Biomedical research: inlook and outlook[1]

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I would like to introduce a new word that I learned only recently, and find to be especially relevant to research and Research Day. That word is *immutology*, defined as the study of things that should not change. Simply stated, the very nature of science and scientific investigation is change, but the underpinnings of the scientific process should be immutable. I must give full credit for the origin of the notion of immutology as applied to science to one of our Cleveland Clinic security officers, who asked me a rather probing question after finding out I was in the Research Institute.

"Any big breakthroughs you've got over there?"

I responded that science advanced mostly in little steps, but asked where he would like to see breakthroughs. He unhesitatingly responded, "Immutology." I, not immediately grasping the wisdom of his words, rather narrowly responded, "Immunology?" His reply was firm: "Immutology for transplantation. Then every time you wear out a part, you put in a spare." Trying to change the subject a bit, I asked, "Do you like research?"

And to my utter delight, he responded, "Oh, yes! You can't have nothing without good research. Can't even fight a war. And look at Bell Telephone. The reason they got so far ahead was those Bell Laboratories. Bell Laboratories came up with the big winners . . . of course, a good part of it was subsidized by the government."

[1] Opening address presented at the Sixth Annual Research Day, The Cleveland Clinic Foundation, September 6, 1986. Bernadine Healy, M.D. is the Chairman of the Research Institute, The Cleveland Clinic Foundation.

Editor's note: See also the Archives article about the status of the Research Division in 1961 by Irvine H. Page, M.D., begining on page 153.

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By now, rather grateful and fully convinced of this man's wisdom, I asked him where else he would like to see breakthroughs. Without a pause, he said, "The big C. No doubt about that." And as I was on my way to an American Heart Association meeting, I asked him finally, with a little concern, "What about the heart?" He replied, "They're doing pretty well on that. And if they get immutology down, they will have got that REALLY licked."

This rather well-articulated view tells me vividly what the Harris polls have been saying: namely, that the public loves research. It says even more, though. It says that the public really understands what they love about research: that any productive enterprise—be it medicine or telecommunications—must invest in research to stay ahead because that's where the winning breakthroughs are.

Indeed, the security officer expressed rather clearly, and possibly more convincingly, what Louis Pasteur meant when he said:

> Science is the highest personification of the nation because that nation will remain first which carries furthest the works of thought and intelligence.[1]

But, back to *immutology*. This word is relevant to science and important to scientific breakthroughs. Society's support of scientific research (both economic and intellectual) and the responsiveness of scientific research to the needs of society should fall under the protective mantle of immutology.

We hear a great deal these days about how gloomy the prospects are for support of science and how insecure and uncertain its future is. Perhaps, in my new lingo, *mutology*, not *immutology*, prevails. I would like to examine this perception at the national level and also look locally at our research enterprise here at The Cleveland Clinic.

Research and development: a national perspective

If we examine what has happened in the United States in the post–World War II era, we will see unequivocal *steady* support of science that moved decidedly upward in two periods. These phases are not boom-bust, although they may be systole-diastole. We can subdivide this modern era rather precisely into four phases, the first three lasting a little over a decade. These phases correspond to what I call the "Inlook" and "Outlook" cycles that we as a nation have passed through.

The first phase was clearly an inlook time. Right after the war we were ready to focus on the home front. We had seen the benefits of science directed toward the war effort, ranging from antibiotics to aerospace, leading to far greater federal expenditure in science and technology during this time. But most of the money was spent in government laboratories.

Then came a shock: Sputnik was launched in 1957, and we were forced to look *outward* again. International competitiveness and national chauvinism were aroused, and there was much concern about why we were not ahead, and maybe even behind, in science and technology. This outlook phase triggered a huge investment in basic research, and rather importantly, served to reinforce the notion that science must develop unfettered—that a diverse science base must grow in our universities and academic centers and that, for them to succeed, government should not manipulate those efforts directly. This was a heyday for U.S. science. It brought enormous return: control of most bacterial diseases, polio vaccines, open heart surgery, valve replacements, vascular bypass procedures for the heart and limbs, renal hemodialysis and renal transplantation, and drugs for hypertension. Despite these achievements, the lag between basic science and its application was often long and circuitous. Basic science breakthroughs with immediate application to society were not coming daily, and major diseases, like heart attacks, strokes, and cancer, were still widespread. Superimposed upon this, the momentum of Sputnik was spent, and an *inlook* cycle again took over.

In 1966 President Johnson expressed this sentiment when he said:

> Presidents need to show more interest in what the specific results of research are in this lifetime—and in their administration. A great deal of basic research has been done . . . but I think the time has come to zero in on the targets by trying to get our knowledge fully applied. . . . We must make sure that no lifesaving discovery is locked up in the laboratory.[2]

Investment in science shifted focus from the heavens to our backyards—to concerns about health, welfare, housing, energy, and crime. For biomedical research it meant a shift of focus toward immediate application to patients of what was already known. This led to a plateau in federal funding of basic research that lasted throughout the decade of the 1970s. A plateau, not a decline. A diastole, not a bust. Nevertheless, a diastole at a time when the engorged pipelines were starting to deliver increasing numbers of scientists, providing increasing demand on a nonexpanding pool of funds.

It took another "Sputnik" to move our *outlook* again. But this time it was an *economic* jolt, a recognition that we were falling behind in international *economic* competitiveness. Japan and Europe were challenging our economic leadership, and it was fully recognized that economic leadership and industrial competitiveness were linked to R & D. In this outlook phase, which we are currently experiencing, unlike any of the previous phases, is the full recognition that basic science is vital to both *economic* and *social* welfare, not just to intellectual stature or to keeping up in the arms race. Fortunately, the issue is now not basic versus applied science, but rather how to assure the proper means for technology transfer to occur between these two vital enterprises.

It is evident from *Figure 1*, which shows investment in nondefense R & D as a percent of GNP, that science and technology have become recognized major forces in economic competitiveness. After a plateau phase in the 1970s, the nations of the industrially developed world have all increased their investments in research, and it seems that Japan and West Germany have led that increase.

Biomedical research as a part of the research and development base

What does this mean for the biological sciences and for biomedical research in this era of outlook? Biomedical research has done extremely well. The National Institutes of Health (NIH) have seen, on the average, better than a 10% rise in budget per year. The NIH budget has gone from $3.18 billion in 1980, to $4.3 billion in 1983, to $5.4 billion in 1986. And in 1987 we

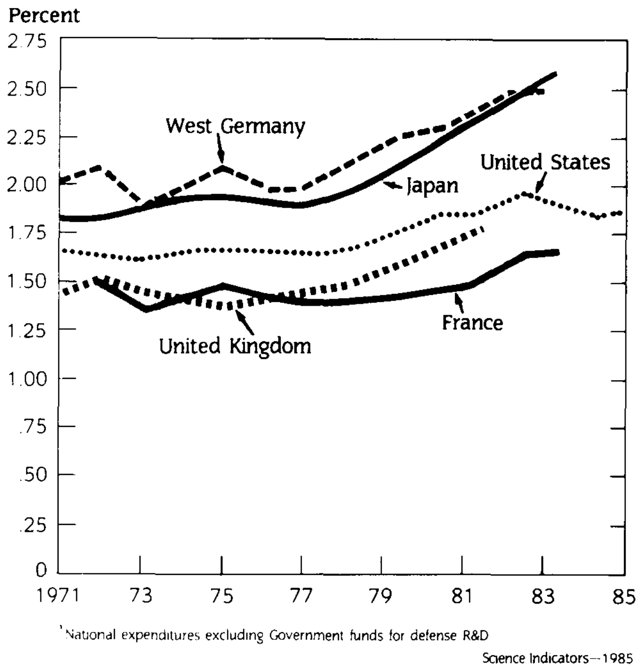


Fig. 1. Estimated ratios of nondefense R & D expenditures to gross national product (GNP) for selected countries.

are expecting more than $6.1 billion. That is almost a doubling of the NIH budget since 1980.[3]

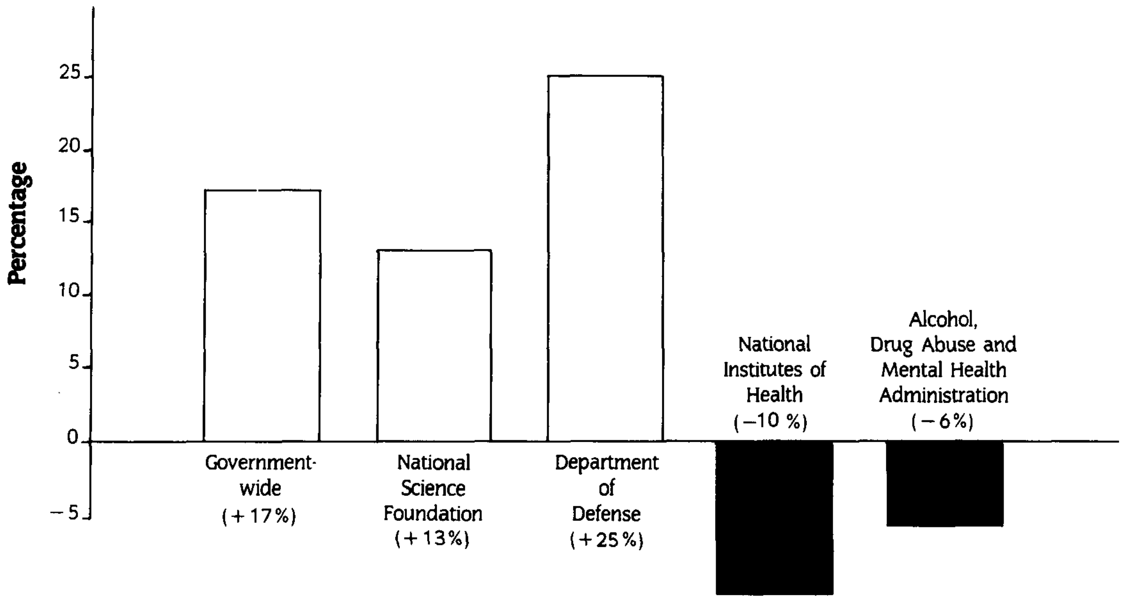
With these rather impressive increases in the NIH budget during the outlook era of the 1980s, why is there a heavy perception that the sky is falling in on biomedical research? There are a number of reasons for this, and I will touch on them briefly. One major reason is macroeconomic: the demand is outstripping even the much-increased supply. The number of grants submitted to NIH, and their budgets, are outpacing even this impressive increase in dollars, so that the funding rate is slowly falling. Second, priority scores at NIH have undergone inflation—that is, the mean score is shifting downward. A score of 150 to 175 today may be closer to a score of 225 years ago. A third reason is that now over 90% of grants are approved for funding, and percentiles are based only on approved grants. A decade or so ago the percentage was closer to 60% to 70% approved, yielding a higher relative percent funding of approved applications.

Another very important factor is micromanagement. Micromanagement, increasingly by the Congress and more recently by the Office of Management and Budget (OMB), has led to a rigidity and effective decrease in the NIH budget. Roughly 25% of the NIH budget is earmarked for special disease-oriented programs.[4] Some might be funded, but many will not be. This means that although 35% of approved grants might be funded, an individual investigator could have a grant in the 25th percentile and not be funded. The Nursing Institute and the Arthritis Institute have been established with the hope of increasing funds in these fields, but without new funds being added for them.

The OMB has also fallen into micromanagement. It has started to dictate limits on numbers of grants per category, making the juggling of the grants by the institute director increasingly difficult. The OMB has tried repeatedly over the past three years to reduce the prior year's Congressional appropriation. In the Fiscal Year (FY) 1987 budget, it tried to rescind 600 grants. (Now, OMB is trying to carry over $334 million to FY 1988—in effect, a rescission.)

Also worrisome are attempts to take dollars for research out of the NIH budget to be disbursed by the Assistant Secretary of Health and Human Services. In the FY 1987 budget, about $150 million was pulled out of the NIH budget, earmarked for AIDS, and placed in the Office of the Assistant Secretary for Health. Technically, this money could thus bypass the NIH peer review system completely, based on the wish of the Assistant Secretary, a political appointee. This set-aside would also not necessarily include the AIDS-related work coming through the NIH grants system. Other politically motivated set-asides of the NIH budget, supported by both Congress and the White House, are the set-asides for small business, as well as some for proposed facilities. Both these set-asides serve to directly reduce the portion of the NIH budget that funds investigator-initiated research grants.

Indeed, these trends are all worrisome and account for a perception of limits based on reality. But there are other elements of the perception that are clearly based on charade: namely, the budget-adjustment game played by the administration and Congress each year. For biomedical research the President's budget *always* comes in low, and the Congress *always* adds major increases. And this game is played regardless of what political party occupies the White House or what party controls Congress. Even though the OMB has been especially active in this administration, the opposite seems to be happening in the Defense budget: The President comes in high, and Congress knocks the figure down.



Source: Budget of the U.S. Government, FY 1987 Special Analysis K. ADAMHA data adjusted to exclude Community Programs in accordance with stated congressional preference.

Fig. 2. Federal support for R & D. Proposed percentage increases FY 1987 *v* FY 1986 obligations.

Figure 2 illustrates how this ritual leads not just to a perception of a funding problem, but possibly to sheer panic. This bar graph of federal support for R & D for 1987 compared with 1986 appeared in the very fine document prepared by the Ad Hoc Group for Medical Research Funding.[5] This document is distributed widely to the biomedical research community and is extremely helpful in lobbying efforts. This presentation of the budget shows a 17% increase in spending governmentwide, a 13% increase in the National Science Foundation (NSF); a 25% increase in the Department of Defense (DOD); and a *decrease* of 10% for the NIH and 6% for the Alcohol, Drug Abuse, and Mental Health Administration (ADAMHA). This is surely enough to enrage, anger, and incite to action any struggling scientist, grateful patient, or well-informed security officer. And that is exactly what the writers of this lobbying document hope will occur. But the reality is, and always has been in the entire history of the NIH, that Congress's *role* is to set the figure for NIH. And the real numbers for FY 1987 will show an NIH bar that is a little *higher* than that of the NSF, as always. (The DOD bar may well be a little lower than the NSF bar. I might also add that the FY 1988 bar graph will look quite similar, with about a 10% proposed decrease in NIH over FY 1987 Congressional appropriations.)

Table. NIH budget

	$ billion
1985 Appropriation	5.1
1986 Appropriation	5.4
1986 Postsequestration	5.26
1987 Budget	
President	5.08 (4.9 to NIH)
House	6.15
Senate	6.08

* Conference Floor Vote: September–October, 1986

This *Table* shows what really happened with NIH funding for 1987. The NIH appropriation was a little less than $5.1 billion in 1985. The 1986 appropriation was approximately $5.4 billion. But a Congressional triumph on the deficit came along in the name of the Gramm-Rudman bill, which caused the agencies to recalculate their budgets based on a so-called sequestration, which may be unconstitutional. This moved the figure to $5.26 billion—the base for the President's budget. In typical fashion the President's budget came in absurdly low—essentially a freeze of the FY 1985 budget and a 6% decrease over the 1986 budget—in the spirit of Gramm-Rudman. But OMB then earmarked about $150 million for AIDS research to be spent by the Assistant Secretary. Thus, the technical NIH figure was down 10%, not 6%, the figure shown on the bar graph. Over the summer, in predictable fashion,

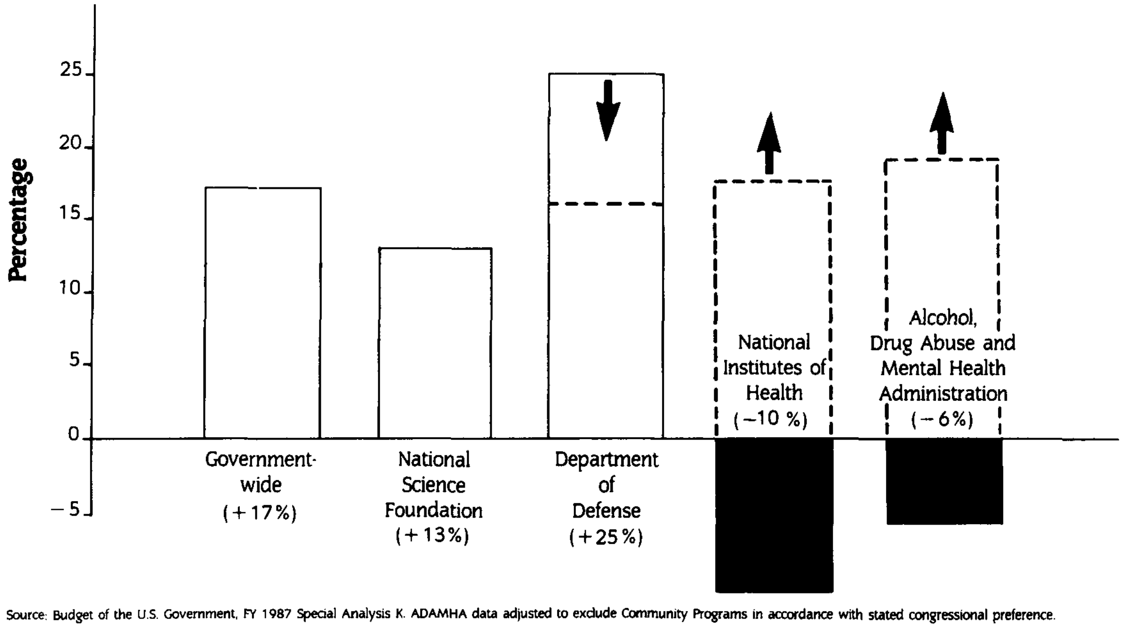


Fig. 3. Federal support for R & D. Projected actual percentage increases FY 1987 *v* FY 1986 obligations.

the House voted out a budget of $6.15 billion—21% over the President's request and 14% over the FY 1986 figure. The Senate came in slightly lower, but close, as it always does. And, in September, there was a conference and final floor vote. Congress added $1 billion to the NIH budget, bringing the 1987 request of $5.08 billion up to over $6 billion.

The bar graph in *Figure 3* has been corrected for the likely real outcome: NIH and ADAMHA up about 18%, Defense taking a real 2% loss over 1986, even lower than the cut by the Senate. This repeats history—NIH tops the list.

This is surely a mind-bending game. It understandably creates panic in the research community at large, which tends to accept numbers, bar graphs, and the written word as written. But why this game? I asked it many times when I was at the White House. Aside from the fact that it seemed politically foolish for the White House to give Congress the credit for bailing out the NIH, I found it somewhat silly to go through the motions of creating, printing, and defending a position you well knew wasn't intended in the first place. The argument went this way, however: Congress wants to get the credit for increasing the NIH budget. If the President's budget is realistic, then Congress will still add over that figure, and NIH will see a 30%, 40%, or 60% increase per year—something neither Congress nor the OMB wants, even if it would be a great happening for biomedical research. Indeed, in a way this happened with President Nixon's "war on cancer," which took the NCI far ahead of all the other institutes.

So in brief, what is the *outlook* for biomedical research and the NIH? It is generally good in terms of dollars: strong funding trends; a rock stable base and a steadily increasing slope of funds. (By the way—this game will continue in 1987. The latest chapter is the President's FY 1988 budget, which will try to pull out $334 million from the 1987 budget, reducing the $6.13 billion to $5.85 billion and resetting the FY 1988 budget at the same level. This would be more than a 10% *decrease* in the NIH budget, at a time when the NSF is at a 17% *increase*. Congress will battle with the administration on both the FY 1987 rescission and the FY 1988 cut—and the 1986 scenario I have described will repeat itself.)

The Cleveland Clinic Foundation and biomedical research

And now for a brief inlook. What about the Cleveland Clinic Foundation's research effort?

Historical perspective

Research at The Cleveland Clinic Foundation also has a good history. Throughout well over

40 years, The Cleveland Clinic Foundation has *recognized* the importance of medical research to continuously improving medical care, based upon its mission: excellence in medicine in response to public need. With that mission, research is viewed as essential. The Clinic realized that belief by establishing our focused research effort independent of, but closely allied to, the practice setting. This commitment has been expressed in many ways:

First, by identifying, reviewing, and reaffirming at regular intervals research priorities of the Foundation, priorities based on the major problems of the sick cared for here—but, by setting those priorities broadly enough—the Clinic has not micromanaged research or constrained the process of uncharted discovery.

Second, by setting aside a portion of operating funds to support research, it has afforded research a modest but stable financial base from which to build and acquire additional outside competitive funds.

Third, by creating a dedicated infrastructure for research with aggregated space, state-of-the-art equipment and willingness to upgrade and expand both in response to opportunity, the Clinic has given the research effort a stable physical base.

Fourth, by nurturing a cohesive Research Institute composed of professional biomedical scientists dedicating all or most of their time to basic and to clinical research, the Clinic has freed these scientists from many constraints on their time that are unrelated to research.

This approach to research at The Cleveland Clinic Foundation has been a successful enterprise. The Division of Research has grown and expanded to become a consequential effort within the institution, a major biomedical research organization within our Cleveland community, and a recognized entity in the national biomedical research arena.

The Research Institute today

The Research Institute now comprises a scientific staff of 70 Ph.D.s and M.D.s, approximately 70 pre- and postdoctoral fellows-trainees, and a support staff of roughly 150 technical and other personnel, housed in our research building and several satellite locations and devoted to research in several major targeted areas: heart disease and hypertension; brain and vascular disease; cancer and immunology; artificial organs; musculoskeletal disease; and epidemiology and clinical trials. We are also planning a new department in molecular biology. Our research effort has grown as much by The Cleveland Clinic Foundation's investment as it has by the ability of the research effort to compete for outside funds. In 1986, our research budget was roughly $23 million, with almost $13 million of that coming from outside our institution in the form of competitive grants and contracts, mostly from NIH. (In 1987 we expect a budget of almost $28 million, with outside grants bringing in more than $15 million.)

It should be noted that the evolution of a successful research enterprise here occurred within the context of an organizational structure that is still the less common one among institutions conducting biomedical research today. Most basic and clinical research, by tradition, has been carried out in universities. The Cleveland Clinic Foundation approach (also seen in such efforts as the Sloan-Kettering Institute, the Rockefeller Institute, the Scripps Clinic, and the Clinical Research Institute of Montreal) has some advantages, as well as disadvantages, compared with the more prevalent university model. The research institute model has a leaner, less costly bureaucracy, can be more responsive to change, can more readily focus its resources toward strategic goals, and by design can be more interdisciplinary, more collaborative, and more sharing of facilities and talent, from the most basic to applied levels. The university, which clearly has the benefit of a broader intellectual life, a wider range of disciplines, and the excitement and stimulation of students, sometimes suffers from its size and the need to be all things to all scholars, its separation of disciplines by rigid departmental structures, its removal of research from the hospital setting, and its separation of preclinical from clinical science. Although both research models have been successful, the research institute model established here at the Clinic may be particularly well suited to modern biomedical research and may be a model for the future. Let me cite a few reasons for this.

First, biomedical science has become extraordinarily complex and multidisciplinary. Multidisciplinary science requires aggregated teams of professional scientists working in close proximity, committed to collaboration and interchange. Second, the sophistication inflation of the technology of modern science carries a heavy price tag. It is crucial that we be efficient in utilizing resources, particularly expensive equipment and methods, avoiding redundancy or "exclusive use" situations. Third, the rapid pace and complexity of modern biology means that medical scientists must be able to focus most of their professional time on research. The classical model I grew up with, where the M.D. scientist teaches, has a heavy clinical practice, administers a department or division of clinical medicine, and also runs a research laboratory, is becoming impossible, if not obsolete. An unequivocal strength of the Clinic's Research Institute is that most of its scientists are committed to research, its clinicians to practice, and both are committed (at least in spirit) to being part of a continuum, bringing basic research problems and developments from the laboratory to the bedside when appropriate.

The next steps

Now finally, what about the next steps? Where should we be going? The Foundation has recently reaffirmed its commitment to research as an essential element of its present and future success. Along with its major expansion of clinical efforts and facilities has been enhanced commitment to *research*. The institution has established a substantial research and education endowment, plans to increase it, and has embarked on needed facilities expansion.

As we focus on the future, we must ask, "Where must we go—and how?" We are clearly planning to get bigger, but bigness must only be achieved out of "goodness," and by that I mean quality. Let me draw on the wisdom of Irvine Page. He warned against the opposite—mainly bigness bound for decadence—when size comes haphazardly and without purpose. Bigness alone can lead to a uniformity of persons and a value scale that gives recognition to those who conduct themselves appropriately, not to those who get things done. In contrast is bigness based only on vigor—especially important for science. And here bigness must be driven by individuality, creativity, and innovating energy.

As we get bigger we must strive more than ever to create a healthy research environment and to know and agree on what a healthy research environment is. The five major ingredients that we must keep in mind are these:

- a clear mission
- well-thought-out goals: short- and long-term
- linkages: interdisciplinary, synergism, and technology transfer
- stability in commitment
- talent

First, we must never lose sight of our broad mission: excellence in medicine in response to public need. We must have well-thought-out goals, long- and short-term, that give focus and efficiency to our energy. Here more than anywhere we must preserve our linkages and create new ones between the many scientific disciplines *within* research, as well as with our clinical colleagues. Such synergy is essential to *technology transfer*, the buzzword of the 1980s, but, nevertheless, a vital concern in biomedical research.

Stability in commitment to research is here and should be appreciated to help avoid the panic that seems to abound. And last, and most important, is talent. That is what makes any institution—and in research it is its very essence. We have good talent now, and we are actively recruiting more talent to increase our depth and breadth in our priority areas.

And, finally, leadership is important. We must have talented leaders of our individual research programs, of our departments, and of our division—leaders who are dedicated, energetic, who can work together, and who can be generous and inspire the younger talent coming along to do even better. But I must warn you that leadership can be tough. Those in the hot seat are especially susceptible to the stresses, strains, ups and downs, systoles and diastoles. And they must become resistant, one way or another, to what I have been told by a friend at the Mayo Clinic (John Shepherd, M.D., personal communication) is the *typical* life cycle of institutional leaders—the so-called Three Stages of Man: elevation, approbation, and castration. I sure am glad that I'm a woman.

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