Virus Infections—What of the Future?

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The rate of progress in virus research today is so rapid that for many the present is the future. Consequently, in order to discuss the future in comprehensible fashion, I must talk about the present state of affairs—to discuss current knowledge which furnishes the basis for contemporary enormous interest in viruses. It is precisely those considerations which will furnish the springboard for future progress in understanding and controlling the effects of virus infections.

Virology has developed into a special, rather new, bioscience which has implications for all branches of biology and medicine. In addition, previously unimagined new viruses have been found infecting virtually all living things, including plants, insects, fish, fowl, and mammals. It is now clear that viruses are major sources of economic loss in agronomy, in animal husbandry, and work loss in all the industries and businesses on which America's 90 million industrial and agricultural work force depends. Billions are now known to be lost for lack of sufficient understanding to control what should be controllable infectious diseases, and millions are spent in attempts to control them.

This is a relatively recent development. No more than 15 years ago the number of viruses known specifically to infect men could be counted on the fingers and toes, and virus research laboratories devoted to virus diseases were uncommon; today there are over 100 different known viruses in one generic group alone—the total number of human viruses is well over 200. A large proportion of these were discovered and characterized only very recently. Each month and year witnesses the discovery in many new virus laboratories scattered over the earth of additional new viruses, and the problem of identifying and classifying so many of them has produced a taxonomic crisis which appears to be insoluble, except by national and international collaboration on the production and use of standard viral reagents.

Fortunately the newer technologies which opened this Pandora's box have also provided considerable understanding of the nature and behavior of many new viruses. Methods for quick identification and classification have permitted extensive long term follow-up studies of virus infections of selected human populations. To this end, virologists, clinicians and epidemiologists are now observing virus infection in certain human populations. For instance, my associates and I have observed multiple and repeated infections with more than 80 different kinds of viruses in infants housed in a District of Columbia nursery; this group has been under constant surveillance for more than seven years. In the course of these studies, thousands of separate virus isolations were made, and all of them had to be identified. Such an eventuality was technologically impossible less than a decade ago, and the actual observations on viruses and illnesses which were made could not have been imagined then. Many of the virus infections caused only mild or severe illnesses; many other infections, however, were silent, i.e., not associated with any measurable contemporary illnesses. In still other studies and under other circumstances, those same viruses apparently caused severe and occasionally fatal illnesses, differing conditions apparently playing a decisive role in whether illness was absent, mild, severe, or fatal.

Thus, while these viruses most frequently cause uncountable numbers of mild to moderate illnesses in infants and children, many of them are now known, under certain conditions, to be able to cause:

1. paralytic disease in humans (polioviruses and certain other enteroviruses);
2. aseptic meningitis and encephalitis (Echo and Coxsackie viruses);
3. heart disease (myocarditis), frequently fatal in infants (Coxsackie B virus);
4. central nervous system disease—hydrocephalus (salivary gland virus);
5. eye diseases—corneal lesions and blindness (herpes, adenovirus 3);
6. fatal pneumonias and croup illnesses (respiratory syncytial virus, influenzas, para-influenzas, adenoviruses);
7. fatal cancer in hamsters, rats and mice (adenoviruses 7, 12, 18).

Effect of Large and Crowded Populations

Other groups, as well as my associates and I, have also studied virus infections in different military cadres, especially in recruit camps, schools, and colleges, where those susceptible to infection are brought together in large groups. At the same time, studies were done on naturally occurring virus infections in man's nearest animal associates, domestic and commensal animals (table 1), revealing a remarkable similarity in viral flora in all these species to those observed in man, a flora not generally observed in wild animals or in commensal animals living in the "wild" state.

The results of all these studies serve to re-emphasize the enormous importance of crowding—the effects of large and dense populations—on the prevalence, spread, persistence, and evolution of numerous different virus infections.

TABLE 1
Comparative Virus Experiences* of Man and His Domestic Animals (Mice, Cattle, and Chickens)

Virus Category	Man	Monkey	Mice	Cattle	Chickens
Myxoviruses	3 influenzas 4 para-influenzas Mumps	Para-influenza 3 SV 5	Para-influenza 1 (Sendai)	Para-influenza 3	Newcastle Fowl plague SV 5
Measles virus	Measles	Monkey measles	Not known	Rinderpest	Not known
Picorna viruses	3 polio 28 Echo's 29 Coxsackie's 30 rhinoviruses	Many serotypes	Theiler's EMC	Foot and mouth disease Numerous enteroviruses	Several serotypes reported
Reoviruses	Types 1, 2, 3	Types 1, 3	Types 2, 3	Types 1, 2, 3	?
Adenoviruses	28 serotypes	Many serotypes	I serotype to date	2 serotypes	Gal virus
Papovaviruses	+	SV 40	Polyoma	+	Not known
Herpes virus	Herpes simplex	B virus	Not known	IBR	Not known
Salivary gland virus	+	+	+	+	?
Pox virus	Smallpox	Monkey pox	Ectromelia	Vaccinia	Fowlpox
Ornithosis	Psittacosis LGV	Probable	MPV	Encephalomyelitis of calves	Several acute and chronic respiratory disease agents

Other domestic animals – hogs, horses, dogs, and cats – also share similar viruses with man.

*These have almost never been studied in the same ecological environment.

Indeed, since viruses, like all other species, are products of evolution, the "virus explosion" we are currently witnessing must in great part result from the "population explosion" itself.

Importance of Viruses

What are viruses? They are definable biophysical and biochemical entities that can be taken apart—nucleic acid and protein can be separated and put together again. There is no question that some day soon chemists will be able to synthesize some of the simpler viruses. If this is so, can we think of viruses as being really alive? I think we must decide that they are. Viruses are the smallest entities capable of independent existence in the sense that they carry their own duplicating machines, genetic information (DNA or RNA) which orders their replication within susceptible cells. Although completely dependent on sympathetic living plant or animal cells for reproduction and continuous existence, they are probably no more dependent than the cell itself, or for that matter, the organ or host which also depends upon sympathetic milieu for persistent existence. These arrangements are apparently reflections of different orders of adaptive mechanisms which guarantee the survival of species and subspecies.

What, in a more specific sense, is so important about viruses that they command some of our best scientific minds and millions of dollars of research funds? Primarily, of course, because they are known to be responsible for much disease, and are suspected to cause even more. Most modern virus disease investigations are currently focused on one of four important virus disease problems:

1. delineation and prevention of acute respiratory diseases, including the common cold—man's most frequent illness;
2. delineation of the role of viruses in the cause of cancer—man's most dreaded illness;
3. definition and prevention of viral causes of birth defects—perhaps man's most devastating and irrevocable illness;
4. determination of the possible role of viruses in chronic and degenerative diseases.

The recognition, by scientists and laymen alike, of the enormous importance of these problems to human health has led to unprecedented nationally financed efforts to solve them. However, the overriding importance of viruses may turn out to be something much more fundamental, namely, their possible role in the evolution or natural selection of higher species. Animal viruses, as well as bacterial and plant viruses, are now known to carry genetic information which frequently alters host cells, and effects fundamental changes in inheritable characteristics of cells. Thus, numerous viruses are now known to transform normal cells into cancer cells whose progeny continue to reflect specific virus effects and carry specific virus markers indefinitely. Although in many cases the changes may be largely functional, other changes are almost certainly genotypic.

As I pointed out above, viruses are unique biochemical, biophysical and biological entities, and have different meanings for the biochemist and biophysicist, the biologist and the medical virologist. While they apparently do not contain enzymes, hormones and other synthesizing materials which enable them to achieve independent existence, i.e., to multiply and mature through feeding on non-living substrates, they do contain genetic materials in the form of DNA's or RNA's which are capable of ordering cells to reproduce their own prototypes. Although viruses usually require more than nucleic acid, namely a protein coat, in order to fully mature and survive as nomadic living particles in the natural order (and it is this protein coat which allows us at present to see them in the electron microscope and more easily identify them in laboratory systems), it is now clear that the naked nucleic acids (DNA or RNA) of viruses can, by themselves, carry out the total functions of intact viruses once they gain a foothold inside cells. In other words, the essential part of a virus is its nucleic acid core, which, like the genetic apparatus (chromosomes) of the male sperm once it gains entry to a susceptible cell, is fully competent. Indeed, some viruses (bacterial viruses) insert their internal genetic material into their host cells without themselves entering the cell. However, like spermatozoa, viruses in order to continue in their nomadic existence, i.e., to leave one host and discover another, require ancillary equipment—namely, specific protein coats.

Molecular Biology, Molecular Disease, and Virology

The twin concepts of molecular disease and molecular biology did not appear in any electric or immediate sense; they are the products of a unifying idea which has been growing in the minds of biomedical investigators for a long time. They are not based on a single theory and cannot be simply stated; they are often called the "molecular basis for disease" and depend primarily on biochemical, biophysical and genetic concepts of how living cells come into being, operate and respond to outside influences. These theories recognize many identifiable particles involved in the great adventure expressed in the term "life"—particles which are smaller than living cells, most frequently subunits and products of living cells, such as genes, enzymes, and hormones. What are they? The first are made up of nucleic acids, which apparently order the others around. Important scientific disciplines are now devoted to the study of enzyme, hormone and nucleic acid chemistry. However, it seems there are also nomadic particles that are sinister as well as interesting—viruses which frequently gain entry to cells, and which actually depend entirely for their existence on their ability, once inside the cell, to create a revolution, to establish an entirely new order for the cell, which results sometimes in death of the cell. This happens when poliovirus affects a motor nerve cell. More often, death may not be the outcome of virus infection; the cell remains alive but vitally changed, something as radical and as devastating as a cancer cell. Or, in other circumstances, viruses can produce defective cells and organs, resulting in something as pitiful as a deformed baby, a crippled child, and perhaps even a chronically ill or demented adult. It is obvious, therefore, at this comparatively advanced stage of medical knowledge, that it will prove difficult to avoid the now well known "microbial" concept of disease in looking for causes of so-called "non-infectious diseases." While frustrating to many scientists, the prospects for progress in prevention of infectious illnesses, including viral diseases, are immeasurably greater than for diseases having causes that are less well understood. After all, the techniques for treatment and prevention of infectious diseases were developed, tried, sharpened and proven over a period of nearly 100 years—ever since Pasteur managed to diagnose and cure the infectious illnesses of French wines and devised a preventive vaccine for rabies. These techniques range from administration of wonder pills stemming from Erlich's magic bullet, of vaccines stemming from Jenner's early observations on the unblemished complexions of milkmaids, to simple but community and nationwide application of the principles of sanitation and hygiene.

What Does the Future Hold?

Perhaps final answers to the questions and problems discussed in the foregoing; perhaps the prevention and cure of some types of chronic diseases and cancer. We can look for newly conceived and highly sophisticated research approaches to the prevention or cure of virus infection.

Taking a long view of scientific progress, the first half of the 20th century doubtless will be most remembered as the age of the conquest of the atom; but it might better be regarded as the period when fatal infectious diseases were finally conquered, and man's life expectancy greatly increased as a result. It is likely that the second half of the 20th century will be heralded as the age of the conquest of space, but equally possible, and perhaps more importantly for human destiny, it may become noted as the period during which the "molecular" basis for life was first defined, the age during which the mysteries of subcellular dysfunctions responsible for cancer, chronic disease, genetic defects, mental disease, and perhaps even aging, were finally understood. The latter part of the 20th century could therefore also become famous as the period in which the microscopic world of living cells, constantly beset by ultramicroscopic particles (viruses) which behave as if they were also living, was discovered to have more meaning, and in a certain sense, larger dimensions, than the cosmos itself.