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When Hans Stetten called me some months ago and asked me to participate in the program I thought, to paraphrase Mark Anthony, that it would be my job to praise the NIGMS rather than to bury it. But the times, unhappily, make it difficult to concentrate on simple eulogy over past accomplishments. Besides, I have a personal predilection against dwelling on past laurels—there is too much work to do ahead. I could take a very gratifying several hours to begin to review the scientific excitement of the past decade. Here again, there is a personal idiosyncracy that gets in the way. I find it extraordinarily difficult to lecture to my classes or to make a presentation to a group of this kind when I know that there is such splendid material in writing that you could read at your leisure which would do a much more beautiful job of reviewing the recent history of the contributions of biology and the general medical sciences to human welfare and to medicine in particular.

At the risk of appearing to be a press agent for my predecessor, I would like to remind you of the volume that Phil Handler edited for a group of committees on the National Academy of Sciences, *Biology in the Future of Man.* Another, more modest and more recent collection of material very pertinent to the subject which I think that everyone in this room should be aware of, appeared as a supplement to the Federation proceedings last November entitled *Contributions of the Biological Sciences to Human Welfare.* These are two splendid documents and they document in very, very great detail how the substance of programs (of which NIGMS is the base and the core) has contributed to human welfare and to medicine and the improvement of health during precisely the period of its first decade.

I'll just bring one small item to your attention from the economic analyses of the period, in part as justifications for the programs in which we are all interested. I was a little startled to notice that—for a disease too commonly passed off as rather trivial, like measles—one can make a very solid case that the simple advent of the vaccination program for this one disease can be attributed an economic advantage during that interval of one billion dollars in terms of prevention of the time, cost of medical care, and the prevention of losses from lost income that stem from it.

This is, of course, a story that can be replicated innumerable times over, for in situation after situation we have grown quite accustomed to all the benefits of past researches, tending to discount them . . . not in an economic sense but in a psychological sense . . . and to ignore that where we are

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today—on a rather relatively comfortable and complacent platform of health advance—is derived from the product of generations of our predecessors. Even so, these calculations of costs are in rather narrow economic terms. They take no account of the aches and the pains that are less threatening to actual life and limb than the major diseases for which, to alleviate, we freely spend billions of dollars each year, and do not appear readily in the economic accounts of health advantage.

Besides these first order health utilities, the studies of this decade have also opened review on many basic issues of the foundations of heredity, of mind, of the emotions, and the pathologies thereof. And we've at least laid the groundwork for such aspirations as the control of cancer, of coronary disease, of schizophrenia, perhaps even of aging, although it would be arrogant to pretend that we know enough to lay out a clearcut engineering blueprint for the successes in these areas which are almost within our grasp.

To my own view—which is obviously a biased one—the most startling development of the decade, and the one most replete, both with opportunities and with policy dilemmas has been the rapid development of fetal diagnosis . . . the detection of hereditary disease *in utero* which can now be accompanied by the sampling of cells from the amniotic fluid . . . and which is available for a limited number of conditions of hereditary origin—both chromosomal and metabolic in their impact. There is the possibility that this, of course, can now be legally coupled with selective abortion on rational principles to prevent the birth of wretchedly unhealthy children—for example, those with Tay-Sachs disease who would otherwise be absolutely doomed to die within a few years of neurological deterioration.

The decade has also seen the explosive spread of oral steroids for contraception—a technology whose impact on knotty problems of population growth is at least less ambiguous than its influence on the liberation of sexual mores, and whose long range consequences on the relationships of men and women is quite incalculable. These are not necessarily the issues that would be brought up in a simple eulogy of past accomplishments because they also point to some of the troubles and some of the difficulties that scientific effort also generate. But they are also very much on the public mind and they should be very much on ours too—the double-edged nature of the kind of sword that we fabricate in our research shops.

And I think that we do have here prototypes of some of science's most crucial problems for the near future. On the one hand we must answer the scoffers who, forgetful of the complacent platform on which we now stand, question the payoff of research. On the other, in the very process of answering the most urgent of human demands—be it for health, for freedom from anxiety, as I have mentioned, or for efficiency in transportation or for national defense . . . to speak to other examples, and you can imagine what I mean . . . science may pose new dilemmas of personal and social decisions just in proportion to their success and to their efficacy, from a strictly technical standpoint.

Undoubtedly, one of our more urgent challenges for the next decade is to learn how to project more accurately the second and third order consequences of technological investments in different fields. This process may be completely futile insofar as a crystal ball is the indicated instrument. Our biotechnology programs are not capable of generating that kind of prognosticative device. But in many areas it is obvious that technical advances have uncovered previously patched-over areas of pure and simple scientific and technical ignorance, that are remediable by the investigative process.

Despite the examples that I've put on the top of my list—concerning fetal medicine and contraceptive techniques—the last decade is likely to be remembered above all as the era of the ecological revolution . . . of the penetration into the public consciousness and into legislative action . . . of an awareness of the changes that large scale human technology has introduced into our environment . . . and in very large part very deep concerns—new concerns—about the role of those environmental factors on our own health. We have a long list of environmental additives whose consequences for human welfare have been the subject of great public hysteria—certainly a great deal of controversy—and where we have incurred enormous expense as the result of our ignorance about how to evaluate the costs to human health of these additives.

We can top the list of these consequences of ignorance just by talking about cigarette smoking. We certainly pay a price on the order of at least $5 billion a year, as the health cost of smoking. Now you may think, in what respect is that the result of ignorance? It's very simple. We don't know the active ingredient of tobacco which is responsible for many of its several pathological effects in man. Yet it might, indeed, be a very simple proposition to reconcile the habit and the pleasures that many people continue to spend large sums for, with a much more healthy environment for them to enjoy, if we but had

some additional scientific knowledge. And I would put it very plainly that our bill for that ignorance is certainly much larger than those five billions.

We've had a whole series of crises of policy judgments with respect to environmental additives where decisions have been made on one side of the fence or on another, on the basis of highly fragmentary and incomplete information . . . where honest men may disagree . . . about the extent to which risks would continue to be sustained. But whether you accept the risk and thereby accept the possible health cost, or whether you deny the risk and deny yourself the economic advantage of a particular additive—in both cases a very heavy price is paid. This may be unavoidable in some cases; it is certain to be sheer waste in others. By this analysis you can see, again, that we are spending billions in a context of incompletely ascertained and incompletely scientifically founded policy decisions that have run from arenas such as cyclamates and from air pollution to the question of whether lead from gasoline additives is or is not a serious health hazard.

The evaluation of drugs—the extremely long procedures that are now imposed on their validation and their availability in health . . . even questions about whether potatoes are serious sources of teratology . . . and such issues as the health consequences of the SST . . . the very large arena of the health consequences surrounding nuclear energy . . . all of these which run into actual economic costs into the tens of billions of dollars every year are, at bottom, founded on incomplete biological, biochemical, embryological, and genetic information about the consequences of these environmental additives for our own health consequences.

These costs of ignorance are enormous. Now you might say that science is also very expensive. It's expensive to do it in that to uncover the answers to many of these questions might cost a significant fraction of the economic advantages of responding to them. However, when you consider that these are costs that are compounded year after year after year—whether they are denied opportunities with respect to nuclear energy, or whether all the political complications that surround our efforts to find secondary and tertiary solutions to problems like those of energy—they do accumulate in a very large measure.

But I think that to some science seems even more expensive precisely because it uncovers these problems. Perhaps there are some who wish we didn't know that radiation is mutagenic and carcinogenic. We could then use our atmosphere and other resources as sinks for our waste in that sphere, and get at least a short-term advantage of the economic utility of the procedures. Unfortunately, you cannot play those kinds of games with nature for very long. Those costs will be incurred to the extent that they are real . . . to the extent that there are actual health hazards . . . connected with them whether you know about them or not. Merely to be ignorant of them is simply to defer your recognition of them into the future—in no way to blunt yourself to the actual impact.

Another source of resistance to health research is only beginning to surface in overt expression. Medical people are arrogant enough to hold to the consistent belief that life and health are precious, worth sacrificing a great deal of their own energies to help preserve. But this tenet should not be taken for granted. One prominent attorney has asserted that research on life-sustaining heart devices should perhaps be curtailed, since society has not yet given its "informed consent" to the extension of life span—and indeed we must foresee many economic and social adjustments if we could generally look forward to another twenty or thirty years of active, healthy life after the customary age of retirement. (This is a pattern some of our youngsters are anticipating by retiring even before they enter the establishment's "labor force," while others are forced into it by our clumsy arrangements for providing useful employment for everyone who is eager to work, much less those who have a reasonable distain for it if it can be avoided.) But I would be happy to see the plebiscite that is indicated by such criticisms, except that we just may not be able to deliver on the implied promises within the lifetime of many of the voters. Much mischief has already been done by promises to solve cancer or heart disease according to fixed, and unjustifiable timetables. Our caution about the potential reach of discovery can be overzealous too, if the public then fails to understand the level of human sacrifice that flows from the failure to support basic, far-reaching research in the health sciences.

Moreover, science so often carries bad news with respect to the impact of a new environmental agent that I think we scientists get it both ways. We're blamed, on the one hand, for promoting the introduction of a technology by providing the ultimate basis for its happening; and then we're the people who tell the world, well, you had better worry about asbestos in your talcum powder.

We have just come to realize that asbestos, too, must be added to the list of potentially serious carcinogens. So we therefore face the

task of justifying social investment in science in the face of skepticism, both from a new right as well as a new left.

Some say, however, perhaps we should set our sights on a new direction. If there are very large economic values involved in the pursuit of science, perhaps one should return to the mechanism of the free market as has been advocated with respect to training procedures in science. We should perhaps explore more dispassionately the consequences of accepting the free enterprise ideology in this sphere as we have been advised to do so. To do this properly, I do think we need some new institutions. I will attempt to be reasonably objective and dispassionate and not indulge in angry polemics or comolaints about the sources of the policies that have been suggested here. In these new institutional arrangements, above all, if we're to have a valid basis for the assumption that the payoff for higher education should be regarded as the fruit of a personal investment, then we ought to establish much more clearly property rights in knowledge.

This would imply going beyond the existing patent system, which recognizes property rights in inventions which can be justified primarily because of the need to protect the kind of investment involved in the exploitation of a new invention. If we are to demand of the individual student that he regard his own education as a capital investment on which there are to be fruits for the future, then we should protect his property right in what he has learned, and we should protect his property right in what he has discovered and what he has later communicated.

This will have a number of interesting consequences. The cost of transactions will be very high. I may demand a release from each of you that you will not make exploitative use of the information that I transmit to you in a lecture of this kind. It will mean that I can tax you with a royalty for any further implications derived from any of the ideas that I transmit to you—require an entrance fee that most of you will be unwilling to pay in order to have access to those goods. But that would be setting it up on a reasonable economic base entirely consistent with the notion of a free enterprise system carried to its logical extremes, which is of course an absurdity.

In the medical field it also would have other interesting consequences, because it would imply that a man who has invested or has gotten another venture capitalist to invest in him . . . in his education . . . should have a right to have the fruits of success as he does in other areas, and that payoffs be properly rewarded. If, therefore, I discover a new drug or a new procedure—the basic principle of free enterprise capitalism, one which is extremely successful and works very smoothly in market allocation processes in other arenas, should be applied here too: *"charge all that the traffic will bear"* under any and all circumstances, since that is the absolute paradigm of the recovery of investments in risky enterprises. That means that when a drug is first introduced—if it has any significant utility whatsoever—that it would of course be available only to the rich, would be advertised at the highest possible price. Thus, the first doses of a penicillin ought to go at ten or one hundred thousand or million dollars per dose, which would be a very good bargain in some situations, in some circumstances, for life-saving purposes to those who can afford it.

Also, let the process of free competition by other innovators, who may emulate the same procedures, increase the supply of those goods until the appropriate market equilibrium is established and the poor can also benefit equally with the rest. I think I'm not making too much of a parody of Milton Friedman to suggest this approach in solving those problems. Rather, I think the answer is very simple. We simply would not stand for such a system. It would be very much against our moral feelings that there are limits to what the traffic can bear where human life and health are concerned. And the fact is, we have other kinds of obligations, of one to another, so that we simply do not have a free market system in issues that relate to knowledge relevant to life and health.

There is, of course, something of a market in arenas of the medical specialties, where services are indeed bid up, where some groups who work very hard for their incomes can achieve very high incomes in pathology, in radiology, and so forth . . . where there is, indeed, an obvious scarcity of specialists just in terms of how the market evaluates those particular services. And in these areas it would be hard to see why the Government should turn away from an opportunity to reduce its eventual cost in health insurance, and in whatever role it plays in the maintenance of public health, by pushing up the supply and reducing the cost by appropriate manipulation of the market, which would be far less intrusive than whatever it undertakes in many other arenas.

But that question—that we simply will not ask all that the traffic can bear—is not really the basic difficulty in creating an open market in knowledge. The basic difficulty is that the transaction cost is simply too high. If we had to depend on the recovery of an economic

yield every time there was an exchange of fact, an exchange of information, and collect a royalty for the promotion of ideas—the overhead would exceed the intrinsic value of each item by many, many fold. And I simply do not know of any economist who has examined this issue in any explicit detail who would begin to advocate application of the principle of a free enterprise economy in the knowledge field, in the way in which it may be entirely appropriate in many others, as a means of allocating resources.

Yet, at bottom, that is the implication of the statement that the training of graduate research specialists should be subject to market forces in order to determine the distribution of individuals who go into it. Now you may say that I've made a parody of the situation—that this was not what was intended by those policy implications concerning training grants. Still, I think they were inasmuch as the suggestion and the imposition of policies with respect to the termination of these programs are simply part and parcel of the total government commitment with respect to research funding. So it is indeed a self-fulfilling prophecy to say that there will not be sufficient positions to occupy the graduates of our research programs when the same market controller—in something that is very, very different from the free market—has also determined what the overall role of those research programs will be in our economy.

All in all, considering the transaction costs of any hindered system—of any economically-tagged system of exchange of knowledge—it would seem that the social support of free science—I stress free—is about the best bargain that a society can get.

Obviously, this view is not held unanimously or we would not be in our present difficulties of funding and of the public image of science today. The ultimate motives for the recrudescence of the war against science are difficult for me to rationalize. My speculations deserve to be tested with empirical evidence and theoretical analysis in fields of social science with which few of us here pretend to be expert. Some of us may view the present campaign as simply the renewal of a centuries-old conflict between science and theology, issues that others believe had been laid to rest at least 100 years ago. Many years ago the sociologist Robert K. Merton pointed out a number of ways in which the methodology of science conflicts with the cultural style of the community in a fashion that he predicted would cause some of the troubles we are now experiencing. As scientists we pride ourselves about our universalism, disinterestedness, the socialization of knowledge, and our role as a community dedicated to organized skepticism. These are all uncomfortable burdens to be borne by a social system which has few other precedents for dedication to these aims and methods. In addition, we tolerate as a necessary evil a level of specialization of knowledge that may already be the limiting factor in the communication within, and growth of, science as a whole, and which seems to bar the average citizen from very direct participation in the intellectual excitement of scientific advance. When this acceptance of arcane jargon becomes transformed into sanctimonius self-superiority about the qualifications of technical experts for guiding human affairs, we are, of course, raising still greater difficulties for ourselves.

Whatever *a priori* norms we might have about the responsibilities of science to the Republic, it is a plain empirical fact, that the present budgetary crisis reflects, that we simply have not done a sufficiently effective job of communicating our values, our utilities, and our ethos to the public at large. In addition, the organization of our scientific disciplines and the academic institutions that go along with them, although ideal for preserving the integrity of scientific criticism in established areas, may tend to have a dampening effect in cultivating an overall perspective about the values of the scientific enterprise as a whole, as well, perhaps, sometimes even in the promotion of new kinds of ventures within the framework of science itself.

The seeming incapability of scientific expertise to reach reassuringly precise conclusions about the costs and benefits of investments in environmental modifications of various kinds, in the introduction of new drugs and additives, and even in the evaluation of investment of basic research itself, furnish all too ample ammunition for the critics of laboratory science who, naturally, come from other sorts of intellectual background. It should be perfectly obvious that problems of, for example, environmental hazards cannot possibly be resolved by the isolated application of the techniques of biology and experimental medicine any better than they can be dealt with by applying abstract formulations from economics or political science; and we surely must develop new institutions that can more effectively bring both kinds of inquiry to bear on crucial policy questions of this kind.

Up to this point, the ultimate future applications of our scientific knowledge have appeared as the main justifications for our social investments in such science. So economists can ask questions like "what is the

appropriate discount rate?" And there will be some deferral of payoffs. But when we talk about long-range goals—if those are to be the justified purposes of present investment—we have to think, are we discounting our present investment at two percent, at five percent, at 10 or 20? And one often thinks of this type of process—wherein you say that if the eventual payoff is going to be the saving of 'x' lives, in some future year, and you have to discount that at 10 percent—anything that is 20 or 30 years off becomes very difficult to justify an investment in . . . just by the laws of compound interest.

Now this is an entirely appropriate way to begin a system analysis and a comparison of competing programs within a given sphere. If you want to ask yourself, "is it better to put 'x' dollars into education," having some idea of what the payoff will be with respect to cigarette smoking habits, or put the dollars into the design of better helmets for motorcyclists—with a whole set of competing alternatives—there really is no substitute for this kind of economic analysis . . . provided it's done rationally and provided it takes into account all of the economic factors in the situation within a given sphere. But it's a very poor system to use in trying to compare vastly different kinds of programs. And I can only illustrate by asking you what you think is the dollar value of national security compared to a given level of health. It may be a reasonable question to ask, in that it may expose some of the assumptions that underly your value judgments, but it's not one to which the economist or anyone else can possibly give a prescriptive answer. He can observe how you behave in your market choices—when you choose aircraft carriers over health research. But we must also ask how well informed such decisions are.

There is one element in the analysis that, as far as I know, has been overlooked by every economic analyst of the situation. The effort to derogate the ultimate value of future benefits of present day health research by invoking a discount rate totally overlooks the fact that, as a matter of historical record, the economic value that we place on life has been growing very rapidly as well. Its future value is increasing and should so discounting equations . . . because it's not a fixed good, not a fixed quantity of potatoes, or gold. or even labor, or other kinds of productivity. The value of life has always been judged extremely flexibly in every society, and it is roughly infinite; that is to say, it is in fact worth roughly what any individual has at his disposal from his resources at a time when he actually confronts the situation as to whether or not he should make an investment for the preservation of his life. (It is not precisely infinite, of course.)

But even looking at it from the point of view of the social valuation of life in terms of the investments that communities have been willing to make . . . how many million dollars to prevent how many deaths in a given circumstance . . . the historical record is perfectly plain showing a progressive increase in that valuation—both in real money and in the inflated values of a constant currency over the years, which just about beats out any discounting of current investments at any rate that one could reasonably propose.

All this is to suggest that most economic analysis in this area are, at bottom, faulty; that when they're pushed beyond the limits of the capability to express meaningful equations, they're going to give nonsensical results. Within an arena of competing programs for related goals, the translation of lives into dollars, as of some particular contemporary period, serves a very useful purpose in focusing attention on the most cost-effective kinds of programs. But that translation factor is, inevitably, an arbitrary one—it reflects the mores of the moment, it reflects what the community at a given time is willing to invest, and it is by no means the fixed price of a given commodity or a given product that the economist would have to have if he is to make comparisons of lives today and lives in the future . . . or lives today and other goods today . . . in the way that he would seek to do in other arenas.

In the long run, the value of a life is what well informed people will pay for it. And we know that this is a highly variable coefficient determined by many, many aspects of the history of a given individual (as, of course, many such valuations are) but which can be very large indeed in circumstances where the customer knows that he can have a useful outcome from making a specific investment. Besides the direct economically evaluated goods that are the results of our research investments, we must not ignore the side effects, even though these (the latter) are even more difficult to put dollar figures on. We thus have in essence what one might call the Newtonian as against the Baconian justification for science. At the very pinnacle of the pyramid, the process of pure research—the fact that there are people who are engaged in this struggle with ignorance and this struggle with nature—brings a unique intellectual, moral, and aesthetic value to any community. It's rather easy to scoff at that, and it's hard to put a dollar value on. But the very fact that there are still long waiting lists of applicants

for admission to institutions like Harvard and Yale and Stanford—who represent an adherence to those kinds of goals—tells that there is still a public interest in these aspects of the intellectual life that are reflected by investment in science as well as in the raw payoffs which might be better reflected in the technological academies. Here, too, we don't charge just what the traffic will bear in the exchange of these commodities nor could we possibly survive without doing so this way in a free enterprise economy.

Essential to the integrity of science is a process of internal criticism, of the demand for public validation of experimental results, which is, in effect, manifested by the peer review system. I know one can make many criticisms of it, as it works out in some detailed examples, but these do not stand up very well to very close scrutiny. The worst abuses that I can think of have to do with taking too simplistic a view of the consequences of a peer review analysis. I have had the privilege, pleasure, and agony of sitting on some Councils and have often debated whether anyone really understood the meaning of a number like 134 when it appeared in a priority score and has to be matched up to a 128 priority score, say, from another study section. These evaluations are simply not as unilinear as would be necessary to justify a single dimensional scale, and I think there is a certain distortion in the process—the intellectual and evaluative process of peer review—that demands that it be expressed in terms of a single number. No one can say that, ultimately, there is a single number. In fact it ends up being one bit of information, yes or no. So there has to be a dividing line that will separate sheep from goats.

But I think at any stage—where judgment still has to be applied to the judgments of a set of peers—that to transmit information about evaluation by a single numeric is a distortion. And it's one that gets to be reflected back in the internal processes of the peers who are doing the reviewing; back to the investigators at the point where they write their application; and to the Councils and the staff who have to cope with this overly-constricted format in which information is transmitted. I would hope that at the same time there is a re-examination of the distribution of goals and responsibilities among various Institutes, and that there also be some very serious attention to the process of peer review itself.

While there are, of course, always many possibilities for the further perfection of any system, peer review included, it is hard to see any viable alternative that could preserve the scientific integrity of research programs. The main competitors, as possible approaches to resource allocation, would be the free market and pressure group politics. Some of the problems of applying free enterprise models to the development of scientific knowledge have already been summarized. In any case, I doubt that we are about to offer incentive contracts that include pecuniary bonuses to the investigators whose work is proven to have the highest economic payoff. Were we to adopt such a crude system of incentives we would be encouraging an overweening attention to priority and to depriving other workers in the field of access to current information. The peer review is, nevertheless, a muted form of reward for performance that depends on the judgments of a large and visible group of experts to make determinations about the probable relative utility of a variety of competing proposals. The success of efforts to use bureaucratic planning for guiding large-scale investment in technological projects, subject to the influence of pressure groups from different regions and specific industries has had such painful outcomes that one would hardly believe them to be good models for changing the policies of NIH which have been so outstandingly successful in promoting research of high quality. Administrators who believe that the process of grants administration will be simplified by dispensing with scientific expert judgment have failed to take into account the intrusion of many other pressures against which peer review has been an effective buffer.

Nevertheless, peer review can be improved, especially by looking more realistically at the nature of the judgments that group is capable of making and capable of transmitting as this information goes down the chain. It is still somewhat deficient these days in terms of the feedback to the applicants, and we should be looking for better ways to take advantage of the enormous effort and critical intellectual judgment that goes into the peer study of research proposals under the present system.

Now of course, there is one very serious danger about the continued success of all of these processes and that is that our investment in basic research may help to cultivate free and critical minds.