Nobel Foundation's Centennial Speech

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The following talk was given as part of the Nobel Foundation's Centennial Symposia at which Nobel Laureates and other prominent researchers offered scientific, scholarly and popular talks. Dr. Varmus spoke as part of the program "Beyond Genes," held December 6-8, 2001, at the Karolinska Institutet, Stockholm.

Introduction

This symposium occurs at a moment that is both symbolically and historically significant for biology and medicine---and also one that highlights the world's inequities and tensions.

On the one hand, we are here this week to celebrate a century of Nobel Prizes and the remarkable discoveries for which they were awarded. We in biology are also celebrating the centenary of the rediscovery of Gregor Mendel's principles and a century of progress in the study of genes, now capped by the full sequencing of many genomes, including the human genome.

In the century just concluded, biology has been transformed from an observational to an analytic science, thanks largely to new methods, such as molecular biology, and the application of established principles of chemistry and physics to biology---for instance, for analysis of macromolecular structures. Science has also dramatically affected life expectancy and quality of health. Many of the improvements in health can be traced, or even linked directly, to work that has won Nobel Prizes, fulfilling Nobel's directive to reward those who have made discoveries "for the benefit of mankind."

But we also meet in the wake of a cataclysm in NYC and terrorism world-wide. These things can easily make us question the role of science in the world, now and in the future. Will it continue to contribute to the benefit of mankind? Are the benefits of science experienced by the poor as well as the rich? Might science accentuate, rather than diminish, the large differences in the quality of life experienced by the rich and the poor? Might these differences contribute to the resentments that fuel terrorism? And, if so, is there anything we can do as scientists to reverse such trends?

"Beyond Genes": A Reprise

Before returning to consider these important questions, I would like to spend a few minutes on the task I was assigned---to comment on the series of extraordinary lectures we have heard during the past two and a half days. It is useful to begin with the modern literary strategy of deconstructing the title of the symposium, "Beyond Genes."

At the most elementary level, this title seems to ask: what remains after genes and whole genomes have been sequenced? It probably came as no surprise to anyone in this audience to find that the answer is "a lot." In fact, many of the exciting things we heard were probably not very different from what we'd have heard if genomes had not been sequenced---including discussions of molecular machines at work in the cell division cycle, mechanisms that allow the central nervous system to perceive and remember, and biochemical pathways that lead to cell death, cell growth, and development.

So, yes, there is plenty "beyond genes" ---and still plenty "before genes." In fact, it is easy to argue that it is not yet appropriate to talk about being "beyond genes" since we are far from finished with the most obvious issues in genomics. The sequencing of few genomes---and certainly none from multicellular organisms---is truly finished. The gene annotation process is just beginning for the most complex genomes; even the rough number of human genes is still unknown, as are the fundamental properties of most of the genes already identified. For all genomes, including those as small as viral and bacterial genomes, we are just beginning to catalog and make sense of genetic variations, and the implications of such variations for an understanding of evolutionary events are only dimly perceived.

Still, undeniably, we are far enough along with genomics and our understanding of genes to begin to appreciate the ways in which genetics will profoundly affect the practice of medicine. In my own field of cancer, it is certain that an understanding of the genes that participate in carcinogenesis will affect all phases of oncology---assessment of cancer risk, detection and classification of cancers, and strategies for prevention and treatment. The remarkable new drug, STI-571 (Gleevac), discussed in several talks, illustrates the importance of learning the genetic basis of cancer, but also teaches us the need to apply many other disciplines---biochemistry, structural biology, pharmacology, and pathology---to solve the world's major health problems.

For a fuller account of what is possible in the next century, I urge you to look at the February 7, 2001, issue of the Journal of the American Medical Association, which contains a series of essays entitled "Opportunities for Medical Research in the 21st Century." Anyone who reads those essays is likely to be struck with the distance that seems to lie between the beautiful science we have heard presented here and the changes in medical practice that advances in biological science prompt us to envision. This "lag time" between scientific discovery and the first application of discoveries to medical practice is another way to interpret the phrase "beyond genes." Moreover, there is another "lag time" beyond discovery that is all too often ignored---the delay between medical progress and its application more generally to public welfare. This is particularly so beyond the borders of the advanced countries represented in this room. And it is so not just for health, but also for other goals such as food production, environmental sustainability, and other things.

Science and Public Health

For the purposes of today's discussion, I will focus primarily on the question of what our science has done to advance public health. Many of the evident improvements in health during the past 100 years can be at least partly attributed to scientific progress: the marked reduction in infectious and perinatal disease, as a consequence of more and better vaccines, the discovery of antibiotics, and improved maternal care; the many new surgical procedures that cure diseases, diminish symptoms, and reduce post-operative mortality; and the increased activity and improved quality of life for the elderly, resulting, for instance, from the treatment and prevention of cardiovascular diseases, mental disorders, and musculo-skeletal ailments. As a result, much longer life spans are common in both developed and developing world, there are more old people in nearly all countries, and the most dramatic aging of populations has occurred in some of the poorer countries.

Still, in many ways, the news is not so good. Despite the award of Nobel Prizes in the first decade of the 20th century for discoveries about the causes of malaria (to Ronald Ross in 1902) and of tuberculosis (to Robert Koch in 1906)---and for effective treatment of tuberculosis with streptomycin (to Selman Waksman in 1952)---malaria still affects over 300 million people each year, killing 1 to 2 million, and tuberculosis kills about 3 million people worldwide each year. Moreover, these numbers are worse now than they were forty years ago; we still lack effective vaccines for either of these common infectious agents; and the available drugs have become less effective because of the increased prevalence of drug resistant organisms.

The toll taken by these two major infectious diseases is much greater in the developing than in the developed world. This pattern holds true for many ailments, as carefully documented in the epidemiological survey, *The Global Burden of Disease*, published a few years ago by the World Health Organization, the World Bank, and the Harvard School of Public Health. This survey shows dramatic differences in health status in different regions of the world, with Sub-Saharan Africa faring the worst by far, and the advanced economies (in Europe, North America, and Japan) faring the best. For example, the risk of death in the first five years of life is forty times greater in the five least healthy countries than in the five healthiest, and life expectancy differs by over forty years (about 78 years in the advanced countries versus about 38 years in the least advanced). But, even within the United States, studies by the Centers for Disease Control reveal remarkable differences in life span----up to twenty years and more---between citizens in different regions of the country and even in different counties in the same state. And despite overall improvements in all categories over the past few decades, the differences in life expectancy have persisted.

Determinants of Health

Obviously, then, many factors other than just the growth of scientific knowledge must affect health status in different populations. These include political stability and population dynamics; social, economic, and educational status; the prevalence of preventive practices; and the delivery of health care to the sick. But inadequate investment in research on some conditions also seems likely to have a role. In particular, little has been spent in recent years on tuberculosis and malaria compared to investment in chronic and acute illnesses that are more common in the developed nations.

In contrast, large sums have been spent on research on HIV/AIDS, a medical problem common in both poor and rich parts of the world, and the outcome has been complex. For many in the developed world, the rewards have been substantial, illustrating the power of modern science to identify rapidly the cause of a mysterious new illness, to dissect the infectious agent, and to produce new drugs that interfere with the growth of the agent by inhibiting enzymes required for its replication. Such progress is remarkable because it depended fully on biological principles that were unknown a century---or even a few decades---ago.

Still, despite these scientific triumphs, control of HIV infection and AIDS has been incomplete even in the advanced countries, less effective in minority than in majority populations in the United States, and nearly inconsequential in the poorer countries of the world. Recent reports from Eastern Europe, India, China, and large parts of Africa indicate that HIV continues to spread at alarming rates, due to inadequate financial investments in health systems, poor public education about the virus and its consequences, and high prices of drugs that might be used for treatment or prevention.

A Forecast for the Next Century

It seems unlikely that the current disparities in health status between the rich and the poor will diminish any time soon. By the end of the 21st century, there will be many more people on this planet; current estimates predict that the world's current population, six billion, will grow to at least nine billion by mid-century. With this growth, many more people are likely to be old (both rich and poor), poor (in the rich countries too), hungry, at high risk of infectious diseases, crowded, exposed to environmental pollution, and resentful of those without complaints (other than age).

Of course, these dire conditions will not be uniformly distributed among the nations and peoples of the world. This prediction is based on an observation germane to many considerations of the future: namely that most of the world's leaders do not view what many would hold to be the most important human goals---health, education, a clean environment---as universal human rights.

Where political leaders have failed, the scientific community should be asking: what can be done? While acknowledging that there are many factors that contribute substantially to health over which we have little control, we should also remember that medical science has very significant roles to play. I would like to speak about three of these: (i) placing greater emphasis in our scientific work on issues that affect public health; (ii) advocating for more financial aid designated to improve health, especially in poor countries; and (iii) supporting the development of a global culture of science, so that even the poor countries can contribute to the amelioration of the diseases that afflict their citizens.

(i) **Emphasizing public health.**
To draw attention to the most prevalent and devastating diseases as subjects for both increased investments in health and further scientific work, it will be important to enhance epidemiological efforts in all parts of the world and to identify the underlying causes of disease. It is apparent that efforts to bring the most important sources of morbidity and mortality under control will demand actions in addition to scientific progress, including public health measures and provision of better care. A rigorous accounting of the major obstacles to health in each region of the world helps to focus these efforts appropriately. But for virtually any country, the major public health challenges will include most or all of the items on the following list: uncontrolled infectious diseases; use of tobacco, alcohol, and other addictive drugs; sexual practices; unsafe transportation; population growth; contaminated water and poor hygiene; inadequate food supplies; poor training (especially of women) in health practices; and access to medicines and vaccines.

(ii) **Advocating foreign aid for the health sector**.
Medical scientists can take an important role in promoting financial aid to poor countries to improve health and health-related sciences in those countries. The dire need for such assistance is dramatically portrayed in a report to be issued by the World Health Organization's Commission on Macroeconomics and Health on December 20th. The report argues strongly for the principle that improvements in a nation's health will produce beneficial effects on a nation's economy---and that better health should not be treated simply as a secondary benefit of economic improvements. Moreover, it documents the reprehensibly low levels of foreign aid---for health and everything else----provided by many of the advanced countries, most glaringly the United States; only a few northern European countries, such as Sweden, approximate the United Nations' development goals by providing 0.7% of their gross national product (GNP) to support improvements in poorer countries. By carefully analyzing the medical conditions responsible for the major burdens of disease and making informed estimates of the impact of increased investments in health, by donor and recipient nations alike, the Commission concludes that several million lives could be spared and economic returns would be many fold if donor spending on health in the developing world was increased from the current $7 billion to approximately $27 billion per year by 2007. We in the medical and scientific communities should become familiar with these arguments and exercise our responsibilities to influence them.

(iii) **Globalizing the culture of science.**
Perhaps most relevant to this week's symposium and most important in the long view, we need to make greater efforts to establish science as a mainstay of global culture. Eric Lander has described how the Human Genome Project has incorporated findings from many nations and disseminated its results for all to use through the Internet. These are exciting steps but the opportunities must be extended much more broadly, both topically and geographically. Science as it has been practiced in the advanced economies over the past century should be viewed as a global public good, the key to successful globalization of economies, allowing all nations more than access to the products of other countries but also the processes required for discovery, invention, and production.

The United Nations recognized the opportunity to extend the domain of modern biological science in the early 1990's when it promulgated Agenda 21, a manifesto that advertised the potential benefits of biotechnology---a form of biological research that is relatively simple and cheap to perform, can be used for a wide range of local applications (for medicine, agriculture, environmental science, law, and others), is a powerful tool for training scientists, and has the potential to generate substantial revenues. Because of its obvious appeal, Agenda 21 has many signatories but there are few manifestations of its effects outside of the advanced economies. For instance, biotechnology has had a much smaller role in globalization than has information technology, with its closer links to commercial activity. The slow growth of science in parts of the world that might benefit most from it should concern all of us, because our collective failure to disseminate the methods and lessons of our disciplines is contributing to the growing distance between the rich and the poor.

So how should we approach this difficult problem of globalizing science? The principles are simple. The efforts should be designed at the local level---bottom up, not top down. And the emphasis must be placed on providing the tools for doing science ("infrastructure") and on training individuals who can lead local efforts. Enthusiasm in governments for building scientific capacity requires demonstrations of local practical benefits---improved agriculture, control of infectious diseases and other medical problems, environmental remediation, expanded industrial production, etc. The feasibility of conducting modern and meaningful research throughout the world has been greatly enhanced by the development of the Internet and the prospect of electronic access to colleagues (by e-mail) and to the current scientific literature and other data, such as the human genome, through public archives. This means that promotion of biological science must proceed hand-in-hand with Internet connectivity, Web access, and adequate provision of hardware, software, and technical assistance for computer-based activities. Efforts to develop a global culture of science should not be focused solely on the poorest countries, where the prospective gains may seem greatest but the difficulties of establishing science are also great. Instead a campaign to promote the growth of science should specifically include countries with lower middle incomes---countries that are often much better prepared to incorporate scientific activities and train scientists.

A Proposal for a Global Science Corps

But formulas and recommendations for advancing science throughout the world will have little effect if they are not accompanied by missionary zeal---and by means to exercise such convictions. For that reason, I propose establishing an International Corps for Global Science to allow science missionaries, young and old, to help build a global culture of science by working in those parts of the world that are underserved by science now. How would this work? Obviously it would require funds from public or private sectors. It would need some administrative structure, perhaps provided by the United Nations or by another existing or newly created multi-national group. It would need eager participants. They could range from newly-minted science graduates, looking for an experience akin to that offered by the U.S. Peace Corps, to more senior scientists, not unlike many of the speakers at this symposium, who would enjoy working on new problems in an unusual setting, with the prospect of contributing to a better world. Finally, it would be essential to link this new initiative with other on-going efforts to nurture science in the developing world. A zeal for science will not suffice. Our missionaries will need a reasonable context in which to work, one that includes trained nationals, appropriate equipment, and a friendly political environment.

An Example: Malaria Research in Mali

It is likely that many of the countries best suited to benefit from this Global Science Corps will be among the more affluent of the developing countries, not the poorest. But even some of the poorest may be---or can become---sites where science and its missionaries might flourish. Consider Mali, one of the world's poorest countries, with an annual income of about $300 per person. Several years ago, the U.S. National Institute of Allergy and Infectious Diseases and the U.S. Agency for International Development established the Malaria Research and Training Center in Bamako, the capital of Mali. The Center has become a very significant force in malaria research in Africa, with several well-trained Malian staff scientists, extensive collaborations throughout the world, electronic connectivity, and the capacity to study the malarial parasite, its insect host, and the clinical disorder with a variety of modern techniques.

Malaria itself represents one of the most attractive targets for building global science. As discussed earlier, it remains a disease of monumental proportions, and the economic benefits of controlling it are legion. Although funds for research on malaria have been relatively meager, a international cohort of investigators, including several in Africa, Asia, and South America, has emerged, displaying an eagerness for collaborative work, as manifested in the Multilateral Initiative on Malaria. The scientific opportunities have also grown, building on the triumphs of 20th Century biology described in this Symposium. The decipherings of Plasmodia, Anopheles, and human genomes are completed or nearing completion. The biological features of the Plasmodial life cycle and infectious process are fascinating and approachable. And there are many potential applications of biotechnology to important practical issues---surveillance, prevention, and treatment of the disease.

Conclusion

If there is a simple message here, it is this: We have a moral and political imperative to use the scientific knowledge produced in the past century to promote better health in neglected parts of the world during the next century. The power and beauty of science can help us pursue that imperative and improve the lives of many. But, to succeed, we must harness our enthusiasm for science, mobilize the talented young and old, and establish its culture in poor as well as rich nations.