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Keynote Address

VIRUSES AND HUMANKIND:  
INTRACELLULAR SYMBIOSIS AND EVOLUTIONARY COMPETITION

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Thank you, Dick [Krause]. I am glad you put in that last bit about your historic association with the Rockefeller University. in that regard.

Some of Steve [Morse]'s first words were that we are ever vigilant. I wish that were true. Dick said, we just had to sit back and wait. I am afraid that from the point of view of public policy and the major health establishments of the world, that is much more closer to their reaction, even to this day, to the prospects of emergent disease.

Fortunately, in this room, we have the investigators who are the most preoccupied with the biology of viruses, who have a very personal and intimate acquaintanceship with how they tick and are therefore much more sensitive to their potentialities for evolutionary change for the evolution of their symbiotic relations with their hosts. Never has there been a more concentrated collection of intellect devoted to that kind of question.

I am deeply gratified at the number and quality of investigators who have responded to the call for this symposium. I do marvel that an examination of this kind is, as far as I know, essentially without precedent. Of course, there have been many symposia on viruses covering every aspect of their biology and epidemiology. For the most part, these have been sharply focused on particular categories, whether of the host, the vectors or the taxonomic location of the virus itself. But the historiography of epidemic disease is one of the last refuges of the concept of special creationism, with scant attention to dynamic change on the part of the agents of disease.

It is not hard to imagine the sources of resistance: it is scary to imagine the emergence of new infectious agents as threats to human existence, especially threatening to view pandemic as a recurrent, natural phenomenon. In reaction to the daunting pace of technological change, and the sudden alteration of balance -- in 50 years, the earth has become so small on the scale of technological alterations of the environment; the atmosphere, the oceans, our aquifers are no longer infinite sinks -- the natural has been extolled. Many people find it difficult to accommodate to the reality that Nature is far from benign, at least it has no special sentiment for the welfare of the human versus other species. Those who are horrified at any tinge of our "tampering with natural evolution" need to be reminded that this has been intrinsic to human culture since Prometheus: the invention of fire, or agriculture, of language, of human settlements, of an overall peopling of the planet perhaps a thousand-fold denser than we had been evolved for. Not to mention a sudden doubling of life span in one century that leaves the latter half of it beyond the scope of what had ever been shaped by natural selection. So contemporary man is a manmade species. In a biological sense, we may achieve new genomic equilibria with these radically altered environments; but the price of natural selection

is so high I doubt we would find it ethically acceptable: it conflicts violently with the nominally infinite worth that we place on every individual. So we have drastically tampered with human evolution, in large measure by suspending that process in favor of artifice.

That artifice has of course been the greatest threat to every other plant and animal species, as we crowd them out in our own quest for Lebensraum. A few vermin aside, *Homo sapiens* has undisputed dominion -- and we could, where we choose, even eradicate rodent and insect pests in confined areas we choose to make oligo-xenic -- at the expense of some of the birds and the bees and some marginal chemical poisoning of ourselves, and an irrevocable loss of evolutionary diversity among other species, an eventual narrowing of the options for our own survival.

Bacterial and protozoan parasites linger a bit longer; but they do have distinctive metabolism, and our ingenuity in devising antibiotics will certainly outpace theirs in evolving resistance, (albeit not without some struggle) provided only that we apply the needed technological resources. And for the most part, still more appropriate technologies of hygiene and vaccination will do most of the job. Out only real competitors remain the viruses; for it is by no means clear that antiviral antibiotics can generally be achieved in principle: the very essence of the virus is its fundamental entanglement with the genetic and metabolic machinery of the host.

Our main recourse has been prophylactic vaccination; and for a number of viruses this will surely work, though very few share the idiosyncrasies of variola that made it the most rational target for our initial effort at global eradication, at an evolutionary victory of the first order. But as we will hear in abundance at this conference, many viruses are more adroit than variola in antigenic evolution, and we shall have to be very nimble indeed to keep up with the diversification of influenza, particularly when we get a recurrence of more lethal strains, e.g. of neurotropism already well known in bird strains.

Other viruses will adapt by changes of range of host or of vector -- the more threatening as we know so little of the biochemical bases of that specificity. And some vector-borne agents will surely learn the tricks of direct aerosol transmission, as has been claimed for pneumonic transmission of bacterial plagues. Why not?! For the few cases of anti-viral drugs we are of course already seeing the emergence of resistant viral strains, just as with bacteria. The viruses I know best, the bacteriophages, are of course no threat to Public Health. They may occasionally be pests in the fermentation industry; D'Herelle and Martin Arrowsmith once thought they might have some merit in therapeutics. They have conveyed to me dramatic images of the wipeout of large populations, sometimes as a result of host range mutations. They have also taught us a great deal about the basic biology of viruses, lessons that can be extrapolated at first hand -- for example the transduction of host genes by viruses, and the integration of viral genomes into the host chromosomes. We will also hear arguments of the intrinsic hypervariability of certain categories of viruses; and we know this will be aggravated further in maladjusted genetic complexes. It is after all genetic stability that has had to be meticulously evolved; we will see mutation rates as high as are compatible with generational viability when the regulatory controls are disrupted. The vertebrate immune system illustrates how the hypermutability of immunoglobulin genes is a trick relearned in evolution -- and matched by the trypanosome's versatility in its surface antigens.

Our view of virus as a parasite is complicated by that of a virus as a genetic element, a two way channel. The viruses are routinely subject to phenotypic modification by the host cells and, from time to time, the viruses incorporate host genes in their standard genomes and vice versa.

This view still looks at host and parasite as independent and autonomous genetic systems. Let us examine their relationship still more broadly.

When we try to classify the genetic elements within cells we find a continuum, with the nucleus and its macrochromosomes at one pole, a range of other particles in between, the frank extraneous cytocidal and cytolytic viruses at the other. Even among the chromosomes, especially in plants, we find micro or B chromosomal elements which share every attribute of a parasite except that they show vertical transmission rather than, as far as we know, routine lateral mobility, and their highly attenuated pathogenicity.

Other particles occupy the cytoplasm. We know most of all today about the mitochondria and the chloroplasts. The eukaryotic cell is now recognized as a symbiosis, those elements very likely having been evolved from what were once free living microbes. Indeed, it is not difficult to cure yeast of their mitochondria with acriflavine, and *Chlamydomonas* and other green plant cells of their chloroplasts with streptomycin.

Conversely, we know of many "viruses" in plants and animals that display vertical transmission. The rodent leukemogenic viruses and, close by, the mouse mammary tumor milk factor, and abundant examples in plants. It will be astounding if we were not to find still other viruses that have become routinized as cytoplasmic organelles in parallel with the mitochondrial and chloroplast systems, like some of the endosymbiotic bacteria of insects that have become indispensable to the normal economy of their specific host.

At one time much polemical energy was spent arguing whether some of these entities were viruses, on the one hand, or cytogenes on the other, as if these were logically exclusive concepts. The word plasmid was invented in 1952 {1} to help moot a logically empty controversy. The expression has come to be used mainly in the narrower sense of the small circular DNAs that abound in bacteria, (it is hard to find bacteria that don't have them). However, it was intended to apply as well to mitochondria and to temperate viruses. I make a confident prediction that we are going to discover many, many more entities like that in the cytoplasm of eukaryote cells as well. {2}.

To look still more broadly, we have discovered that terrestrial life is a dense web of genetic interactions. The plant cell is an intracellular symbiosis, the photosynthetic chloroplast fixing solar energy for the benefit of the host. And I will not take time to articulate how the tree repays than debt. Then, when I eat a green plant and sow its seeds, our genetic systems are also interacting to mutual benefit. The lichen is not much different: the cell boundaries are likewise still intact between algae and fungus. One can find intermediate interactions, even across broad species lines, of hyperparasitism, the nuclei of one fungus parasitizing the cytoplasm of another. This blends into heterokaryosis within a species, with the regular dikaryons of the basidiomycetes, the mushrooms. In the laboratory there is an easy and elegant demonstration of nutritional symbiosis of complementary auxotrophic mutants in

heterokaryons. In streptomycetes it is difficult to distinguish these internuclear interactions from chromosomal ones.

We can thus see the continuum of interaction of genetic systems we have co-evolved. There is a synecology at the very top level that is absolutely undeniable, the exchange of what are ultimately gene products, the metabolites, the energy that is fixed in green plants. Syncytia form more abundantly than most people realize where these interactions become possible at a more intimate level, and one can see polymers, enzymes, RNA messages and so on as the units. And then synkaryosis, the primitive step in sexual recombination is a further step in that continuum. Consider further the interrelationships of still smaller autonomous genetic elements like viruses and plasmids, and mitochondria, as falling at different points on this spectrum with no sharp line between them.

This pattern of mutualism must have prevailed from the very earliest stages of biosynthetic evolution, perhaps even prior to the organization of the cell as we now know it. The recombination of self replicating molecules to facilitate biosynthetic complementation would have accelerated primitive chemical evolution from the earliest times.

Refocussing on the pathogenic interactions, we recall that since Theobald Smith (3), Frank Burnet (4) and others, we have understood that evolutionary equilibrium favors mutualistic rather than parasitic, rather than unilaterally destructive interactions. Natural selection, in the long run, favors host resistance on the one hand, and temperate virulence and immunogenic masking on the part of the parasite on the other. But I garner limited assurance from those precedents. Yes, demographic obliteration is not the most likely outcome of a novel introduction of the emergence of a major new virus. Most likely, the outcome of those exigencies will not be worse than what happened to the rabbits in Australia after the introduction of myxovirus.

But apart from the personal human catastrophe that such a pandemic would entail, (short of prompt species obliteration), I would also question whether human society could survive left on the beach with only a few percent of survivors. Could they function at any level of culture higher than that of the rabbits? And, if reduced to that, would we compete very well with kangaroos?

Let me summarize: the units of natural selection are DNA, sometimes RNA elements, by no means neatly packaged in discrete organisms. They all share the entire biosphere. The survival of the human species is not a preordained evolutionary program. Abundant sources of genetic variation exist for viruses to learn new tricks, not necessarily confined to what happens routinely or even frequently.

The first inklings that genetic recombination could occur at all in bacteria, in F+ E. coli, were at a rate of  $10^{-7}$  and one had to look very hard to have any evidence that they existed at all. And some bamboo plants flower only once per century and the careless observer might think that they never recombine. Some generalizations to the limits of genetic change in viruses are equally hasty.

Thank you very much.

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--- Cite Temin re retrons?

Also C-Smith re junk dna?