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VIRUSES: Tiny Mysteries

An Honors Thesis (ID 499)

by

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Introduction

A virus, consisting of genetic material enclosed in a protective coating, is one of the simplest entities able to reproduce. Viruses have no metabolic systems, they have no intrinsic mobility, they cannot respond to stimuli and they do not grow in the usual sense(Allen,242). The ability to maintain genetic continunity with the possibility for mutation is the only basis for considering viurses to be alive(Forbisher,304).

The mechanism by which viruses reproduce are unique in biology. This seems to be true whetner one is talking about a virus of green plants, bacteria, mushrooms, algae, insects, higher animals, or humans. In all cases, during the reproductive cycle the genetic material of viruses becomes a functional part of the cell it has infected (Dale ,60). The genes added to the cell by the virus either cause the infected cell to produce more viruses with cell death usually the end result, or to become changed and acquire new characteristics (Locke,102).

Discovery

The term 'virus' is derived from latin, meaning 'poison', 'venom' or 'slimy liquid' (Hughes,109). Rather than defining a virus the latin meaning actually describes aspects of viral diseases. The first definitions of viruses were presented in negative terms: "They were not retained by bacterial filters, not visible in a microscope, and not cultivatable on any nutrient media in vitro (Frankel-Conrat)." The current definition of a virus however, is facilitated by the defini-

tion of life. Viruses are defined presently as a state of biophysical and biochemical organization which enables (a) enzymes to synthesize macromolecules and (b) nucleic acids to carry encoded information for production of those macromolecules(Frankel-Conrat,4).

It is not surprising that research in the early decades focused primarily on viral diseases rather than the precise nature of viruses, for this area is a relatively recent introduction into the world of the physician. The manifestation of viral disease (some of the major infectious diseases of the world) were far easier to identify than their causal agents.

The great names of early medicine --- Hippocrates, who about 400 B.C. taught that all illness had a cause; Galen, who in A.D. 200 said that man could learn about the body only by dissecting it; and even William Harvey, who in 1628 demonstrated the circulation of the blood --- none of these knew that disease was often caused by living organisms too small to perceive (Brock,15). Supernatural and cosmic phenomenon were originally deemed to be the cause of infectious disease. As man gained knowledge of the natural world, these beliefs were replaced by the idea that infectious substances produced diseases in living creatures.

With the development of the microscope in the seventeenth century things began to change (Bradbury,108). Only with further discoveries on the nature of bacteria in the middle of the nineteenth century did the principle difference between bacteria and viruses appear. Viruses were recognized as a seperate class of microorganism in 1898 by Beijerinck (Locke,20).

The list of contributions and contributors to the study of viruses is much too long a list to include however a few of the major landmarks in viral research and their researchers follow:

LANDMARKS IN RESEARCH

(Hughes,75)

1798	E. Jenner	Empirical development of smallpox vaccine.
1892	D.I. Ivanowski	First description of the filterability of a virus.
1898	F. Loeffler	First description of the filterability of an animal virus.
1898	E. Nocard	Discovery of the mycoplasma.
1898	G. Sanarelli	Discovery of the virus Myxomatosis.
1898	M.W. Beijerinck	Description of the TMV as a contagious living fluid;discovery of it's mode of reproduction.
1900	J. McFadyean	Discovery of the virus of African horse sickness.
1901	W. Reed et al.	Discovery of the virus of Yellow fever.
1903	D.I. Ivanovski	Microscopical observation and description of crystalline inclusions of TMV.
1903	P. Remlinger	Discovery of the virus of rabies.
1909	S. Flexner	Discovery of the virus of Polio.
1911	J.Goldberger	Discovery of the virus of Measles.
1911	R. Rous	Transmission of a tumor by means of cell-free filtrate.
1913	E. Stienhart and C. Israeli	One of the first propagations of a virus in tissue culture.
1915	F.W. Twort	Discovery of a virus infecting and lysing bacteria.
1917	F. d'Herelle	Named Twort's virus'bacteriophage.'
1930	M. Theiler	Demonstration of the usefulness of mice in viral research.
1931	W.J. Elford	Description of the use of graded collodion membranes for determination of viral size.

1931	A.M. Woodruff and E. Goodpasture	Cultivation of a virus in developing chick embryos.
1934	C. Johnson and E. Goodpasture	Discovery of the virus of mumps.
1935	W.M. Stanley	The first artificial crystallization of a virus (TMV).
1935	M. Hoskins	The first experimental demonstration of interference between animal viruses.
1938	Y. Hiro	Discovery of the virus of rubella.
1939	G. Kausche and E. Pfankuch	First us of the electron microscope for visualization of viruses.
1946	M. Delbruck	Discovery of genetic recombination in bacteriophage.
1949	J. Enders, and F. Robbins	In vitro cultivation of polio virus in non-neural tissues.
1953	A. Hershey	Demonstration that DNA is the infective component of bacteriophage vectors.
1953	Watson and Crick	Description of the molecular structure a replicative mechanism of DNA.
1956	A. Gierer and G. Schramm	Demonstration that RNA is the infective component of TMV.
1957	A. Isaacs and J. Lindenmann	Discovery of interferon.
1962	T. Diener	Discovery of the viroid.

Stanley's crystallization of the Tobacco Mosaic Virus, TMV, in 1935 was a major milestone on the road to understanding viruses (Locke, 65). TMV, which causes a mottling of the tobacco leaf, was the first virus in which the amino acid sequence of the viral coat protein was determined (Frankel-Conrat, 53). Stanley like many other researchers, noted the paradoxical nature of viruses. Their ability to infect and multiply suggested a microorganism. But their filterability and resistance to alcohol,

weak formalin and dessication were usually characteristics of non-living material (Goodhart,243).

Physical Features

The question of the size of viruses had been of interest from the beginning. Pasteur had deduced that the rabies virus was ultra microscopic and Beijerinck had concluded that TMV might be molecular size (Elford, 450). One thing was for certain, viral particles were small enough to past through the smallest holes in ceramic filters used to filter bacteria. In fact, viral particles are now known to be smaller and simpler than any other disease producing agents (Locke,1). A bacterium is approximately 1 micrometer in diameter while a large virus measures only 12 nanometers in diameter (Locke,2).

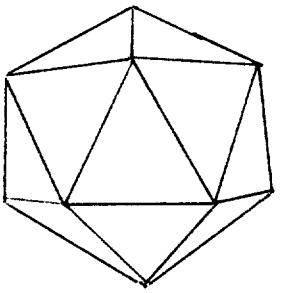
It was in 1939 that the eletron microscope was enlisted in the cause of virology by G. Kausche, E. Pfankuch and Helmut Ruska when they micrographed TMV (Bradbury, 101). Until then, all viral particles appeared as spherical structures. It is now evident that viruses seen in electron microscopy have one of several forms. To understand these forms a little more must be known about viral composition.

Viruses are composed of only two substances in most cases: a nucleic acid which contains the essential genetic information of the virus, and a protein coat which (a) protects the nucleic acid from enzymes (b) helps the virus penetrate the defense of host cells and (c) form themselves into progeny virus within the infected cells (Locke,64). Some also include molecules of other kinds such as membranes and appendages. It is the arrangement of protein subunits in the protein coat which determines the 3-dimensional shape of the particle (Watson,740). This arrangement is very much like the molecules or atoms of a crystal.

The key factor in the virus structure is the regular, crystal-like arrangement of identical repeating protein subunits. Two principle patterns predominate; spherical

and helical. Both patterns approximate those dictated by the laws of symmetry that determine crystal structures (Baltimore,52). The viral structures are essentially a closed shell to house the nucleic acids.

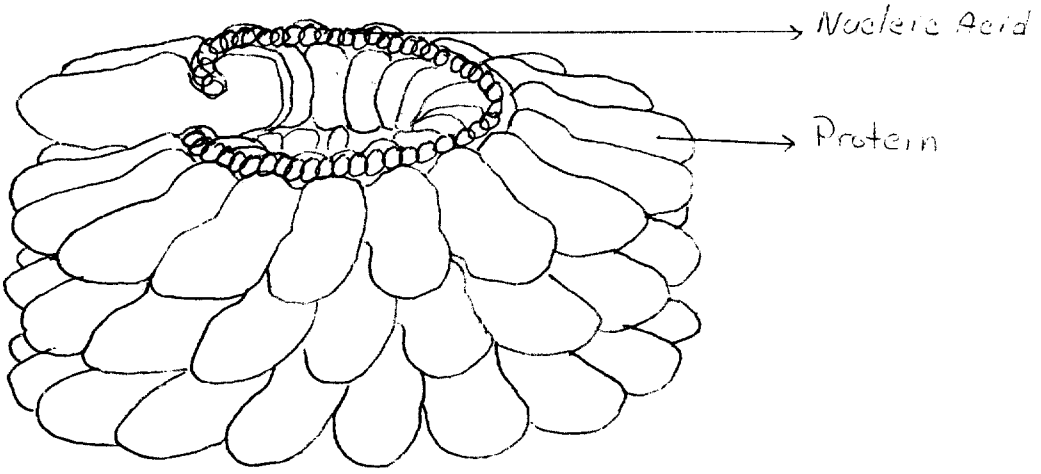
Spherical viruses do not have perfectly spherical structures, rather they are regular polyhedra, solid objects who faces are made of regular polygons (Locke,67). Because the polyhedral viruses typically have many faces they appear spherical at first glance. One can think of these viruses as resembling the geodesic domes of Buckminster Fuller, which appears spherical from a distance. Below is an illustration of a typical spherical virus (Locke,69)



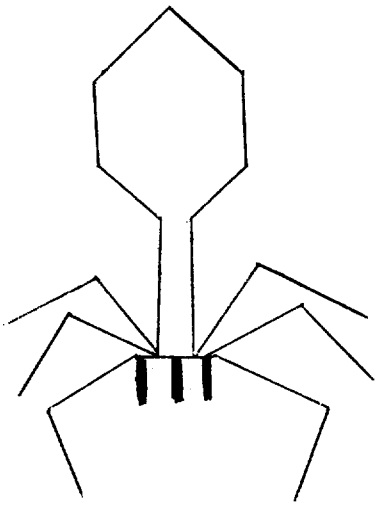
The polyhedron which forms the basis for spherical structure is the icosahedron (20 faces of equilateral triangles). Each face is composed of a specific number of capsomers--structural subunits. The smallest icosahedral virus is phi-X174 which contains 12 capsomers while the largest one known is Tipula irridescent virus which has 1,112 capsomers (Dubos, 121).

In helical viruses the shape is that of a tube---a spiral of constant diameter. The protein components of a helical virus are stacked in spiraling rows, each unit with the same dimensions and each at the same distance from the units on every side of it. The best known helical virus is TMV (Locke,75). The helical chain of protein subunits spiral up the outside of the particle forming a hollow tube. The nucleic acid is wound into a long helical

channel made by a groove in each protein subunit. Thus, the nucleic acid is inside the viral particle but not within the hollow at the center of the virus (see diagram bel ow) (Fenner,6).



Although most viral particles conform to one or the other of these basic patterns, variations and elaborations are common. For example some have multiple protein shells, some are bullet shaped, some have various types of appendages, and many are surrounded by a lipid membrane or envelope. Some interesting variations are the T-even bacteriophages T2,T4, and so on). They have polyhedral heads and elaborate rod-like tails as shown below (Locke,76):



The tail itself consist of an outer tube, an inner core and a tail plate which bears 6 short prongs and 6 long appendages. The head still resembles an icosahedral shell

and portions of the tail have helical subunits.

One of the chief advantages to simple icosahedral or helical structures is that subunits can come together by themselves to form viral particles (Locke,90). Not all viruses can do this however, specifically the highly complex structures such as T-even bacteriophages which are assembled in stages. Viruses with membranes seem to acquire them by moving through the cellular membrane picking up coating as it does so---a process called 'budding' (Locke,81).

Classification

Classification of viruses presents a particular problem to virologist. Presently no rational means exist for classification of viruses since they lack recognizable common evolutionary relationships (Frankel-Conrat, 18). Viruses were originally named for the diseases they caused. After 1965 viruses were grouped by structural similarities, irregardless of their hosts, and given latinized names (Kohler, 103). This was done because the host and the pathological symptoms produced by the virus were not fundamental in classification. One of the more common methods of classification is one in which the virus is classified according to (a) whether they contain DNA or RNA (b) whether the virus had icosahedral or helical symmetry and (c) the presence of an envelope or membrane (Locke, 103).

Life Cycles

In its free state -- outside the host cell -- a virus exist as the kinds described earlier. This particle as such is immobile. Viruses are carried to and from their specified destinations by other natural forces or living creatures (Allen,241). Essential body fluids in plants and animals serve as excellent transports. The chief problem however, is transport from host to host.

Replication of a virus is preceeded by entry into the host cell and removal of their coat protein and/or envelopes. Animal cells probably provide the least formidable defense against virus invasion, since they do not have the heavy cell walls which plants and bacteria have (Rhodes, 117). Viruses such as the T-even bacteriophages have become specialized to penetrate the heavy cell walls. Plant viruses rely on accidental breaks in the cell wall or take advantage of the action of insects that penetrate the plant cells. They then pass from cell to cell by way of tiny plasmodesmos channels (Rhodes,119).

Once inside the cell the virus cannot simply split itself in two, bud off little offspring or produce viral spores. What it does do is to take over the cell's machinery for producing protein and nucleic acid (Locke,4). This machinery is then used to make new viral protein and nucleic acid. For this reason, it may be said that viral infected cells should be viewed as a new entity, not a cell with a virus in it, but a <u>virus-cell system</u> (Locke,7). After the nucleic acid directs the manufacture of the necessary components, the components self-assemble into new viral progeny.

In most cases multiplication occurs in the cytoplasm, but some have been known to replicate in the nucleus. Although viruses are known to replicate in both procaryotic and eucaryotic cells, no one viral particle can replicate in both (Frankel-Conrat,182).

When one speaks of the 'growth' and nourishment' of a virus these terms don't quite fit, for a virus really needs no 'nourishment' from the host--being a simple collection of chemicals. It doesn't really 'grow' in the usual sense of the word, it is assembled. Once this assembly is complete the virus is released from the cell into the enviroment. It is unable to function or multiply outside the living cell since there is no machinery for the production of components outside the living cell (Locke,33).

As a result of the protein coat 3-Dimensional conformation, most viruses damage only certain specific kinds of cells, such as the lining of the mucuous membrane of man's nose and throat in the case of the common cold (Adams,63). The most striking example of viruses which have a wide host range are those plant viruses that replicate in insects which transmit them (Frankel-Conrat,182).

If a single celled organism is infected by a virus the virus will kill the organism and release hundreds of new viruses. Loss of one cell in a multicellular organism however, may go unnoticed or be unimportant as far as the parent organism is concerned. If every one of the new viruses infects a new cell, destruction may continue at such an alarming rate that the organism cannot shrug off it's losses and sickness occurs. If the infection is bad enough and enough cells die the organism ultimately dies.

Viral Diseases

A virus is not a disease although commonly referred to as one (Locke,21). The virus is simply the agent by which viral infections are caused. Therefore there is no special symptomology that sets viruses apart. For example viral pneumonia appears no different from one of the more common bacterial pneumonias (Adams,73). The symptoms of viral diseases are as varied as the viruses that cause them and the organ which they attack. A virus invasion may prove to be as innocuous as a wart or a terrible as rabies. The invasion may in fact attain considerable viral quantities in the body with out causing any outward symptoms.

Most common of all viral diseases are those of the respiratory tract which range from the common cold to influenza (Adams,84). The common contagious childhood diseases are also viral in nature. Included are such ailments as German measles, mumps, smallpox, chicken pox, hepititus, polio, herpes, and yellow fever.

The symptoms of infection by one particular kind of virus are not always the same in all people. Nor do viruses affect the different species they attack in the same way. In general most viral diseases are acute; once the symptoms begin, they develop quickly, rage for a day or two, and then subside (Forbisher,16). Viruses also tend to be self-limiting; in the normal course of events they more or less cure themselves(Adams,101). The common cold is a good example of this; however, there are many exceptions such as rabies. Other viral illnesses may eventually subside but leaving behind serious permanent damage which is the case with polio.

Finally, viral diseases bring with them a certain measure of immunity to further attacks. In typical childhood illness--mumps, measles, chickenpox--the immunity is lifelong. With influenza however, the immunity may only last for a few months or years. And it's possible to catch colds several times a year.

Transport

Every virus must enter the body if it is to produce an infection. Viruses are discharged from bodies of infected host in the skin, nasopharyngeal secretions, conjunctival secretions, urine and feces (Rhodes,98). In many diseases viruses circulate in the blood. Viurses can be spread by direct contact, inhalation, intermediate articles, food or drink or by vectors such as mosquitoes, mites, ticks, or fleas.

Viral diseases, spread by droplets of secretions include influenza, atypical pneumonia, measles, rubella, mumps, smallpox and polio (Rhodes, 100). These droplets can be secreted in the air by coughing and noseblowing. It is important to note also that viral diseases are spread by fully developed cases, by persons with mild abortive illnesses, and by healthy carriers (Rhodes, 98). The latter two are more important than the first since they tend to have more contacts with uninfected people (Adams,301).

Cell Defenses

The 'parasitic' nature of viruses and their intergration into normal cellular activity represent major obstacles in chemotherapeutic control of viral disease (Frankel-Conrat,4). The human body does however, have some defense against viruses: (a) physical and chemical processes such as dead cells on the body surface or ciliary processes and mucous movements of the nasopharyngeal membranes for example help prevent viral infections; (b) specialized cells of the blood, lymph and tissues tend to engulf viruses and digest them (this process also may serve as a breeding ground for some types of viruses); (c) the formation of antibodies help to prevent absorption of viruses into the host cells; and (d) interferon action in which one virus prevents the growth of other viruses by interaction with host cells (Locke,143).

Conclusion

In summary, viruses which have aptly been described as structures 'at the threshold of life,' are stable complexes containing a nucleic acid molecule and many protein subunits organized into a characteristic three-dimensional arrangement. Virus particles have no power to reproduce themselves in the test tube. However, when a viral particle gains access to the interior of a specific host cell, it has the capacity to direct its own replication. The viral nucleic acid, which the infective part of the virus can 'monopolize' the biosynthetic machinery of the host cell, forcing it to synthesize the molecular components of virus molecules rather than the normal host cell components.

Because of the nature of viruses, they are playing an increasing role in research areas such as genetic engineering, cancer and tumor preventatives. The information scientist derive today from viruses may drastically change the medical field as we know it.

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