
ROBERT POLLACK

The Human Genome and the Human Community

Advances in genetics highlight the individual, but medicine should be directing its attention to the community.

In 1957, the year I entered college, the American Medical Association issued its "Principles of Medical Ethics." Section 10 stated "The honored ideals of the medical profession imply that the responsibility of the physician extends not only to the individual, but also to society, and these responsibilities deserve his interest and participation in activities that have the purpose of improving both the health and the well-being of the individual and the community [my italics]." Improving the health and well-being of the individual remains an honored ideal of the medical profession, and one that has also served as the guiding principle behind government funding of basic biomedical research. Improving the health of the community, however, has always depended on the shifting fortunes of the very notion of community in our deeply individualistic society, and it remains, in many ways, an ideal more easily articulated than put into practice.

This year, the interlocking worlds of international politics, the stock market, the National Institutes of

Robert Pollack (pollack@columbia.edu), is professor of biological sciences and director of the Center for the Study of Science and Religion at Columbia University.

Health, and the medical profession all joined in celebration of what was widely touted as the most significant—and possibly the culminating—creative act of our society: the transfer from molecule to database of one or more DNA sequences for most or all of the coding sequences in the human genome. To my eye, the current

wave of enthusiasm for genomic research seems to distance medicine even further from its responsibility to the community. Ironically, the promises of genetic medicine that have the potential to separate us all into more- or less-extended families, encouraging us to care only for ourselves and our genetic constituencies, have appeared at a time when medical practice is already in crisis. Deeply immersed in delayed intervention, fiscal befuddlement, and contentious insurance regulation, neither those who practice medicine nor those on whom it is practiced should turn to the decoded human genome for solace or solution.

In the United States, the cost of medical care for 84 percent of the people has grown to about \$1 trillion per year, but there is still no national commitment to the 16 percent of Americans who have no health insurance. It is unlikely that the uninsured will receive adequate care without a renewal of interest in public, community-directed, preventive medicine. But what is

to be prevented? Prevention has two meanings, depending on what is meant by a healthy person. If health is given a functional definition—you're healthy if you are free to work and think and play to the best of your born abilities—then preventive medicine such as a vaccine is preventive because it lowers the risk of developing a disease later in life. If, on the other hand, one imagines that there is an ideal of human form and function to which we all must aspire, then preventive medicine coupled with the data from the Human Genome Project takes on a different, perhaps alluring but in the end sinister, purpose: the elimination of avoidable deviation from this ideal.

In fact, disease, morbidity, and mortality are generated by a mix of environment and genetic propensity. The surge of interest in genetic medicine has led us to forget that we are each part of the environment of a host of strangers, and that this crowd is part of our own environment in turn. Our society seems best able to remember this fact and accept its responsibility for simple preventive medicine only when a contagious disease threatens. To put the case most simply, we are in each others' hands at all times, not just when contagion threatens. A medicine that waits to treat people one at a time is defaulting on the responsibility each of us has to preserve not only our own health but the health of perfect strangers as well.

Basic biomedical science has a responsibility for helping medicine to return to its obligations to the communities in which we all (doctor, scientist and patient alike) must for better or worse live together. I want to suggest some ways in which medical science might work now and in the immediate future to meet those principles of ethical medicine so well stated almost 50 years ago. None require any patents held by Celera nor any technologies not now available; all do require, however, the will to do the right thing.

Create a vaccine initiative

Infectious diseases caused by ancient and emergent microbes are and will remain the major threat to our species' health and life. Vaccines are our best way to deal with this problem. A government that absorbs the costs of producing and distributing vaccines has made the most prudent possible investment in the health of its citizens: a government that does too little too late has no excuse for the consequent avoidable loss of health and life.

Microbes do not respect national boundaries: the strongest ally infectious agents have is the human notion of national sovereignty. International cooperation was a prerequisite to the elimination of smallpox as a human pathogen. If every person on the planet could simply be vaccinated with the vaccines we already have, hundreds of millions of people, a good fraction of them babies, would be saved from dying.

Given these facts, it is disturbing that only a few agents of infectious disease (yellow fever, an insect-borne virus; Lassa viral hemorrhagic disease; smallpox; cholera; diphtheria; tuberculosis; and plague) cause illnesses that must be reported to the U.S. government today. All others, including malaria and all antibiotic-resistant strains of common infectious microbes, come and go unremarked.

Many other diseases used to be reported; the shortsighted decision to save a small amount of Centers for Disease Control and Prevention money a decade ago guaranteed the fast and extensive spread of any outbreak of antibiotic-resistant infection. It also mistakenly presumed that the United States had no need to worry about tropical diseases such as malaria, even though the climate of the southeastern United States would suit the insect vector quite well.

To pay for a more rational and comprehensive defense against microbes, we might consider using a version of the military model that aims to contain, not annihilate, an enemy. There is a pleasing symmetry to extending the notion of subsidy for the sake of security from the production and purchase of lethal weapons to the production and distribution of life-saving vaccines. I propose the creation of a Strategic Vaccine Initiative (SVI), designed to help our immune systems turn microbial mutability to our advantage by domesticating the microbes that get inside us.

SVI could work only if it were the product of total international cooperation. Political, religious, and ideological differences make no difference to tuberculosis or malaria; they have no place in a species-wide SVI. National sovereignty may seem an impermeable barrier to the necessary transnational attitudes and actions, but we have a precedent at our fingertips for the permeability of national borders to new technologies.

Ideas and information that get onto the Internet travel around the planet, crossing national bound-

aries with impunity. Organized and run from the beginning on the Internet, an internationally funded SVI would not need to have a single location in any one nation. That would be an appropriate organizational strategy for the kind of international effort it will take to respond as a species to the invisible species that will always threaten us. Like the immune system in any of our bodies, the Internet is widely distributed, rapidly adaptable, and quick to learn. A new idea that travels through the Web is quite like a new antigen that stimulates a strong immune response. And like the chemicals and cells in a person's immune system, ideas that move through the Web may be what keep our species going, especially if one or more of the microbes we live among gets going in us in a serious new way.

Edible vaccines

The ideal vaccine for any infectious agent should be safe, oral, and effective when given in a few doses early in life. The new technologies and insights of molecular biology can and should be brought to the task of creating such vaccines. Only 20 or so vaccines are available in clinics today. Bringing any of them closer to this ideal would be a way to save a lot of young lives.

Oral vaccines available today are prepared from infected cultured cells. Although it is attenuated, the Sabin live polio vaccine can be taken by mouth because it can still infect the lining of the intestines. It is safe because its genome differs from that of the pathogenic polio virus in enough places to ensure that it will not revert to its ancestral capacity to go into neural cells. Another way to make an oral vaccine would be to put a few of a pathogen's genes into the germ line of an edible plant, forcing offspring plants to produce antigenic foreign proteins and thereby make them into edible, even nutritious, vaccines. Transgenic plants are now being tested for their ability to serve as cheap, stable oral vaccines against hepatitis and cholera.

The main limitation so far seems to be tolerance: The intestinal immune cells presented with a recom-

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binant foreign protein as part of a digested mass of plant material cannot always respond to it with a full-blown immune response. The trick seems to be packaging the immunity-inducing genetic material as part of a larger, more obviously microbe-like structure.

If the ideal preventive medicine for infectious diseases would be the delivery of an optimal vaccine for all the major infectious diseases, women of childbearing age should be the first to receive these

vaccines. A baby fed on breast milk winds up with a 50-fold enrichment of immune-protective molecules from its mother. Milk also carries natural drugs to fight infection, in particular the anti-inflammatory agent lactoferrin and the antibiotic lactoferritin, as well as sugars that trick bacteria into binding to them rather than to the surfaces of a baby's cells. A baby's immune system is set for life by the mother's milk.

A complete response to microbial disease must be built out of a national policy—an extension of current maternal leave policy—to encourage and assist every mother to nurse her newborn child before it is exposed to any vaccines, let alone any antibiotics. Breast-feeding so enhances the immune system that societies in which mothers do not breast-feed have a 10-fold excess of infant mortality over those that do. This difference is due to the absence of similar enhancers of the immune response in any other foods and to the relative contamination of all foods compared to milk from the breast, which is sterilized by the mother's immune system.

Treat cancer as preventable

A cancer cell and an infectious microbe have a surprising amount in common, even though no cancer cell ever gets beyond the body in which it was born except when it becomes the object of a scientist's passion and is kept alive in a dish. Microbes and cancer cells are both able to use the victim's body as a culture medium in which to grow indefinitely, both can stimulate an immune response, both are genetically malleable enough to provide for the chance of Darwinian selection of variants able to escape the immune response they stimulate, and in both even

one escaped cell may be the source of later disease.

For at least the past 50 years, the main thrust of biomedical science has been to describe the molecular differences between normal differentiating cells and their mutant, cancerous cousins and then to use that information to devise more precise ways to kill the latter while sparing the former. Current techniques for killing tumor cells with radiation and chemicals create the same Darwinian natural selection that takes place in the body of a person struggling with malaria or tuberculosis. As the tumor grows, throwing off a cloud of genetic variants, any mutant cells that can survive the body's defenses and medicine's assaults become the seeds of new, resistant tumors. Sometimes such mutants are overcome, and the tumor is eradicated. In other cases, the downhill slide ends with a painful death, a Darwinian catastrophe for tumor and victim alike.

One aspect of cancer makes it a different sort of medical problem from any infectious disease. Cancers arise by mutation, and most mutations can be kept from happening in the first place. As a result, most cancers, unlike most infectious diseases, are avoidable. Only a few percent of new cancers are the consequence of an inherited condition, and only a few more percent are the product of infectious agents. The ones that arise from infection can be prevented as well, by curing the infection. Eliminating the bacterial cause of stomach ulcers, for instance, also eliminates the associated risk of later stomach cancer.

All remaining new cancers (9 out of 10, or more) will be neither caught nor inherited. They will be the result of avoidable habits and preventable exposures that, given the will, can be changed at any time without the need for any further basic research. Tobacco smoke is the classic avoidable inducer of cancers but is far from the only one. Foods laced with pesticides, pollutants in the air and water (both at work and at home), and radiation and drugs that cause mutation all cause cancer, and all can be avoided. The risks of cancer from any of them are cumulative, so cancers tend to appear in older people. Thus, prevention requires the earliest possible intervention. The same mother's milk that concentrates protective immune cells and antibodies also concentrates these chemicals and delivers them to a nursing infant, where they can reach much higher concentrations than are typically found in adult tissue.

The irony is that the science of preventing cancer is simpler and easier than the science of curing it. Prevention works, and it has no clinical side effects. With very little in the way of either cash or cachet, the strategy of prevention (through changes in diet, reduction in tobacco use, and exercise programs) has led to a modest overall reduction in cancer deaths in the 1990s. Four percent fewer men and one percent fewer women died of cancer in 1995 than in 1991. Perhaps a few lives were saved by genetic detection coupled with prophylactic surgery, but most were saved because people changed their habits to avoid cancer in the first place. Most escaped by staying away from tobacco. The different behaviors of men and women demonstrate this. A few decades ago, women took to cigarettes in great numbers as men were pulling back. In the 1990s, as the rate of lung cancer in men declined by more than 6 percent, it increased by almost the same percentage in women.

Every cell's DNA is vulnerable to mutation by any chemical that can bind to it and either break it or shift around some of the bonds that hold it together. Mutagens that can do this get to the tissues of our body in the food we eat, the fluids we drink, the air we breathe, and the materials we handle. Some mutagens, such as those in the nitrogen compounds we breathe when the air is smoggy, are artifacts of our technology. Many others are "all natural" and oblige us to protect ourselves from them by the very sorts of chemicals that may cause further damage. One natural substance, the potent molecule aflatoxin, is made by a mold that lives on damp stored peanuts. Aflatoxin will mutate genes in the liver cells that try to detoxify it; liver cancer can result from eating peanuts that have not been treated with the chemical pesticides that—so far—kill the mold.

The current absence of commitment to the well-being of the community is plainly visible in our country's budget for cancer research. Prevention is hardly mentioned. Instead, genes associated with higher risk are sought on the premise that one day the information will provide better drugs to kill every last cell of the tumor that will inevitably arise. This agenda is woefully incomplete at best and absurd at worst. For instance, to discover precisely which chemicals will cause cancer when they enter the bloodstream and then, instead of working to remove these chemicals from everyone's food, air, and water,

to study the genetics of the liver proteins that detoxify them, is to be in a waking dream.

A cancer prevention agenda for basic research would begin with a planetary review of differences in the incidence of various cancers, because some regions and cultures are hot spots for some cancers, whereas in others the same cancers are exceedingly rare. From this international effort, governments and companies worldwide would have the information necessary to plan a planetary strategy for the prevention of cancer: planetwide optima for low-mutagen food, air, and water and clear guidelines for behaviors that would, together, ensure the lowest possible frequency of avoidable cancers. In this context, the current emphasis on the genes responsible for a tumor would be seen for what it is: an interesting sidelight to the real problem of cancer, not the main issue.

At present, we search for populations at high risk for inherited cancers only to tell families what their fates will be. We spend relatively little time and money understanding the origins and consequences of the habits that bring on the majority of fatal cancers and reaching out to the entire population with help in avoiding these habits. A 1996 study by the Harvard School of Public Health found that only about 10 percent of people who had died of cancer were born with versions of genes that made the disease inevitable. About 70 percent of the lethal cancers were brought on by choices such as smoking, poor diet, and obesity, and most of the remaining 20 percent could be attributed to alcohol, workplace carcinogens, and infectious agents. Smoking is optional, but eating, drinking, and breathing are not. The task of understanding why people act against their own best interest even after they learn how to act prudently is not part of today's agenda for cancer research, but it should be.

Don't kill a tumor cell, renormalize it

Setting prevention aside—not because it is impossible, but because in scientific terms it is so easy that one is embarrassed to say more about it—in the near

The insights of molecular biology can and should be brought to the task of creating effective oral vaccines.

future, cancers are likely to be dealt with by a slowly evolving combination of genetic, immunologic, and antibiotic interventions. The lessons of microbial research apply here. The immune system, not the genome, is the body's first line of defense.

The development of the technology to read the future in a person's DNA has been so rapid and diffuse that it has some of the properties of an infection. We are now at risk of knowing our future without wanting to, without know-

ing why we must, and without any idea of how we will deal with the knowledge. For example, what will our options be when we are confronted with germline genetic information about ourselves that could lead to termination of employment, if known by our employer? This question, with no simple answer, is being addressed by more and more families each year as the versions of genes responsible for hundreds of inherited diseases are read and the differences converted into easy DNA diagnoses.

Human germline genetics and the genetic approach to cancer treatment should not have much overlap, since cancer is so common. The commonness of cancer and the fact that all families are susceptible to it to a greater or lesser extent tell us that cancer usually will not arise because of a recessive difference in a single gene. Yet the search for genes associated with a higher than average likelihood of developing a tumor has been vested with magically high expectations on the premise that some day it will somehow lead to better treatments.

One day everyone will be a candidate for a germline DNA test for cancer susceptibility. But to what avail? The genetic differences that may lead to a better understanding of how to treat a tumor are simply not the same as the genetic differences among people that can be used only to predict someone's future health. A blurring of this distinction is understandable as the wishful thinking of a frightened group of scientists unconsciously trying to keep cancer from striking their own bodies, but that does not make it right. The distinction needs to be made quite clear before it leads to great mischief. Better DNA prog-

nosis with neither explanation nor treatment is the worst of all possibilities.

Today, for example, a DNA analysis of the defective versions of the breast cancer-associated genes BRCA1 and BRCA2 has hardly any function at all, except to divide women into a minority who will almost certainly get a breast tumor and the rest, who have a one-in-nine chance of the same fate. Neither group can make much use of the information, because women in both groups still must undergo constant self-examination and because, in either group, detection of a tumor must be followed by the same harsh and painful treatment.

If the normal activity of the BRCA1 or BRCA2 gene products were somehow to be returned to the cells of a breast tumor, these cells ought to revert to their normal nonproliferative state, curing the disease without the side effects of current treatments that try to kill every last tumor cell. However, there is a catch. Most growth-controlling genes work through proteins that switch other genes on or off. These proteins never leave the nuclear sanctum of the cell they keep quiescent. Any drug designed to mimic such a protein would have to get to the tumor cells — every last one of them — get inside each, get to each nucleus, and find the same set of other genes to turn on or off. This seems unlikely, and in fact to date no laboratory has been able to mimic the effect of an absent tumor-suppressing gene except by introducing the gene itself into a tumor cell, a trick unlikely to work in a clinical setting, where even one untreated tumor cell would be able to seed a brand new tumor.

Embryonic stem cells may provide the information needed for solving these problems. It might be possible to grow any differentiated tissue in a dish and have it be wholly acceptable to the donor. In this way it might be possible to replace a tissue such as the liver after excising the original to rid the body of all traces of a liver tumor. More generally, it ought to be possible to rebuild a person's immune system in a dish this way and even to stimulate it in advance to at-

tack the pathogen that is attacking the body, whether microbe or tumor.

In order to begin to integrate the Human Genome Project's success into a comprehensive program of public medicine, physicians, scientists, and managers of our health care delivery systems all need to accept that we are all the products of past mistakes. The genetic variations in ancestral species that natural selection chose in order to solve the problem of the survival of our own species were mistakes when they occurred. These ancient mistakes provide us today with, among other things, a brain capable of imagining its own death. Some of the many ways in which past mistakes live on in us are individual, such as a mutation in the DNA of a parent: every new case of Huntington's disease is the expression of such a very recent and wholly unavoidable mistake in the human germ line. Other mistakes are more widely shared, such as a mutation in a far-distant ancestor or infection by an inadvertently selected resistant strain of microbes. Still others are shared by all of us. They are all the mixed blessing of our species' birthright.

We are intrinsically social beings. The mind is the product of social interactions: there would not be enough DNA in the world to encode a single mind. From birth on, minds develop in brains by the imitation of other minds, partly but not solely the minds of biological parents. The few behaviors wired into our genes at birth are all designed to maintain and thicken the bonds through which this imitation can proceed. The current biomedical model of a person as an autonomous object lacks a proper respect for these social interactions. It severs the patient from family and social context, and it devalues preventive—social—medicine to an afterthought or a charity. This denial of the reality of the social bond is an avoidable mistake of science. The strains it has opened between scientific medicine and society are not simply matters of resource allocation. They are signs that the dreams of science are no longer satisfying even the dreamers.