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HEALTH IN THE WORLD OF TOMORROW

Third PAHO/WHO
Lecture on the
Biomedical Sciences

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PAN AMERICAN HEALTH ORGANIZATION
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HEALTH IN THE WORLD OF TOMORROW

Joshua Lederberg

*Third in the series of PAHO/WHO Lectures on the
Biomedical Sciences, delivered at the Headquarters
of the Pan American Health Organization,
in Washington, D. C., on 28 March 1968*

*With an introduction by Dr. Abraham Horwitz,
Director of the Pan American Sanitary Bureau*



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INTRODUCTION

Presentation at the Third PAHO/WHO Lecture on the Biomedical Sciences, 28 March 1968, in Washington, D.C.

Dr. Abraham Horwitz
Director, Pan American Sanitary Bureau

There are those who create knowledge and those who apply it. The former, in the search for truth, endeavor to define reality with precision. The latter hope to elicit the need for new knowledge. Those who investigate foresee the benefits for mankind of the results of their studies. Those who apply them enjoy the well-being derived, but dream of the new frontiers further research could attain. Both are part of a never-ending process to the service of man, a true example of complementarity. Ideas, feelings, and elements in apparent contradiction have a greater harmony and are indispensable to explain phenomena and to foster progress. As explained so well by Tuve, "Modern physics, unexpectedly, and in the experimental world of the laboratory, has provided an unequivocal demonstration of the finite or limited nature of our human possibilities for 'understanding' the world in which, unasked and without choice, we find ourselves. The message is clear and direct, and leads both to confidence, to faith, and to humility. There *are* different ways, conflicting ways too, in their very essence, by which we view the world around and in us, but the true answers will be framed in terms which fit the questions which we ask." ¹

As it is for human beings, so it is for societies and their institutions in the fostering of progress. It is with this philosophical view that we need to

¹Tuve, Merle A. "Physics and the Humanities—The Verification of Complementarity." (Remarks by Dr. Tuve on receiving the Third Cosmos Club Award.) Washington, D.C., 9 May 1966, p. 16.

appraise the transcendence of the purpose of the World Health Organization. In the short span of twenty years, it has come to be a true forum for the exchange of ideas concerned with the fostering of activities for the improvement of the living conditions of humanity. It has become a most effective instrument for the dissemination of knowledge that will enable the positive experience of one community to be applied in other places where problems, although having the same origin, manifest themselves in different circumstances. In furnishing advisory services to Governments, it recommends techniques that have proved their worth and acquires further experience of which other countries can avail themselves. By means of a broad program of development of human resources, it is opening up new opportunities for those who, in response to a laudable spiritual concern, wish to become better qualified in order more meaningfully to serve their fellowmen. It is offering increasing possibilities for exploring fresh approaches to the phenomena of health and sickness, whether the quest is for new interpretations, new methods, or new solutions.

As part of the celebrations of the Twentieth Anniversary of WHO, we have devoted this Third Lecture on the Biomedical Sciences to the subject which is the theme selected for World Health Day: "Health in the World of Tomorrow." As the speaker, we are honored to have Professor Joshua Lederberg, who has distinguished himself in investigating the creation of life while, at the same time, he has sought to establish a functional relationship of science with the structures, tendencies, and paths of societies and their interactions.

Professor Joshua Lederberg, as we all know, received the Nobel Prize in 1958 for his discoveries concerning genetic recombination and the organization of the genetic apparatus of bacteria.

In his Nobel Lecture, "A View of Genetics," he speculated about the context of contemporary science in which bacterial genetics can be better understood. "That genetics should now be recognized," he stated, "is also timely—for its axial role in the conceptual structure of biology, and for its ripening yield for the theory and practice of medicine."² In pointing out the true coalescence between genetics and biochemistry, for the experimental creation of life, he considers it as one example of the

²Lederberg, Joshua. *Physiology of Medicine, 1942-1962. Nobel Lectures*. Elsevier Publishing Company, Amsterdam-London-New York, p. 615.

coordination of so many adjacent sciences which will be a cogent challenge to the intellectual powers of our successors. But we face the same formidable challenge in understanding modern societies and the same need in establishing the relationship and mutual influences of different sciences, among them, biology, sociology, and economics.

In discussing the world of tomorrow, Professor Lederberg said that "man's unique quality is his self-conscious awareness of history. Every man looks back at a cultural tradition that, whether he understands it or not, has molded his personality, his language, his capacity to cope with the external world. He looks ahead to a posterity and around himself to a community of other men on whom his own life inevitably impinges.

"Religion is this consciousness of the species, the insight that man in complete isolation is nothing, that his life can have a meaning only in communication across time and space with his past and future traditions and with his fellows."³

This vision of human nature, as well as Professor Lederberg's concern for the future of mankind, impresses us greatly. He has emphasized the power of science and technology as it relates to men and their wisdom, and proclaimed that the highest possible investment of modern societies should be in the education of their citizens. We have understood his concept of education as the process that nurtures the ability of each person to form and pass judgments, that is, to apply a scale of values to the phenomena of social life. And it is in the university that this kind of education can best be fostered, provided that it emphasizes principles rather than techniques; fundamentals rather than methods; concepts rather than precepts. In sum, the education we speak about must endow the student with those notions that will enable him, throughout his life, to interpret his own experience in terms of reality.

The greater the attempt of a society to base decisions on public opinion, the greater the responsibility of scientists to analyze in rational and simple terms all issues affecting human beings. It becomes a matter of ethics, a true moral imperative, to cooperate with the political power which is the authority that takes decisions so that these should be guided to the realization of the ideals and higher purposes of every society. Great

³Lederberg, Joshua. "Science and Man—The World of the Future." *The Washington Post*, 8 July 1967, p. A-13.

progress has been made in the last twenty years in this respect, but we are still far from an order of relationship between government and science that ensures that the national interest and the well-being of the people will prevail.

It has been in this role precisely that we have come to admire Professor Lederberg, because he has shown wisdom and courage in analyzing the most complex issues of our present-day societies and has clarified the role of the scientist as a member of society interested in the welfare of man.

What is then his image of health in the world of tomorrow? We feel that the spread of his ideas in the context of health in the immediate future would be a most appropriate way to celebrate the Twentieth Anniversary of the World Health Organization.

It is my pleasure and honor to introduce Professor Lederberg.

HEALTH IN THE WORLD OF TOMORROW

Prof. Joshua Lederberg
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I find it a somewhat traumatic experience to be transplanted from my academic habitat to an environment of international public health policy. My attempts to ignore the implications of this environment were shortlived. Most of my speculations have concerned the frontier of biological progress in a self-reportedly advanced society. They might appear to be very remote from the massive, contemporary problems of my hosts and sponsors, the World Health Organization and the Pan American Health Organization. Nevertheless, "Pan American" includes the United States of America. To be sure, many of the nations in this union dedicated to the progress of public health suffer from some underdevelopment of their economic advance; in many respects the U. S. part of this union is, perhaps, an overdeveloped society. So we have our own problems of glut: too many automobiles, overmedication, overbuilt urban environments, and overnutrition—problems which many other countries aspire to share. These are problems of growing world significance as companions of economic progress. I will try to shed some timidity in presenting some of the challenges and opportunities that may now seem to be relevant only to countries that have a surfeit of medical progress and medical care by international health standards.

My topic is the nature of the biological revolution and its impact on our perception of health in the world of tomorrow. Recent months have

seen a great deal of publicity given to this. There is now a much wider public understanding of some of the very important advances that are taking place in the laboratories of the biochemists, virologists, and microbiologists. One of the outstanding feats of 20th Century science was, unquestionably, the replication of DNA in the test tube, news that broke in the world press last December. This information is not new to scientists who have been interested in molecular biology over the last five or ten years. In fact the trend of reaction when Professor Kornberg's experiments were announced was "what took it so long?"

The basic principles on which this exceedingly important and technically difficult result was achieved were very well understood at least ten years ago. On the other hand, the successful demonstration that a biologically active DNA could indeed be replicated or, as some spoke, "synthesized in the test tube" did, of course, open, to a much wider arena of interest, speculations about the early biological or medical exploitation of this kind of technology. But in fact the biological revolution (and I think it is fair to describe the intellectual currents of the last ten to twenty years in revolutionary terms) does not consist of tangible advances now suddenly made possible in the "engineering of human beings." The biological revolution is a philosophical one based on a new depth of scientific understanding about the nature of life. It is the realization that while many mysteries of detail remain about the way in which cells are constructed, there are no longer any *fundamental* mysteries; that it is feasible to think of creating a model of the cell and a model of life, essentially on mechanistic terms; that we can describe the essential substances that participate in the chain of life; that we have indeed filled in the most crucial important gaps in our detailed understanding of the way in which the cell replicates, the way in which it passes this information from generation to generation, the way in which it controls the synthesis of proteins in its development, and so on.

The cardinal element of this revolution is one of understanding the central significance of the role of DNA, of information transfer from DNA to RNA, and from RNA to protein. It is almost not important that you know in any detail what these words mean; it is important that you recognize them, that you know that they will come up again and again and again in your life and your children's life in the future; and most important, simply that they are substances amenable to detailed chemical investigation in the laboratory, and that life can only be understood in terms of these substances.

This support for an utterly non-vitalistic interpretation of life may seem to have some interesting philosophical consequences. But what does it have to do with such tangible questions as health in the world of tomorrow; what should we anticipate for its practical impact on public health; what processes should we be setting in motion at the present time? It has become fashionable in recent weeks and months to worry about "tampering with the genetic code," with genetic engineering, with modifying human DNA, and to concern oneself with the ethics of this kind of intervention and so on. These matters of individual ethics are not our immediate and present public health concern. There is, however—to borrow a phrase from Senator Harris—a macro problem behind the micro problems to which I have just alluded. The main health implication of the biological revolution is the confidence, entertained by scientists, in the eventual technical solubility of any biological problem, now that we have passed the boundary of mysticism in our interpretation of biological processes. This was not true twenty years ago, when we still had only rather vague ideas about the chemical basis of heredity. If one asked the question "Will we ever conquer the problem of aging?" we would have had to say only in very general terms: "Well, if we work hard enough maybe we will get an idea that is relevant to it." We were not able to assert any arrogant confidence that problems of this kind were unqualifiedly within the arena of human competence. I believe we are in a position to express such confidence today. There are a thousand self-evident experiments waiting to be done. The field suffers only from a plethora of hypotheses about the details of the aging process among which one must make a choice. And from a shortage of funds and skilled manpower to do the experiments.

This is a philosophical innovation; the innovation is the certainty that given a requisite investment—and by requisite I mean quite within the potential resources of government-supported health research today—this is going to be solved, and that we had better start gearing ourselves to the consequences of success in this and in a number of other areas. In fact, we perhaps had better start attending to questions of priorities concerning not merely which problems are the most grievous but also which have solutions we can assimilate with least violence to our deepest values.

The prototype for this remark is, of course, the central success of world health in the suppression of infant and child mortality. We were certainly reacting to an extremely urgent human problem but we did nothing to anticipate our success, so we have a whole new set of problems generated

by the successful achievement of solutions to the old one.

I have heard very little thinking about how we are going to cope with the inevitable *success* of our health research programs in fields like cancer, heart disease, and aging in general. This is natural; we are so preoccupied with the solution of these very urgent problems, problems that touch every one of us, that success seems almost out of the question.

I am reminded of a discussion some five or six years ago in which I tried to prod some of my surgeon friends about how they would cope with the success that we mutually anticipated in the transplantation of organs. Until it was actually done, it was difficult to evoke any realistic thought that hearts would be movable from one individual to another, and further that the success of this operation would itself pose a new set of problems.

We will survive the dilemmas that pertain to the successful transplantation of hearts; we may find it more difficult to survive the dilemmas that will pertain to the global conquest of aging, cancer, and heart disease unless we give a great deal of hard thought in advance about what they will mean to the nature of the population in which we live and to the nature of our own lives.

Will life be tolerable without death? Nothing more nor less than this is the inevitable fruit of our modern knowledge of molecular biology.

These questions are in fact not totally out of discussion in contemporary policy. Urgent medical problems, like severe chronic renal failure, or even cardiac failure, have technical solutions, either immediately visible and apparent, or just around the corner; I refer to artificial kidneys and artificial hearts, respectively. Our experience with artificial kidneys has been and is a very trying one, and it is particularly so in the present interval of technical success, and economic and social failure to take full advantage of it. As all of you know, the availability of this method of solving the problem of the individual with no functional kidney is sharply limited by the economic considerations, that there are not enough such machines to go around, not enough hospitals and care centers in which to accommodate them, not enough trained personnel and not enough money to pay them—all this in a country that prides itself on being able to furnish the highest level of medical care.

Artificial kidneys are not necessarily the most cost-effective use of the

next increment of medical investment. My point is the vagueness of the value judgments for reaching such decisions. If a very large investment is made it will be taken from somewhere else. Is it in fact a matter of the highest priority to prolong life of individuals who are suffering from chronic disease, or should areas like infant health, or preschool education and nutrition, or other areas receive a higher priority?

The only complaint that I have to make about the present debate on this subject is that it is not forthrightly stated, even by the protagonists, and it is certainly not one in which the public is playing any perceivable role. It is of the utmost importance that our citizenry be educated about these possibilities and that they do participate in these very difficult choices about where we are going to put our resources, what quality of life we seek first in the solution of our medical problems of the very near tomorrow. And where, if anywhere, do we ever reach the break-even point for such investment?

I will turn to some micro issues. These are amusing and interesting to speculate about; they represent very short hops out of the biochemical laboratory into health concerns. What near-term use can we make of present knowledge of DNA? Just coming down the elevator to this podium it occurred to me that perhaps there has not been a great deal of thought about moving the frontier of molecular biology to the large-scale public health programs which occupy so much of your thought, energy, and resources. My companions tell me we might classify these problems under four major headings: malaria; population control; malnutrition; and water supply.

I make no pretensions about expert knowledge of any of these fields, which makes it easy for me to speculate.

Consider malaria. The principal technique is mosquito control by annual spraying of houses with chemical pesticides. This is a procedure that has to be maintained month after month or year after year; very large amounts of money are spent throughout the world using now commonplace agents like DDT. What is the budget now spent for this purpose? I would hope some hundreds of millions of dollars a year around the world; perhaps that is an overestimate.

I am sure that no commensurate attention—say 1 per cent of that budget—has been given to the possibility of adapting viruses for the

purpose of mosquito control, and even less to the fabrication of a virus to attack *Plasmodium falciparum*. The capacity to manipulate the genetic composition of viruses is one that is essentially upon us at the present time.

Many approaches to this kind of problem have not left the biochemical research laboratory. Not because they are any secret—they are enthusiastically and loudly published by their discoverers. But applied effects like this are always under-funded in the first place, and too little is left to support sufficiently broad and imaginative bridging research of the scope relevant to the problem.

For malnutrition I may be able to make a more concrete suggestion along somewhat similar lines. This is a very confusing subject; the experts have confused us by lumping together a large variety of different diseases under one particular heading. Whenever this is done medicine and health suffer, and I believe that this is true in the field of malnutrition. There are some fifteen or twenty essential ingredients in our diets, any of which may be missing in the diet of some particular individual. There are nine or ten essential amino acids, there are perhaps half a dozen vitamins, and there are a number of minerals. Some of these do not pose consequential health problems anywhere; many of them do, but differently in different localities, depending on the diets that are available. And it does no good to solve the lysine deficiency that may be present in one population by providing grains supplemented with materials that have quite a lot of extra threonine but not the lysine, and vice-versa.

For the Biafran airlift, the quality of the cargo was measured in lives per pound. Was it, could it have been, scientifically matched to the actual needs of the starving population? Do we know the best regimen to save the most lives during such emergencies?

Malnutrition is, in fact, a rather particular kind of genetic deficiency disease. This is a rather odd way to put it, and it rarely is expressed in this fashion, but I have to do so for the further extension of my argument. Man has evolved from precursors which had the capacity to synthesize all of the essential nutrients from rather simple sources in the diet. We now rely on plants, which make every one of the amino acids and every one of the vitamins. The requirement by man for specific food components, amino acids and so on, can be stated as an evolved defect in his genetic apparatus. We lack whole sets of genes needed for the manufacture of

tryptophan, of lysine, of threonine, and so on. These genes are, however, present in other organisms; they are present in many bacteria, they are present in most plants. It is then plausible to foresee virological solutions to the problems of specific malnutrition that might be in the aggregate far less expensive than maintaining an agriculture which is capable of producing an optimum variety of amino acids.

As soon as the problem is formulated in this way we can visualize the following steps: we first of all have to learn, in a rather general way, how to graft viruses with genetic material of other origin. (We are certainly very close to doing this.) We then have to have isolated just one molecule of the genetic information needed for the synthesis of tryptophan from a cell of *E. coli*, or from the cell of a maize plant, or whatever you like; and we have to now introduce a virus that carries the genetic information for the internal synthesis of tryptophan into a child genetically deficient, as we all are, for the ability to produce that specific amino acid. Once the preliminary work on this is done, and I have absolutely no doubt that it will be done over the next dozen years (or months) or so, I will have to ask our world international health experts whether it would be cheaper to vaccinate children against malnutrition or to teach them and their mothers how to maintain adequate and satisfactory diets. As far as I know no one has even attempted to obtain a research grant on this particular program, and I am not sure I would approve it if I had the discretion to do so. But I do want to point out that there is an avenue for the application of new knowledge of biochemistry into this kind of health problem.

It would be equally plausible to engineer viruses to modify crops so as to exaggerate their yield of scarce amino acids. This is merely an extension of ideas already being slowly diffused for the rational breeding of crop plants and animals to meet the actual needs of the population, not just give the most bushels per acre or the most butterfat in the milk.

Population is, I realize, an extremely complex problem in which sociological and psychological factors play a central role; we have to face much more than the technicalities of temporary sterilization. Nevertheless, the costs of the dissemination of these techniques are important in many countries that desperately need the respite for a start toward industrial sufficiency. By the same logic as for dealing with malnutrition, we should also be able to produce a virus that will simply reduce the excessive fertility of the human species. In fact, viruses of this general kind are already known in some of the insects; and I do not know why they should

be smarter than we are in finding techniques of family planning.

To approach this problem would entail the most fundamental studies of tissue specificity in the attack of viruses on cells; but the gonads should be as interesting as the central nervous system, which has usually been the point of application of our concern about tissue specificity.

Moral problems of social process in fields like population control already press heavily upon us. New techniques will bring their own dilemmas but they are not abruptly different from the ones we already encounter. Mass infection with viruses is a consistent extrapolation of mass indoctrination with propaganda, particularly so long as the target population remains too poorly educated to form truly independent and critical judgments.

Now, I was not able to think of a way in which DNA could be used to make water. (Perhaps I have already demonstrated how it could be used to make "hot air.") But we might try to turn the problem around. The economics of a bulk commodity is a different proposition from that of a hormone or an insecticide. But what about mitigating the need for water? Here we are in fact talking about the development of crop plants capable of surviving in more arid climatic conditions, and I do not understand why we do not rocket off the ground on that. Let me just say briefly, and rather dogmatically, that this is another area which is grossly undercapitalized in basic research in relation to the most obvious human needs and benefits.

Well, will anyone refute me about the currency of projects of this kind? Have I overlooked existing, imaginative uses of molecular biology in these areas?

There are many other ways by which a knowledge of DNA is going to be used in a human context; and in the fullness of time they will also represent world health problems. I have already given away part of the story, as one of the fantasies about the application of synthesized viruses for malnutrition. However, the same principle to which I alluded, with respect to the repair of genetic deficiency for the autogenous synthesis of amino acids, should of course be available for other kinds of genetic defects, as has been urged for some time by Dr. Stanfield Rogers of Oak Ridge.

The more visible application of new knowledge, of the cellular machinery for protein synthesis, has already been started in a very empirical way, and this is the realization of the enormous possibilities of tissue and organ transplantation with the help of immunosuppressive drugs. The agents that are used at the present time are mainly by-products of cancer research. They have been incidentally and empirically noted to be rather dangerous because they suppress tissue functions in the marrow and some of them have been found to have particularly toxic effects on those cells that have to do with antibody formation and graft rejections. We are just beginning to get a clear insight into the fundamentals of antibody formation, and it seems inevitable that we will soon have a detailed rationale for specific interference with the immune response to foreign tissues, which is what interrupts transplantation experiments at the present time.

Now, I do not think that heart transplantation is going to be the major application of this technique in the future. This is of course an important and a dramatic one, but I rather hope that mechanical hearts will solve some of the problems brought to us by the very success of the heart transplantation technique. But I would like to point out that transplantation of organs is now inappropriately regarded as a rather heroic therapeutic measure. We think of replacing a completely failed organ, missing kidney, a missing or completely deteriorated liver, a heart that is about to cease to function. Much more important than this in the aggregate would be the use of organ transplantation for rather minor ailments. If my liver is not producing enough bile, perhaps I ought to have some augmentation of it; if my kidneys are not quite up to par and they have to do a little better clearing of alcohol, perhaps I ought to have an improved model; if I am a hemophiliac perhaps I ought to have an extra lobe added to my liver in order to make the clotting factors. If my temperament is not what it ought to be perhaps I ought to have another adrenal gland or thyroid or another pituitary that might be more effective as a homeostat than the one I have at the present time, and so on. There are many, many less dramatic functions where events can go out of whack, where transplantation will be easier, or particularly those cases in which we are dealing with small organs with soluble products where the question of integration into the old site is not that important; and I have no doubt at all about where the action really is going to be. The *Wall Street Journal* a few days ago carried a story that illustrates my point beautifully: I have no doubt whatsoever that the transplantation of patches of hair to eggheads like me will probably be the major transplant industry, once the

immune rejection phenomenon is countered. So, there are some glorious consequences from understanding the genetic code.

There is a great deal said that implies that we are on the brink of an immediate and incisive intervention in existing genetic information; as if we had some way in which we could go into the fertilized egg, discover some defective or missing nucleotide, and replace it with the right one; that we have some way of repairing it genetically *in situ* in the developing organism. This is a lovely idea; I wish I were bright enough to see how to do such miracles. The problem is not the intervention; it is not hard to see ways in which one might at least some time exchange one nucleotide for another; the problem is to know where to go with it! There are some four or five billion nucleotide pairs in a human nucleus; and you had better get the right one or you will be doing more harm than good in the process. It seems to me extremely unlikely that we will have achieved this particular pattern of intervention without having passed a number of other milestones on the road first, and among these, for example, would be manipulation of intact nuclei, exchanging nuclei from one tissue to another and from somatic tissues into the fertilized egg. These will already raise some interesting possibilities of vegetative reproduction in man as a mechanism of producing a new generation that undoubtedly will continue to operate in parallel with the familiar techniques that you know about at the present time. I do not think this should be shrugged off too quickly as a bizarre anomaly. I want to remind you that the vegetative propagation of individuals is habitual throughout the plant world; it goes on through many of the lower animals—you can cut an earthworm in half and very happily get two—it is something which has been lost as a latter day event in the specialization in the biology of the higher vertebrates. A number of us might express some concern about the evolutionary consequences of preventing diversification of genotypes, the diversification that arises from sexual recombination, but this would only be a serious problem if vegetative reproduction preempted the gamblers' choice which is the consequence of such a reproduction at the present time.

I put this more as a social fantasy than a biological one; it raises some rather provocative ideas about the nature of our culture and these may be already sufficient to postulate the validity of this as a biological proposition. The end result, you see, of a procedure of the re-nucleation of eggs with nuclei, each of them derived from a different cell of the same donor, would be the production of a clone of individuals all having the same genetic constitution—identical to the donor's at the time of his birth.

We then face the application of our deepest insights into just what is the role of differential environment and the role of differential heredity in the definition and growth of human personality. If for no other reason than to do these experiments (to find out something about education, for example, which can only be done in any incisive way by controlling the genetic composition of individuals party to these experiments), we will see an effort to produce batteries of genetically similar or identical individuals. Now, this already happens, we have twins and triplets. They unfortunately happen too sporadically for us to be able to use them effectively for this kind of environmental experimentation, although perhaps one might prefer to think of ways of performing such observations on natural clones, before we went too deeply in the business of making them artificially.

I do not have the vision to detail the world health implications of clonal reproduction; perhaps we will not have to face it on a large scale, and I do not know that it is a problem we need to face during WHO's next twenty years; but I am sure it is typical of the problems that the next generation of world health workers will have to think about. My shakiest assumption is categorical optimism: that there will be such a generation, given the world's perils from nuclear weapons (which everyone knows and fears), and pandemic disease (which we know well and do not say enough about). Certainly our central responsibility is toward the realization of this categorical optimism.