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In thinking of strategies for the direction of research, we should keep in mind a multi-dimensional matrix: roughly of needs, scientific opportunities, resources, and constraints: not to mention time and space.

The scientific opportunities have been dealt with in the discussion of principal themes for the Human Frontiers Effort. The planning document is an excellent survey of the current frontiers of the life sciences.

I have been involved in many such projections especially during the last 25 years. They are indispensable for giving a tangible sense of direction in a comprehensive plan. They will help guide the establishment of organizational and management structures and give a sense of scale. They should not be taken too seriously: unfortunately scientists too often make discoveries that require a constant redirection.

This Green book is the annual report of The Rockefeller University (formerly The Rockefeller Institute for Medical Research). Our program is developed incrementally especially by the choice of the most skilled people and they shape the details of the scientific program which in fact is of almost identical content and objectives as the Human Frontiers Project. In fact, our motto is "Pro Bono Humani Generis". Besides being a model of a management approach, the scope of the R.U. may also indicate what can be achieved with an annual budget of $90MM. But this is only about 1% the US annual expenditure in health related research (all sectors).

Needs will bring us into philosophical discussion, where our priorities in different spheres must be examined as "tradeoffs", e.g. of industrial prosperity vs. pollution. Resources are very much concerned with the organization and management of programs; and I will discuss that at the end of my talk. Constraints arise in the ethical and political sphere, for example in the attention we must pay to the ethical problems of research involving human subjects. In the U.S. today there is great controversy over the conflicting desires for privacy of the individual and the public health interest in acquiring all possible information about, for example, AIDS. But most of my further remarks will be about the dimension of NEEDS, how we will target the application of advances in biological knowledge. In this field more than most areas of science, the relationship of basic to applied science is a reciprocal: that is, biology has as much to learn from "the experiments of nature", that is the examination of disease, as vice versa.

There is much to be said in favor of bringing an international focus to a consideration of where technological advance is leading global society and the measures that we must undertake in order to alleviate techno-stress. Consistent with that general aspiration, I suggest that there are two or three focussed aims which are relatively neglected in the research activity going on today. These would be of very great benefit not only to industrial societies but to the much larger portion of the world population that is now struggling to enter into the modern industrial age.

We know very well what the most acute historic challenges to human survival have been: they are war, pestilence and hunger. Today we can add the chemical and radioactive pollution of the environment.

The prevention of war I will accept to be primarily a problem of political management although one in which scientists continue to play a preeminent role. I am not here to make political speeches but I do want to comment my positive expectations for a truly global participation in this idealistic program. It has the possibility of bringing together the scientists from every country to deal with the problems of every country in a way that may mitigate tensions and improve understanding within that international scientific culture. In particular a more generous attention to the urgent problems of the less developed countries is an absolute prerequisite to the maintenance of peace to the next century. During that interval the aspirations of these countries are inevitably going to put increasing stress on the fabric of peaceful international relations even independently of the difficulties faced by the super-powers in their confrontation.

There are many neglected challenges of world health -- the apocalyptic pestilence to which the best of modern science needs be addressed. I need but mention the names of diseases like malaria, schistosomiasis, and leprosy and so many other parasitic infections which remain rampant throughout the Third World. Precisely because they have been relatively neglected for so many years they present extraordinary opportunities for the prompt application of innovations of the most modern biotechnology, and the understanding of pathogenesis in the development of vaccines and of other means of interrupting the spread of these infestations and of their damage to the human host. These diseases are reckoned as the most important scourges of mankind Together with diarrheal disease in children they kill so many more millions of people throughout the world than those diseases that figure so highly in our own imagination and fear. I'm glad to refer to important progress during the last decade under the leadership of the Tropical Disease Research Program within the World Health Organization, and the diarrheal diseases efforts and the universal immunization of children done in collaboration with UNICEF and many other collaborating international organizations. I know many idealistic young American scientists who have now been motivated to a career of interest in these organisms to which they know they can apply their very sophisticated skills with the most marvelous effect. I invite Japan to join this effort and take its share of responsibility in helping to be among the scientific saviors of the Third World in this arena. There are comparable problems of the development and improvement of new crops to help take care of the nutritional needs of those same populations. Of course we cannot be promoting the health and survivability of children without at the same time attending to effective and humane methods of family planning and population control. This would enable these same families and these same countries to make a fresh start in garnering the capital resources so that their economy can reach a standard of living comparable to that of the now industrialized world.

We should not believe that this is a merely unilateral benefit. To our great pain we are discovering right now that our oblivious neglect of viral disease in Africa has allowed the fomenting of the very serious family of viruses, the HIVs (Human ImmunoDeficiency

Disease Virus) which are causing such severe stress in Central Africa. But this has now spread to every other country of the world and is being heralded as the great plague of the 20th century. I am not one of those who feels optimistic enough to minimize the eventual impact of this epidemic: we do not know how far it will go. Even if it is merely confined to sexual channels of transmission, and then dirty needles and an occasional accident, we are still going to face a human toll of unprecedented dimensions. And why should we believe that this is the only nasty trick that nature has up her sleeve when we turn our back to the evolution of disease and its spread in those populations where we permit this to occur unchecked.

HIV has of course the most insidious characteristic of any known infection in having such a long latent period during which its carriers are presumably fully capable of transmitting the disease; and in having no known mode of prophylactic vaccination at the present time. Other virus diseases have had much more rapid spread but one more visible with shorter latent periods and lifelong immunity. Hopefully at some time in the next decade or two we will have chemotherapeutic methods of treatment as well as vaccine prophylaxis for this virus but there is no telling what the human toll will be in the interval. There is certainly more than ample need and challenge in answering this immediate threat to our own direct health and tranquility.

The other field that I advocate for emphasis has to do immediately with techno-stress. I'm going to use a startling phrase that I learned from Professor William Baxter of Stanford University: that is that we need to learn how to optimize pollution. This may be a startling statement to some who have the fantasy that we can somehow reduce pollution to zero but this is contrary to the daily fact of human existence. Every breath that every human takes depletes the atmosphere of its lifegiving oxygen. These natural processes are multiplied by industrial activity, which necessarily results in some pollution of our environment. When we treat our water supplies we try to exchange one form of pollution with the potential for another: namely we chlorinate polluted waters in order to eliminate infectious bacteria and are willing to take a much lower but still residual risk of the chemical consequences of chlorination. In order to optimize pollution we need a much deeper technical understanding of exactly what are the costs to human health and to of the environment of each of a very large family of chemicals (and of course physical agents). It is not good enough to say that we want to wipe them out completely: it is too late for that. One can calculate that in every breath we take there is at least one molecule of the perfume in Queen Nefertiti's vial over 3,000 years ago; and of course many, many molecules of every pollutant that has ever been emitted in every industrial process. There is no way that we can reduce those numbers to zero nor could we ever have even in anticipation. So we must learn how to set reasonable standards and to do that we need to have far more precise knowledge of the quantitative aspects of toxicity of every substance importantly involved as a product or byproduct of industrial activity. Then eventually we must also know not only the first order effects of these materials but their interactions with another, with other disease to which given individuals may be prone, to the effects of extreme youth or extreme age on vulnerability to toxins and so on and so forth.

Obviously it would be both morally repugnant and technically impossible to acquire this information by the observation of human beings exposed to chemicals. Although of course we have almost a moral obligation to exploit every occasion, after the fact, when there has been inadvertent exposure of a human being to an exotic chemical in order to acquire information of benefit to all the rest of society. The only reasonable way that we can acquire the requisite information is through the enhancement of a discipline that I would call comparative toxicology. This is a conceptual framework that embraces most of what is already done today in toxicological work: namely the use of laboratory systems (exposing enzymes or microbes or tissues cells or laboratory animals to greater doses of a given chemical and observing the inhibition of biological processes that result). Unfortunately, partly as a result of the way in which government regulation has evolved, almost all of this work has been done in a crude and rote fashion, and very little more is learned or observed than whether the animals become sick or die. In many cases that fact alone is enough to discourage any further mechanistic investigation as to how a toxic chemical was exerting its effect. Now we must try to extrapolate from the limited laboratory observations to the human population in assessing the practical risk and as a way to establish socially appropriate standards. The way to approach a better concept for the mechanistic understanding of toxic actions is to relate these experiments to comparative biology: how the processes of a human organism do or do not parallel, can or cannot be extrapolated, from simple laboratory systems or mice or rats. We do not at the present time have even well validated concepts of scaling: that is how to calculate from the toxic doses seen in mice or rats what the corresponding threshholds would be for the human. Lacking that scientific knowledge our judgements about the hazards of environmental pollutants tend to be all or none; to excite great controversy between the parties at interest and to frustrate efforts at optimal solutions. The costs are not only in economic wastes or foregone economic opportunity, nor in the abuses of human health and the environment on the other side. They also reflect on the confidence that people will have in the social order and in turn on civility and on the unity of peoples within nations and throughout the world.

To answer these concerns we need to enhance two extremes of investigation: a deeper mechanistic understanding of how toxic chemicals exert their effect -- this cuts to the core of modern molecular biological understanding, and a conceptual framework based on evolutionary principles of how the human response may resemble or may differ from that of other organisms. Here we have to be concerned about intrinsic differences in cellular response -- and there are species specific differences even of cells in culture but must also deal with much more subtle variables of the physiological and pharmacological disposition of materials that enter the body from the environment. Here, they are subject to the disposal mechanisms that have been evolved precisely to deal with such environmental insults. Keep in mind that the smoking flame is more toxic than the one that burns more brightly: that imperfectly oxidized intermediates (subjected to the P-450 cytochrome system of the liver) are often far more toxic than their precursors or their finally oxidized end-products. Then we see what a deep understanding we must have of the details of physiological organization in order to make reliable extrapolations. Within this framework, however, comparative toxicology can emerge as one of the most exciting scientific challenges and at the same time one

with the broadest of applications of the present era.

These programs of world health with respect to infectious disease and of comparative toxicology would have the advantage that any knowledge we achieve is instantly of universal benefit: there can be no question of competitive advantage in the acquisition of this new information. Let us do it and the world will be grateful.

May I add one comment: implied in the language of the January 1987 report, and in many other statements that I have heard from Japanese, is some sense that the creativity of Japanese basic science does not match your extraordinary accomplishments in applied technology. Because they have indeed been so extraordinary and in the process have generated some economic problems for the rest of the world! -- that would be a difficult standard to meet across the board. I do not know whether I agree with that self characterization: certainly I know any number of individual Japanese scientists whose own brilliance answers the question as to whether Japanese scientists are capable of the peak of creative capacity. Some will bring up certain cultural attributes, perhaps just the respect for older generations and established and traditional modes of thought as some explanation for that hypothetical shortfall. If there is a shortfall, I think there may be a very simple explanation: namely that the Japanese Government has never as a matter of policy provided funding for basic research activities at its universities in a fashion commensurate to that which has nourished the growth of science in the United States since 1950. Before resorting to more radical restructuring of Japanese culture, perhaps the experiment ought to be tried of simply providing those kinds of funds in a measure comparable to and to mechanisms similar to those which have been so successful in the United States. I do not however necessarily do you, my Japanese friends, a service by glossing over this question: it is one that recurs over and over again. My urgent suggestion is that we examine it more objectively and more critically: there are many problems of definition and measurement of "creativity". More specifically I would suggest that we have an international conference that critically examines the sociology of Japanese science with this issue of patterns of scientific productivity very much in the forefront. This would put particular emphasis on the international comparison of scientific productivity and patterns of research and might well include countries other than Japan and the United States. We should then include issues of funding, institutional strength, the role of young talent in relation to established bureaucracies, cultural differences in the approach to critical reexamination of established ideas and other related factors. If we could do this we could get a much deeper understanding of the role of contextual factors in the nurturing and inspiration of young scientists as influenced by all of these matters of funding, organization, culture and so forth.

I have for example my own deep concerns about the extent to which cumulative changes in the detailed style of research grant administration in the United States may be quite counterproductive in discouraging bold initiatives. Short term grants that are subject to capricious withdrawal at each renewal period may oblige young scientists to forego attempting venturesome and large leaps. They may instead concentrate on the obvious, which can be more readily demonstrated before the fact, in writing up grant

applications.

As to the organization of your effort: I most strongly endorse the proposed emphasis on international exchange of fellows. The United States already participates in this on a large scale mostly without a formal structure. A robust national research program conducted in an open way has made room for thousands of Japanese research fellows and tens of thousands of students at US universities and research institutes.

We are glad to have them and we would welcome steps to encourage a reciprocal flow of US students to Japan. There are formidable problems of housing as well as travel and maintenance expense and language training.

However any calculation of the US contribution to international funding of such exchanges must take account of what is taking place today.

An international center could serve as a very useful clearing house for scientific exchanges and be a vehicle for some of the funding -- especially incremental funding.

I do not believe however that an international foundation is an efficient mechanism for the distribution of grants for research projects nor for the collection of funds except for special circumstances.

In my opinion Japan's first priority for human frontiers is the strengthening of its internal activities in life sciences. If 1/5 as much money was spent here as in space and in nuclear energy Japan would be a formidable partner in our world effort.