AT THE EDGE OF LIFE: AN INTRODUCTION TO VIRUSES

A Report from the National Institute of Allergy and Infectious Diseases

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health · Public Health Service

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A REPORT FROM THE NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES

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PREFACE

According to health surveys, viruses cause the most common acute infectious illnesses in the United States; and there is growing evidence to suggest that they may cause many different chronic diseases as well.

Three years ago, I reported to the U.S. Congress on the extent of the burden of these infectious agents on the people of this country and the world in terms of human suffering, reduced productivity, and medical costs. At the same time, I established a Task Force to review the field of virology and to assist our Institute in developing a strategy for improving the diagnosis, treatment, and prevention of viral infections.

The Virology Task Force, ably led by Dr. Igor Tamm of the Rockefeller University, with the assistance of 81 virologists from throughout the country, produced a six-volume scientific report for use by our staff at the National Institutes of Health as well as by investigators worldwide. This report highlighted the medical importance of virology research and called for a plan to develop antiviral drugs and new vaccines. The report also stressed the importance of viruses in basic research on life processes.

In an effort to convey to the general public some of the excitement of virology research and to describe where we are and where we need to go in our conquest of viral diseases, I also requested that this shorter, less technical report be written. For that purpose, we were fortunate in securing the services of Elaine Blume Wilson, an experienced freelance medical writer who had at one time been a member of our staff.

As you read this report, I hope you will understand more clearly the new avenues opening up in medical research. Looking ahead to the 1980's, I believe we will see a decade during which the traditional research approaches to all kinds of infection will be revolutionized. The revolution will come through a *chemical* explanation of infectious disease processes—and such knowledge must precede innovative approaches to new drugs and vaccines.

To me, one of the most remarkable aspects of virology is our ability to use viruses as tools with which to probe the secrets of the cell, and in the end, this may be the most important legacy of research that began nearly a century ago with Pasteur. Viruses, so frequently described as being *at the edge of life,* have become a key to unlock the hidden passages to the nature of life itself.

Richard M. Krause, M.D.
Director, National Institute of Allergy and Infectious Diseases

INTRODUCTION

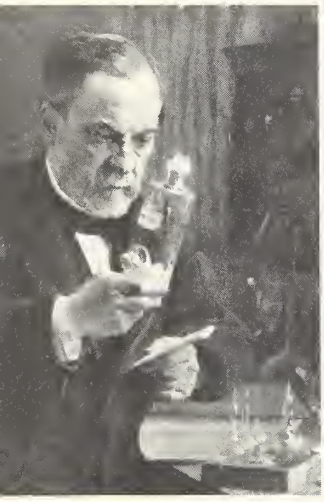
Colds, flu, rabies, smallpox, mumps. Polio, measles, herpes, and warts. A witch's incantation? No, but it might easily serve as one. It is a list of just a few of the *virus**-caused ills of man. Viruses plague humans from conception to death, from the tropics to the far north. Some are mere nuisances, causing noses to run or spots to appear. Others, such as yellow fever and influenza, can bring death on a massive scale. Most fit somewhere in between, striking many but harming few, or touching only rare individuals but with devastating results.

Long before the nature of viruses was understood, people began to fight back against the diseases these agents caused. The contest began in the Far East where, centuries ago, it became the custom to infect individuals with scabs from persons with mild cases of smallpox (variola). The ensuing infection was usually mild but resulted in permanent immunity against the then-rampant, disfiguring, and frequently fatal disease. In 1717, a similar practice was introduced into England, where it came to be known as *variolation.* It proved worthwhile and was widely adopted. Still, an individual submitting himself to the procedure could never be certain of what lay ahead. He might emerge pockmarked—or fail to survive. So when in the late 18th century an English physician, Edward Jenner, convinced the public that a benign illness known as cowpox furnished immunity against smallpox, *vaccination* (deliberate infection with cowpox) quickly became a standard and highly successful practice throughout much of the world—

Edward Jenner convinced the public that inoculation with cowpox vaccine could protect against smallpox.

*Italicized words are defined in Glossary.

Early vaccination procedures attract curious onlookers (circa 1870).



Louis Pasteur.

Martin Biejerinck.

Wendell Stanley.

in fact, one of the earliest triumphs of preventive medicine.

The next victory over a virus took place in 1885 when Louis Pasteur used a painstakingly prepared live rabies virus *vaccine* to treat a 9-year-old boy. The child, Joseph Meister, had been so severely bitten by a rabid dog that all physicians consulted agreed he was certain to contract the always fatal disease. Under Pasteur's direction, Joseph received 12 doses of increasingly *virulent* rabies virus over the course of 11 days. Pasteur became more and more anxious as the treatment continued. He dreaded the last shot and had a nightmare in which he saw Joseph in the same mad and desperate state as the luckless child from whom he had obtained the vaccine virus. But Joseph slept peacefully, ate well, and played happily. He suffered no harm from the vaccine, and he did not develop rabies. Instead, he grew up to become the gatekeeper of the Pasteur Institute in Paris, so grateful for the scientist's gift of life that when in 1940 the invading German army demanded that he open Pasteur's crypt, Meister, then 64, committed suicide rather than obey.

While Pasteur was striking his blow against rabies, whose basic cause at that time was completely unknown, he also, along with others, was developing the science of *microbiology* and thereby laying the groundwork for the discovery of viruses and the new science of *virology*. The breakthrough came in 1898 when the Dutch scientist Martinus Beijerinck showed that mosaic disease of tobacco plants was caused by an infectious agent. This agent passed through filters designed to trap bacteria and could reproduce itself only in the presence of living cells.* Beijerinck called his discovery a "virus," the Latin word for poison. A short time later, two German scientists showed that foot-and-mouth disease of cattle was caused by an agent with the same properties that distinguished Beijerinck's virus, and in the next 2 decades, scientists discovered and extensively studied human, insect, bacterial, and tumor viruses.

In 1935, an American, Wendell Stanley, prepared tobacco mosaic virus in such pure form that he was able to crystallize it, and the crystals, when dissolved in water, were still able to infect tobacco plants. This achievement generated enormous controversy. Were viruses living organisms or merely chemicals? It did not seem possible that chemicals could produce infection. On the other hand, it was inconceivable that living organisms could take the form of crystals. The answer emerged only gradually, but in the meantime, both Stanley's achievement and the controversy surrounding it inspired chemists to apply their skills to the new field. During the next decades, they studied a number of viruses in

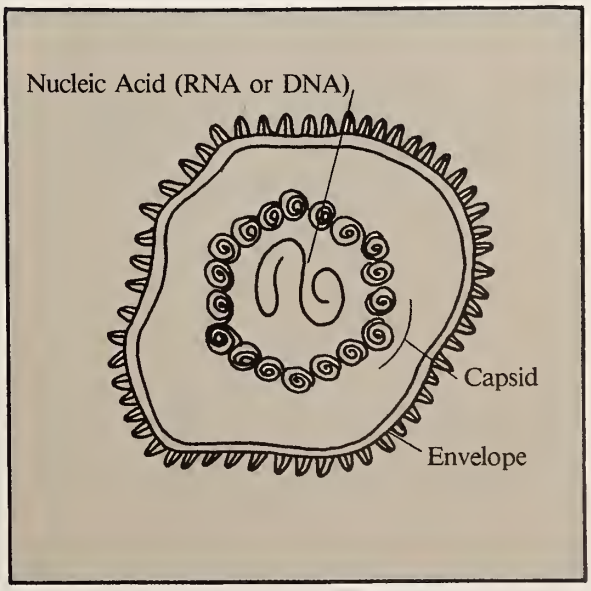
*A Russian scientist, Dimitri Ivanovski, had earlier shown that sap from leaves with mosaic disease remained infective after filtration, but he misinterpreted the significance of his findings.

detail, gaining knowledge that formed the foundation of the emerging sciences of molecular virology and viral genetics.

WHAT ARE VIRUSES?

The chemists who studied viruses* found virus particles to be minute packets of genetic (hereditary) material wrapped in protein coats or *capsids*. They also found that these *particles* were not cells and were not made up of cells. Since all known living things were composed of cells, this again raised the question of whether viruses could be considered alive.

Today, we still have no simple answer to this question, but the facts are clear enough. Outside of cells, viruses are inert—no more alive than a fragment of glass or your pet rock. But once they gain entry into cells, viruses are able to reproduce, displaying a prime characteristic of living beings. Thus, as one textbook** suggests, these agents can be viewed "both as exceptionally simple microbes and as exceptionally complex chemicals." Or we may simply choose to think of viruses as existing at the uncertain edge of life.



Schematic diagram of a simple form of virus particle.

*The term virus is used in this booklet to refer to a viral species. Individual virus units are called "particles" or "virions."

**Microbiology (2nd ed.) by Davis, et al.; Harper & Row, 1973.

The genetic material of a particular virus may be either *ribonucleic acid* (RNA) or *deoxyribonucleic acid* (DNA), but no virus contains both. (In contrast, living cells, whether bacterial, plant, or animal, always contain both DNA and RNA.) The nucleic acid forms the central core of the virus particle, and protein coat subunits (*capsomers*) surround this core like kernels of corn on a cob. Some viruses are further encased in an envelope—a hand-me-down wrap made from the membrane of the cell in which the virus particle was formed.

Viruses range in size from about 17 to about 300 *millimicrons* in diameter. For purposes of comparison, human red blood cells are about 8,000 millimicrons (8 *microns*) or 0.0003 inches in diameter. Size is one characteristic used to classify viruses. Others include type of genetic material (DNA or RNA), presence or absence of an envelope, and arrangement of the capsomers.

Relative Sizes and Shapes of Different Viruses

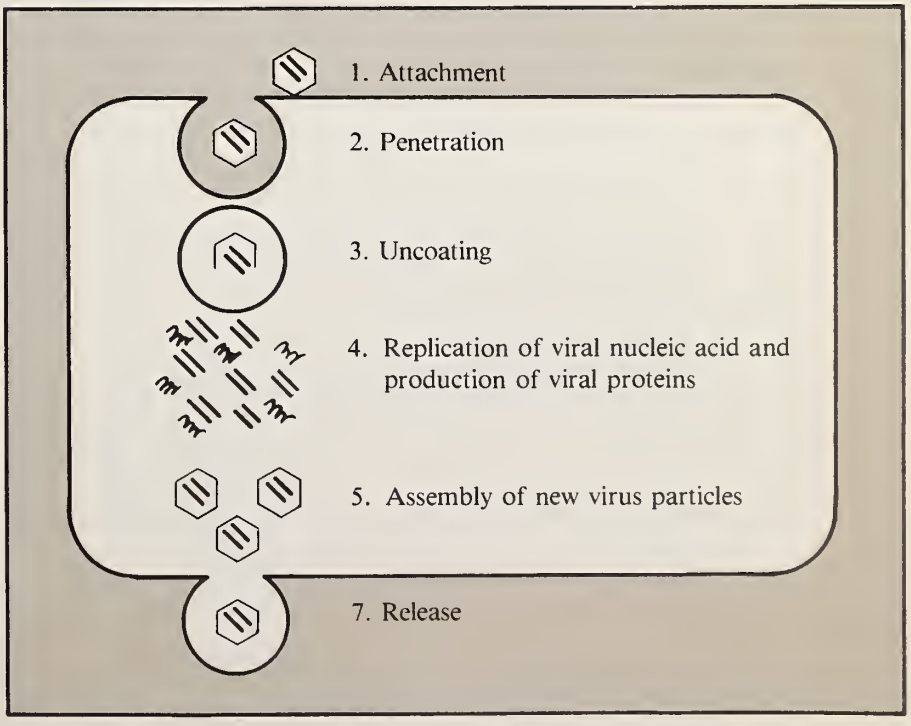
While studying viruses, scientists have found that they offer a valuable means of approaching many of the key questions of biology. Because they are so simple, and because they can be "switched on" at will by bringing them into contact with susceptible cells, the tiny agents present researchers with unique opportunities to study the most basic processes of life.

The contribution of viruses to modern biological research may not make up for the damage they have inflicted, but it certainly tends to even the score. And it seems likely that in the future viruses will also serve man directly, infecting and destroying insect pests, for example, and carrying missing genes to the cells of patients with inherited defects.

VIRUS AND HOST

Viruses are submicroscopic hijackers; they reproduce by taking over living cells and redirecting cell functions toward their own ends. For a virus particle to enter a cell, it must first attach itself to the cell surface, and it can do so only if the cell has specific receptor sites for the particular virus. Viruses thus have restricted *host* and tissue ranges. A *bacteriophage* (bacterial virus) may be able to infect only bacteria of a single species, and various human viruses specifically attack particular tissues or organs—for example, the intestines, glands, nerves in the spinal cord, or nerves in the brain.

Once the virus particle (*virion*) is inside a cell, it commandeers the cell's raw materials, energy, and machinery to make new copies of the viral genetic material and capsomers. The cell's contributions are indispensable, since the virion lacks many of the components needed for these tasks.



Simplified diagram shows how virions are produced within a cell.

As the new viral parts are formed, they are assembled into complete virions that are released either one by one, without major damage to the cell, or all at once, as the cell bursts open and dies. The newly released virions may attach to receptor sites on intact cells and begin the infection cycle anew.

The reaction of the invaded host depends upon the amount of infecting virus and its site of entry, the number and kinds of cells infected, the nature of the cell-virus interaction, and the host's state of resistance. Even within a single host species, the effect of a given virus in different individuals may range from inapparent infection to death.

VIRUSES AND SOCIETY

The average American probably experiences between two and six viral infections each year—more than 200 in a lifetime. Nationwide, these illnesses cost billions of dollars annually in medical expenses and lost productivity; in addition, they cause untold personal misery. Viral diseases of plants and animals hurt people, too, by destroying valuable crops and livestock as well as pets and ornamental shrubs. Losses suffered by farmers, ranchers, and animal breeders can be enormous. And even bacteriophages are sometimes harmful to man; diphtheria bacteria produce human disease only when they are carrying certain *phages.*

The fight against viral diseases begun by Jenner and Pasteur has continued. Scientists have applied their research findings to the development of effective vaccines against yellow fever, polio, measles, mumps, and rubella (German measles), as well as other viral diseases. These vaccines have saved the American public over $2 billion a year in addition to the immeasurable personal costs of the averted illnesses. But many other viral diseases either cannot readily be controlled by vaccines or present major obstacles to vaccine production, and in many cases, no practical alternative means of prevention or treatment now exists. Conquest of these diseases will depend upon the successful conduct of additional research.

Estimated Annual Cost of Selected Viral Diseases in the Absence of Immunization

Disease	Projected Approximate Annual Cost in 1980 ($)
Hepatitis	1,500,000,000
Influenza A	3,600,000,000
Measles	700,000,000
Poliomyelitis	3,100,000,000
Rubella	400-600,000,000

Virus Burden of Contemporary Man

Major Virus Groups	No. of Distinct Types	No. of Types That Commonly Infect Man	Usual Proportion of Individuals Infected During Lifetime
Adenovirus	32	7	90%
Herpesvirus	5	5	
Type 1			50-100%
Type 2			10-70%
Varicella (chickenpox)			100%
Cytomegalovirus			90%
EB virus			90%
Orthomyxovirus	3	3	
Influenza A,B, and C			100%
Paramyxovirus	6	6	
Parainfluenza	4	4	100% of all 4 types
Mumps			100%
Measles			100%
Respiratory Syncytial	1	1	100% by two years
Picornavirus			
Echovirus	30	30	40%
Coxsackie A	24	24	40%
Coxsackie B	5	5	40%
Rhinovirus	110	110	70% for each type
Coronavirus	3	3	50-70%
Rubella	1	1	85%
Rotavirus	2	2	100% by 2-3 years
Unclassified			
Hepatitis A	1	1	40%
Hepatitis B	1	1	10-15%
Epidemic gastroenteritis	3	3	70-100%
Total	231	206	

ACUTE VIRAL INFECTIONS

CHILDHOOD DISEASES

Our acquaintanceship with viruses begins very early in life. In fact, a number of viruses affect children far more often than adults or cause more serious disease in the young. There are even a few viruses that do most of their damage to the unborn.

Not very many years ago, almost every American child could expect to have measles, mumps, chickenpox, and rubella before he or she reached adulthood. These "childhood diseases" were a normal, predictable part of growing up. Adults were rarely affected because almost all were already immune.

The situation is very different today. Because of the development and widespread use of vaccines against measles, mumps, and rubella, most children in this country now reach adulthood without experiencing

Selected Viral Infections by Age of Major Impact

Before Birth	At Birth	Infants	Children	Adolescents & young adults	Senior citizens
	Herpes 1				
	Herpes 2	Respiratory syncytial	Rhinovirus	Herpes 2	
Cytomegalovirus		Parainfluenza	Coronavirus	Hepatitis B	
Rubella	Hepatitis B	Adenovirus	Measles	including post-infectious encephalitis	
			Rubella		
			Mumps		
		Influenza			
		Poliovirus and enterovirus			
		Infant diarrhea (rotavirus)	Hepatitis A	infectious mononucleosis	St. Louis encephalitis
			Epidemic gastroenteritis (Norwalk agent)		
			Varicella (chickenpox)		Herpes zoster (shingles)

Young boy with measles.

these illnesses. Chickenpox is the only member of the group properly immunized American children are still very likely to contract.

All of these diseases create a fair amount of discomfort. They all cause children to have fever and feel ill. In addition, measles and rubella are marked by rashes, and chickenpox by a troublesome eruption of small blisters over much of the body, while mumps attacks salivary and other glands, causing them to swell.

But the campaigns against measles, mumps, and rubella have not been inspired by the wish to spare children a few days of discomfort. Rather, they took shape because of the realization that these illnesses can have very serious consequences. About one out of every 300 to 400 youngsters recovering from mumps, for example, is left with some permanent damage to his hearing; in fact, before development and use of the vaccine, mumps was one of the leading causes of deafness in children. This infection can also cause meningitis (inflammation of the membranes covering the brain and spinal cord) or encephalitis (inflammation of the brain), which on rare occasions proves fatal.

Measles is potentially even more serious. Its complications include pneumonia, deafness, blindness, and encephalitis that sometimes results in mental retardation. Before a vaccine became available, measles caused about 400 deaths in the U.S. each year.

Chickenpox

Chickenpox (varicella) can also have serious consequences on occasion, but because of the peculiar behavior of the virus most experts oppose any plan for routine vaccination against this illness. The virus—varicella-zoster or VZ—is responsible not only for chickenpox but also for herpes zoster ("shingles"), a painful and debilitating disease that often afflicts the elderly. After an attack of chickenpox, VZ virus apparently may remain *latent* (hidden) in nerve cells for many years until lowered resistance or other circumstances cause it to become active again, producing a case of shingles. Scientists are concerned that while a live virus vaccine against VZ virus might protect against chickenpox, it might at the same time make those vaccinated more susceptible to shingles. VZ virus also belongs to a class of viruses that has been associated with cancer production in animals and humans, and for this reason even use of a killed VZ vaccine in normal children may involve an unacceptable risk.

However, in children and adults whose immune systems are below par—leukemia patients, for example—VZ infection poses a major threat, and vaccination against the virus could prove lifesaving. A VZ vaccine developed in Japan appears very promising for this purpose and is presently being tested with support from the National Institute of Allergy and Infectious Diseases (NIAID).

Rubella

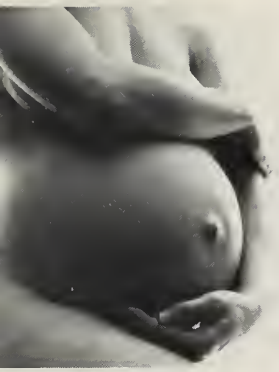
Unlike mumps, measles, and chickenpox, rubella poses little serious threat to children, but it can cause great harm to the unborn. If a woman contracts this infection early in pregnancy, she may miscarry or her infant may be stillborn; if the baby survives, it may suffer from blindness, deafness, heart defects, or mental retardation. It has been estimated that the last major rubella *epidemic*, which occurred in 1964, caused between 20,000 and 30,000 babies to be born with severe defects. Children today are given rubella vaccine much less for their own protection than for the sake of their as yet unborn brothers and sisters and for their own future children.

The mother of these twin girls had rubella early in pregnancy. The larger twin is normal. The smaller has a hearing loss, heart disease, and eye problems.

Cytomegalovirus

Although one important viral cause of birth defects—rubella—can now be prevented, another—cytomegalovirus or CMV—remains a serious problem. It is estimated that CMV is responsible for congenital defects and damage in more than 3,000 infants each year in the United States; it is the leading viral cause of developmental disability—including mental retardation—in this country today.

CMV infection is often chronic or *persistent,* and many individuals



Both rubella virus and cytomegalovirus can be serious problems for the pregnant woman.

carry the virus for long periods without showing signs of illness. As many as 15 percent of pregnant women may be infected, as are about 1 percent of newborn infants. Most of these infants will not show any ill effects, but about 10 percent will go on to develop neurologic problems such as deafness or some degree of retardation.

Scientists would like to know why some infants are harmed by prenatal CMV infection while many more are infected but not damaged. Possibly, the damaging infections are those that occur early in the pregnancy. Some researchers have suggested that CMV infection in the mother is normally suppressed during the first trimester and that failure of this suppression to occur may be the critical event leading to early fetal infection and subsequent damage. If this hypothesis is confirmed, additional research aimed at understanding the normal mechanism of suppression (which may involve the immune system, hormones, or other factors) could lead to methods for preventing damage from CMV.

Although CMV infection acquired after birth rarely causes significant illness in otherwise healthy individuals, it does pose a threat to those whose immune systems are defective or have been medically suppressed. Almost all kidney transplant recipients, for example, become infected with CMV. Although not all become ill, some patients suffer serious damage to their eyes or develop inflammation of the lungs (pneumonitis) that is often fatal. Patients receiving bone marrow transplants are also highly vulnerable to CMV infection. Scientists are now looking for ways to enhance the immunity of transplant recipients against CMV and thus reduce the chances of serious infection.

Surgeon prepares to transplant a kidney. Almost all kidney transplant recipients become infected with cytomegalovirus.

RS and Parainfluenza

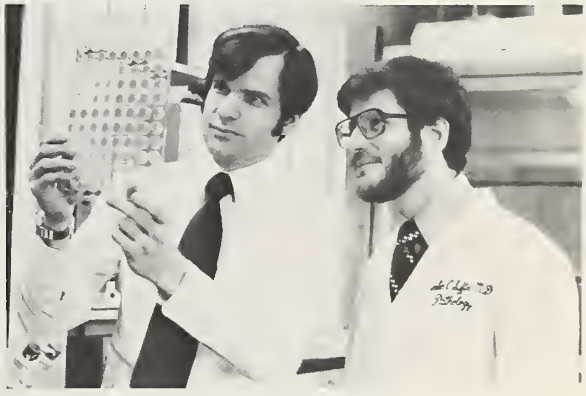
Two other strange-sounding viruses—respiratory syncytial (RS) and parainfluenza—are particular foes of the very young. Now that measles, mumps, and rubella can be prevented with vaccines, RS and parainfluenza infections rank with chickenpox as the major childhood diseases in this country. RS virus (RSV) is the most important cause of pneumonia during infancy and early childhood; its peak incidence occurs at 2 months of age. About half of all infants become infected before they are a year old and most of the rest before they are 2, but they do not develop lasting immunity. Beyond the age of 2 months, however, the infection is increasingly less likely to be serious.

Respiratory syncytial virus infects about half of all infants before their first birthday.

RSV is unique in that it is the only one of the many viruses affecting humans that is particularly damaging during the earliest months of life. Why RSV should have this property is a mystery that greatly intrigues medical scientists. Some have theorized that circulating *(serum) antibody* acquired by infants from their mothers before birth may interfere with the child's own immune response, leading to severe illness. Although this particular theory may not be correct, it is obvious that serum antibody is not always protective. For instance, infants with RS infection who are admitted to hospitals often show high levels of serum antibody. Serum antibody in response to inactivated vaccine was also associated with a paradoxical effect during RSV vaccine trials in the 1960's. Instead of being protected against RS infection, infants receiving the vaccine subsequently developed severe disease when naturally exposed to the virus.

Unlike other respiratory viruses, which usually cause epidemics once every 2 years or at irregular intervals, RSV produces sizeable epidemics

every year in large urban centers throughout the world. It attracted much notice in early 1979 when an international panel of experts, which included two NIAID scientists, identified it as the probable cause of a serious illness afflicting newborn infants in Naples, Italy. Over the course of a few months, the Naples outbreak, dubbed the "dark disease," took the lives of more than 50 infants and affected many others.



Two NIAID scientists helped identify respiratory syncytial virus as the probable cause of a 1979 epidemic in Naples, Italy.

The parainfluenza viruses are second only to RSV as causes of lower respiratory tract disease in young children, and they also frequently cause upper respiratory illness in older children and adults. The most characteristic condition these agents produce in infants and young children is croup—swelling of the larynx leading to obstructed breathing and a hoarse cough. These symptoms can be very frightening, although most children recover completely.

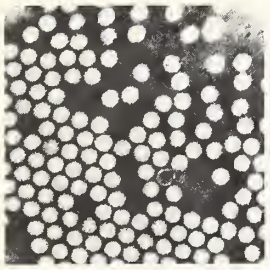
Parainfluenza viruses cause illness throughout the world. Though most children are exposed to these agents very early in life, they develop only partial immunity to them. Like RSV, parainfluenza is especially troublesome in hospitals, where it can cause serious illness in many children who have been admitted for unrelated problems.

Poliomyelitis

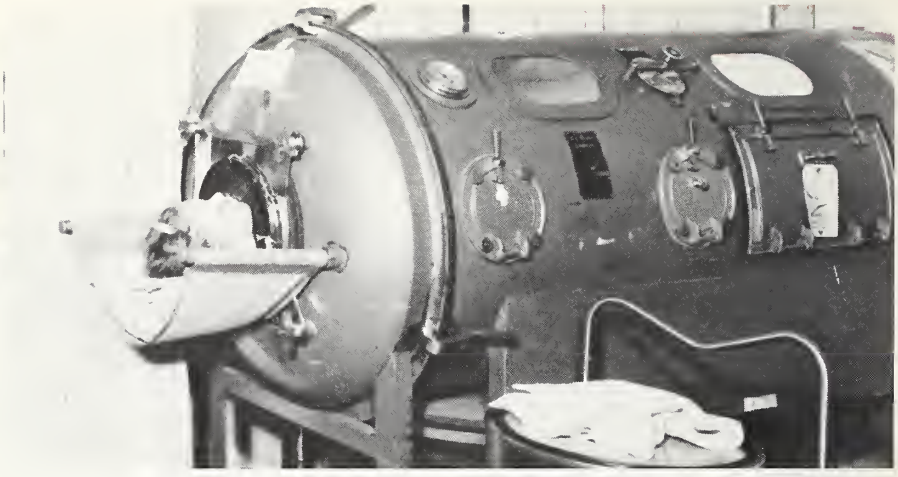
Many viruses cause disease in children. But of all these diseases, by far the most dreaded has been poliomyelitis, a scourge that can with shocking suddenness kill a young person, cripple him for life, or confine him permanently to an iron lung.*

Polio is a disease of paradoxes. Despite the terror that it inspired for many years, during most of those years its real impact was comparatively small. Yet in spite of its fearsome reputation and apparent rarity, polio was actually extremely common in the prevaccine era; most cases were simply so mild as to pass unnoticed. When it does

*respirator



Electron micrograph of a poliovirus.



A picture of a child in an iron lung was a heart-rending symbol of the tragedy of polio. Today it is used to remind parents not to neglect immunization.

make its presence known, polio is a disease of the spinal cord and brain, but the normal habitat of the virus is the human intestinal tract. And unlike the many infectious diseases that do most of their damage among poor people and in poor countries, polio becomes an increasing threat as nations develop modern habits of sanitation and hygiene—this even though the virus is spread by fecal contamination.

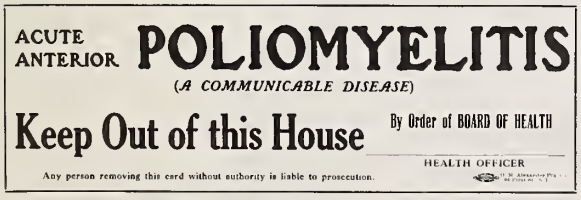
Scientists studying polio have explained these paradoxes. They have found that, although almost everyone in a poor country develops one or more poliovirus infections early in life, the virus usually multiplies only within the intestines and nearby lymph nodes and does not cause illness. Only rarely does poliovirus become established in the nervous system, causing paralytic disease, but the older the affected individual, the more likely this is to occur. That is why polio is a relatively minor problem in countries where, because of poor sanitation, almost everyone is infected soon after birth but becomes a more serious threat in areas where many persons are not exposed in their earliest years. From 1900 until 1930, up to 90 percent of polio victims were younger than 5 years old, with the majority under 2, and the disease was truly "infantile paralysis." But as sanitation improved in many countries, the peak incidence of paralysis tended to occur in the 5-to 14-year-old age group.

Fortunately, polio is now a preventable disease. Emotional reactions to those left crippled by polio, including many children and an extremely popular president, produced tremendous public support for the March of Dimes, a fund-raising campaign founded by President Franklin Delano Roosevelt in the early 1940's. Money cannot always

buy research success, but in this case it did. The intensive effort funded by the March of Dimes led to development of the inactivated (killed) Salk vaccine introduced nationwide in 1955. A few years later the live Sabin vaccine became available. After introduction of the Salk vaccine, the number of cases of paralytic polio in the United States fell from about 15,000 per year to about 4,000; with widespread use of the Sabin vaccine, the number dropped below 100—almost all among unvaccinated individuals.

Both of these vaccines were made possible by the success of John Enders and his associates at Harvard Medical School in growing polioviruses in tissue culture. In the course of the research that led to the vaccines, the polioviruses (there are three slightly different types) were studied so thoroughly that the work became a model for the investigation of other viruses.

But, distressingly, though American parents of the 1940's would have done almost anything to protect their children from polio, many today neglect to give their children this protection, now readily available at little or no cost. The false belief that polio, as well as measles, mumps, and rubella, no longer pose threats has led to complacency, with the result that many children are not being fully immunized against these preventable diseases. In 1978, more than 26,000 cases of measles were reported in this country, and in some areas large numbers of children remain susceptible to polio, mumps, and rubella as well. There is a real danger that new epidemics of these diseases could occur at any time.



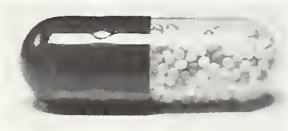
Every family dreaded seeing this sign on the door.

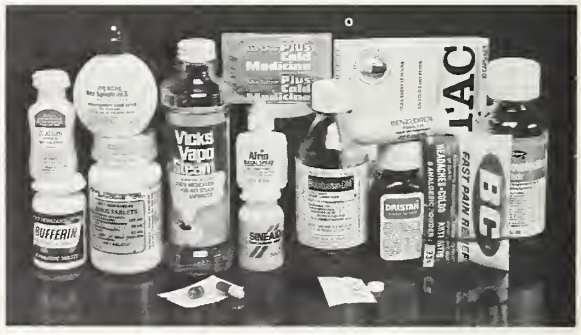
Physical therapy was the principal treatment of polio during convalescence. Although the greatest return of muscle function occurred in the first six months, improvement could continue for two years.

RUNNY NOSES AND STOMACH ACHES

"It's just a virus." Most of us have grown accustomed to hearing that phrase when we are suffering from such symptoms as sore throat, fever, cough, or diarrhea. Often we accept the explanation but wonder, in some frustration, why our doctor doesn't name the virus or offer us any specific remedy.

Well, the doctor is frustrated, too. He must deal with the fact that a particular illness may be produced by any one of many possible viruses—and that many viruses can give rise to more than one illness. He also knows that using lab tests to pinpoint the exact cause of a viral infection is time-consuming, expensive, and often unrewarding. For, besides the fact that the patient is usually restored to health by the time a laboratory diagnosis can be made, the near total lack of effective treatments for viral infections means that even rapid diagnosis would be of little use to the individual.





One can treat the symptoms, but there is still no cure for the common cold.

Colds

A survey conducted between 1971 and 1974 produced the estimate that, on the average, each 100 Americans experienced between 92 and 121 acute respiratory illnesses per year. Some epidemiologic studies estimate that each American has as many as six such infections each year. Which viruses cause these infections? Why do we get so many of them? And why don't we become immune?

A number of groups of viruses, each containing several to many members, can cause the common cold or related illnesses. The human coronavirus group, for example, which contains at least three distinct viruses, is responsible for many of the colds occurring in adults during the late fall, winter, and early spring. Colds caused by rhinoviruses, on the other hand, occur throughout the year but peak in the fall and spring. More than 90 distinct rhinoviruses have been recognized, and it is probable that many more remain to be identified.

The rhinoviruses belong to an "umbrella group" of small RNA-containing viruses known as the picornaviruses ("pico" implying small,

plus "RNA"). The other members of this group normally inhabit the human intestinal tract and are known as enteroviruses, a category that includes the polioviruses, the echoviruses, and the coxsackieviruses.

Most enterovirus infections pass unnoticed or produce mild symptoms, such as those of a cold. But echoviruses and coxsackieviruses can, like polioviruses, occasionally cause distressing illness.

Respiratory Illnesses and Predominant Causative Viruses

Respiratory Tract Illness	Important Etiologic Agents
Upper Tract Illness	
Common Cold	
Without fever	Rhinovirus, parainfluenza, adenovirus, coronavirus, respiratory syncytial, coxsackie A21
With fever	Rhinovirus, parainfluenza, adenovirus, coronavirus, respiratory syncytial, influenza A and B, coxsackie A21
Sore Throat	
Without white spots	Adenovirus types 1,2,3,4,5 and 7; coxsackie A2,4,5,6,8,10 and B2,3,5; herpes hominis type 1
With white spots	Adenovirus types 1,2,3,4,5 and 7
With blisters	Coxsackie A2,4,5,6,8
Ear Infection	Adenovirus types 1,2,3,5 and 7; parainfluenza; respiratory syncytial
Conjunctivitis	Adenovirus types 3,7,8 and 19; enterovirus 70
Lower Tract Illness	
Laryngitis/Croup	Parainfluenza types 1,2 and 3; influenza A and B
Tracheobronchitis	Parainfluenza types 1,2 and 3; influenza A and B; adenovirus types 1,2,3,4,5 and 7
Bronchiolitis	Respiratory syncytial; parainfluenza types 1 and 3
Pneumonia	Respiratory syncytial; parainfluenza types 1,2 and 3; adenovirus types 1,2,3,5 and 7; influenza A and B

Symptoms may include blistering of the mouth and throat, meningitis, encephalitis, gripping chest pain, rashes, and inflammation of the heart. There is also evidence that coxsackievirus infection of the unborn can cause congenital heart defects. Fortunately, most patients with echovirus or coxsackievirus infections recover quickly and completely.

Another viral group responsible for colds and other respiratory infections is the adenoviruses, of which 31 types are known to infect humans. In addition to producing colds, adenoviruses sometimes can cause more severe respiratory illness, with sore throat, cough, fever, and even pneumonia. In addition, certain adenoviruses produce inflammation of the eye or its lining.

Adenoviruses are a special problem in the military, where certain types used to cause yearly epidemics of acute respiratory disease, especially among recruits, interfering with training programs. Since development of a live adenovirus vaccine by Robert Chanock and his co-workers at NIAID and the routine use by the armed services of a related vaccine, respiratory illness due to adenoviruses is no longer a serious problem in the military.

A number of other viruses, including mumps, respiratory syncytial, and parainfluenza, also cause colds at times, though they are better known for the more distinctive illnesses they often produce.

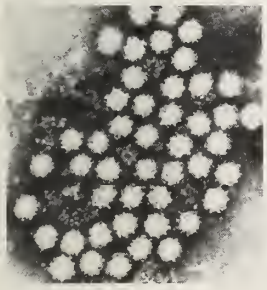
Because so many different viruses can cause colds, development of immunity to one or even several respiratory viruses does not furnish much protection. Although susceptibility does tend to decrease with age because of increased immunity as well as other factors, there are always cold-producing viruses going around to which any given individual has not yet been exposed. That is why we get so many colds and why we don't seem to become immune.

Any discussion of colds must confront the strongly held belief, expressed even in the name, that if you get chilled or wet a cold is likely to follow. Scientists have tried and failed to prove this. Their findings may make some parents more relaxed about permitting children to dress as they please and play where they wish in the winter, but others will no doubt continue to heed folk wisdom in preference to that of science.

Diarrhea

In the United States, diarrheal disease caused by viruses ("nonbacterial gastroenteritis" or "intestinal flu") is very common, especially among infants and young children; in poorer countries, it is frequently fatal as well. But in spite of the magnitude of this problem and the strides made in other areas of virology, the mircrobes responsible for most episodes of nonbacterial diarrheal disease remained unknown until 1972. In that year, NIAID scientist Albert Z. Kapikian used the technique of *immune*

A special technique using the electron microscope enabled Dr. Kapikian to identify a virus causing gastroenteritis.

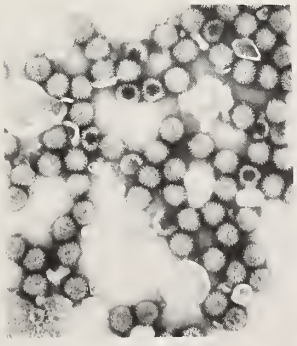


Electron micrograph of Norwalk agent.

electron microscopy to identify the agent responsible for an outbreak of gastroenteritis at an elementary school in Norwalk, Ohio. Virus particles resembling the Norwalk agent have since been found in stool samples from a number of other family-wide or community-wide outbreaks of diarrheal disease.

There is another common form of diarrheal disease that is different from the type associated with the Norwalk agent. This second form occurs mostly in infants and young children, is frequently severe enough to require hospitalization, and often does not cause illness in other family members. In 1973, scientists reported seeing, through the *electron microscope*, wheel-shaped virus particles in stool samples from young Australian patients with this type of gastroenteritis. Other investigators later found similar particles in stool samples from almost half of 143 infants and children admitted to Children's Hospital in Washington, D.C., with diarrheal illness. Because of their wheel-like appearance, these agents were dubbed "rotaviruses" ("rota" meaning "wheel" in Latin).

Scientists have not yet been able to grow any of the Norwalk group of agents in such *in vitro* systems as tissue cultures or eggs; but investigators at NIAID have recently succeeded in getting one of the two types of human rotaviruses to grow well in tissue culture. Eventually, researchers hope to grow all of these agents efficiently in the laboratory as a first step toward devising means for their control.



Electron micrograph of rotavirus.

NIAID scientist performs immunofluorescence test to detect human rotavirus.

FLU, JAUNDICE, AND POX

Flu

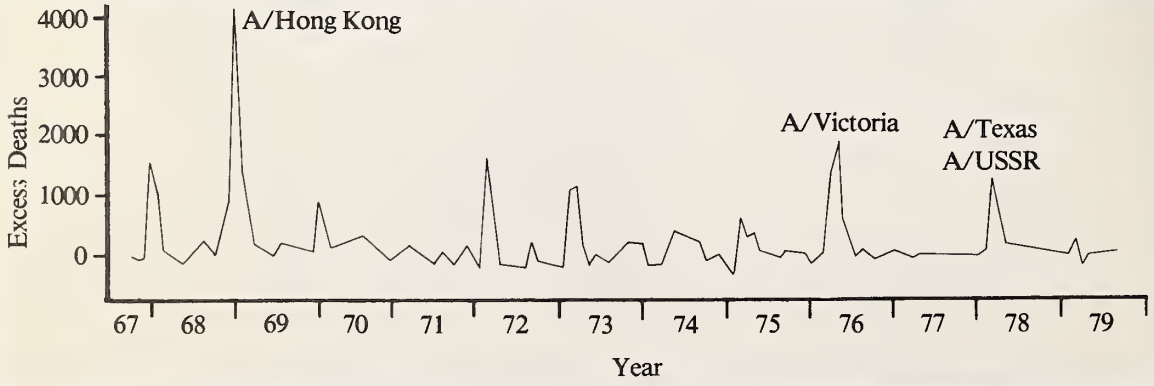
Although many viruses we encounter fortunately cause only relatively mild illness, some viral diseases are serious as well as common. A prime example is influenza ("flu"), which has periodically swept over the world leaving more or less devastation in its wake. The worst of these pandemics (worldwide epidemics) occurred in 1918-19, killing some 20 million persons and afflicting a large fraction of the world's population. Since that time, flu has been less ravaging in its effects, but it still remains a major problem. In epidemic years it causes widespread illness and many deaths, particularly among the elderly and the chronically ill. Pregnant women are also especially susceptible. Although flu virus itself sometimes causes fatal pneumonia, most flu-related deaths result from bacterial invasion of virus-weakened lungs.

Pneumonia-influenza ward at Base Hospital #82 in Toul, France, 1918.

There are three types of flu virus—A, B, and C—with type A the most prevalent and most destructive. The protein coat of type A flu virus (and, to a lesser extent, of types B and C) has the remarkable property of changing over time so that individuals who develop immunity against the virus in one year are likely to find themselves susceptible to it again some years later. The change in the virus may occur slowly ("antigenic drift") or abruptly ("antigenic shift"), though only a few instances of the latter are known.

Many experts believe that major flu epidemics occur when the virus has changed enough—whether by antigenic drift or antigenic shift—so that a large fraction of the population is again vulnerable. Of course, even if the virus does not change greatly over the course of a number of years, the susceptibility of the population will increase as immune individuals die and are replaced by others who have never had flu. Eventually, a new epidemic will occur.

Excess Deaths From Pneumonia/Influenza (1968-1979) Related to Influenza A Epidemics

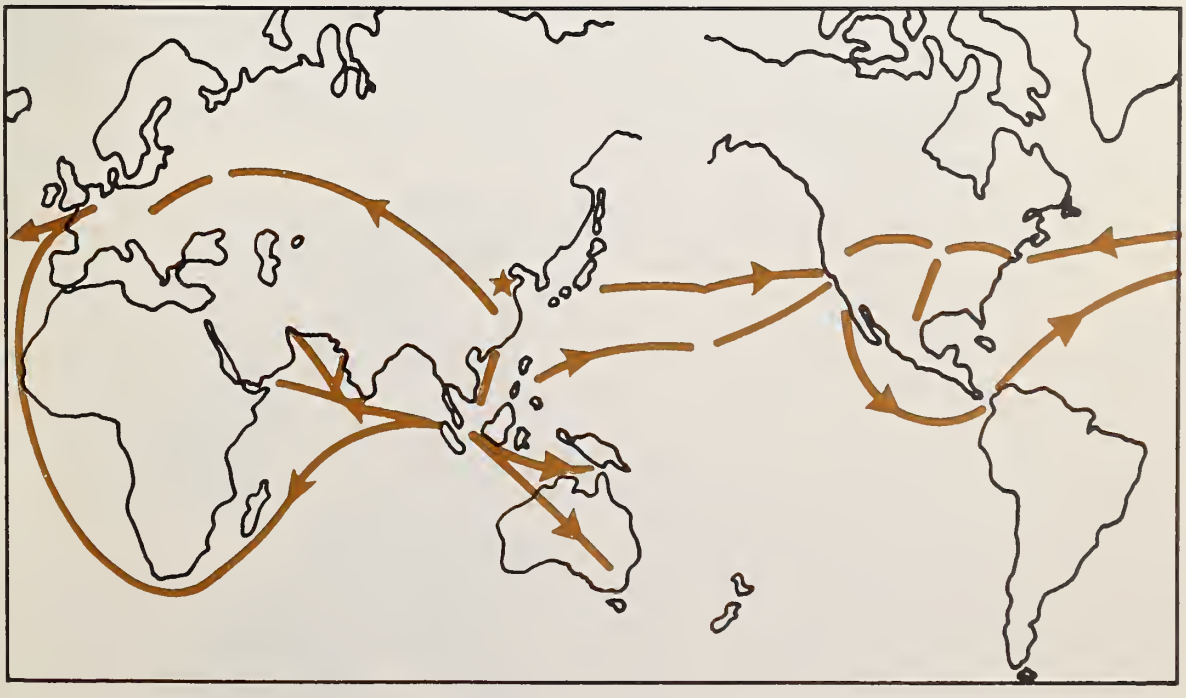


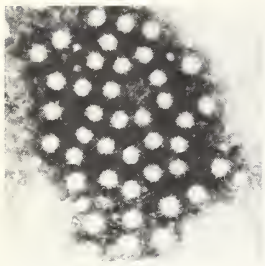
Flu virus grown in fertilized eggs is harvested for use in vaccine development.

The changeable nature of flu viruses naturally increases the difficulties involved in fending off the disease with vaccines. A vaccine that is effective in one year may be much less effective the next because different strains are more prevalent. This not only means that those who have had vaccine one year may need to be "shot" again the following year, but also that an entirely new vaccine may need to be developed and manufactured. It is both time-consuming and expensive to do this, and because of the wildfire manner in which flu often spreads, an epidemic may well have peaked and passed by the time a new vaccine can be produced and distributed.

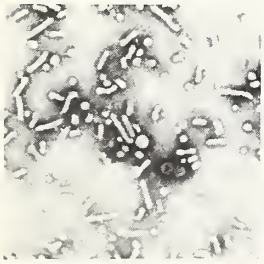
But flu not only poses a threat in itself; on rare occasions it triggers another illness known as Reye's syndrome, a severe form of encephalitis coupled with liver disease. The cause of this ailment is not understood, but it generally strikes children in the wake of a virus infection, especially flu or chickenpox. A variety of treatments, including exchange transfusion (complete replacement of the patient's blood) have been used to combat Reye's syndrome. But although these techniques work well for some patients, they fail to help others, and the fatality rate remains high.

Map showing how Asian influenza spread worldwide from its probable origin in central China in 1957.





Electron micrograph of hepatitis A virus.



Electron micrograph of hepatitis B virus.

Hepatitis

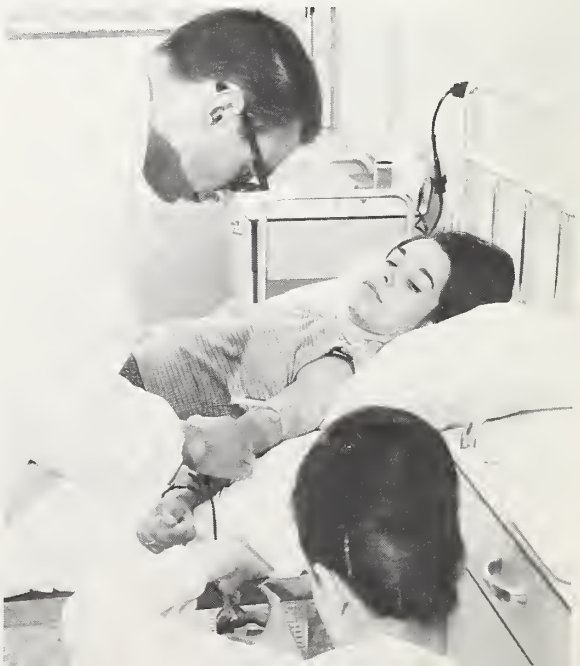
Another grand-scale viral threat is hepatitis (inflammation of the liver), commonly called jaundice because of the characteristic yellowing of the skin that occurs. It is estimated that more than 500,000 cases of this disease occur each year in the United States alone, causing much disability and more than 1,000 deaths. Worldwide, viral hepatitis takes an enormous toll.

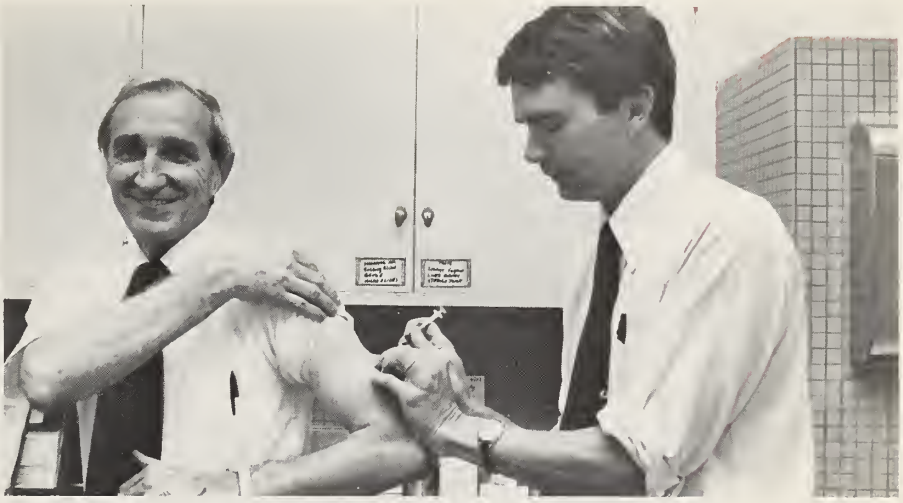
The term "viral hepatitis" refers to at least three different types of the disease: type A, type B, and type non-A, non-B. Type A, long known as "infectious hepatitis," usually spreads by the so-called "fecal-oral route" and is the type involved in almost all hepatitis epidemics associated with contaminated food, water, or shellfish. Type A also accounts for most rapidly progressive institutional epidemics as well as for many apparently isolated cases.

Type B was formerly known as serum hepatitis because doctors believed that it could be transmitted only via direct inoculation of the virus, as in transfused blood or serum or on improperly sterilized hypodermic syringe needles. Hepatitis B usually is transmitted in these ways, but it is now known that it can be spread by other means as well.

Recently, blood testing of patients with hepatitis seen at a large hospital showed that about half had type B and another quarter had type A, but the remaining fourth had neither. Their form of hepatitis has, for the time being, been labeled simply "non-A, non-B," since it is unclear just how many viruses may be involved. Scientists now have evidence of at least two separate viruses. The pattern of transmission resembles that of type B: for example, non-A, non-B often follows blood transfusions.

Use of more blood from volunteer blood donors and less from paid donors has decreased the risk of hepatitis from blood transfusions.





Experimental hepatitis B vaccine is given to volunteer NIAID scientist.

Both type A and type B hepatitis infect a majority of the population in developing countries and a large fraction of the populace in wealthier countries as well. Most of these infections are inapparent or mild, but when infected individuals become ill they may remain disabled for weeks or months, especially with hepatitis B. Mortality with hepatitis A is less than one percent, but with type B it is somewhat greater, and it may reach up to 20 percent among the elderly. Some patients suffering from hepatitis B rapidly develop acute liver failure, and about three quarters of this group die. Also, as many as one out of ten hepatitis B patients develops mild or severe chronic hepatitis, which in certain cases may lead to cirrhosis or, possibly, liver cancer. Although less is known about non-A, non-B infections, whose existence has only been known for a few years, it is clear that they account for a significant proportion of hepatitis cases in the United States, quite possibly including many that produce chronic liver damage.

Individuals infected with type B or type non-A, non-B hepatitis may continue to carry virus in their blood for months or years while appearing perfectly healthy. These *carriers* are the source of the contaminated blood and blood products that lead to post-transfusion hepatitis.

The fact that transfusions carry with them a substantial risk of hepatitis has presented a major challenge to medical researchers. In recent years, they have succeeded in developing a sensitive test for hepatitis B virus, and the widespread adoption of this test by blood banks has noticeably reduced the incidence of post-transfusion hepatitis. Use of more blood from volunteers and less from paid donors has also decreased the risk since volunteer donors are far less likely to be

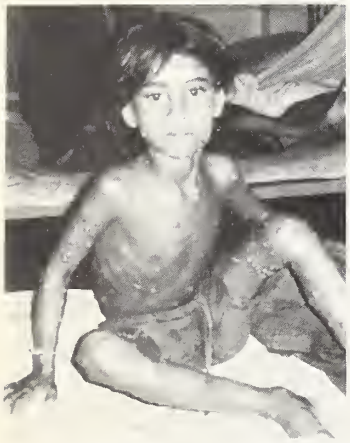
carriers. Unfortunately, there is no way as yet to screen blood for the presence of non-A, non-B viruses, so as type B post-transfusion hepatitis has come under greater control, non-A, non-B infections have become relatively more important; currently, approximately 8 to 10 percent of patients receiving multiple blood transfusions develop post-transfusion hepatitis, and about 90 percent of these cases are type non-A, non-B.

Although there is no specific treatment for any form of viral hepatitis once it has become established, *gamma globulin*—a fraction of blood that contains antibodies—can prevent or ameliorate hepatitis A infection if given shortly after exposure to the virus. Ordinary gamma globulin is not generally effective in preventing hepatitis B, but a special preparation known as hepatitis B immune globulin is now recommended for short-term protection of individuals who have been exposed to the virus. Also, both interferon and the antiviral chemical known as ara-A have recently been found effective in either eliminating hepatitis B virus from the blood of many otherwise normal carriers or at least in reducing the amount of virus sufficiently so that serum from these individuals is no longer infectious. Elimination of the carrier state by these methods can help limit spread of hepatitis B.

Scientists have recently succeeded in growing hepatitis A virus *in vitro* but have not yet done so with hepatitis B virus or any non-A, non-B virus. By growing the viruses, researchers will be able to learn more about them and move closer to full-scale production of vaccines.

Smallpox

Historically, no viral disease has been more prevalent and destructive than smallpox. In addition to spreading like wildfire and causing many deaths, this illness has the striking property of leaving many of its victims disfigured by pitted scars called pockmarks.



One of the last patients with smallpox.

Because of the enormous impact and distinctive character of smallpox, the records of its ravages are unusually complete. These records show repeated severe epidemics occurring from earliest times. By 1800, the infection was so prevalent in Europe and the British Isles, that according to one source, every tenth person was killed, crippled, or disfigured by it, and "no man dared count his children as his own until after they had had the disease."

Remarkably, this greatest of viral scourges was not only the first to come under some measure of control (through vaccination), but it is also the first infectious disease to have been totally eliminated. An eradication program started by the World Health Organization (WHO) in 1958 now appears to have been a complete success; except for accidental laboratory infections, no cases are known to have occurred since October 1977.

BUGS AND BITES

While many human viruses spread by person-to-person contact or by fecal contamination of food and water, a number of others—the *arthropod*-borne viruses or arboviruses—are transmitted by ticks or by mosquitoes or other bloodsucking insects. These viruses produce a variety of illnesses, ranging from minor feverish episodes to terrifying tropical plagues. Among the arbovirus infections that are presently or potentially important in the United States are Colorado tick fever, several forms of encephalitis, dengue, and yellow fever.

Arboviruses are transmitted in cycles that involve a host animal or bird and an insect or tick *vector*. During at least some of the time that it is infected, an arbovirus' principal host will have significant amounts of virus in its blood. When the vector feeds on the host it also picks up virus that multiplies within the vector, travels to its salivary glands, and is deposited in the blood of the next creature it feeds upon.

Sometimes a vector will infect an animal that does not develop sufficient *viremia* (virus in the blood) to permit further spread of the virus. The animal is an *incidental* or *dead-end host* for that virus. With the exception of the agents of yellow fever, dengue, and sandfly fever, all the arboviruses to which man is susceptible involve him only as an incidental host.

After multiplying in their hosts' bloodstreams, arboviruses may attack particular organs or tissues, leading to one of the following disease patterns: mild illness with fever; a more serious infection with jaundice and other signs of liver damage; central nervous system involvement, showing up as encephalitis or meningitis; or "hemorrhagic fever," marked by skin rashes and bleeding from mucous membranes and internal organs. Arboviruses also cause many inapparent infections that are only detected after the fact by epidemiologic studies.

Colorado Tick Fever

In most years, this tick-borne disease is the most commonly reported arboviral infection in this country; 170 cases were reported in 1978, and the actual number may well have been 10 times greater.

Ticks transmit diseases to man.

The illness is marked by the sudden onset of fever, chills, headache, and severe pain behind the eyes and in the muscles of the back and legs, followed by loss of appetite and, often, nausea. Symptoms continue for about 2 days, then disappear for a similar period of time, only to recur and persist for a few days more. Serious complications—most often taking the form of encephalitis or hemorrhage—are rare, and they occur almost exclusively in children. After a patient recovers, however, the virus may persist for months in red blood cells and can be transmitted by transfusions. Even mild infections are followed by lasting, probably lifelong, immunity.

Dermacentor andersoni, the tick that transmits Colorado tick fever, is found in the Rocky Mountain region of the United States, and the disease occurs in the same area. The natural cycle of the virus involves squirrels, chipmunks, and other small rodents, with man serving merely as an incidental host. Humans can prevent infection by avoiding tick-infested areas or by wearing protective clothing and using tick repellants.

Mouth parts of a tick greatly enlarged.

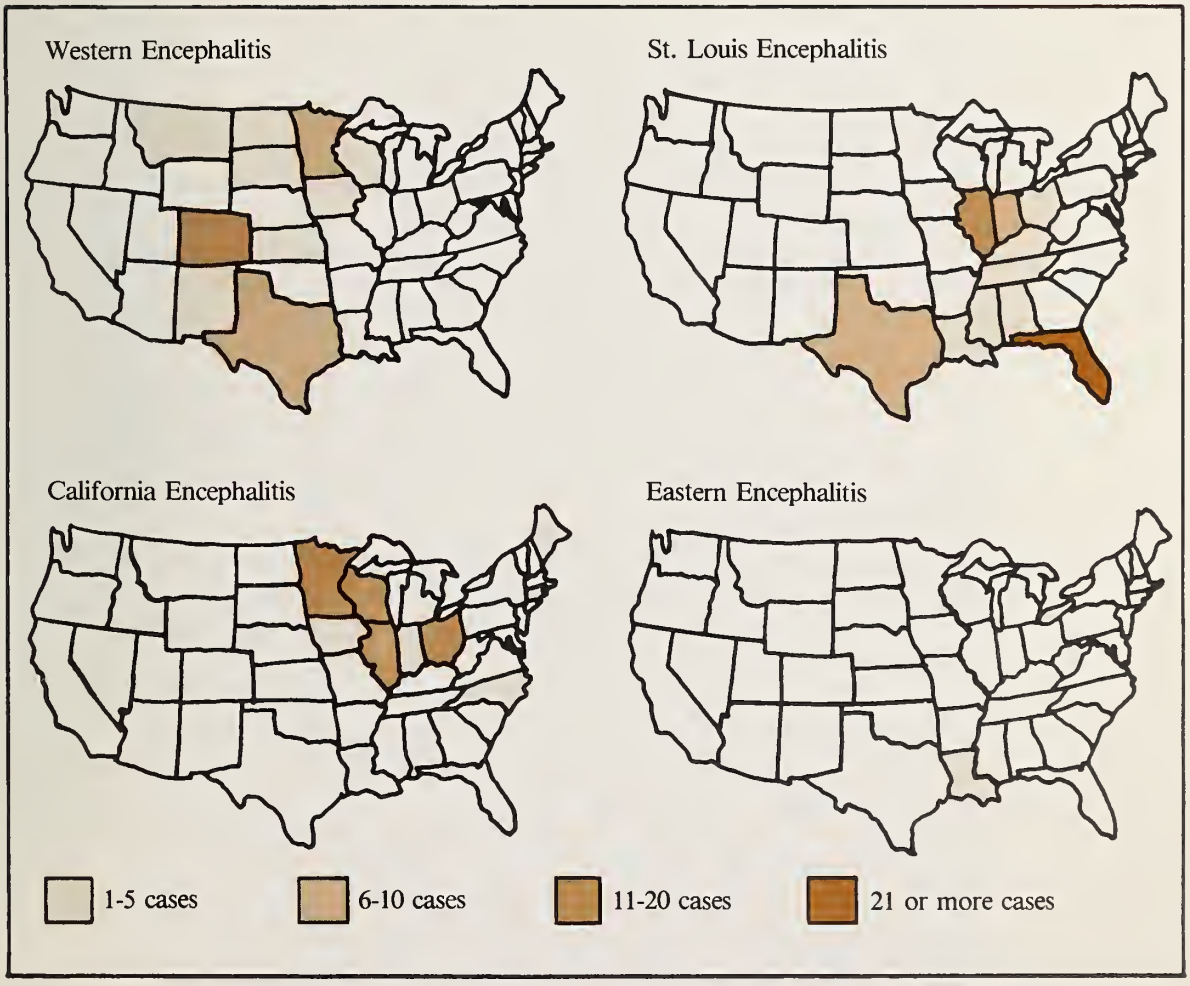
A piece of flannel is dragged across a field to collect ticks for early laboratory studies.

Encephalitis

Several varieties of mosquito-borne viral encephalitis occur in the United States. Of these, St. Louis encephalitis (SLE) poses the biggest threat because it is relatively common and often causes serious illness. In 1975, there were 1,815 recognized cases of SLE, the largest outbreak of mosquito-borne encephalitis in this Nation's history. The disease occurs most often and is most severe in older persons. Its geographic distribution includes the Pacific Coast, the Plains States, Florida, Texas, New Jersey, and Pennsylvania. During the 1975 outbreak, for the first time, SLE spread as far north as Ontario, Canada.

SLE virus, which is closely related to the viruses of yellow fever and dengue, is transmitted by various *Culex* mosquitoes, and its natural cycles involve these insects and wild birds. Humans are only incidental hosts; they are not part of any SLE virus cycle or chain of infection.

Western, eastern, and Venezuelan equine encephalitis (WEE, EEE, and VEE, respectively), caused by three closely related viruses, are other



Distribution of arthropod-borne encephalitis in the United States in 1977, by state.

mosquito-borne forms of encephalitis that threaten humans in the United States. EEE occurs in small outbreaks in the East and South; it causes many inapparent infections, but there is a high fatality rate in obvious cases. WEE outbreaks, in the western United States and Canada, are much larger, involving as many as 3,000 individuals but with a lower fatality rate and an even higher ratio of inapparent to apparent cases. VEE virus is present in the Florida Everglades and the Southwest, as well as in Mexico, but it has only rarely caused human infections in this country. All of these viruses are also found in Central and South America as well as in other locales outside the United States.

Despite the word "equine" in their names, the main vertebrate hosts

for WEE and EEE are birds; horses (and rodents) are important hosts only for VEE. As with SLE, human infection with any of the three viruses is accidental and does not help to maintain the virus in nature.

A person bitten by a mosquito infected with one of these viruses may become immune without ever showing signs of disease or may develop a generalized illness with fever. Of those who become ill, a few go on to develop symptoms of encephalitis. This is more likely to happen with WEE or EEE; VEE usually does not cause encephalitis in humans. When encephalitis does occur, there is often permanent brain damage which may take one of several forms, including emotional instability, mental retardation, or paralysis.

Efforts to control these diseases include anti-mosquito campaigns and, in the case of VEE, vaccination of horses. The cost of these efforts runs into the millions annually in the United States alone. Fortunately, infection with one of the encephalitis viruses confers lasting, solid immunity against that virus.

In recent years, another important cause of mosquito-borne encephalitis in this country (responsible for between 45 and 90 cases in most years) has been California encephalitis (CE) virus. CE infections have occurred in all regions of the United States as well as in many other parts of the world. Although most patients recover completely, some are left with learning problems or other difficulties, and a few die. The related La Crosse (LAC) virus causes milder disease and affects children and young adults almost exclusively.

CE virus has been found in *Aedes* and *Culex* mosquitoes, but it is not certain whether either of these is the mosquito chiefly responsible for the virus's transmission. LAC virus is carried by forest mosquitoes and typically infects campers, foresters, and persons living in rural areas.

In California, mosquito control has effectively limited spread of SLE

Vaccination of horse against Venezuelan equine encephalitis.

and WEE, but increasing resistance of the mosquitoes to insecticides may make such control impossible in the future unless new biological or other methods of insect eradication are developed. Research along these lines is essential for the ultimate control of arboviral infections, and other kinds of research are needed as well. Many questions remain, for example, about which insects can serve as vectors for particular viruses, which animals can serve as hosts, and how the viruses survive the winter. Answers to these questions may be instrumental in the development of effective means of encephalitis control. Public health officials would also like to have simpler and less expensive ways of predicting SLE epidemics than the present approach of annually surveying mosquitoes and birds for signs of infection.

Research on vaccines offers real promise for the control of certain encephalitis viruses. An experimental VEE vaccine has been tested and found effective in humans; it is already being used for vaccination of laboratory workers. An SLE vaccine that produced long-lasting immunity would be a boon to vulnerable individuals, such as elderly persons in high-risk areas. Development of such a vaccine is likely to depend on basic research in arboviral genetics as well as applied research directed toward producing vaccine virus strains.

Dengue

Dengue and yellow fever have not occurred recently in the United States because of modern sanitation and control of the vector mosquito, *Aedes aegypti.* In 1968, however, the U.S. stopped its campaign against *A. aegypti,* and the mosquito is again abundant in such Southern cities as New Orleans, Miami, and Houston. Should dengue or yellow fever virus be introduced into these areas, outbreaks and even epidemics could occur.

Most cases of dengue (sometimes called "breakbone fever") are caused by true dengue viruses, but several other arboviruses cause virtually identical symptoms. Frequently, dengue takes the form of a mild illness with fever, but in more serious cases there is also headache, backache, and pains in muscles, joints, and behind the eyes—all very severe—as well as blood changes and a skin rash. Convalescence is slow, and the recovering patient may be incapacitated for several weeks. In some outbreaks in Oriental populations, many victims show bleeding tendencies, and there are numerous fatalities, especially among children. This form of the disease is known as dengue hemorrhagic fever.

During the 19th century, dengue was rife throughout tropical and subtropical regions of the world. Today the disease is still *endemic* in large areas of the tropics, and since 1920, epidemics have occurred in the United States, Australia, Greece, and Japan.

Vaccines against dengue would be extremely useful, but this approach to protection is complicated by the fact that there are least four different types of true dengue virus in addition to the other viruses that cause dengue-like disease. In the absence of vaccines, mosquito eradication is the only practicable control measure.

Yellow Fever

Elimination of mosquitoes—specifically *A. aegypti*—is now recognized as an important control measure for yellow fever as well as denque, but it took many years and a risk-laden research effort before the role of mosquitoes in spreading yellow fever was understood.

Like many arbovirus infections, yellow fever may be inapparent, mild, or severe. Most attacks pass unnoticed or take the form of an illness with headache and low fever lasting less than a week. Severe cases, though, have two phases. The first lasts about three days and is marked by high fever, headache and other pains, dizziness, nausea, and vomiting. After a brief lull the patient's temperature again rises while his pulse falls, and signs of heart, kidney, and liver involvement, including some jaundice, develop. There is abnormal bleeding, including stomach hemorrhage resulting in black vomit. The victim may lapse into a coma or become wildly delirious, and death may follow in either case. About half of those who develop severe yellow fever die, but patients who survive recover completely, and even a mild case usually confers lifelong immunity.

A. aegypti, the mosquito that transmits yellow fever in cities, is thought to have been imported into the New World from Africa and was responsible for major epidemics in the Americas from the 17th to the 19th centuries. During this period yellow fever was one of the great plagues of the world, decimating populations and leading the French to abandon work on the Panama Canal. Nor was the disease purely tropical; in the 19th century an epidemic in the Mississippi Valley caused 13,000 deaths,and other epidemics occurred as far north as Boston.

Major William C. Gorgas eradicated yellow fever from Panama, enabling work on the Canal to be completed.

The magnitude of yellow fever epidemics and the terrible symptoms of the disease were enough to incite terror in threatened populations. This terror was intensified by the fever's mysterious pattern of spread. Even extensive contact with a patient did not seem to increase the risk of illness, yet the disease was clearly communicable in some fashion and even tended to travel locally from one house to the next.

Major Walter Reed.

During the Spanish-American War in Cuba (1898), yellow fever had a disastrous impact on American troops, leading to the establishment in 1900 of the U.S. Army Yellow Fever Commission, headed by Army doctor Major Walter Reed. Building on the observations of a Cuban physician, the Commission used human volunteers to demonstrate that mosquitoes transmit yellow fever. Also, by showing that the infectious agent was filterable, the Commission for the first time established a virus as the cause of a human disease.

A campaign against *A. aegypti* was promptly launched under the direction of U.S. Army Major William C. Gorgas, and it met with great success. Yellow fever was eliminated from Havana and other large centers in the Americas. Gorgas also eradicated both yellow fever and malaria from Panama, enabling work on the Canal to resume. In 1928, however, a yellow fever epidemic occurred in Rio de Janeiro, leading to the discovery that the disease is maintained in nature by a woodland or jungle cycle involving monkeys and forest mosquitoes.

Major William C. Gorgas.

Today yellow fever remains endemic in central Africa, Central America, northern South America, and the Caribbean Islands. Though the disease has not so far moved into India or Malaysia, *A. aegypti* is abundant in those areas, and populations there are potentially vulnerable. As already mentioned, the southern United States also remains at risk. Unfortunately, there is no possible way of eliminating yellow fever from the vast jungles of Africa and South America, so constant vigilance is needed to avoid its spread into urban areas.

Although it appears that yellow fever cannot be entirely eliminated, individuals at risk can now be protected. In the mid-1930's, two different live *attenuated* (weakened) yellow fever virus vaccines were introduced: the 17D vaccine developed in the New York City laboratory of South African-born bacteriologist Max Theiler, and the so-called French strain, also made possible by Theiler's fundamental work. The first virus vaccines developed since Pasteur's rabies vaccine in 1885, they saved vast numbers of lives throughout the world and also eliminated the serious problem of laboratory infections. Although the French strain is more protective and has been widely and for the most part safely used in Africa, the 17D vaccine produces fewer serious complications and also provides good protection.

The story of yellow fever control is a dramatic example of the rewards that may be reaped by placing adequate resources in the hands of trained, talented researchers. It illustrates the necessary interplay of basic research and applied research and the combining of approaches to achieve a desired end. There is every reason to believe that well-directed research efforts mounted against present-day viral threats could achieve comparable successes.

EXOTIC VIRAL DISEASES AND LCM

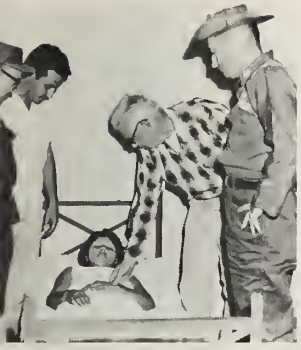
A number of arbovirus diseases normally occur only in distant parts of the world but pose a potential threat to American travelers and, in some cases, to the United States as a whole. Some of the more important of these diseases are Rocio encephalitis, found in Brazil and first recognized during an epidemic in 1975; Crimean hemorrhagic fever, which occurs as epidemics in Bulgaria and the U.S.S.R. and sporadically in Pakistan and East Africa, and which is probably transmitted by ticks; Rift Valley fever in Africa, a mosquito-borne disease of humans and sheep that recently caused a major outbreak in Egypt; and phlebotomus (sandfly) fever, which caused large outbreaks among U.S. Army troops in the Mediterranean area during World War II.

Mosquitoes transmit several serious diseases, including yellow fever.

Marburg and Ebola viruses, which originate in Africa, cause hemorrhagic fevers not transmitted by ticks or mosquitoes. The natural *reservoirs* (carriers) of these viruses are unknown, though Marburg virus has been contracted from monkeys, and both viruses can spread from person to person to a limited extent.

The arenaviruses are a group of mostly *exotic* viruses, four of which—Lassa, Machupo, Junin, and lymphocytic choriomeningitis (LCM) viruses—cause disease in humans. The natural reservoirs of these viruses are rodents, and the diseases probably spread via the animals' excretions. Lassa virus has been found only in West Africa, while Junin and Machupo viruses occur in certain parts of South America; all three cause hemorrhagic fevers in humans that are often fatal. LCM virus is found in the United States and throughout the world in mice, guinea pigs, and other animals. Through contact with the excretions of these animals (as with pet rodents or in mouse-infested buildings), humans occasionally become infected with the virus, displaying flu-like symptoms infrequently followed by severe meningitis. Rodent eradication has proven effective on some occasions in combating epidemics caused by these agents.

Most of these viruses deserve increased public awareness and federally sponsored surveillance and research because of their potential to be introduced into the United States and cause epidemic disease. In particular, more information is needed about the life cycles of these

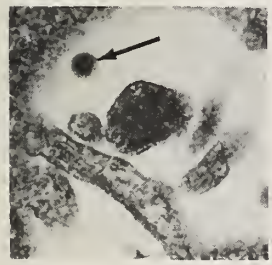


Physicians from Middle America Research Unit check pulse of a young victim of Bolivian hemorrhagic fever.

agents. Such knowledge would enable public health workers to act more efficiently in trying to control them. Scientists also need to know much more about human immune responses to these viruses and how best to induce artificial immunity against them.

Important research on arenaviruses and other infectious agents was conducted in the past at NIAID's field laboratory in Panama, known as the Middle America Research Unit or MARU. The laboratory was instrumental in virtually ridding Bolivia of Bolivian hemorrhagic fever, following isolation and identification of the causative virus and elimination of the rodent carrier. Although MARU was officially disbanded in 1972, much of the laboratory's work continues under the auspices of the Gorgas Memorial Laboratory with significant support from the National Institutes of Health (NIH).

Other important work on arenaviruses and arboviruses is being carried out at the Yale Arbovirus Research Unit (YARU), which is substantially funded by NIAID. YARU serves as a world reference center for arboviruses. In addition, its staff, which includes several world-famous *virologists,* conducts research and is currently collaborating with Egyptian scientists on studies of Rift Valley fever, in response to the recent serious epidemic in Egypt.



Rift Valley fever virus.

Rift Valley fever (RVF) virus is a serious threat to this Egyptian farmer. Traditionally, RVF epidemics in Sub-Saharan Africa affected domestic animals on which villagers depend for their livelihood. In 1977 and 1978, widespread RVF affected animals in Egypt and, unlike previous outbreaks, also caused serious human disease.

RABIES

Like the arboviruses and arenaviruses, rabies virus most often infects animals, though in many underdeveloped countries it is an important cause of human disease as well. Since rabies of dogs and cats has been virtually eliminated in the United States, the threat to humans here is now from infected wildlife, especially skunks, raccoons, foxes, and bats. Most human rabies follows a bite from an infected animal, but contaminated air, such as that in bat caves, can also spread the disease.

Scientists learn about rabies by studying the disease in bats.

The incubation period of rabies is usually from 3 weeks to 2 months, but it is occasionally much longer. The illness itself lasts a few days and is almost always fatal. Fever, headache, malaise, and other general symptoms are the first to appear. These are followed by tingling pain at the wound site; increased sensitivity to such stimuli as touch, light, and noise; muscle spasms; and profuse sweating and salivation. Most patients become increasingly agitated as the disease progresses, but those who survive this phase become quiet, paralyzed, and stuporous before death. One symptom of rabies—fear of drinking fluids—is so striking that the disease is sometimes called hydrophobia (fear of water). This fear develops because the rabid patient's attempts to drink stimulate painful spasms of the muscles involved in swallowing as well as some used in breathing. Instead of being swallowed, liquid is forcibly expelled, and the associated muscle spasms may so interfere with the patient's ability to breathe that he becomes desperate. All in all, it is difficult to think of a disease that one would be more eager to avoid.

Fortunately, it is possible to prevent rabies. In the late 19th century, Louis Pasteur developed a rabies vaccine by attenuating the live virus, and a number of improved vaccines have been prepared since that time. But because these vaccines all pose dangers, and because a standard course of rabies vaccination is relatively lengthy and uncomfortable, rabies vaccine is given routinely only to animal handlers and others who are at unusually high risk; otherwise, it is used only after an individual has been exposed. Such post-exposure immunization is often effective because of the relatively long incubation period of the disease. For

Rabies vaccine is injected into the abdomen.

Widespread vaccination of domestic animals has made rabid dogs, such as this one, a rarity in the United States.

added protection, antibody-containing serum *(antiserum)* from rabies-immune horses or gamma globulin from immune humans is given along with vaccine treatment. Unlike vaccine, these offer the patient immediate protection, fending off the disease while the vaccine has time to take effect.

Antirabies treatment, with its attendant risks and discomforts, can often be avoided if the biting animal is available for examination by experts. Pets should be observed to see whether they become ill or die, and wild animals should be killed and their brains examined for telltale formations known as *Negri bodies*. If the animal proves healthy, vaccine need not be administered to the bitten person. To avoid unnecessary rabies treatment, every effort should be made to kill, capture, or in the case of pets, locate any animal that bites an individual without provocation.

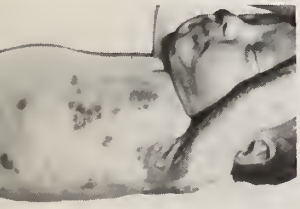
VIRUSES THAT LINGER

PERSISTENT VIRAL INFECTIONS

Although rabies may take a long time to show up, the illness progresses very rapidly once symptoms appear. But some viruses that persist in their hosts' bodies for long periods cause very slowly developing disease. And others persist but rarely or never cause symptoms.

Cold sores on the lip are common type 1 herpes simplex virus infections.

Herpes simplex types 1 and 2 are classic examples of persistent viruses that cause recurrent infections. Type 1 herpes simplex virus (HSV-1) produces cold sores (fever blisters) and, occasionally, a serious eye infection known as herpetic keratitis; HSV-2 is responsible for genital herpes, a major sexually transmitted disease. After symptoms of the initial infection die down, these viruses remain as hidden saboteurs in nerves that serve the site of infection, giving no sign of their presence until the balance between virus and host is upset, inducing viral multiplication and recurrent disease. Recurrences may be brought on by virtually any sort of physical or emotional stress, and they may also occur without any apparent explanation.



This infant, born to a mother with genital herpes, developed a serious generalized infection.

Infants born to mothers with genital herpes may develop a generalized infection, which is often fatal. In older infants, too, and in children and adults with deficient immune systems, herpes infection may sometimes produce fatal illness, often marked by meningitis or encephalitis.

The herpesvirus family also includes varicella-zoster virus, cytomegalovirus, and Epstein-Barr virus, all of which can produce persistent infections. Varicella-zoster virus produces the acute infection we recognize as chickenpox, but it also causes herpes zoster ("shingles")

many years after the original infection (see page 15). Cytomegaloviruses (CMV's or salivary gland viruses), best known for their capacity to injure a developing fetus, cause such injury so frequently because they are often present in a latent state in pregnant women, as well as in the rest of the population. Although CMV infection rarely produces obvious symptoms in otherwise healthy children or adults, work with animals suggests that these viruses can cause suppression of the immune system. Thus it is possible that long-term carriers of CMV may have reduced resistance to other infections.

Epstein-Barr virus (EBV) is believed to be the cause of infectious mononucleosis ("mono")—the long-lasting and debilitating "kissing disease" familiar to college students. It is also suspected of playing a role in two fatal malignancies—Burkitt's lymphoma in Central Africa and nasopharyngeal carcinoma in East Asia. EBV transforms lymphocytes (a variety of white blood cell also found in lymph nodes) in laboratory cultures, causing them to grow in the relatively unrestrained manner characteristic of cancer cells. Excessive multiplication of lymphocytes also occurs in all three diseases believed to be caused by EBV.

Burkitt's lymphoma cases occur across a wide belt in Africa that encompasses the hot and wet areas below 5000 feet altitude.

But members of the herpesvirus family are not the only viruses that frequently or occasionally cause persistent infection. Hepatitis B virus (HBV) infections, for example, often become chronic, sometimes causing mild persistent hepatitis or the more serious chronic active hepatitis. And, as long as they remain infected, patients with persistent HBV continue to be potential sources of infection for others.

"SLOW VIRUS" INFECTIONS

A number of persistent, slowly developing viral infections ("slow virus" infections) cause damage to the brains of humans or animals. Among those affecting humans are subacute sclerosing panencephalitis (SSPE) and progressive rubella panencephalitis (PRP), rare fatal disorders caused by measles and rubella viruses, respectively. Another rare brain disease, progressive multifocal leukoencephalopathy (PML) has been associated with two agents of the papovavirus *family* (polyomavirus *genus*), one of which—SV40 virus—is usually found only in monkeys. Both SV40 and a related virus (polyoma) produce malignant tumors in experimental animals—another outcome of persistent infection. The other genus of the papovavirus family, the papillomaviruses, includes the agent responsible for the benign tumors we recognize as warts.

Mink, susceptible to slow virus diseases such as Aleutian mink disease and encephalopathy, are excellent animal models.

Goats serve as animal models for slow virus diseases. The animal on the right has scrapie.

Two other slowly progressing fatal brain disorders—kuru and Creutzfeldt-Jakob disease—are caused by so-called "unconventional viruses."* Creutzfeldt-Jakob disease causes its victims to become increasingly demented, then stuporous, and finally to lapse into a coma before death. About one person in a million, worldwide, is struck by this illness. Its usual means of spread remains a mystery, although about 10 percent of patients have a family history of the disease, and a few cases have occurred in medical personnel and in patients following such procedures as corneal transplantation or brain surgery.

Kuru primarily affects the portion of the brain that maintains coordination and balance (the cerebellum), so that its victims exhibit disturbed movements and clumsy gait. The disease has been found only in the primitive Fore people of New Guinea, among whom, in the 1950's, it had become the commonest cause of death.

In 1959, William J. Hadlow of NIAID's Rocky Mountain Laboratory pointed out many similarities between kuru and scrapie, a progressive disease of sheep caused by an unconventional virus, and suggested that kuru, like scrapie, might be caused by a virus-like agent. Building on this clue, NIH researchers D. Carleton Gajdusek and Clarence J. Gibbs, Jr., investigated the Fore plague and established that kuru was indeed transmitted by an unconventional virus. The Fore people had been practicing ritual cannibalism within their own group. Evidently, individuals contracted the disease in the process of removing, cooking,

*These agents behave like viruses in many ways, but both their chemistry and their behavior differ sufficiently from that of ordinary viruses to justify placing them in a separate class.

and eating infected brains from tribe members who had died from kuru. Probably, infection also took place through cuts and sores on the skin. Since it was primarily women and children who took part in the post-mortem rituals, they were the ones who usually fell victim to kuru, while the adult males remained unaffected. With the suppression of cannibalism by governmental authorities, kuru gradually died out. Dr. Gajdusek subsequently won the Nobel Prize for his studies of this unusual illness—studies that may eventually help us to understand the causes of such other mysterious ailments as multiple sclerosis and Parkinson's disease.

An eight-year old girl of the Fore tribe of New Guinea has the progressive disease called kuru.

SUBTLE VIRAL DISEASE

Marek's disease is a common viral infection of chickens marked by multiple tumors. It has been successfully controlled worldwide by a vaccine. An unexpected benefit of the vaccine was the increased productivity of vaccinated chickens. They are not only protected against Marek's disease but are generally healthier, grow faster, and produce more eggs than unvaccinated birds, even when the latter show no overt signs of illness. Apparently, the virus produces low-grade disease in the chickens it infects, even though the birds appear relatively normal.

It seems possible that known (for example, CMV) or unknown persistent viruses of humans may act similarly to impair the health of their hosts in subtle ways, perhaps by interfering with immune responsiveness. Identification of such viruses, if they exist, and the adoption of control measures against them might lead to improved life quality for many individuals.

DISEASES OF UNKNOWN CAUSE

Sheep with progressive pneumonia, a virus-caused chronic lung disease.

Several persistent viral infections of animals are of special interest to scientists. These infections produce diseases that resemble human illnesses whose causes are unknown, and the fact that viruses cause the animal diseases suggests that the human ailments might be caused by viruses, too.

Maedi (Icelandic dyspnea, progressive pneumonia) is a chronic lung disease of sheep occurring in Iceland (until a recent successful eradication program) and elsewhere, and visna is a progressive paralytic disease also found in Icelandic sheep. After some years of uncertainty, scientists found that both of these diseases were caused by a single agent, now known as the visna-maedi virus. Visna, in particular, interests medical researchers because it resembles multiple sclerosis (MS), a chronic, crippling illness that attacks humans in their prime. Several pieces of evidence suggest that MS may be caused by measles or some other virus, and study of visna might show scientists how to uncover the viral cause of MS, if one exists.

Amyotrophic lateral sclerosis (ALS or Lou Gehrig's disease) somewhat resembles MS but is much more rapidly progressive. It has features in common with certain known viral infections of mice and, for this and other reasons, it is suspected of being caused by a virus.

Mice have also furnished clues that are helping researchers to understand the origin of juvenile-onset diabetes. This severe form of diabetes, which accounts for nearly 10 percent of all cases, generally starts earlier in life and more abruptly than the adult-onset disease. Several features of juvenile-onset diabetes led scientists to suspect that it might result from an infection, and the demonstration, within the past decade, that several viruses can produce diabetes-like disease in

Lou Gehrig, a first baseman for the New York Yankees and an extraordinary athlete, was called "Iron Horse" because he appeared in 2130 consecutive games from 1925 to 1939. While in his thirties, he was stricken with amyotrophic lateral sclerosis (ALS) and died in 1941 at the age of 38. Since then, ALS is sometimes called Lou Gehrig's disease.

Guinea pig with tumor is an animal model for studies of viruses and cancer.

susceptible mice gave added impetus to this theory. Recently, researchers at the NIH isolated a coxsackie virus from a 10-year-old boy with a fatal case of diabetes. The virus from the boy also produced diabetes in test mice. Other evidence suggests that this coxsackie virus may trigger juvenile-onset diabetes.

For many years, scientists have speculated that viruses and cancer might be intimately related. Indeed, a number of viruses are known to cause cancer in animals—some in nature, others only under special laboratory conditions. In humans, though, no virus has been definitely established as the cause of any cancer, and there are relatively few candidate viruses with any credibility. One of these few—Epstein-Barr virus—has been implicated in the development of both Burkitt's lymphoma and nasopharyngeal carcinoma, though it seems that these cancers develop only when other factors act in concert with the virus. There is also some evidence associating type 2 herpes simplex virus with development of cancer of the cervix and hepatitis B virus with cancer of the liver. Whether or not viruses will eventually prove to be an important cause of cancer in humans is a question that at this time remains completely unresolved.

VIRAL DISEASES OF ANIMALS AND PLANTS

Viral diseases of animals are important to man not only as models of human diseases but because of the economic losses and the damage to pets that they cause. Canine and feline distemper are two of the many viral diseases that threaten pets, while swine and equine influenza, Newcastle disease of fowl, and bovine rhinotracheitis are just a few of the acute viral infections that cause serious economic losses to farmers, ranchers, and others. Persistent viruses that threaten domestic animals in the United States include the agents of Marek's disease of chickens, avian leukosis, bovine infectious anemia, and scrapie and progressive pneumonia of sheep. Marek's disease alone cost the poultry industry in this country $100 to $200 million annually before it was controlled. Although vaccines and other measures have proven effective against many of these viruses, the costs of control may themselves be considerable.

Plants, too, are subject to viral infections, some of which cause great economic losses. Tobacco plants, many vegetables, citrus and other fruits, cereals, sugar beets, and sugar cane all serve as hosts for one or more viruses that can cause markedly reduced crop yields.

Within the past 10 years, scientists have discovered a new class of

virus-like particles in plants. These *viroids* are small, highly infectious molecules of RNA; they are the smallest known agents of infectious disease. To date, six plant diseases are known to be caused by viroids, and recent evidence indicates that related agents may turn out to be the causes of certain animal and human diseases, including kuru and scrapie. How viroids reproduce and how they cause disease remain mysteries. Possibly, they upset normal host cell processes by acting in the guise of regulatory molecules.

The larger potato plant is healthy; the smaller one is blighted by a viroid-caused disease.

VIRUS-HOST INTERACTIONS

VIRUS AND CELL

An encounter between a virus and a cell may have one of several outcomes depending both on the properties of the virus and the susceptibility of the cell. If the cell surface does not have specific receptor sites for a particular virus, that virus will not gain entry. But even if cell and virus do have matching surfaces, the cell may be *nonpermissive* for that virus, meaning that it will not support the virus's reproduction, and the infection will be *abortive* or *nonproductive.*

Abortive infections are less likely than others to cause cell damage or death, but even *productive* infections do not always kill cells. In fact, a particular virus may be highly virulent (deadly) for one type of cell and totally innocuous for another, though both cell types are *permissive.* Some of the mosquito-borne encephalitis viruses, for example, cause great damage to human or animal cells but none at all to mosquito cells,

though the viruses multiply equally well in both cell types.

Viruses can not only multiply successfully without affecting their host cells, they can also greatly alter cells while failing to multiply at all. This occurs when cells are transformed by an *oncogenic* (cancer-causing) virus. Genes from the virus become a part of the genetic material of the cell. Each time the cell divides, the viral genes replicate along with those of the cell, but no new virus particles are formed. The cell and its progeny do, however, show definite effects from the genetic intrusion. They become transformed, growing in multiple rather than single layers in laboratory cultures, producing tumors when they are inoculated into animals, and otherwise behaving like cancer cells.

HOST RESPONSES

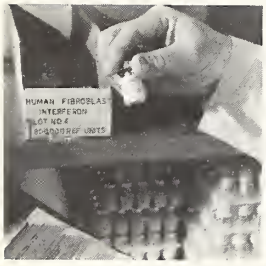
A viral infection may pass unnoticed, cause mild discomfort, or result in overwhelming illness. In part, the outcome depends upon the nature and amount of the infecting agent. Equally important, though, is the host's state of resistance and response to the infection.

Humans and animals generally react to viral infections by manufacturing specific antibodies and *immune cells*. These are produced in response to foreign molecules called *antigens* that are present on the surface of the virions as well as within them. The antibodies may combine with and inactivate (neutralize) virus particles, while the immune cells engulf and digest them.

The host's response to infection not only helps him to overcome his current illness but usually leads to increased resistance in future encounters with the same or related viruses. Often, the immunity produced is solid and lifelong, completely preventing any recurrence of the illness. In other cases, it may simply permit the individual to respond rapidly to a repeat infection, causing it to be shorter and less severe. Some viruses, however, fail to produce a detectable immune response, or they produce one that is very short-lived; and a few give rise to paradoxical immune responses that cause future infections to be more rather than less serious.

Human milk supplies antibodies and immune cells to protect nursing babies from many diseases.

Experiencing infections is an important way of acquiring immunity, but it is not the only way. Infants are born with *passive immunity* against the same viruses to which their mothers are immune. This infantile immunity develops because antibodies from the mother's blood enter the fetal circulation during pregnancy; it lasts for several months before the donated antibodies are lost to metabolic wear and tear. Human milk, too, furnishes protective antibodies—and immune cells as well—to nursing infants and children. Breast milk is particularly rich in "local" antibodies that perform their work in the intestinal tract rather

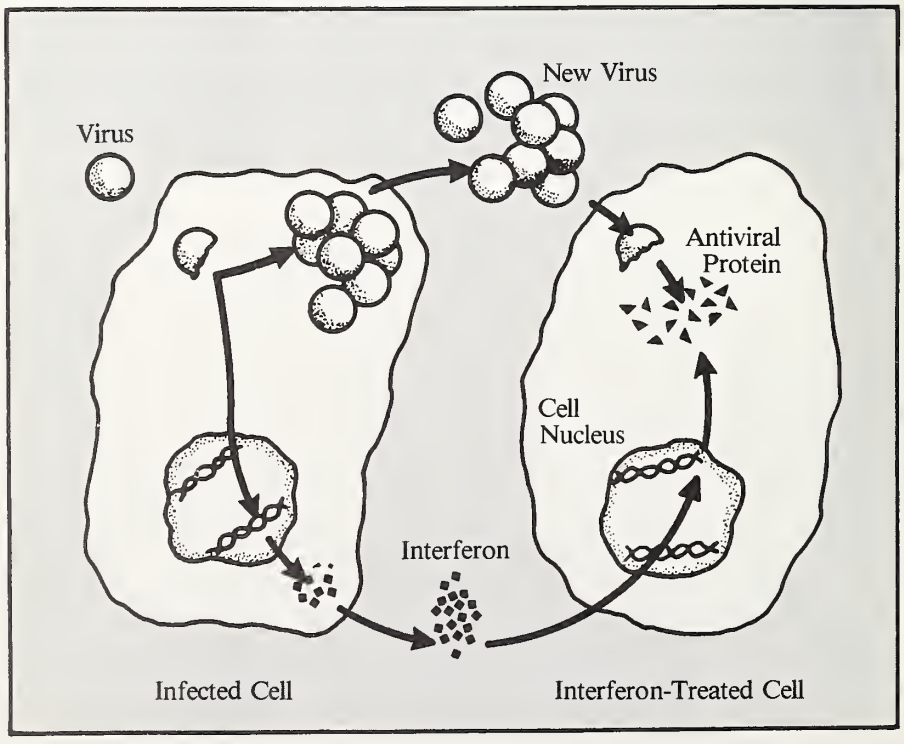


Small quantities of interferon are available to scientists who are studying its remarkable properties and its effectiveness in treating disease.

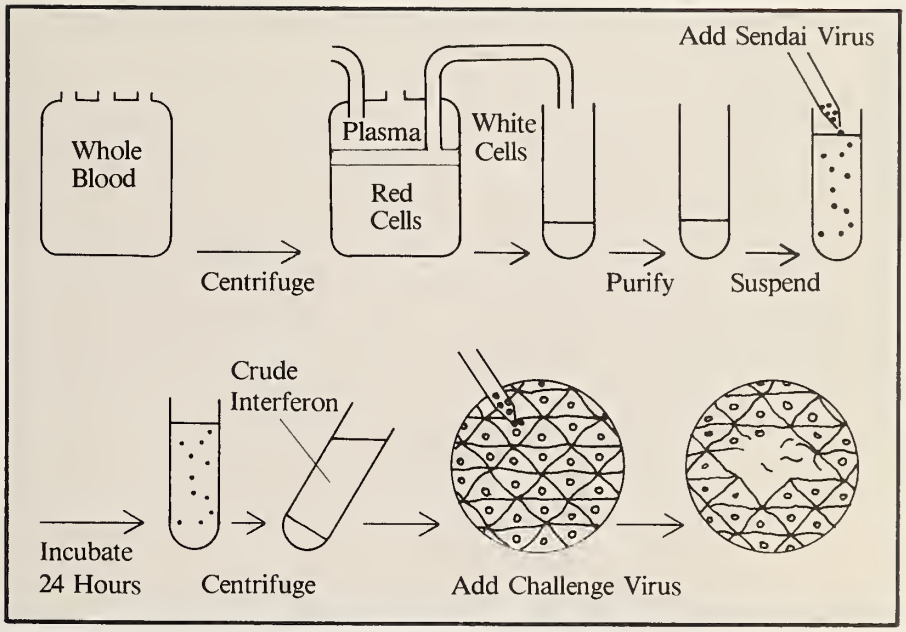
than the bloodstream and that afford protection against the diarrheal diseases that can be so disastrous to infants. Finally, artificial immunization—either active, via vaccination, or passive, by the inoculation of immune serum—can provide an individual with immunity against a virus to which he has never been exposed.

However it is acquired, specific immunity generally gives a host animal or human a big edge in fighting off a virus, but this is not always the case. Scientists now recognize instances in which the host suffers more damage from his own immune response than from the virus itself. Such damage may occur, for example, when aggregates of virus and antibody deposit in and obstruct capillaries in the kidneys and elsewhere, causing *immune complex disease*. This result of certain viral infections has been observed in animals and may also account for the findings in a number of serious human diseases, including systemic lupus erythematosus.

Viruses may also interact with the host's immune system in other destructive ways. They may, for example, infect cells belonging to this system and either depress or enhance their functioning to a harmful degree. In other instances, antibodies or immune cells sensitized to a virus may react with and injure the host's own virus-infected tissue.



When a virus attacks a cell, it forces the cell to produce new virus particles that eventually can leave the original cell and go on to infect other cells. However, the first virus attack also stimulates the cell's nucleus to activate a gene for producing interferon. Interferon is released and stimulates nearby cells to produce proteins that inhibit virus multiplication.



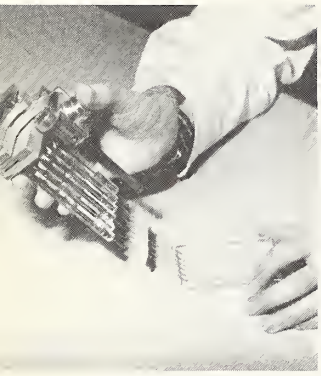
Large scale production of interferon is a painstaking process. According to one method, developed in Finland, human white blood cell interferon can be removed from whole blood and purified. The blood, which is obtained from blood banks, is centrifuged, the white cells removed and purified. The cells are suspended in a culture medium containing blood serum, and virus is added to induce interferon production by the cells. Cells and virus are removed leaving crude interferon. The final step is to measure the potency of the interferon by testing its ability to reduce the areas of killed cells in a culture exposed to a challenge virus.

Clearly, immune responsiveness is a double-edged sword that cannot always be counted on to work in the best interest of the host.

Interferon, on the other hand, under normal conditions appears to be purely benevolent from the host's point of view. This remarkable protein (strictly, class of proteins) is produced by *vertebrates* in response to viral infection and acts on cells to inhibit reproduction within those cells of viruses, even those unrelated to the infecting agent. Interferon is manufactured not only by cells of the immune system but also by many other cell types, and its appearance represents one of the body's earliest protective responses to viral invasion.

Animals and humans also react to microbial invasion with an *inflammatory response,* the body's attempt to localize infection and repair damage. This response is marked by fever, increased acidity, and changes in capillary permeability, all of which influence the subsequent course of events.

Both our specific and nonspecific responses to infection are controlled by a combination of environmental and hereditary factors that scientists only partly understand. Nutrition, for example, undoubtedly affects the ability of our bodies to produce antibodies and interferon, and our relative lack of knowledge in this area has opened the way for an ongoing debate on the merits of Vitamin C as a common cold preventive. Certain illnesses, including some cancers and many infections, are known to depress the immune system, and a variety of



Tissue typing tray with reagents is used to match HLA types for organ donors and recipients.

drugs and medications alter our natural responses to infection. Cigarette smoking, too, has been clearly shown to decrease resistance to respiratory infections, probably at least partly because smoking tends to inhibit the movement of cilia—tiny hairlike structures that line the respiratory tract and normally act to sweep mucus and microbes up and out of the body.

The role of hereditary factors in host response to infection is most strikingly seen in individuals born with seriously defective resistance. A number of different immune system defects have been identified, and there must also be a wide range of genetically determined normal variations in immune response. The capacity for interferon production is no doubt under genetic control, too, as are various anatomic factors that affect resistance to viral infections.

Just as different individuals have genetically different blood types, so, too, do we have different cell types—known as HLA types—the reason why donated organs cannot be randomly transplanted. Within the past decade, scientists have learned that individuals with certain HLA types are particularly susceptible to some diseases. (HLA-A3 and HLA-B7 individuals, for example, are especially prone to develop paralytic polio.) This is a very new and very promising area of exploration in our effort to understand and control viral diseases.

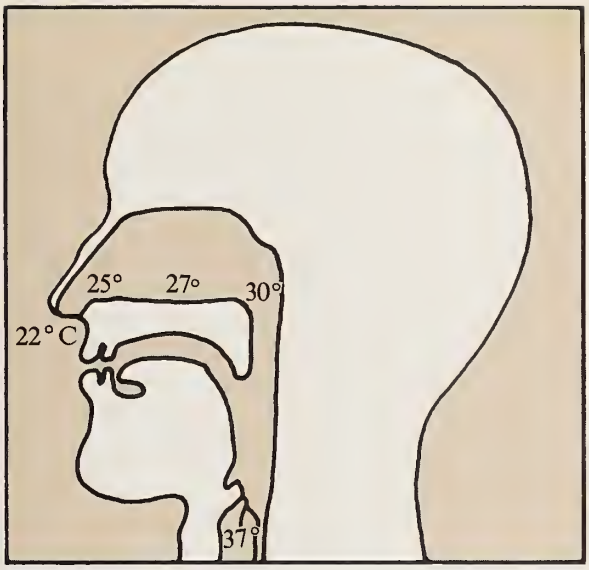
MECHANISMS OF PERSISTENCE

While it is comparatively simple to envisage how a virulent virus can overwhelm all defenses and kill a host, or how a host may successfully fight back and eliminate the invader, it is more difficult to understand how host and virus can coexist uneasily for months, years, or decades with neither gaining the upper hand. Yet this is the situation that prevails in the many known chronic or persistent viral infections and probably also in a number of other illnesses that are suspected to be of viral origin.

According to NIAID's Virology Task Force: "There are probably as many potential mechanisms for . . . virus persistence as there are stages of interaction between tissues and cells and infecting viruses." Some of these mechanisms have been clearly demonstrated in animals or in cell cultures; others, at present, can only be guessed at with a greater or lesser degree of conviction. Of course, in many persistent infections, several mechanisms may operate either simultaneously or in succession.

In one type of persistent infection, the majority of cells are resistant (nonpermissive), but some permissive *mutant* cells continually appear, allowing a limited amount of virus to be produced. Systems of this type often develop after the initial viral attack has destroyed most of the original, largely permissive, cell population.

In other cell-virus systems, the development of persistent infection



Temperatures in the nose and throat are cooler than those in the lungs. Taking advantage of this difference, NIAID scientists are using temperature-sensitive (ts) mutants of influenza viruses to develop a live virus vaccine. The vaccine grows well enough in the cooler temperatures of the upper respiratory tract to stimulate protective antibodies. However, it does not grow enough in the warmer temperatures of the lower respiratory tract to cause the pneumonia, cough, and fever produced by the naturally occurring virus.

seems to result from the appearance of viral mutants known as *defective interfering particles.* These incomplete virions are defective in that a portion of the usual viral genetic material is absent. They can thus reproduce only in the presence of standard "helper" virus; at the same time they interfere with reproduction of the standard virus.

Temperature-sensitive (ts) viral mutants, which can reproduce only at certain temperatures, may play a somewhat similar role in the establishment and maintenance of persistent infections. In some systems, the ts particles interfere strongly with the multiplication of standard virus both at permissive and nonpermissive temperatures.

In some cases, the ability of a virus to initiate persistent infection seems related either to its failure to induce interferon or to the absence of an immune response. In certain persistent viral infections of cells in culture, for example, interferon neither is produced nor acts. And such "unconventional viruses" as the agents of kuru, Creutzfeldt-Jakob disease, and scrapie fail to stimulate any detectable immune response in their hosts.

In contrast, many persistent viral infections appear to be maintained by the presence of one or more antiviral substances in the fluid surrounding the infected cells. These antiviral factors (the one found most often has been antibody) keep the concentration of infectious virus at a low enough level so that the susceptible cell population is not wholly destroyed, yet in these systems the virus is not completely eliminated either.

Other, more complex, interactions between virus particles and antibodies or immune cells also play a role in some persistent infections.

Antigenic drift is one example of such an interaction. In this context, the term refers to the preferential multiplication (selection) of viral mutants whose antigens do not match antibodies already present in the host. As the host develops antibodies against the mutants, other mutants may become predominant. By continually changing in this fashion, the virus may outrun the host's immune response.

VIRAL LATENCY AND CANCER

Of all the known and suspected mechanisms of viral persistence, the most interesting is the strange association between cell and virus known as latent infection. In such an infection, a copy of viral genetic material links up with the genetic material of the cell and multiplies along with it. No virus can be detected as long as the infection remains latent, but from time to time it may become active, and virus again appears. Herpes simplex is one example of a virus that produces latent infections marked by occasional periods of activity.

Although in a latent infection the virus itself remains hidden, its presence may be revealed by changes in the infected cell. Some cells carrying viral genes produce new antigens that disappear if the viral genes are eliminated.

As mentioned earlier, certain latent infections cause cells to become transformed (cancerous). How this occurs is still unknown, though some scientists believe transformation may result from production within the cell of a "transforming protein" coded for by a viral gene. In fact, researchers have observed certain proteins to be associated with transformation. One of these is found in cells transformed by SV40 virus; some molecules of the protein appear to attach to the cell's nucleic acid, while others localize on the cell surface where they act as tumor-specific antigens.

If transformed cells bear new surface antigens that should identify them as "foreign" to the host immune system, why are they not destroyed by the host's immune response? Scientists believe that most transformed cells are destroyed. Those that escape immune surveillance and go on to establish tumors may succeed for one of the following reasons: (1) No strong antigens are produced by the transformed cells, or if they are produced, they are masked by *blocking antibody;* (2) The transformed cells multiply so rapidly that they outrun the immune response; (3) The transforming virus is *immunosuppressive* and thus interferes with the immune response of the host; or (4) The host's immune system is already suppressed at the time of infection with the transforming virus. Such immunosuppression may result from a preexisting infection or other illness, or from drugs, such as those taken by transplant recipients to prevent rejection of donated organs.

DIAGNOSIS OF VIRAL INFECTIONS

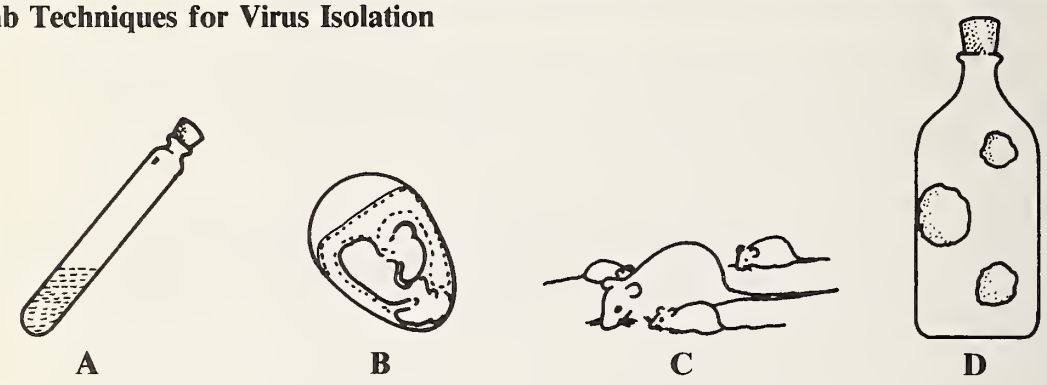
There are several circumstances in which physicians or virologists may wish to diagnose a viral disease. These include illness in an individual patient; outbreaks and epidemics; monitoring of a disease that can be controlled by public health measures such as vaccination; and research. In each of these situations, the reason for making the diagnosis is somewhat different, and procedures must be selected accordingly.

The two broad ways in which viral infections may be diagnosed are through isolation and identification of the virus and by measurement of specific antibodies in the patient's blood. Virus isolation is likely to be more specific and reliable than the antibody-measuring or *serologic* techniques, but it is also generally more difficult, time-consuming, and expensive. The procedure involves inoculating appropriate specimens (e.g., throat swabs in the case of a respiratory infection, stool samples if the patient has diarrhea) into one or more test systems, usually tissue cultures, embryonated hen's eggs, or laboratory animals.

In tissue cultures, virus activity often shows up in the form of a characteristic *cytopathic effect* (CPE) or visible abnormality; in other cases, the presence of virus in the tissue culture may be demonstrated by immunologic tests. Certain viruses produce distinctive *pocks* on the membranes of embryonated eggs. And many viruses produce signs of infection in one or more laboratory animals. But a major stumbling block in efforts to identify a virus is the need to match the proper system

Flu viruses are sometimes grown in tissue culture tubes like these, as well as in eggs.

Lab Techniques for Virus Isolation

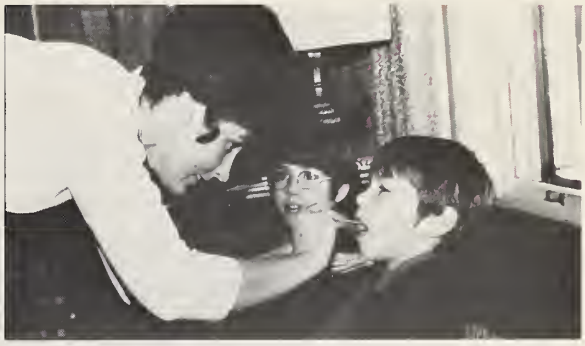


A, Tissue culture system
B, Embryonated egg inoculation.
C, Infant mouse inoculation.
D, Tissue culture system for plaque formation.

with an unknown virus. Even if a specimen is loaded with virus, unless it is inoculated into the appropriate cell culture, embryo, or animal (that is, one that supports growth of that virus in some recognizable way), the virus may go undetected. Choosing appropriate test systems may present little difficulty in cases where an illness is almost certain to have been caused by one of just a few viruses, but it is a major problem when the cause is totally unknown. And, in general, the need to keep a large variety of systems on hand makes virus isolation impractical in all but a few highly specialized laboratories.

Serologic diagnosis, like virus isolation, usually yields its results too late to be of any practical use to the individual patient, but its comparative simplicity makes it very useful for *epidemiologic* studies. Most often, doctors using this approach compare antibody levels present in a patient's serum early in an infection and about two to three weeks later. If antibodies against a particular virus show a marked rise in concentration (titer) during this period, that virus is presumed to have caused the infection.

In order to measure particular antibodies, the laboratory must have on hand stocks of corresponding viral antigens. Depending on the system, the reaction between antigen and antibody may be detected in a variety of ingenious ways. *Neutralizing antibody,* for example, may be recognized and measured by its ability to prevent a known virus from



Nurse takes a throat swab as the first step in isolating the virus that is causing this child's respiratory infection.

infecting a test animal or cell culture. In other cases, one of the *reagents* used in serologic tests may be fluorescent or radioactive, making it easy to locate and measure antigen-antibody complexes.

Because so few therapeutic agents are effective against viruses, diagnosis of specific viral infections has often been of more interest to the researcher than to the physician. In recent years, though, several antiviral drugs have become available, and it seems likely that more will be licensed within the next few years. As this occurs, the need for rapid diagnosis will increase greatly.

The NIAID is supporting development of techniques that will enable physicians to diagnose specific viral infections in time to provide the most appropriate treatment for their patients. Immune electron microscopy, for example, which was developed by NIAID scientists, is now being used in some research hospitals to provide specific diagnoses of viral gastroenteritis ("intestinal flu") within 2 hours of obtaining specimens from patients. NIAID is also supporting projects for the rapid diagnosis of certain acute respiratory infections, including those caused by influenza A, respiratory syncytial, and parainfluenza viruses. The Institute is interested, too, in achieving speedy and accurate diagnosis of all forms of viral hepatitis.

TREATMENT OF VIRAL INFECTIONS

At present, the inability of physicians to diagnose viral infections rapidly has little effect on most patients, since specific treatment is in any case rarely available. Unfortunately, viruses are not susceptible to the antibiotics we use to treat bacterial infections. That is why doctors know how to cure pneumonia (if it is a bacterial pneumonia) but cannot cure the common cold. It is also why persuading a physician to prescribe an antibiotic for a viral infection is not likely to prove helpful; on the contrary, taking an antibiotic under these circumstances will subject you

to the risk of allergic reactions and other side effects without providing compensatory benefits.

Although scientists have searched intensively for substances with antiviral properties, they have had a hard time finding ones whose toxicity to humans is low. This is hardly surprising, since viruses are so intimately involved with the cells they infect that trying to destroy one without damaging the other is like trying to gun down criminals on a city street without hurting passersby. At most points in their life cycles, viruses depend on cell components and processes, and any substance that attacks the virus at these points is likely to destroy infected and uninfected cells along with the invader.

In spite of this difficulty, scientists have identified a number of promising antiviral chemicals, a few of which have been licensed by the Food and Drug Administration for the treatment of specific diseases. Adenine arabinoside (ara-A) has been approved for use in encephalitis caused by herpes simplex virus and is being tested, with NIAID support, as a treatment for acute shingles; both ara-A and idoxuridine (IDU) have been licensed for topical (local) use in herpes simplex infections of the eye; and amantadine hydrochloride has been approved for use against type A flu. The fact that these chemicals are in use is exciting, because it hints at the beginning of a new era in the treatment of viral diseases; however, their practical importance is still limited. Eye infections and encephalitis caused by HSV, while extremely serious, are relatively uncommon, and amantadine must be taken before the onset of flu symptoms to be truly effective.

But perhaps the most promising of all the known antiviral substances

Dr. John R. La Montagne (left), NIAID, Sir Charles Stuart-Harris (center), University of Sheffield, England, and Dr. Robert M. Chanock (right), NIAID, participated in a 1979 conference on amantadine at the National Institutes of Health. A panel of experts convened by the NIAID reported that the drug is effective in the treatment and prevention of all type A influenza. They advised that amantadine should be used with vaccines in selected high risk patients and also in certain unvaccinated persons at lower risk.

is interferon. This protein is extremely potent, relatively nontoxic, and active against many viruses. It shows promise of being effective, for example, in treatment of chronic hepatitis B and acute shingles. It is entirely possible that interferon will one day be a mainstay of viral disease therapy, though many obstacles must first be overcome. At present, interferon itself cannot be produced in anything like the amounts that would be needed to make it a practical means of treatment. On the other hand, interferon inducers—complex chemicals that stimulate animal cells to manufacture interferon—are available, but their effectiveness may be poor in certain situations, they are sometimes broken down in the body by enzymes, and they are often quite toxic. Researchers are now trying to find ways of producing more interferon and also to develop safer and more effective interferon inducers.

All of this, though, lies in the future. Right now, doctors can treat a very few viral infections with drugs like ara-A, and a few more with donated immune serum or gamma globulin (fractions of blood containing antibodies) or with vaccine. But in most cases they are likely to recommend "aspirin, bed rest, and plenty of fluids"—in other words, to treat only the symptoms because they cannot cure the disease.

PREVENTION OF VIRAL INFECTIONS

The old saying, "an ounce of prevention is worth a pound of cure," applies with full force to viral infections. It is certainly true today when there are so few means of treating viral diseases. But it will remain true in the future as well, both because more complications are likely to occur in treating a disease than in preventing it, and because a viral infection is apt to be fairly far along and hence difficult to treat by the time a patient gets to the doctor.

Viral diseases can be prevented either by stratagems that keep virus and host from coming into contact with one another or by measures that increase the host's resistance to the point where he can successfully fight off the illness. Which approach will work best depends on the particular virus.

Whenever feasible, scientists would like to eliminate harmful viruses from the environment. They appear to have recently succeeded in doing this with smallpox virus, using a combination of mass vaccination, tracking of cases and *quarantining* of contacts. Unfortunately, for one reason or another most viruses cannot be dealt with in this fashion. Some are not common enough or harmful enough to justify mass vaccination; many others are so widespread in nature that eradicating them is simply not a practical possibility.

But even without totally eliminating a virus, public health workers can often take steps to keep viruses safely apart from man. In the case of viruses carried by domestic animals, for example, health authorities may require that the animals be vaccinated, as has been done with rabies and Venezuelan equine encephalitis. Wild animals carrying viruses usually pose little direct threat to humans, but their potential for harm may be great, as through spread of infection to domestic animals; scientists have been experimenting with baits laced with live virus vaccines as a possible way of controlling such infections as rabies in wild animal populations. Some infections carried by domestic animals can be held in check by a combination of import regulations and quarantine, and slaughter of infected animals has also proved an effective, though expensive, method of controlling certain animal illnesses such as foot-and-mouth disease of cattle.

Jonas Salk vaccinates a little girl against polio.

In the case of the arboviruses, the most effective way to prevent human illness is to control the vector populations. Most often, this involves the use of pesticides, but insects and other pests tend over time to become resistant to most chemicals. Also, increased understanding of our environment has brought with it the realization that most pesticides are damaging to desirable forms of life as well as to the unwanted

Spraying of mosquito breeding sites is a common method of reducing vector populations in order to control human arboviral diseases.

species they are designed to destroy. Both of these problems have led scientists to explore alternative, biological methods of pest control.

Some researchers have been studying the natural development of insects with an eye to pinpointing vital hormones that could be used for control. By exposing insects to these hormones at specific points in their life cycles, it might be possible to hasten the insects' passage through harmful stages or to keep them at a harmless stage indefinitely. Alternatively, scientists might be able to use chemical inhibitors to prevent maturation. Yet another possible method of biological control would make use of sterile male insects which, by taking the place of normal males in matings with fertile females, could substantially reduce the species population. Finally, and most intriguing, we may one day fight pests with pests of their own. Insects are subject to infection with viruses, bacteria, protozoa, and fungi; certain insect viruses, especially, may turn out to be useful weapons in the war against human viral diseases.

Some viral diseases, especially hepatitis A, may be spread by contaminated food or water. This form of spread can be controlled by careful monitoring and treatment of water supplies used for cooking, drinking, bathing, irrigation, or as a source of seafood. Many other viruses spread through the air, and shielded ultraviolet lights, improved ventilation, or frequent cycles of warming and cooling might reduce the danger of infection in such places as schools and hospitals.

Some viruses are carried in the blood and are spread by transfusions and administration of blood products. We have already described the successful steps taken to limit transmission of hepatitis B. Scientists hope to score similar successes in controlling spread of non-A, non-B hepatitis and other blood-borne viruses.

Many viruses, though, spread directly from person to person, and the most useful approach to their control is to increase host resistance. Sometimes, as in flu season or when a patient needs a transfusion, exposure to one or more viruses can be expected. In these cases, short-

Viral Vaccines Licensed in U.S. for Human Use	
Type Of Vaccine	Duration of Immunity
Inactivated	
Rabies (duck egg)	?
Rabies (human cell)	?
Influenza A and B	2-3 Years
Poliovirus 1, 2, 3	5+ Years
Live	
Smallpox (vaccinia)	3-5 Years
Yellow fever	17+ Years
Poliovirus 1, 2, 3	5+ Years
Measles	8-15 Years
Mumps	6-8 Years
Rubella	5-8 Years
Viral Vaccines Now Being Tested	
Influenza (live vaccine)	Hepatitis B
Adenovirus (live vaccine)	Cytomegalovirus
Herpes Simplex Type 2	Varicella-Zoster

term prophylaxis (prevention) with immune serum, gamma globulin, or an antiviral chemical (e.g., amantadine for influenza A) may be worthwhile.

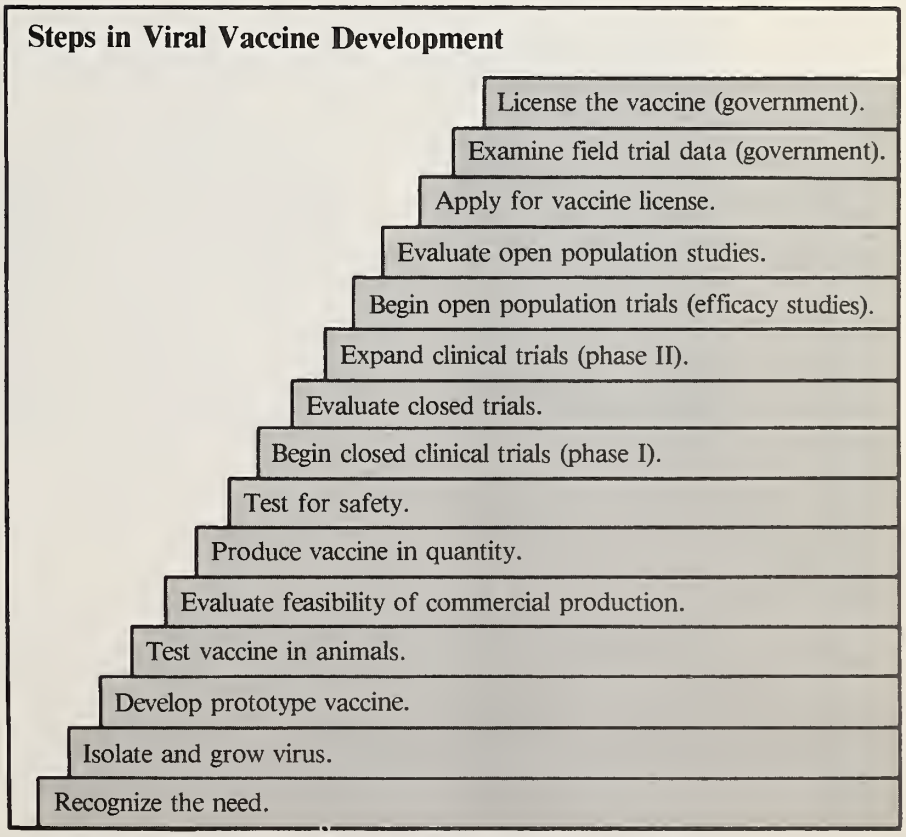
In most cases, though, host resistance is built up by administering vaccines designed to provide long-lasting immunity. These vaccines may contain inactivated virus (i.e., virus that can no longer multiply) or live virus that has been weakened by growing it for many cycles in selected host animals or tissue cultures. In addition, experimental vaccines have been made from natural or synthetic virus parts (subunits) instead of from whole virus as is usual.

Inactivated (killed) vaccines do have several distinct advantages. They are relatively simple to prepare—exposure to formalin, for example, will kill most viruses, and natural virus can be used. A big safety plus is that multiplication of both the vaccine virus and viral contaminants is ruled out. On the other hand, the immunity produced by a killed vaccine is less complete and less lasting than that produced by a live vaccine or by the natural infection. And killed vaccines have proved more likely than live ones to stimulate an abnormal immune response that may set the stage for severe disease if a vaccinated individual later becomes infected with the natural virus.

Live vaccines generally provide good protective immunity, and sometimes, as with oral polio vaccines, they offer a welcome alternative to shots. But these vaccines have frightening aspects as well. There is always some risk that the virus may, by mutating, become dangerous

once again or that it may persist in the host's body in a latent state and eventually produce serious illness. Also, there is the possibility that the virus may spread from vaccinated persons to others to whom it may present dangers.*

But the wave of the future in vaccine development seems to be vaccines made from selected viral subunits or from synthetic antigens. If properly designed, these can produce excellent immunity with a minimum of risks and side effects. They also lend themselves to the development of *multivalent* vaccines containing antigens from many different viruses—e.g., the many rhinoviruses responsible for colds. Synthetic vaccines are still very much in the idea stage, but some subunit vaccines are close to becoming practical realities.



*Because scientists are aware of these hazards, they are able to take steps to avert them. The rigorous and expensive process of testing is designed to make vaccines as safe as possible before they are approved for distribution, and they are recommended only when the expected benefit far outweighs the possible risk. Nevertheless, vaccine researchers and manufacturers labor under the knowledge that some element of risk must always remain.

WAYS OF STUDYING VIRUSES

Viruses present formidable challenges to scientists who wish to study them. They are far too small to be seen with the naked eye; too small even to be visible under an ordinary microscope. As for their chemistry, how can one analyze entities that never seem to be off by themselves but, rather, are always found intimately associated with cells? Brilliant minds, hard work, and special techniques have provided answers. Working primarily with plant viruses at first, because they were easier to obtain in large amounts and in high concentration, researchers used high speed *centrifuges (ultracentrifuges)* to separate out virus particles and determine their sizes (by the speed with which they moved outward

The electron microscope enabled scientists to see viruses for the first time.

This centrifuge is used to purify specimens of respiratory viruses, such as influenza, parainfluenza, and respiratory syncytial, for various studies including vaccine development.

as they were spun). Meanwhile, in the 1930's the electron microscope also appeared on the scene, enabling virologists to see the objects of their study for the first time. They found that some virus particles appeared very simple and uniform, while others had more complex structures with distinctive parts such as tails, tail fibers, and envelopes. Using the ultracentrifuge and the electron microscope, along with chemical techniques that had been applied earlier to the purification of proteins and other substances, virologists then learned how to obtain pure preparations of virus particles. The next steps were, first, to establish that viruses are made up of protein and nucleic acid and then to learn more about these basic components, often through various forms of *chromatography*. Chemical studies have now progressed to the

point where the complete sequence of nucleic acid building blocks is known for a few viruses and will soon be known for many more.

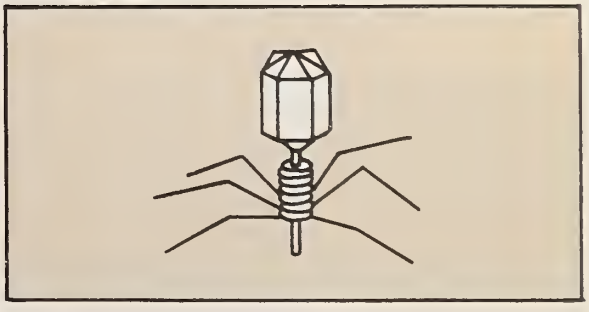
On the biological level, researchers study viruses and viral diseases with the same techniques physicians use to diagnose infections. Depending on the virus and its properties, they may use any of a number of different immunological methods, or they may observe the results of viral growth in tissue culture, animals, or embryos. All of these techniques can be standardized and quantified, creating *assays* that can be used to measure the amount of virus present in particular animals or body parts under a variety of conditions.

BACTERIOPHAGES

Nature, which on the one hand made viruses exceedingly small and difficult to study, has on the other hand provided virus researchers with extraordinary assistance in the form of "model viruses." Because of their simplicity and accessibility, bacterial viruses or phages were deliberately chosen as model systems by a confederation of brilliant researchers in the 1940's. Since then, phages have functioned as a set of master keys enabling scientists to unlock the secrets of viral structure and behavior. Their role in the development of virology and, indeed, of all modern biology, has been without parallel. In addition, research on phages has permitted virologists to hone their thinking and techniques to a fine edge before tackling the trickier animal and human viruses.

Given the minute size of bacteria and the role many of them play as parasites of higher organisms, it may seem surprising that these microbes are subject in turn to parasites of their own. But not only do such parasites—the bacteriophages—exist, but they make up a varied and complicated tribe. There are DNA phages and RNA phages; phages with double-stranded DNA and others whose DNA has but a single strand; some with long tails and some with tails that are short and stubby.

But it is not only their structure that is complex and variable; phage behavior is complicated, too. Phage heads contain the virus's genetic material. The tails attach to receptor sites on bacteria and serve as tubes



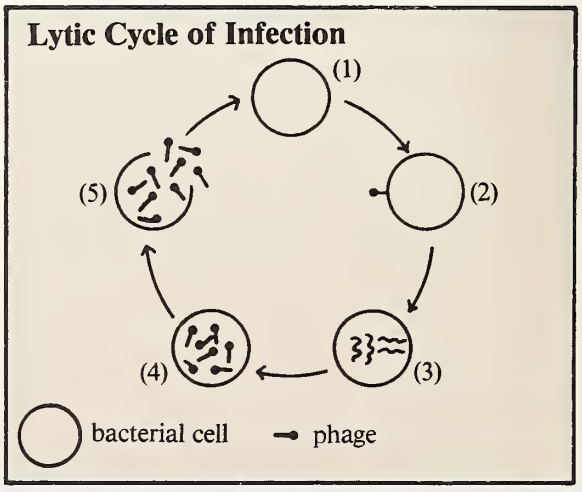
A bacteriophage is a virus that attacks bacteria, and its simplicity makes it a useful tool in studies of virus structure and behavior.

through which the genetic material from the head is injected into the bacterial cells. One of two things may happen next. Often the phage—or more strictly, its nucleic acid—will take over the cell, inducing it to manufacture viral rather than bacterial proteins and nucleic acids. Up to several hundred new virus particles will be produced until, finally, the bacterial cell bursts, or *lyses,* releasing the new generation of infectious phage. This *lytic cycle* of infection resembles the cell-virus interaction in many acute infections of plants, animals, and humans.

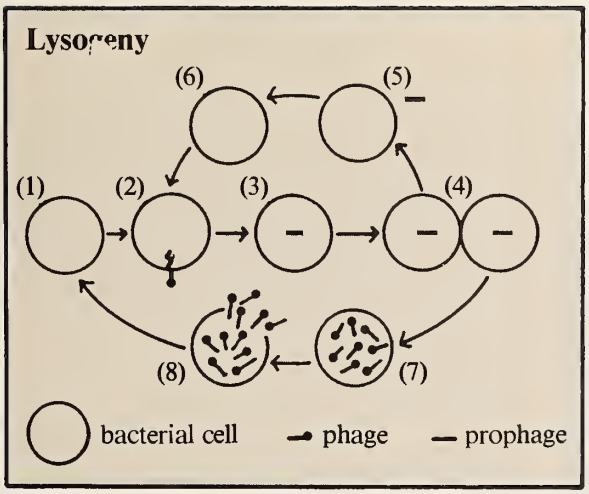
Some phages, however, are *temperate.* After infection, they can choose between lysing the cell or uniting with it in a long-term relationship known as *lysogeny.* Lysogenic bacteria carry phage DNA along with their own, and the phage's genetic message is reproduced along with that of the bacterial cell. As long as the lysogenic state continues, however, no new phage particles are produced.

The phage DNA carried in a lysogenic bacterium is known as a *prophage,* and it is kept from entering a fully active state by the presence in the cell of a *repressor protein* coded for by the prophage itself. Any condition (e.g., exposure to ultraviolet light) that interferes with production of the repressor protein induces the lysogenic cell to make infectious phage particles and lyse.

Lysogenic bacteria and latently infected animal cells obviously have much in common. And just as a latently infected cell may produce new surface antigens or show other virus-induced changes, a lysogenic bacterium may display properties it lacks in its uninfected state. The



Normal bacterial cell (1) becomes infected with phage (2). Phage DNA takes over cell DNA (3) producing new virus particles (4) until cell bursts (5) releasing a new generation of infectious phage that can then infect other normal cells.



Normal bacterial cell (1) becomes infected with phage (2). Phage DNA becomes harmlessly integrated with cell DNA (lysogenic response) (3). Lysogenized cell divides normally carrying latent phage, called prophage (4). Cell may lose prophage (5) and again be susceptible to infection (6) or cell may be induced to make phage particles (7) and lyse (8). The new infectious phage can infect other normal cells that may then exhibit the lytic response or the lysogenic response.

most dramatic example of such *lysogenic conversion* occurs in diphtheria-causing bacteria. Only if they carry certain phages do these bacteria synthesize diphtheria toxin and produce illness. In a certain sense, then, diphtheria is not the bacterial disease it appears to be but is, rather, a viral disease in disguise.

ANIMAL MODELS

Bacteriophages have served as simple models from which scientists have been able to learn general truths about viruses, including those that infect humans. In a similar fashion, animal models of human viral diseases have provided insights that could never have been obtained by working with human patients, given the inevitable practical and ethical restraints. These models include animals naturally subject to diseases that also affect humans (e.g., rabies); animals subject to diseases that resemble human illnesses caused by similar viruses (e.g., equine influenza, which resembles human flu); and animals to which human viruses can be adapted in the laboratory, with the resultant diseases resembling the human ones (e.g., hepatitis B in chimpanzees). Animal models have proved invaluable to virologists in the past, and the need for additional ones is keenly felt by researchers today.

Chimpanzees, like this one from the Holloman Air Force Base breeding colony, were used to show the safety and effectiveness of hepatitis B vaccine before human trials could begin.

RESEARCH

If you have read this far, you cannot help but be aware of the many questions about viruses that have yet to be answered and the many viral disease problems that have yet to be solved. Some of these problems and questions are quite practical, as: Is multiple sclerosis caused by a virus? or: How can flu vaccines be improved? The answers to such questions can be sought with research directed toward specific goals. But in order to solve many problems in virology, often including "practical" ones, basic research is needed.

Basic research sometimes appears to be trying to answer questions "just because they are there" instead of aiming at an immediately useful result. Often it is viewed as the pursuit of knowledge for its own sake, and to some extent it is and should be exactly that. But it is also true that, lacking fundamental knowledge, scientists are working in the dark. Each advance in basic research, by adding to the general level of illumination, helps much other work to proceed.

Research on phages, for example, might well have seemed like an ivory tower exercise. (Think of it—research on viruses that infect bacteria!) Instead, this work has furnished a solid bedrock for almost all areas of research on viruses. To cite just one instance, the discovery of temperate phages and lysogeny, which could hardly have been anticipated, opened the way to a sophisticated understanding of viral latency that is giving direction to current research on tumor viruses.

In the case of vaccines, too, the role of basic research has been critical. Although it was Jonas Salk who won public acclaim for developing the first polio vaccine, it was John Enders, Thomas Weller, and Frederick Robbins whose Nobel Prize-winning basic research on growing poliovirus in tissue culture made possible Salk's achievements and many subsequent ones.

One of many other areas where basic research on viruses may be expected to have a significant payoff is in the development of antiviral substances. By understanding in detail the way in which viruses invade cells and new virus particles are synthesized, researchers may learn how to interrupt the process with "magic bullets" whose action is so precise that they do not damage uninfected cells.

VIRUSES AS PROBES

Many scientists are interested in studying viruses for their own sake. But other basic researchers use viruses as probes with which to gain insight into the biology of cells.

The entry of a virus into a cell sets in motion a sequence of events that is at the very heart of life itself. Genes are replicated; protein is

synthesized. These components are assembled into functional units and, sometimes, wrapped in an outer membrane. All of these processes, while directed by viral genes, are carried out by the infected cell, and thus offer an opportunity to study the workings of that cell.

Almost any problem in cell biology can be approached with viruses. One basic question, for example, is how cells *differentiate*. That is, why does one cell become a muscle fiber and another a blood cell when both (assuming they belong to a single organism) have the identical genetic constitution? Researchers believe that part of the answer will be revealed by temperate phages and other persistent viruses as they help shed light on the ways in which repressor proteins and other regulatory molecules can switch genes on and off, causing cells to take one developmental direction or another.

Studied in conjunction with viruses, cell mutants can greatly increase scientists' understanding of cell biology. For example, by isolating mutant cells that will not support virus growth and comparing them with normal, permissive cells, researchers may be able to pinpoint essential steps in protein or nucleic acid synthesis.

Although basic research on any type of cell may furnish insights that apply to all cells, medical scientists are especially interested in studying human and some bacterial cells. Study of human cells is necessary in order to learn more about a number of "molecular diseases" that are specific to humans and whose basis is a cellular defect. Once these diseases are thoroughly understood, it is possible that cures may be devised. Basic research on medically important bacteria, on the other hand, may lead to improved methods for combating these microbes and the diseases they produce. Viruses can help us to understand both of these kinds of cells.

But we are now on the threshold of an era in which viruses may act, not merely as reconnaissance agents furnishing intelligence, but as actual combatants in the war against disease. If genetic engineering fulfills its promise, missing genes will be supplied to defective cells, and in some cases, cells will be given extra genes to extend their capabilities beyond the normal range. And where would viruses fit in? They would be the vectors, postal carriers conveying genetic packages from test tubes into the hearts of cells.

Certain bacterial viruses spontaneously give rise to variants, called *transducing phages,* in which a segment of viral DNA has been replaced with DNA from the bacterial host. These phages have demonstrated the possibility of gene transference and have played a crucial role in this area of research. Scientists expect that they will soon be able to adapt the process to viruses capable of transferring genes into animal and,

ultimately, human cells. Once this can be done, the way will be open to correcting such inherited molecular diseases as hemophilia, sickle cell anemia, and defects in immunity.

Viewed from almost any angle, virology may be seen as a science whose time has come. It rests on a solid foundation of basic knowledge, has already delivered many stunning achievements, and stands at the very center of modern biomedical research. Yet every accomplishment is matched by a problem that remains unsolved and whose solution might pay major dividends. The study of viruses today awaits the further effort that will enable us to tame—even harness—these minute entities that exist at the edge of life.

GLOSSARY

abortive—nonproductive; an abortive viral infection is one in which no new infectious virus particles are produced.

antibody—a protein molecule produced within an animal in response to a foreign substance (antigen) and which can unite with that substance in lock-and-key fashion, often rendering it inactive.

antigen—substance that can induce the formation of antibodies against itself.

antiserum—serum containing antibodies against a particular microbe.

arthropod—member of the phylum Arthropoda, a major biologic subdivision that includes organisms with a hard, jointed, outer skeleton, among them, insects and ticks.

assay—standardized test used to measure the amount or activity of a substance.

attenuated—weakened or made less virulent; viruses are often attenuated so that they can be used as vaccines which will induce immunity without producing disease.

bacteriophage—virus that infects bacteria.

blocking antibody—antibody that combines with an antigen in such a way as to prevent a different antibody from combining with the antigen.

capsid—protein coat of a virus.

capsomer—subunit of the protein coat of a virus.

carrier—individual who harbors disease organisms in his body without manifesting symptoms and thus acts as a distributor of the infection.

centrifuge—machine that spins rapidly, separating the lighter portions of suspensions from the heavier portions by centrifugal force.

chromatography—technique for separating mixtures into their components on the basis of preferential adsorption.

cytopathic effect (CPE)—visible change in cells resulting from virus-caused damage.

dead-end host—animal or plant that harbors a parasite, but from which the parasite cannot be transmitted further.

defective interfering particle—virus particle that lacks some genetic material; defective interfering particles can reproduce only in the presence of standard virus, but they interfere with the reproduction of the latter so that less standard virus is produced when defective interfering particles are present.

deoxyribonucleic acid (DNA)—very long molecule that serves as genetic material in plant, animal, bacterial, and other cells and in many viruses.

differentiate—to develop specialized form or function.

electron microscope—microscope that forms images with beams of electrons instead of visible light, enabling scientists to observe much finer detail than is possible with a light microscope.

endemic (disease)—one that is constantly present in a human community but that is clinically obvious in only relatively few individuals at any one time.

epidemic (disease)—one affecting many people in a region at the same time.

epidemiologic—pertaining to the study of the frequency and distribution of diseases.

exotic—of foreign origin.

family—biologic subdivision subordinate to an order (or suborder).

gamma globulin—group of plasma proteins with antibody activity.

genus—biologic subdivision subordinate to a family and superior to a species.

host—animal or plant that harbors or nourishes another organism.

immune cell—cell that is specifically sensitized to an antigen and can react with that antigen in lock-and-key fashion.

immune complex disease—disease produced by the formation of antigen-antibody aggregates (complexes) in the circulation and by their deposition in and around small blood vessels.

immune electron microscopy—electron microscope studies using immunologic reactions to identify viral or other antigens.

immunosuppressive—tending to suppress the immune system and its response.

incidental (or accidental) host—animal or plant that harbors an organism that is not ordinarily parasitic in the particular species.

inflammatory response—protective response elicited by injury or destruction of tissue and marked by localized pain, redness, swelling, and elevated temperature.

in vitro—literally, "within a glass"; occurring in a test tube or other artificial environment rather than in a living organism.

latent—present but not manifest; a latent viral infection is one in which no virus can be found but in which the infected cells retain the potential to produce virus under certain circumstances.

lyse—to destroy or be destroyed.

lysogenic conversion—alteration of a cell's properties by a prophage carried within it.

lysogeny—state of a bacterium harboring a prophage, but not producing phage.

lytic cycle—viral life cycle involving infection of a cell and multiplication of virus within the cell resulting in cell death (lysis) with release of infectious virus particles.

microbiology—the study of minute living organisms (microbes),particularly those capable of causing disease in animals, and including bacteria, protozoa, and fungi.

micron—0.001 millimeter or 0.000001 meter.

millimicron—0.001 micron.

multivalent—having several specificities; a multivalent vaccine is one which produces antibodies against three or more organisms or types of one organism.

mutant—cell or organism that has undergone a sudden genetic change; genetic variant.

Negri bodies—accumulations of viral particles showing up as oval or round bodies in nerve cells of rabid animals.

neutralizing antibody—antibody that, when mixed with the corresponding infectious agent, reduces its infectivity.

nonpermissive—not supportive of the multiplication of a particular virus.

nonproductive (infection)—one that does not result in the production of infectious virus particles.

oncogenic—producing tumors.

particle—single unit of virus.

passive immunity—immunity produced by the administration of preformed antibody or immune cells.

permissive—supportive of the multiplication of a particular virus.

persistent—long-term, chronic.

phage—short form of "bacteriophage" (a virus that infects bacteria).

pock—mark or spot made by poxviruses on embryonic membranes, skin, etc.

productive (infection)—one that results in the production of infectious virus particles.

prophage—the latent stage of a phage in a lysogenic bacterium.

quarantining—isolating because of known or suspected infection with a contagious disease.

reagent—substance used to produce a chemical reaction.

repressor protein—molecule that acts to prevent the expression of one or more genes or of a prophage.

reservoir—carrier of a virus (or other parasite) which does not itself show signs of illness, but from which the virus may be transmitted to individuals who then do show signs of infection.

ribonucleic acid (RNA)—long molecule that serves as the genetic material in many viruses, plays an important part in protein synthesis in cells.

serologic—pertaining to the observation of antigen-antibody reactions *in vitro*.

serum—liquid portion of blood remaining after clot has formed.

temperate (virus)—a virus able to become a prophage.

transducing phage—lysogenic phage that carries genes from one bacterial cell to another.

ultracentrifuge—centrifuge with such a high rotational speed that it can separate the large molecules of a mixture.

vaccination—originally, the injection of cowpox vaccine for the purpose of inducing immunity against smallpox; later generalized to refer to the administration of any vaccine.

vaccine—suspension of weakened or killed microorganisms administered for the prevention or treatment of an infectious disease.

variolation—deliberate inoculation with unmodified smallpox virus to produce immunity to the naturally occurring disease.

vector—carrier, especially the insect or other agent that transfers an infective agent from one host to another.

vertebrate—animal with a vertebral column (backbone) or internal skeleton; member of the subphylum Vertebrata.

viremia—the presence of virus in the blood.

virion—individual particle or unit of virus.

viroid—minute infectious agent made up of RNA.

virologist—scientist engaged in the study of viruses.

virology—the study of viruses.

virulent—highly infective; malignant, deadly.

virus—one of a group of minute infectious agents, usually too small to be seen under the light microscope and characterized by a lack of independent metabolism.

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