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EUGENE GARFIELD

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AIDS and Beyond: Living with the Inevitability of Virulent Disease

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When I read the following article by Joshua Lederberg, I vowed immediately to reprint it in *Current Contents*®. Josh's literary style is elegantly poetic—I'm always at a loss in trying to describe its unique rhythms. What is all the more remarkable—and this can be known only from personal experience—is that he speaks in that same manner extemporaneously. He is a superb popularizer and, as I have observed on many occasions, interprets the often-technical jargon of The Rockefeller University faculty to the delight and benefit of the audience.

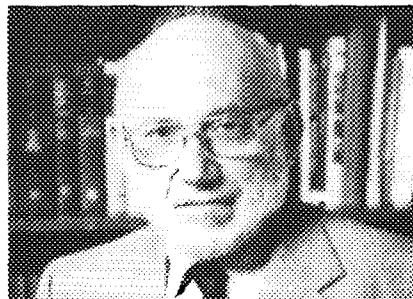
I don't dare interpret his essay for you. It reminds us eloquently of the fragile relationship between humankind and nature, particularly between humans and virulent microorganisms. And of the continuous need to replenish our fund of basic research knowledge. Indeed, of our need to foster that

same goal throughout our interdependent world.

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Medical Science, Infectious Disease, and the Unity of Humankind

Joshua Lederberg, PhD
Office of the President
The Rockefeller University
New York, NY 10021

In this commentary, Joshua Lederberg considers our relationship with the microbes that share our world. Advances in antibiotics and the control of contagious disease have engendered complacency and overoptimism about the prospect of global epidemics, such as the AIDS crisis. These attitudes ignore the fact that such phenomena are an unavoidable consequence of our place in nature. Given the inevitable threat to humanity of widespread infectious disease borne by agents yet unknown, virus research employing recombinant DNA must become a worldwide priority, transcending national and ideological boundaries.

The ravaging epidemic of acquired immunodeficiency syndrome has shocked the world. It is still not comprehended widely that it is a natural, almost predictable, phenomenon. We will face

From the Office of the President, The Rockefeller University, New York. Dr. Lederberg won the Nobel prize in physiology or medicine in 1958. This article was adapted from a presentation at a conference of Nobel laureates sponsored by François Mitterrand and Elie Wiesel, Paris, January 1988.

similar catastrophes again, and will be ever more confounded in dealing with them, if we do not come to grips with the realities of the place of our species in nature. A large measure of humanistic progress is dedicated to the subordination of human nature to our ideals of individual perfectibility and autonomy. Human intelligence, culture, and technology have left all other plant and animal species out of the competition. We also may leg-

isolate human behavior. But we have too many illusions that we can, by writ, govern the remaining vital kingdoms, the microbes, that remain our competitors of last resort for dominion of the planet. The bacteria and viruses know nothing of national sovereignties. In that natural evolutionary competition, there is no guarantee that we will find ourselves the survivor.

Some of the great successes of medical science, including the "miracle drugs," the antibiotics of the 1940s, have inculcated premature complacency on the part of the broader culture. Most people today are grossly overoptimistic with respect to the means we have available to fend off global epidemics comparable with the Black Death of the 14th century (or on a lesser scale the influenza of 1918), which took a toll of millions of lives.

Visualize human life on this planet as mirrored in the microcosm of a culture of bacteria; a laboratory test tube can hold ten billion cells, twice the human population of the globe. More than 70 years ago, Frederick William Twort and Felix d'Herelle discovered that bacteria have their own virus parasites, the bacteriophages. It is not unusual to observe a thriving bacterial population of a billion cells undergo a dramatic wipeout, a massive lysis, a sudden clearing of the broth following a spontaneous mutation that extends the host range of a single virus particle. A hundred billion virus particles will succeed the bacteria; but their own fate now is problematic, as they will have exhausted their prey (within that test tube). Perhaps there are a few bacterial survivors: mutant bacteria that now resist the mutant virus. If so, these can repopulate the test tube until perhaps a second round, a mutant-mutant virus, appears.

Such processes are not unique to the test tube. The time scale, the numerical odds, will be different. The fundamental biologic principles are the same.

Humans are more dispersed over the planetary surface than are the "bugs" in a glass tube; there are more diverse sanctuaries, and we have somewhat fewer opportunities to infect one another. The culture medium in the test tube is more hospitable to virus transmission than is the space between people (with the exceptions of sexual contact and transfusion). The ozone shield still lets through enough solar ultraviolet light to hinder aerosol transmission, and most viruses are fairly vulnerable to desiccation in dry air. The unbroken skin is an excellent barrier to infection; the mucous membranes of the respiratory tract are much less so. Our immune defenses are a wonderfully intricate legacy of our own evolutionary history. This enables machinery for producing an indefinite panoply of antibodies, some one of which is (we may hope) a specific match to the antigenic challenge of a particular invading parasite.¹ In the normal, immune-competent individual, each

incipient infection is a mortal race between the penetration and proliferation of the virus within the body and the evolution and expansion of antibodies that may be specific for that infection. Previous vaccination or infection with a related virus will facilitate an early immune response. This in turn provides selective pressure on the virus populations, encouraging the emergence of antigenic variants. We see this most dramatically in the influenza pandemics, and every few years we need to disseminate fresh vaccines to cope with the current generation of the flu virus.

Many defense mechanisms, inherent in our evolved biologic capabilities, thus mitigate the pandemic viral threat. Mitigation also is built into the evolution of the virus: it is a Pyrrhic victory for a virus to eradicate its host! This may have happened historically, but then both the vanquished host and the victorious parasite will have disappeared. Even the death of the single infected individual is relatively disadvantageous, in the long run, to the virus compared with a sustained infection that leaves a carrier free to spread the virus to as many contacts as possible. From the perspective of the virus, the ideal would be a nearly symptomless infection in which the host is oblivious of providing shelter and nourishment for the indefinite propagation of the virus' genes.^{2,3} Our own genome carries hundreds or thousands of such stowaways. The boundary between them and the "normal genome" is quite blurred.⁴ Not much more than 1% of our DNA can be assigned specific physiological functions; most of it is assumed to be a "fossil" legacy of our prior evolutionary history, DNA that is today parasitic on the cell.^{5,6} Further, we know that many viruses can acquire genetic information from their hosts, which from time to time they may transfer to new ones. Hence, intrinsic to our own ancestry and nature are not only Adam and Eve, but any number of invisible germs that have crept into our chromosomes. Some confer incidental and mutual benefit. Others of these symbiotic viruses or "plasmids" have reemerged as oncogenes, with the potential to mutate to a state that we recognize as the dysregulated cell growth of a cancer. This is a form of Darwinian evolution that momentarily enhances the fitness of a cell clone at the expense of the entire organism. Still other segments of "nonfunctional" DNA are available as reserves of genetic potential for further evolution, in a sense more constructive for the individual and the species.

At evolutionary equilibrium we would continue to share the planet with our internal and external parasites, paying some tribute, perhaps sometimes deriving from them some protection against more violent aggression. The terms of that equilibrium are unwelcome: present knowledge does not offer much hope that we can eradicate the compe-

tition. Meanwhile, our parasites and ourselves must share in the dues, payable in a currency of discomfort and precariousness of life. No theory lets us calculate the details; we can hardly be sure that such an equilibrium for earth even includes the human species even as we contrive to eliminate some of the others. Our propensity for technological sophistication harnessed to intraspecies competition adds a further dimension of hazard.

In fact, innumerable perturbations remind us that complex systems often fluctuate far from equilibrium—each individual death of an infected person is a counterexample. Our defense mechanisms do not always work. Viruses are not always as benign as they would be if each particle had the intelligence and altruism to serve the long-term advantage of the group.

Fears of new epidemics as virulent as those of the past have been mollified by the expectation that modern hygiene and medicine would contain any such outbreaks. There is, of course, much merit in those expectations. Influenza in 1918 was undoubtedly complicated by bacterial infections that now can be treated with antibiotics;⁷ vaccines, if we can mobilize them in time, can help prevent the global spread of a new flu. However, the impact of technology is not all on the human side of the struggle. Monoculture of plants and animals has made them more exposed to devastation. The increasing density of human habitations as well as inventions such as the subway and the jet airplane that mix populations all add to the risks of spread of infection. Paradoxically, improvements in sanitation and vaccination sometimes make us the more vulnerable because they leave the larger human herd more innocent of microbial experience.

The opening of wild lands to human occupation also has exposed people to unaccustomed animal viruses, to zoonoses. Yellow fever has sustained reservoirs in jungle primates, and the same source is the probable origin of the human immunodeficiency virus in Africa. It is mystifying that yellow fever has not become endemic in India, where competent mosquitoes and susceptible people abound. We will almost certainly be having

like experiences from the "opening" of the Amazon basin.

Our preoccupation with acquired immunodeficiency syndrome should not obscure the multiplicity of infectious diseases that threaten our future. It is none too soon to start a systematic watch for new viruses before they become so irrevocably lodged. The fundamental bases of virus research can hardly be given too much encouragement. Recombinant DNA, still a scare word in some quarters, is our most potent means of analyzing viruses and developing vaccines.⁸ Such research should be done on a broad international scale to both share the progress made in advanced countries and amplify the opportunities for field work at the earliest appearance of outbreaks in the most afflicted areas.

The basic principles of vaccination were established long ago, but practical means of production of vaccines for viral afflictions like polio had to await the cell and tissue culture advances of the 1950s. The most celebrated example, smallpox, also has the oldest historical roots. That success has encouraged other proposals for the eradication of other infectious agents. Rarely do we have the understanding of its natural history needed to calibrate the feasibility of the goal. This will strain our basic knowledge of the genetics and evolution of the etiologic agents.

For example, our stratagems on malaria, gonococcus, and human immunodeficiency virus are all confounded by the poorly understood capacity of the viruses to undergo further antigenic evolution. We know a bit more about influenza, but not enough to give us more than a few weeks or months of lead time merely to respond to its perennial variations.

As one species, we share a common vulnerability to these scourges. No matter how selfish our motives, we can no longer be indifferent to the suffering of others. The microbe that felled one child in a distant continent yesterday can reach yours today and seed a global pandemic tomorrow. "Never send to know for whom the bell tolls; it tolls for thee."

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