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My title is

Infectious Disease

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MEDICAL SCIENCE and the UNITY of HUMANKIND

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The ravaging AIDS epidemic has shocked the world. Still not clearly understood ^{it} is that is a natural ^{almost predictable} phenomenon! We will face similar catastrophes again and again if we do not come to grips with the realities of man's place in nature -- a conception ^{a poor model to} at odds with the existing political organization of national sovereignties, and a reality that stresses many deeply cherished myths about the autonomy of each individual.

We look back today over a century of biological science that has been impelled by the iconoclastic insights of Charles Darwin and of Louis Pasteur. However, Darwin never quite rectified the anthropomorphic view that man has a privileged place in nature. Man's intelligence, his culture, his technology has of course left all other plant and animal species out of the competition. Pasteur taught, and we should have learned, the hazards of insouciance about the remaining vital kingdoms, the microbes, as our competitors of last resort. Many medical scientists, like Theobald Smith and Rene Dubos have offered us broad perspectives of the natural history of infectious disease -- perspectives that leave no illusions about the infeasibility of eradication of our scourges, of the need for an ongoing struggle. Some of the great successes of medical science, including the "miracle drugs", the antibiotics of the 1940's, 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 global epidemics comparable to the Black Death of the 14th century, (or on a lesser scale the Influenza of 1918) which took a toll of millions of lives! We have no guarantee that the natural evolutionary competition of viruses with the human species will always find ourselves the winner.

^{ask you to}
I ~~often~~ visualize human life on this planet as mirrored in the microcosm of a culture of bacteria: ~~between two fingers one can easily hold~~ a vial ^{with} 5 billions _(like this can hold)

5 billions (Twort & Felix)

of cells. In 1911, 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, in consequence of a spontaneous mutation extending the host range of a single virus particle. The bacteria will be succeeded by a hundred billion viruses -- whose own fate is now problematical, as they will have exhausted their prey (within that test tube). There may, or may not, sometimes be 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.

Is there any reason to believe that such processes are unique to the test tube, that life in the large is exempt from them? Of course not! Only the time scale is certain to be different, by a factor of years to minutes, the disparity of generation time of human to bacteria. The fundamental biological principles are the same. The numerical odds may be different, by a factor hard to estimate.

As crowded as we are, humans are more dispersed over the planetary surface than are the "bugs" in a glass tube, and we have somewhat fewer opportunities to infect one another, jet airplanes notwithstanding. The culture medium in the test tube offers fewer chemical and physical barriers to virus transmission than the space between people -- but you will understand why so many diseases are sexually transmitted. The ozone shield still lets through enough solar ultraviolet light to make aerosol transmission less hospitable; 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 much less so. And we have evolved immune defenses, a wonderfully intricate machinery for producing a panoply of antibodies, each specifically attuned to the chemical makeup of a particular invading parasite. 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 development of antibodies that will dampen or extinguish the infection. If we have been previously vaccinated or infected with a virus related to the current infection, we can mobilize an early immune

response. But 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 quantitative mitigations of the pandemic viral threat are then inherent in our evolved biological capabilities of coping with these competitors. Mitigation is also 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 that 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 to a sustained infection leaving a carrier free to spread the virus to as many contacts as possible. From the virus' perspective, its ideal would be a completely symptomless infection, in which the host is quite oblivious of providing shelter and nourishment for the indefinite propagation of the virus' genes. Our own genome carries hundreds or thousands of such stowaways. The boundary between them and the "normal genome" is quite blurred; 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 of mutating to a state that we recognize as the dysregulated cell growth of a cancer. As much as 99% of our DNA may be "selfish", parasitic in origin.

At evolutionary equilibrium, we would continue to share the planet with our parasites, paying some tribute, but even deriving from them some protection against more violent aggression. Such an equilibrium is unlikely on terms we would voluntarily welcome: at the margin, the comfort and precariousness of life would be evenly shared between the parasites and ourselves. No theory lets us calculate the details; we can hardly be sure that such an equilibrium for earth even includes the human species. Many prophets have foreseen the contrary, given our propensity for technological sophistication harnessed to intra-species competition.

In fact, innumerable perturbations remind us that we cannot rely on "equilibrium" -- each individual death of an infected person is a counter-example. Our defense mechanisms do not always work. Viruses are not always as benign as would be if they had the intelligence to serve their long term advantage.

The historic plagues, the Black Death of the 14th century, the recurrences of cholera, the 1918 influenza, and now AIDS, should be constant reminders of Nature's sword over our head. They have been very much on my mind for the past two decades. However, when I have voiced such fears, they 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: the plague bacillus is susceptible to antibiotics, and today we understand its transmission by rat-borne fleas. Cholera can be treated fairly successfully with simple regimens like oral rehydration (salted water with a touch of sugar). Influenza in 1918 was undoubtedly complicated by bacterial infections that could now be treated with antibiotics; and vaccines, if we can mobilize them in time, can help prevent the global spread of a new flu. But we have been lulled into complacency only recently jarred again.

Technology's impact is not all on the human side of the struggle. Monoculture of plants and animals has, of course, made them more exposed to devastation. In like fashion, the increasing density of human habitations, inventions like the subway^{N.Y.} and the jet airplane^(which I do not compare to the Météo?), all add to the risks of spread of infection. Paradoxically, improvements in sanitation and vaccination leave the larger human herd more innocent of microbial experience, and may in the long run make us the more vulnerable.

Technology, exercised in the opening of wild lands to human occupation, has also 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 HIV 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 AIDS should not obscure the multiplicity of infectious diseases that threaten our future. It is none too soon to start a systematic watch for other new viruses before they become so irrevocably lodged. The fundamental bases of virus research can hardly be given too much encouragement -- and they have made extraordinary leaps, particularly with the help of recombinant DNA technology. Such research should be done on a broad international scale, both to share the progress made in advanced countries, and to amplify the opportunities for field work at the earliest appearance of outbreaks in the most afflicted ones.

The most promising answers to these grievous challenges, the afflictions that today beset so much of the world's populations, and the horrors Nature still has up her sleeve, come from recent research on DNA, and especially its application to infectious disease. "Recombinant DNA", still a scare word in some quarters, is our most potent means of analyzing viruses and developing vaccines.

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 1950's. The most celebrated example, smallpox, also has the oldest historic roots. Political determination and operational know-how were of equal or greater importance compared to recent laboratory investigation for the success within this decade of the world campaign to eradicate smallpox. Most important for any further efforts at eradication of an infectious disease is an understanding of its natural history to calibrate the feasibility of the goal. This will strain our basic knowledge of the genetics and evolution of most virus diseases.

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. How can we procrastinate any further, or have any reservations, about a common cause -- one that responds to every outbreak of disease anywhere as a challenge to all of us.

"~~Ask~~ not for whom the bell tolls ... it tolls but for thee."

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