on the part of both research administrators and the keepers of the public funds.

Basic research is a reflection of a kind of play. This feature tends to be obscured by the technical and planning aspects of research that scientists must make one of their major concerns. Nonetheless, I believe that the spirit of play underlies most basic research efforts. You can't make play efficient without ruining it. If that is true, the imposing question becomes: Why pay scientists to play? My reply is that there is no other way to assure that proper climate in which fundamental discoveries about our world can be made.

The task of basic research is to discover and describe significant new features of the world under the guidance of a surmise, hypothesis, or theory. This is frequently misunderstood. Often I've had graduate students ask in the middle of an experiment, "Why are we doing this? Can't we just go to the library and look it up?" That kind of question from students of science might seem astonishing, but it indicates a point of view that is common even in specialized precincts. The answer is, one can't look it up—one guesses and one tries. Very often there are other misconceptions about the scientific method. Whatever it is, this method is not a formula to calculate discoveries. It is something to tidy up one's fumbling and guesses after one has finally found some

apparently coordinated facts or clues. I shall discuss this a bit by using immunology as an example, in order to give you some sense of the direction of discovery and research in a basic area with which I am familiar.

Curiously enough, backboned animals must do something like this guessing and tidying up in order to protect their individual integrity by means of immunity—in other words, they must recognize foreign molecules by use of their immune systems. Let me indulge in a somewhat lengthy digression and consider how this is done. I think such a digression may be illuminating, for some of the principles that are exemplified by this biological system come close to those that must guide basic research itself.

The problem in immunity is to distinguish self from non-self. To put this in a more sophisticated fashion, the immune system must tell the difference between the shape of foreign molecules and the shape of molecules that belong to a particular individual. The way in which the immune system does this is surprising. The system is distributed throughout one's body in the bone marrow, in the thymus, which lies just behind the breastbone or sternum, in the spleen, which can be found under the left rib cage, and in a variety of small organs called lymph nodes, which are distributed all over the body. The immune system develops during embryological development and early infancy and consists of a rather large number of cells; in a man, perhaps that number exceeds 100 billion. These cells, called lymphocytes, circulate back and forth in the blood and percolate through a variety of organs in the body. They move through various vessels; and finally they police the entire body. The only exception is the brain, which is sealed off by its surrounding bony structure, and must have other ways of handling immune defense. From a narrow point of view, these lymphocytes must deal with this problem of defense. But, as I said before, from a more basic viewpoint, they make the distinction between self and non-self, a fundamental process in more highly developed organisms.

The problem, therefore, comes down to one that was first investigated in chemical detail by Karl Landsteiner, who worked in this University in its early days as an Institute: How is it possible for an

organism to tell the difference in the actual, three-dimensional shape of one molecule as distinguished from another? The rough answer is by means of a very special molecule called immunoglobulin, or antibody. This molecule, which makes the key distinction between self and non-self, resides on the surface of the lymphocyte. Ten-thousand to a hundred-thousand antibody molecules stick out like little fence-posts on the lymphocyte surface. Within the lymphocyte is its nucleus, containing the DNA with all the genetic instructions; on the periphery of the cell is the plasma membrane, which contains the antibodies. It is important to point out how small the immunoglobulin is compared to the cell—the molecule is so small that it can't even be seen in detail by the electron microscope.

In order to know how this molecule works, we must somehow see its structural details. Now, the immunoglobulin molecule has an intriguing structure with which I have been concerned for about twenty years. It is made up of a large number of components, but, as I said before, the molecule is still very small compared to the cell itself. A few of its structural features are particularly important. First of all, it is a T-shaped structure that is symmetrical; the stem of the T sits on the cell. At the end of both arms of the T is a cavity known as the antigen-combining site; this is the place at which the molecule recognizes a foreign shape. To see what this recognition might be, imagine a cookie and a cookie-cutter, if you will, each complementing the other; the invading molecule (the cookie)—or the antigen, as it is called—enters and is bound closely in each of the two cavities (the cookie cutters) of the immunoglobulin molecule. That means that these cavities must have a specific shape. In order to recognize different foreign molecules, the cavities on antibody molecules affixed on different lymphocytes must have different shapes. Perhaps I should change the metaphor—instead of cookies and of cookie cutters, it might be better to imagine these cavities to be a large number of locks into which fit a large variety of unknown keys, which are the foreign molecules.

When the antibody molecules bind foreign molecules, a great number of reactions take place: more cells are made, and a variety of mechanisms are called into play to destroy or break down the foreign

molecules or otherwise entrap them. Obviously, this is a major mechanism for the body's defense against disease. In bacterial or viral invasions, for example, the bacteria or viruses are in some measure destroyed or inactivated as a result of this binding process.

My main concern in trying to do research on immunity has been the question: How does this sytem of locks and keys work? This question is not easy to answer because of the number of "locks" and "keys" one has to deal with. I think you would be startled if I told you that, above a certain size, there is hardly any molecule of defined shape that the immune system cannot respond to, including molecules that have never before existed in the history of the human species or any other species. This statement is a close approximation to the truth, with some allowance for the special manipulations that have to take place within the immune system.

Now, common sense would tell you that, in order to accomplish such a feat, the immune system has to know something about the shape of the key before it puts the shape of the lock into place. This idea, which is called "instruction" in the field of immunology, has turned out to be false and inadequate. During the development of the system, no information whatsoever exists on the shape of a future invader that is going to be recognized by this system. Astonishingly, the system contains all of the necessary potential information before it ever "sees" anything out in the world. This is so because it is a "selective" system. It does not receive instructions in the way dough does when a cookie cutter cuts out a cookie or in the way a master key is made by impression from a lock. In fact, the system has so many different kinds of locks that virtually any key will fit more or less well into one or more than one of them.

Each of the lymphocytes that I've talked about has its own antibody molecules sticking out with their distinctively shaped locks, or cavities, waiting for a foreign molecule, the key. When that foreign molecule comes along—for example, in the form of a virus of a particular shape—it will move along among this collection of cells, and find those that bind it more or less well. When the virus does bind, an amazing mechanism goes into play that says, "Make more of that kind of lock—that is, make more of those kinds of cells and make more of

those kinds of antibody molecules with that particular shape of "lock." According to the experience the animal has had with a variety of foreign molecules, or keys, this command increases the proportion in the system of the kinds of locks that happen to fit these keys. This principle of selection accounts for responses to transplanted skin, to transplanted hearts, to allergies, to typhoid or polio immunizations, and so on. The principle is known as clonal selection; clonal, because the stimulated cell actually divides to form a clone, or asexual progeny, of a single cell.

This is an astonishing principle. It is obvious that, at a particular time, each immune system could not actually have a sufficient number of locks to recognize everything in the world. What it does have is a very large number of different ways of arranging to build the lock portion of different antibody molecules to achieve different shapes. The calculated number of potential locks, or antibodies, that can be made by such a rearrangement is unbelievably enormous. That process is activated very early in each individual's life. When something foreign comes along, it encounters many locks as it circulates, and a reasonable likelihood exists that it will find one that it fits more or less well.

The surprising feature of this system, which is, in effect, a system of discovery, is that it *appears* to be highly efficient. But fundamentally efficiency *cannot* be the issue, for the system must deal with an *unknown* future, one in which the animal cannot tell what foreign material it is going to encounter. And the world is very rich in foreign materials! Therefore, the immune system is apparently a wasteful system at the level of the repertoire of locks that exists in the animal—some will never be used at all. But once a lock is encountered, the system is extraordinarily effective in amplifying that encounter and developing the right kind of antibody. Perhaps it might be called a learning system, in which the body learns how to deal with this world full of foreign molecules as a result of the very effective way in which the selected cells divide and make more kinds of antibodies. The attempt to understand this intriguing process has formed the saga of immunology during the last fifteen or twenty years.

By now we pretty much understand the molecular principles upon

which the extraordinary idea of clonal selection stands. Dr. Lederberg once published an article on what he called at that time "instruction and election" (not instruction and selection), and this article was one of the fundamental contributions to the idea that there is a pre-existing diversity of antibodies. This concept has had deep implications for biology. But the story I have told also has a deep implication for psychology of research. Because of the unpredictable nature of the future and the complex structure of the world, we need in scientific ideas and observations the equivalent of a repertoire of different pre-existing antibodies. Of course, this does not imply that we must not plan, use logic, and instruct ourselves as much as possible. But I believe that, if you study a scientific problem long enough, you come to the conclusion that you will be faced with an irreducible minimum of facts and ideas, which, when first conceived, seem to have little practical meaning. They seem as gratuitous, if you will, as some of these antigen-binding cells with their antibodies. Mind you, the cost of having such a system of antibodies is that most of the cells don't do anything at all. They simply sit there, live, wait, and die. But this "cost" of diversity is the price the organism must pay to get the cells that *are* efficient in their response. The fact that we are all alive in this room indicates just how good such a system can be.

In research, we often don't know the connection between the results of our studies and their practical applications. There is one reassuring historical point, one made by Lewis Thomas and a variety of other knowledgeable and wise people: almost always, apparently inefficient basic research pays off handsomely, efficiently, and in unpredictable ways. It is obvious that a new vaccine which prevents a major incapacitating illness is a vital development in both humane and economic terms. What is not obvious are the humane and economic benefits of a basic discovery that organizes a field, opens new vistas, or makes development of a vaccine possible. What is the dollar-and-cents value of the structure of DNA or, for that matter, the founding of biochemical genetics, a milestone that Dr. Lederberg helped to mark? To take a more personal example, I am always embarrassed when reporters ask me to explain the practical benefits of my own work on immunoglobulin or antibody structure. That work has cured no

disease, but I do think it has helped to reorganize our thinking about all diseases related to the immune process and it also allows us to envision new diagnostic and therapeutic tools. For example, now that we know its structure, the antibody molecule can be cut up in various ways and its properties altered in order to treat people more efficiently, in ways that the body itself has not yet managed to contrive throughout evolution. In other words, this kind of knowledge is basic research capital, which is ready to be invested in useful and humane projects. I must reemphasize that, for the most part, the accumulation of this research capital was not in a straight line or for a predicted end result.

Having digressed so far to make the point that there is a necessary inefficiency in accumulating research capital, I now turn to my second assertion, which is related to real capitalism and the support of research. At the outset, I want to emphasize that I have enormous admiration for what has taken place in this country since World War II in founding and developing various institutions, such as the National Institutes of Health and the National Science Foundation. In particular, I want to praise the whole system of peer-group review, which calls upon scientists to review the merits of other scientists' proposals. Nevertheless, it seems to me that there are two areas in which this system may be in need of larger insights. These are, first, the failure to recognize sufficiently that a fairly large amount of basic research capital is necessary before application is possible. In the absence of this capital, direct mission-oriented pushes or large task-forces almost always fail. Second, to make a more practical point adumbrated in my earlier remarks, research support strikes me as a curious form of capitalism indeed—one which lacks the usual buffers of space, time, or money that a capitalist or a businessman would employ to put his funds to the best use. Basic research funds usually are given via grants after proposals have been reviewed by scientific peers and agency officials, and after the funds have been appropriated by the Congress. The funds usually are given according to strict budgets for defined periods of time, and this is all well and good. But a close scrutiny of the process indicates that if there are any untoward developments in a project, or if needs change during the research period, the scientist has recourse to only one method—he must reapply over time periods

that usually are too long to do him any good or to meet the immediate crisis that he faces. And, at the other end, even if an official at the NIH, for example, has understood what the problem is, he has a very hard time rustling up contingency funds to tide the researcher over. The needs for accountability and the political process in some sense act in conflict with the needs of the researcher.

There are related needs, which are particularly striking these days. One of them is the increasing cost of setting up young researchers in a new research venture—beginning assistant professors, for example. Everybody in our kind of enterprise knows that these young brains are the ones that we can count on for new developments and new imagination. Furthermore, it no longer is possible to have every kind of field represented in every good institution. There must be some fractionation of fields; this principle has been adopted at The Rockefeller University with great success. The question I must ask is, "Given all of these needs, would a businessman run his company without some form of buffering provided by equity, investment capital, and bank loans?" I think it unlikely, and would therefore suggest that perhaps the time has come to consider the idea of a research bank, a place in which government funds are placed to buffer the various situations and contingencies that arise during a research project. Such a bank could serve to meet a number of contingencies that confront the researcher in the course of his basic research. Let me illustrate this a bit by discussing research budgets for a moment.

A typical budget proposal, taken from my own laboratory, demonstrates the definite kind of funding system that requires a specific budget. The budget must account for the time and effort of the various people concerned with a particular project, and include some guesses about the kinds of scientific equipment that are necessary. A fairly healthy part of the budget is dedicated to research animals and general laboratory supplies, as well as to some costs for contracts, publications, and shop expenses. But my main point is that this budget, which in year one started at $67,000 or so for salaries, grew to $78,000 as a result of inflation and other unforeseen contingencies, so that the total proportion of the budget dedicated to salaries has become huge. These days, the remaining unencumbered funds available to a researcher for

a reasonably modest project, such as this one, is a very small percentage of the total. Furthermore, a laboratory like mine must make multiple requests of this kind to different agencies. If anything happens to endanger some of these funds—$11,000 out of a total of $96,000, for instance—the project is in jeopardy. The salaries are paid and increase with the years, but the project cannot go ahead. Here is a typical situation in which a rapid mechanism of buffering of funds insured by a loan from a research bank could be of very great use.

Another area pertinent to this suggestion relates to grant renewal and delays in the grant decision-making process. If I have three or four grants supported by different agencies with different starting and ending periods, a really remarkable juggling act is essential, if a grant ends, to keep a constant flow of money coming to the laboratory. It requires the cooperation of officials in the various agencies, as well as the cooperation of officials in the University. Although a grant is awarded in principle, a grant-decision delay means that the money simply is not there, and some way of buffering that money must be provided. Moreover, as I mentioned earlier, one of the chief challenges to a researcher working in this and other universities is to set up enterprising and brilliant young people in their new laboratories. Unfortunately, because of budget stringencies and delays, this mechanism has not been worked out completely within the usual grant frameworks. Finally, I think there is some merit in considering the establishment of a central clearing house for valuable scientific equipment, which is becoming more and more expensive. A research bank might have some function in such a plan.

Of course, as it stands, this proposal of a research bank is very general, and I am aware that there is a conceptual problem: basic research provides no direct profit and no obvious tangible product. But, as I have tried to show, science has an invisible product with enormous implications for our economy. Indeed, some economists have estimated that over 30 percent of the economic development in this country since World War II can be related in a more or less direct way to the basic research accomplished in that period. Moreover, I am told by people such as Gus Kinzel, former director of research for Union Carbide, that basic research is much less costly than applied or

developmental research. For every dollar dedicated to basic research, he tells me, about $10 must be spent on applied research, about $100 on development, and $1,000 on plant. Basic research, essential basic research, is cheap, given the return.

I know how much work would have to go into thinking through the practical details of a research bank. This is not the place for these matters, and the idea may not be practical in the end because of the political difficulties. All the more reason for institutions like The Rockefeller University, the President's Office of which already serves many of the functions of a research bank, as I suspect Dr. Lederberg has already found out. Indeed, it has always been a local tradition here to provide some of the buffers that I have been talking about, but it is a hard tradition to maintain in the face of mounting costs. Clearly, we must continue to receive support from enlightened private sources, for that support has been one of the key reasons this place has remained excellent. I join with the others here in the justifiably optimistic hope that Dr. Lederberg will deepen and adorn the great tradition of the capitalism of curiosity at The Rockefeller University, a tradition composed of both private and public support, of independent laboratories, of magnificent ancillary services, and of a fervent belief in the intellectual excellence of the workers, tempered by an understanding of how that excellence is achieved. That understanding stands upon the principle that basic research does not run in a direct line from curiosity to achievement and use.

So, as I said to Mr. Warhol, perhaps too lugubriously and with a personal poignancy I needn't discuss, "Science does take a long time to do well." Given that, researchers must have the freedom and the time to pursue their ideas. In an atmosphere of mounting frenzy and push programs, which—at least in the public sector—seem to be more and more prevalent, perhaps it would be well to remember that ideas do not come every day. Certainly good ideas don't come every day. I cannot help paraphrasing in a somewhat inexact but essentially correct way the story about Paul Valéry, the French poet, who went to visit Einstein because he was interested in poetic creativity and scientific creativity. He asked, "What do you do every day?" Einstein said, "Well, I get up and shave and I take a walk and I think, and by that

time it's lunch and then I'm a little tired, and I think a little more in the afternoon, but by that time I'm really tired, and I have supper and I go to bed. Perhaps I have a sail or another walk, but that's about it." Valéry said, "Do you keep a notebook?" Einstein looked at him, startled. "What on earth for?" he said. "You know, to write down your good ideas." Einstein said (and I believe this is a true story), "Look, I don't get many. And don't worry, when I get one, I don't forget it."

Once having assured the quality of a research climate, I believe that the best policy is to leave the researchers alone to their play. That is, do not get in their way, for an excess of zeal leads only to logic rather than to imagination. I would like to end with one comment and one further anecdote. The comment is by William Butler Yeats, who was a great poet but, unfortunately, a great enemy of science. Nonetheless, he obviously understood imagination and creativity. He said that bad art is will substituting for the imagination. This is also true of science. Bad science, fundamentally, is will substituting for the imagination.

The anecdote is told by Freud. During the Napoleonic Wars, an emergency was anticipated and Napoleon called his councils of war and consulted his generals about what should be done. An old general said, "The most urgent thing to do is wait." To my mind, this a good description of the psychological tone of doing basic research. It is dominated by the urgency of waiting. No highly structured or programmatic approach will succeed as well as that form of urgency. In places like The Rockefeller University, with the love that its scientists have for their discipline and their art and their science, we have nothing to fear about the absence of urgency.

Medical Education and Biomedical Research

THEODORE COOPER

Dean, Cornell University Medical College

This is a happy occasion for all of us—for different reasons. We at Cornell are excited and expectant. We congratulate The Rockefeller University; we congratulate President Lederberg; and we even congratulate ourselves. Indeed, we are fortunate to be your close neighbors, your colleagues, and, we hope, your partners in many future scientific and educational endeavors.

Among the many challenges and opportunities that you will consider, some are specific to the York Avenue institutions. Among the greatest of these is the achievement of the promise raised by the proximity of three great institutions with some common heritage, some common purpose, some common programs, some common problems, some common needs, and many uncommon people and ideas. This commonality—an old dream that I have heard ascribed to many of you here today—should take real form now, because in our own ways we all need it; New York needs it; the American systems of biomedical research and education need it, not for survival, but to be able to prepare for the future.

It is not difficult to convert happy occasions such as this into gloomy ones simply by reporting most of the discussions being held by national leaders in medical education and research. The commentary can only be characterized as ambivalent, guilt-ridden pessimism. We are being convinced that we are guilty of fraud, financial irresponsibility, and failure. Indeed, for a system that has done so much good, it is remarkable how it can be perceived as so bad. The explanation of this perplexing and frustrating situation lies in the changing criteria of social justification and evaluation.

We in this country have accepted as appropriate and right that the

government should support medical research and medical education. We have gone further. We have said that, in the public interest, the government should support a very large portion of the costs of medical research and education, and we have attempted to develop a system of public and private institutions that could react to these assumptions as if the institutions—public and private—operate the same way.

The character of medical education has been greatly influenced by research activities in our institutions, even to the extent that faculties have been refashioned and facilities redesigned. The remarkable impact of research can be seen on medical practice. And as medical practice changes, so does the educational process. Thus, research has had both direct and indirect influence on medical education. Financing has been a factor; the character of the faculty has been a factor. No longer is the philosophy dominated by "the practitioner." The students are selected by people with different viewpoints. The emphasis, the orientation, has changed. Medical education presents other unique reflections of the realities of financing. Large and growing amounts of money from practice are underwriting faculty salaries. As federal research funding is increasingly unable to meet the cost patterns that were set ten years ago, practice plans are being looked into in order to bridge the gap between commitments and institutional resources. Faculties are rationalizing these changes by agreeing that perhaps such plans could come close to income parity with the private practitioner.

At the moment, no greater force challenges our philosophies of operation than cost escalation in medical care. So pervasive is this concern that no sector—education and research included—is free from suspicion of "fat," excesses, waste, greed, and irresponsibility. So loudly and often have the charges been made that the allegation is now the conclusion. As a consequence, we are accepting refinancing without changing aspiration or expectation. We are not even willing to suggest that perhaps it is not possible to do all things with less money. We are reluctant to challenge government-mouthed righteousness, because we do not wish to offend those who administer our monies. This is a well-recognized consequence of dependence—the loss of flexibility that accompanies the "emperor's new clothes" syndrome.

Social justification is being interdigitated with scientific evaluation in an interesting but dangerous way. It is one thing for society to decide "it isn't worth it," but quite another to conclude that not being worth it means that it has no intrinsic merit or, worse, that it was undertaken with malicious deceit in mind. In order to attempt to meet every possible objection, every human failing, the government is attempting to direct the system, to achieve social objectives, and to guard against abuses by creating more and more specific restrictive legislation and regulations. In a very real way, the proliferation of rules and reporting systems is a greater problem than are the deficits of funding for our institutions.

As one reviews the forthcoming legislative calendar, no matter what item is encountered, one is faced with recidivism in various ways:

1) The Health Professions Education Bill will lead to requests for more federal direction of who can go to medical school and what should be taught. At the same time, there will be withdrawal of funding and increase in control. The student loan provisions and regulations are already incredible. For a loan of $30+ thousand, the student is expected to pay $140+ thousand.

2) The Research Authorization Bills will attempt to change emphasis, will increase reporting, and will decrease promises of future support. The administration's new "plan" will not have significant impact for the next two years and, if it did, it would be to "cap" the system in the name of stability.

3) The Health Planning Legislation will intensify the regulatory activities of local bodies. Medical colleges will be increasingly involved and ensnarled. As dependence on clinical-practice income increases, our vulnerability to political manipulation increases.

4) Measures to change practice through financing will receive the greatest attention. Reimbursement for teaching hospitals will be changed in efforts to reduce costs. Limits on incomes will be proposed. Limits on services also will be proposed, while at the same time more and better care for everyone through National Health Insurance will be promised.

5) The Drug Reform Act and some recent regulations relating to clinical investigation in academic centers, proposed by the Food and

Drug Administration, will magnify reporting, recording, and reviewing, way out of proportion to any benefit they could possibly obtain.

6) The Federal Trade Commission will pursue the health professions with the doctrine of salvation through competition.

The list is long and, if looked at in isolation, presents a depressing picture. But federal brushes should not be painting the whole canvas. There are several encouraging signs. The most important of these is the revival of intellectual independence in our private institutions. The evidence is substantial: the refusal of capitation funds by several institutions rather than acceptance of federally dictated admission policy; the successful campaign against restrictive DNA legislation; the successful campaign against implementation of Sec. 227 of the Medicare Law; and a meaningful modification of the Office of Management and Budget circular A-21 on overhead determination.

The biomedical researchers, the medical colleges, and the health-science centers are less reluctant to work openly with business, particularly with the industrial world. Part of the reason behind this conversion is financial self-interest. Yet it is a very important evolution. The admirers of the American system of enterprise can come out of the closet. The association with government is no longer free of implications of control and direction. And, in fact, there is growing concern that the directions a required and the controls imposed by government are less and less justified on appropriate social grounds, not to mention scientific and academic critera. We would be well advised to restore independence through balanced pluralistic interaction. We should be making scientists, physicians, and other health professionals aware of the career potential in nonacademic and non-governmental settings.

One can even make the remarkable observation that the academic and practicing wings of the medical profession have come closer together. "Organized medicine" has helped the academic brotherhood in meaningful ways in Washington by lobbying for legislation that is helpful to medical schools and the scientific community, including appropriations for the National Institutes of Health and sound positions for education legislation in the health professions. These have put a different perspective on the "town-gown" situation as we move

into the need for rapid integration of new knowledge into clinical practice through education. The busy practitioner knows he has a reliable friend and critic in the academic scientist-physician who can help sort out the meaning and quality of newly proposed methods of diagnosis and treatment.

Yes, not all the signs are negative. The list of positive trends, like the apparent success of the voluntary cost-containing efforts, is growing. But the most important reason for optimism lies in realizing how much we are going to be able to do for people in the future. Social and scientific forces will insure high interest, growing expectation, and need for innovation, experimentation, and education. Too many people have viewed modern medical technology as approaching the ceiling of possible intervention on disease treatment and prevention. Dr. Lewis Thomas has repeatedly warned of this short-sightedness. If one looks ten years down the road, the possibilities are staggering. From immunology, genetics, neurosciences, behavioral science; from pharmacology; from bioengineering will come great insights and tools for the practice of general medicine, not superspecialty medicine.

The "new-old" panacea for our social-medical ills, i.e., preventive medicine, will take on new meaning because we shall have real tools to find the susceptible, to make predictions far beyond statistical correlations alone. We shall be able to interpret biological response to social ills with confidence.

At our medical college, we have begun the process of preparation for tomorrow. We have recognized that we can no longer do business in the same old, comfortable way. We accept that there are limitations to our resources, but not to our vision. To avoid becoming a part of a seedy, aristocratic home of solid mediocrity, we shall seek to improve our productivity. We shall regain independence of action through reduced dependence on government. Cornell Medical College spends about one-third of its resources on research, one-third on education, and one-third on services. We shall repartition our "hard monies" in favor of the support of education and science. We shall redesign our clinical programs with The New York Hospital and our other affiliates to provide more service to the community at less cost per citizen. The future of clinical teaching will demand diversification, a broader

variety of clinical experience. The aggregate expenditures for clinical service and education will increase, but will derive from various sources. The national refinancing of health services implied in what is called National Health Insurance will offer both opportunities and problems. The problems are conceptually manageable, and we need to get on with preparing how to accommodate them.

Our independence—our productivity and our ability to dream—will come through strong associations with The Rockefeller University and Memorial Sloan-Kettering Cancer Center. Therefore, we wish you success, for we cannot help but grow with you.

The Competing Roles of Basic and Applied Research on Cancer

LEWIS THOMAS

President, Memorial Sloan-Kettering Cancer Center

It is a privilege to be here today, on this great occasion in the life of The Rockefeller University, and a quite special and personal pleasure for me as an alumnus of the venerable Rockefeller Institute, as a trustee, and as a representative of Memorial Sloan-Kettering. My remarks this morning are made in this latter capacity. I want to explain some things about what my institution is up to, just across the street. It is not widely known that Memorial Hospital was placed where it now stands, 40-some years ago, because John D. Rockefeller, Jr. was convinced that cancer research and patient care were going to need this proximity to both The Rockefeller University and Cornell.

First off, I'd like to say something candid, ambitious, and self-interested about the future of Memorial Sloan-Kettering. Obviously, we have a single, very long-range mission as our assignment from society: to do whatever becomes possible to do in order to reduce the threat of cancer, and, in the best of worlds, to get rid of it. This mission is self-evident from our title and charter, and the ambition to get this accomplished is what drives the place along. However, there is another mission and ambition in the back of the minds of many of us. It is to form intellectual linkages as close as possible with both our distinguished neighbors, the Rockefeller and Cornell, so that all of us can capitalize on the lucky creation, here on York Avenue, of as concentrated an aggregation of scientific firepower as exists on a single city corner anywhere in the country.

I am convinced that there are new symbiotic arrangements that can be worked out among these three institutions that could have the effect of greatly enhancing the kind of science done here, particularly

in such times of inadequate funding for biomedical science as surely lie ahead for all of us in the next decade or more. Moreover, I am convinced that closer ties among us, if worked out carefully and with taste—which means, in my view, with a good deal of informality and looseness, and worked out by the faculties concerned—would have the net effect of making it enormous fun to work here, especially for those generations of the brightest young people, in training for careers in science, whom we all hope to see agitating back and forth across 68th Street and across York Avenue. It goes without saying that the quality, braininess, and enthusiasm of the very youngest people, those just beginning their scientific careers, provide the most certain and exacting test of success for institutions like these three, whatever the differences in our structure and mission.

And, of course, there are great differences, needing understanding and frequently needing explanation. Across the street, Memorial Sloan-Kettering is a single-mission institution, dedicated to the conquest of a single disease. This suggests to some observers, at a distance, that our science must be highly targeted, programmed in every detail, and squarely in the area of what is called applied science. It is abundantly not so. On the contrary, virtually all of the research in the Sloan-Kettering Institute, amounting to about $30 million per year, would have to be classed as basic research, if this term is taken to mean, as I mean it, the exploration of tentative hypotheses in an atmosphere of high uncertainty. It is this matter of uncertainty that defines basic research, in my opinion, and differentiates it from applied science. All of us can make guesses about the underlying mechanisms which are responsible for switching a normal cell into the mode of a neoplastic cell, but none of these guesses can be regarded as anything like a sure thing. The research has to be based squarely on making guesses, and for a biological problem as broad and profound as cancer it is necessary to cast a very wide net, and to make up stories, hypotheses for testing, in many different fields of biology. The laboratories of Sloan-Kettering are engaged in this kind of enterprise, covering as wide a cut as is logistically feasible of the fields that seem, at a guess, to be somehow or other relevant to the underlying process of neoplasia.

Research of this kind cannot really be targeted, nor can it even be centrally controlled or run by committees within an institution; it requires the imagination and mind-changing of individual investigators. For instance, there are some pretty good reasons for supposing that immunologic mechanisms may be involved in natural defense against cancer, and it can be imagined that most of us do not develop cancer because of the proper functioning of such mechanisms, but in order to study this matter it is necessary to learn a great many things about immunology itself, in general; the time has not yet arrived for the launching of any kind of applied targeted research program for immunology in cancer; there is nothing resembling certainty here; it is plainly a matter needing basic science of the most uncommitted, undifferentiated kind. The same thing must be said for our programs in virology, in molecular genetics, in cell differentiation, in aging, and all the rest. None of us can predict, with any sort of assurance, whether or when any one of the lines of research will turn out to be actually connected with the cancer problem, in the sense of being useful or usable. It is something like gambling, but there is, in real life, no other way to go about it.

Meanwhile, there is a certain amount of applied research that can be done, and *must* be done. Despite the plain fact that we are nowhere near to the center of things in the problem of cancer, there are some extremely useful measures that can be taken to treat the disease, and these must be tested, tried out, and improved upon if possible. This kind of research consumes the energies and time of a large group of clinical investigators in Memorial Hospital; most of these people hold simultaneous appointments in the Sloan-Kettering Institute and work side by side with their colleagues in the basic research laboratories.

Therapeutic research is the hardest and most demanding of scientific endeavors. It has to be done in a totally different mode from basic research. In the first place, it can only be done well when highly centralized, carefully programmed protocols are laid out in their most intricate details, way in advance; committees are essential for both the planning and the operation. You cannot go around changing your mind whenever your mind feels like changing, which is the greatest difference from what goes on in basic research (which, as I've said,

works by mind-changing). Once a protocol is laid out and agreed upon, everyone involved is expected to follow that protocol with precision until the results come in. Biostatisticians stand as indispensable arbiters, before, during, and after the work.

We do not have a long history of first-rate applied science in medicine, primarily because it is only quite recently that we've had much in the way of genuinely basic information to apply. The best of our achievements thus far have been in the field of infection, and there may be a useful analogy here for the understanding of where we are heading in cancer research.

I was a medical student in the mid-1930s, when tuberculosis was the disease of most concern. Anyone, from infants to the aged, was at risk. If you were lucky, you survived. If the diagnosis was made early enough, and you were admitted to one of the many state hospitals or private sanitaria devoted exclusively to TB patients, your chances of survival increased. Rest was the only treatment—both for the body and for the lung itself—by inducing its temporary or complete collapse. No drugs helped.

It was also lucky if the disease did not spread. If the bacilli reached the central nervous system, that was the end. The doctor's main function in tuberculosis meningitis was to make the end peaceful for the patient and to comfort the survivors.

From the 1890s, when Koch discovered the tuberculosis bacillus, basic research on the disease expanded worldwide well into the 1930s. Gradually, investigators began to understand how tuberculosis spread through communities, and early detection and isolation methods were developed. The still-mysterious mechanisms that enable the tubercle bacillus to destroy living tissue were explored, and environmental factors were identified: crowding, malnutrition, genetic predisposition, immune responsiveness, perhaps even the stress of living.

But throughout forty years, the single, crucial discovery was that the tubercle bacillus was the sole cause of the disease. Other factors, environmental or genetic, might contribute, but at the center, indisputably, lay the bacillus. If it could be killed and the patient live, tuberculosis could be cured. This achievement led ultimately to the work of Selman Waksman, who, like René Dubos, explored the hunch

that certain soil microorganisms might produce chemicals that could curb the growth of competing bacteria.

But streptomycin was not good enough; it cured only those patients in beginning stages of the disease. It could not reverse consistently the devastations of miliary TB or TB meningitis. Also, it produced disorders in hearing and sense of balance if used over long periods or in large doses. Nevertheless, streptomycin proved that the tubercle bacillus was vulnerable in living tissues and, subsequently, research led to para-aminosalicylic acid and then to isoniazid. Tuberculosis became, at last, a curable disease.

We do not yet possess information about cancer with anything like the central significance of the tubercle bacillus in tuberculosis. Of course, today we have clues that were unknown twenty-five years ago. We know for sure that cigarettes are the main cause of lung cancer. We are certain that other environmental pollutants, notably asbestos, are implicated in various forms of the disease, and new agents, from hair dyes to food additives, come under suspicion with remarkable frequency.

But the identification of environmental carcinogens will not by itself solve the problem, when they are as ubiquitous in nature as now appears to be the case. We need to know the nature of the mechanism in the cell which triggers its transformation from normal to neoplastic activity. It has been suggested that a virus or some other infectious agent is involved, although the idea seems less plausible now than it did a few years ago. The switching mechanism remains a mystery, and it is this problem that constitutes the major preoccupation of basic science in cancer research today.

However, there is progress in cancer therapy despite the lack of fundamental information about the process. Twenty-five years ago, very little could be done in the way of specific or selective therapy, and nothing could be done to prevent or restrain the metastatic spread of cancer to other parts of the body.

Then treatment with chemicals became part of the arsenal. The earliest chemotherapy was the use of nitrogen mustard, which is related to the mustard gas of World War I. Some cases of leukemia responded remarkably well, but the side-effects of the treatment were

alarming and sometimes lethal. Modifications of the drug were introduced, then totally novel compounds, all with the capability of interfering with the functions of rapidly dividing cells, and it became clear that certain varieties of cancer were highly vulnerable to these chemicals.

Even ten years ago, leukemia could be arrested in 50 percent of the children affected, and other forms of cancer regressed as a result of chemotherapy, even if only for short periods. The past five years have produced more dramatic results. Hodgkin's disease is now curable when treated in its earliest stage. Combinations of less toxic drugs, or drugs plus radiation therapy, have given reason for hope—as in bone sarcomas of children—that we can talk tentatively of cures. The treatment of testicular cancer by use of platinum salts has recently been spectacularly successful.

Obviously, not all forms of cancer respond equally well. We have not found the right drugs; we have not found the right combination of treatments. Most importantly, that triggering mechanism still eludes us. But discoveries are coming faster and faster.

How did we get to this point? Do the improvements in our technology for treating cancer thus far represent a feat of appled science, or were they based upon basic science? It was, and is, a mixture of both kinds of enterprises. At the outset, it was entirely empirical, and for some years after nitrogen mustard, most of the effort consisted of screening great numbers of compounds for anticancer activity, more or less blindly. In recent years, however, it has become a considerably more sophisticated undertaking, with molecular design now made possible by today's more basic understanding of the kinetics of cell division; it is now feasible to synthesize new drugs that are aimed at interrupting one stage or another in the cell cycle, and both the potency and the reduction of toxicity are problems that are open to research by groups of chemists and basic pharmacologists such as those now working in the Sloan-Kettering Institute, together with the clinical scientists in Memorial Hospital.

The limitation of this line of research is well recognized by everyone concerned. It is not really a specific anticancer therapy at all, any more than radiation, even the extremely precise and effective forms of

radiotherapy now used for Hodgkin's disease, is specific anticancer therapy. The technology is aimed at rapidly dividing cells, and we will be held at this level until we have learned more about the special attributes and points of vulnerability of cancer cells themselves. It is the best we can do at the present time, and it is certainly not the final answer. But it does work, nonetheless, in some patients with some forms of cancer, and it is still open to further improvement by research. This kind of research can only be done by close collaboration between basic and applied scientists, and it cannot be done at all without the resources of clinical institutions like Memorial Hospital.

One very bright piece of news has come from all the work in chemotherapy to date, and is often overlooked by the public, by critics of the National Cancer Program, and especially by those critics who believe (as I do not) that cancer can be reduced to a minor health problem by changing the environment to prevent it; you could, I agree, accomplish a great deal by eliminating cigarettes, and the identification and elimination of industrial carcinogens is clearly a worthwhile activity to which all of us ought to be committed. But it is highly unlikely, I think, that we will ever find them all and, even if we could, it is still more unlikely that we can change the way our lives are lived drastically enough to get rid of them all. We simply do not know enough yet to talk about preventing most forms of cancer, even though this is the most laudable of objectives for applied science in the long-term future. And even when we do know all there is to know about the environmental causes, we are still going to have to face cancer as a formidable health problem, and we are going to have to treat it.

The bright piece of news is that cancer is, really, slowly, gradually, becoming a treatable disease. I do not say this out of any institutional self-satisfaction, nor with anything but discontent with today's forms of treatment; they are not good enough, they do not cure enough patients, and they are not directed at any central, causative mechanism of the disease. Nevertheless, from time to time, much more often today than just five years ago, they *do* work, spectacularly well, and this means something quite tremendous, to me, anyway. Even twenty-five years ago, I would have said that such a thing would be forever

impossible. I believed that cancer was simply a fact of life, a part of the human condition, like mortality, a sort of tax on living in complexity. But today, to observe the rapid vanishing of huge growths in the lung almost overnight, the shrinking almost to nothing of great masses of malignant cells in the brain, is an absolutely extraordinary thing to see, despite the knowledge that some of the cells are still alive in there and will grow back again, sooner or later. We need a new technology, perhaps an array of new technologies, to assure the elimination of those last, still invulnerable, cells, but I have no doubt at all that this can be done. It will not happen easily or quickly, and we have a vast amount of basic science still ahead to do. Then there will have to be other vast efforts in applied science, but I see no reason at all to be skeptical on this issue. Cancer is no longer the blank mystery it seemed, not very long ago. It has become an approachable, ultimately solvable biological problem.

INTRODUCTION OF PRESIDENT LEDERBERG

PATRICK E. HAGGERTY

Chairman of the Board of Trustees, The Rockefeller University

In three-quarters of a century, The Rockefeller University has had but four leaders—Simon Flexner, Herbert Gasser, Detlev Bronk, and Fred Seitz—and it has been fortunate in all of them.

Once again, in Joshua Lederberg, the University is fortunate to have found a leader for the future who is qualified to match the expectations created by this institution's experience with those who have preceded him.

A scientist with a deep concern for improving public understanding of science and its role in society, he comes to us from Stanford University's School of Medicine, where he was chairman of the Department of Medical Genetics and Joseph D. Grant Professor of Genetics. A man of far-ranging interests, he has been active on a variety of advisory committees and boards dealing with an equal breadth of problems, including those of mental health and retardation and environmental health. Winner of a Nobel Prize in 1958 at the age of 33, Dr. Lederberg is an exceptionally gifted scientist of international stature, one of that band of pioneers who has laid the foundations of modern genetics, a field that is furnishing new techniques and valuable insights for the biomedical research so central to the work of our laboratories.

Presidential Address

JOSHUA LEDERBERG

President, The Rockefeller University

First of all, my welcome to you to this exhilarating occasion, and my particular thanks to those of you who have come a long way from all parts of the world. I am also especially pleased to see those of you who have traversed 68th Street or York Avenue in the mood of fellowship and cooperation that should increasingly bind our respective institutions.

Why would so many people go to such trouble for an event of this kind? Anyone who has ever had to arrange for more than a dozen people will respect the fuss and labor that it must entail. From my own perspective, a ceremonial like this mainly gives pause to a new incumbent, and to a venerable institution, for a process of self-examination from which both may profit.

I am reminded of James B. Conant's admonition describing the beginning of his long service as president of Harvard University, after having returned there from a distinguished career as a laboratory organic chemist. How grateful he was, he wrote in his autobiography, that he was inadvertently thwarted in his plan to publish his initial thoughts on entering: "... that would have hung around my neck during the next 20 years like the albatross of the ancient mariner."

But I am going to disregard his implicit advice, as indeed I have tried hard to exhibit other disqualifications for an administrative role, by trying to continue to behave as a laboratory scientist. In the latter role, it is important to bring speculative ideas to the surface, where others, as well as myself, can have a better opportunity to criticize, sometimes even to discard, them. Furthermore, the scientist should be quite fearless about appearing to be naive, ignorant, or even foolish—too often if you think you know the answer, you don't understand the problem! My remarks are, then, in no respect settled truths, but reflect

initial quandaries and dilemmas in my trying to understand the larger aspects of new responsibilities.

The fact is that none of our institutions can evade the most critical examination, in the present climate of skepticism and inquiry about our entire social fabric. If we do not examine and sometimes reform *ourselves*, others will do so with even less information and insight. This is then an apt moment to ask, as we should be prepared to ask at any moment, "Just what would be lost if we disappeared from the face of the earth?"

Perhaps there is even some special advantage in an incumbent's tackling these issues before he is indeed encumbered by his day-to-day obligations, and before he is embraced by the traditions and setting of an institution so manifestly captivating as to prejudice that essential self-examination. In fact, before proceeding more broadly, there are two local elements of our setting worthy of comment.

First, this is the season of the equinox, with its unpredictable alternations of climate and mood. In the ancient traditions of my co-religionists, the community built the harvest tabernacle as a symbol of the indispensibility and frailty of our human constructions, of reliance on a benign Providence for the recurrence of the nourishing rains, and as a shelter against the torrential winds. In pursuing our academic plans, we must still rely both on optimistic faith in ourselves and on the support of a larger community.

In the crass terms of modern industrial society, a one-percent fluctuation in the rate of inflation is the margin between fiscal stability and disciplined growth on the one hand, and an inexorable slide into insolvency on the other. We may congratulate ourselves in being far closer to equilibrium today than are most other private academic institutions. The most onerous and demoralizing adjustments—the painful task of my predecessor Dr. Fred Seitz—are already behind us. With hard work and just moderate good luck, we have a planning framework for vigorous survival. But it would take an egregious hubris to ignore the possibility of still other unforeseeable storms; and we must remind ourselves unremittingly how vulnerable we are to the smallest fluctuation in public understanding of the integrity and necessity of our mission. The task we face is both a material one of

matching our plans and operations to a realistic model of the resources available, and the spiritual one of sustaining our own confidence in the importance of our work, and of communicating and shaping it to the best interests of the human purposes we ultimately serve.

Another element in the setting for my remarks is the 75th Anniversary celebration of The Rockefeller University, held just two years ago. Much of what I would want to say myself was already captured by the statements of others at that time. Those accounts of the transition from The Rockefeller Institute of Medical Research to The Rockefeller University depict what attracted me to this place: not to invoke radical changes, but to *conserve* the most vital traditions of biomedical research to be found anywhere today.

It has become almost tedious to use this indicator, but of course we do take some pride that still another of our research alumni, Dr. Daniel Nathans, was honored with the Nobel Prize, announced just last week. Dr. Nathans graduated from his clinical residency into laboratory research here under the tutelage of Professor Fritz Lipmann from 1959 to 1962, and I am sure that we all join in collegial congratulations to him. We cannot be doing everything wrong with a consistent record of recognition represented by the placement of Rockefeller University graduates in leadership roles in medical research and education throughout the country.

The fundamental agenda of The Rockefeller University is indeed basic biomedical research of substantial breadth in the tradition of the Institute. The biomedical laboratory is the central focus of medical research today: but it must have a still broader perspective—that of the biochemical laboratory. We are fortunate in a faculty of world-recognized excellence in the behavioral sciences, as well as in experimental biology and pathology. And we can be informed by the still different insights of physics and mathematics.

Now, scientific research is one of the most enthralling games that can occupy the human mind, and those of us who can dedicate our lifework to it are privileged indeed. But the private excitement of the chase for new discovery should not obscure the enormous public stakes of the enterprise—stakes that are trivialized by the attribution of mere curiosity or by the better-selling Frankenstein images of the pop media.

What we learn today about the structure of DNA and of cells, and how these are knit together in a functioning organism, is indispensible tomorrow for what is indeed a war against pain, disease, and death. There is no fundamental reason why we cannot learn to prevent all of the major destroyers of long and happy lives that loom over the world today: heart disease, cancer, mental illness, parasitic afflictions, birth defects, even untimely aging. These tragic events are not inexorable laws of matter and energy—they are side-effects of a natural evolutionary process that is both incomplete in its own script and indifferent to the anguish of the human consciousness as we face our own mortality.

Advances against these threats will not come cheaply, and the main ones will, as the history of science has shown again and again, come from the most unexpected and unprogrammed sources. The careers of thousands of investigators are committed to them, and they, in turn, require a level of material support that must be justified in competition with many short-run social needs. They need moral support as well. The ground rules for the ethical involvement of human subjects in medical research are under constant scrutiny and revision, and evoke an ever more cumbersome bureaucracy of supervision. Above all, the lay citizen needs adequate information to be able to confront his own soul about the choices ahead—whether to be a passive victim of natural disease and disability, or to seize the chance to use new knowledge for a rational frame of healthy life. There has been much, sometimes hysterical, concern about the risks of medical research and the need for public involvement. In my view, the most strident shocks to familiar ways will come from the very *success* of our basic programs of health research. No one will cast a vote against "living"; but we have certainly not begun to face up to the social problems inherent in biological solutions for the prolongation of life, even those that have already been achieved in this century.

The primary responsibility that I avow in my new office is to help sustain the traditions of excellence in science for which The Rockefeller Institute and University has been justly famous for many decades. The creative intellect of its carefully selected and gifted individual members is the bedrock of accomplishment of any institution, and

they must be furnished an environment and resources with which to exercise their gifts. The substantial scope, but simple structure and coherent goals, of this University offer a unique and attractive challenge to scientific leadership. Beyond the list of our sixty independent laboratories is an overarching opportunity to bring different specialties of knowledge and styles of critical thinking together, both to enhance scientific excellence and to confront all of these with the practical challenges of human disease. The remarkable aspects of The Rockefeller University: its appropriate size, traditions, setting, and range of studies on one campus—encompassing molecular biology, the behavioral sciences, and the clinic—all offer unparalleled opportunities for intellectual adventure and human service.

This conception of collegial effort is deeply embedded in the motivations both of our original founder and of the many individuals, corporations, and foundations that have continued to support the programs of The Rockefeller University. At its inception, the federal support of biomedical research, mediated primarily through the National Institutes of Health, was implemented according to similar ideals. Such support is absolutely indispensable and government grants now account for half the annual operating budget of this University. It is predictable but lamentable that this level of federal involvement brings along an egregious degree of centralized management. Most of this funding is directed to the "purchase" of specified research results, packaged in projects, as if major discovery could be marketed according to such specifications. The project grant system, as admirably as it has supported major innovations and discoveries in the past, is now administered in ways that threaten to disintegrate institutions, to discourage the confluence of creative ideas, and to impede opportunistic collaborations of basic science and important clinical applications. One of the most important functions of a private endowment is a countercurrent to the services-rendered concept of the support of research. In its place we return to the concept of venture capital toward the identification of creative individuals and of collegial frameworks better able to achieve the same social ends.

The need for collegiality and the attenuation of internal obstacles to its realization also extend to the relationship between institutions.

Happily situated at the center of an extraordinary complex of medical institutions—being literally now in the shadow of New York and Memorial Hospitals, and immediate neighbors to Cornell University Medical College and the Memorial Sloan-Kettering Cancer Center—we have a remarkable opportunity to match our own intellectual style and skills, and dedication to the most basic science, with the diverse problems and resources of our neighbors. They are deeply preoccupied with medical education and the care of patients on a large scale. These are social values of undeniable worth, but distinct from what we can offer in tracing the underlying causes of disease. I believe we have a particular obligation to focus on preventive health applications: but I fear it will be quite a while before the hospitals are no longer needed. We must work together to meet our categorical social responsibilities, and I am delighted that even in the few weeks of my tenure a number of measures for realistic partnership have been started with the equally enthusiastic concurrence of our neighbors.

In closing, may I recall that I was educated in New York, having had the privilege of access to Stuyvesant High School and to Columbia University and Medical School, to the City's public library system and many other institutions that foster intellectual development. Having been away for many years and now returned, I feel especially keenly how rich are these networks of sources. We are really all non-matriculated students in a metropolitan super-university. I will certainly be doing all I can to enjoy this fare for myself and my colleagues, and to seek ways in which our own specialized institution can most efficiently cooperate with others truly "*pro bono humani generis*," for the benefit of mankind. I am indeed grateful to the Board of Trustees, to my colleagues, and to the community of our supporters and well-wishers for having created such an opportunity.

BIOGRAPHIES

DR. THEODORE COOPER is dean of the Cornell University Medical College, Provost of Medical Affairs, and Professor of Surgery and Pharmacology. His contributions as surgeon and educator have been enhanced by his development and implementation of health policy at the highest governmental levels. Prior to his appointment at Cornell, Dr. Cooper was Assistant Secretary for Health, U.S. Department of Health, Education and Welfare. Past government service also includes a six-year tenure as Director of the National Heart and Lung Institute of the National Institutes of Health. He is a member of the governing boards of many health-related foundations and organizations; in addition, he is active on the editorial boards of six medical journals.

DR. GERALD M. EDELMAN, an authority on immunology and protein chemistry, received a Nobel Prize in 1972 for his analysis of the amino acid sequence and internal subunit structure of gamma globulin, the body's primary defense against foreign substances and disease. He has been associated with The Rockefeller University since 1957, when he arrived as a graduate fellow. He received his Ph.D. and a faculty appointment in 1960, and became full professor in 1966. In recognition of past achievements and projected investigations relating to the formation of antibodies—a research focus that may increase understanding of the treatment and prevention of cancer—Dr. Edelman was appointed a Vincent Astor Professor in 1974.

DR. JOSHUA LEDERBERG, who became president of The Rockefeller University on July 1, 1978, is a distinguished geneticist who was born in Montclair, New Jersey, in 1925, attended Stuyvesant High School in New York, and received his B.A. degree from Columbia College in 1944. After two years at Columbia University's College of Physicians and Surgeons, he took a leave of absence to do research with the late Edward L. Tatum at Yale University. He never returned to formal medical studies. At first with Tatum, and later with other co-workers, Lederberg pioneered in bacterial genetics research.

While at Yale, where he received his Ph.D. in 1947, he discovered the mechanism of genetic recombination in bacteria, demonstrating for the first time that a form of sexual reproduction occurs in these microorganisms. Eleven years later, at the age of 33, he was named a co-recipient of the Nobel Prize in Physiology or Medicine for this work and subsequent research on bacterial genetics. The other recipients of the prize that year were Dr. Tatum (who later joined The Rockefeller University faculty) and Dr. George Beadle for their discovery at Stanford in the 1940s that genes act by regulating specific chemical processes.

From 1947 to 1959, Dr. Lederberg was professor of genetics at the University of Wisconsin and served two years (1957–59) as chairman of a new Department of Medical Genetics. In 1959, he joined the faculty of Stanford's School of Medicine,

where he served as chairman of the Department of Genetics and also held the titles of professor of biology and professor of computer science. For four years, beginning in 1974, he was principal investigator and chairman of the executive committee of the Stanford University Medical Experimental Computer-Artificial Intelligence in Medicine project and continues as chairman of the executive committee.

A member of the National Academy of Sciences and a charter member of its Institute of Medicine, Dr. Lederberg has been active on government advisory committees and boards dealing with problems of mental health and retardation. He also was a member of the Advisory Committee for Medical Research of the World Health Organization, and is on the board of trustees of the Natural Resources Defense Council, which is concerned with environmental health.

Dr. Lederberg played an active role in the Mariner and Viking missions to Mars, sponsored by the National Aeronautics and Space Administration. He was a consultant to the Arms Control and Disarmament Agency during the successful negotiation of the treaty on biological weapons disarmament. He is a director of the Center for Advanced Study in the Behavioral Sciences, Stanford, and of the Institute of Scientific Information in Philadelphia. He is also chairman of the board of Annual Reviews of Palo Alto, California, a cooperative, nonprofit scientific publisher.

Dr. Lederberg has been awarded honorary Doctor of Science degrees by Yale, Columbia, University of Wisconsin, and The Mount Sinai and Albert Einstein colleges of medicine, and an honorary M.D. by the University of Turin, Italy. He has also been elected a foreign member of the Royal Society.

His interest in improving communications among scientists, the general public, and government policy makers has led Dr. Lederberg to write extensively for lay audiences, including a series of columns, distributed by the Washington Post Syndicate, on the social impact of scientific programs.

DR. LEWIS THOMAS is President and Chief Executive Officer of Memorial Sloan-Kettering Cancer Center. He also holds appointments as professor of pathology and medicine at Cornell University Medical College, and attending physician at Memorial Hospital. Dr. Thomas has been a specialist in pediatrics as well as in pathology; a hospital administrator; an instructor in many medical schools, including those at Yale and New York University, where he was also dean; a government consultant; and a popular author. Dr. Thomas's collection of essays entitled *The Lives of a Cell* won a National Book Award in 1974. Recognition of his accomplishments is reflected in his election to the boards of many eminent foundations and institutions, including The Rockefeller University.