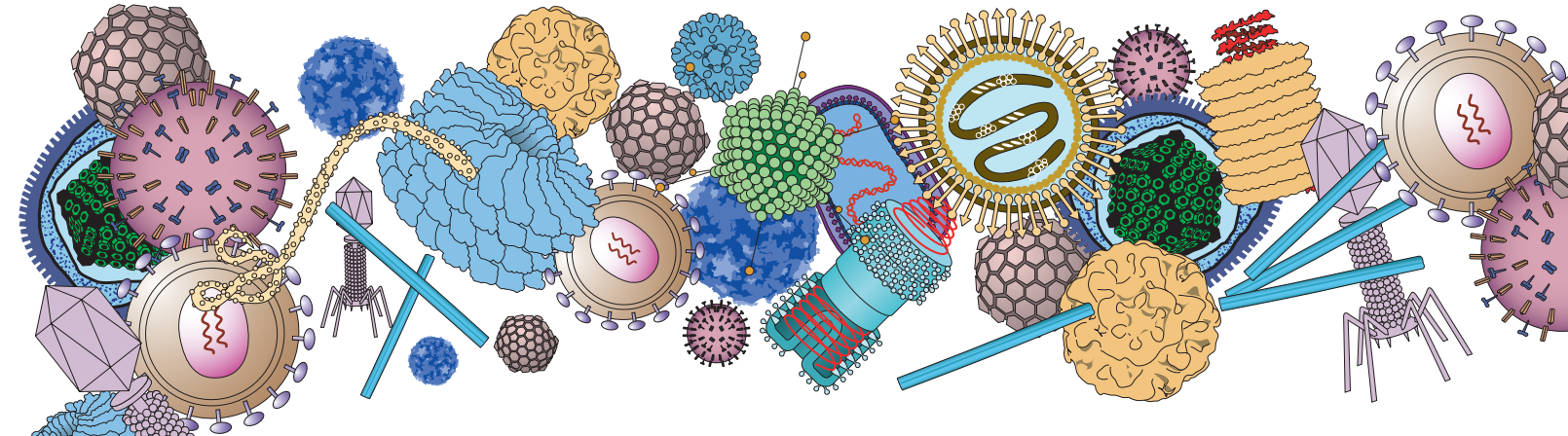
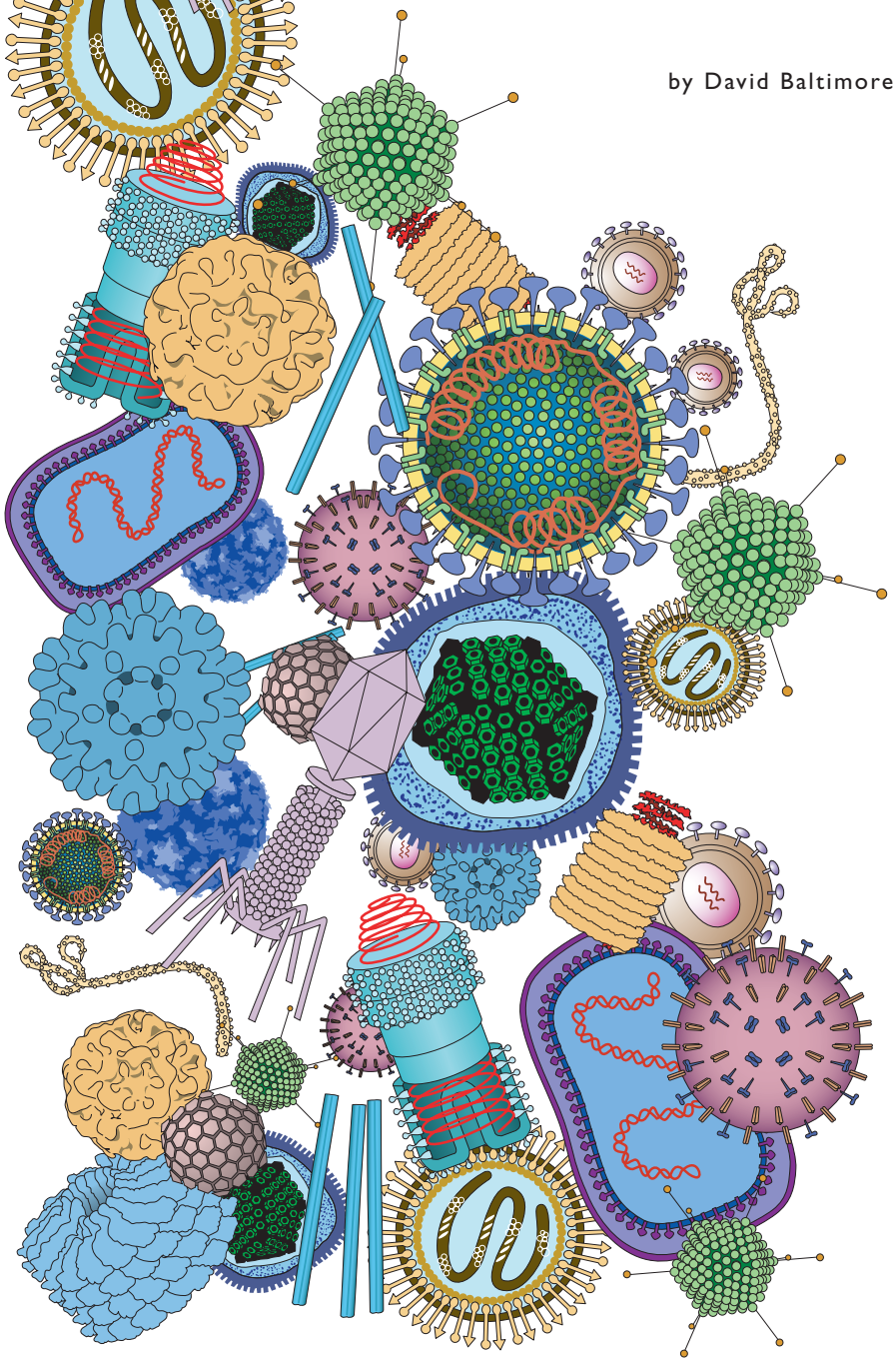


# Viruses, Viruses, Viruses

by David Baltimore



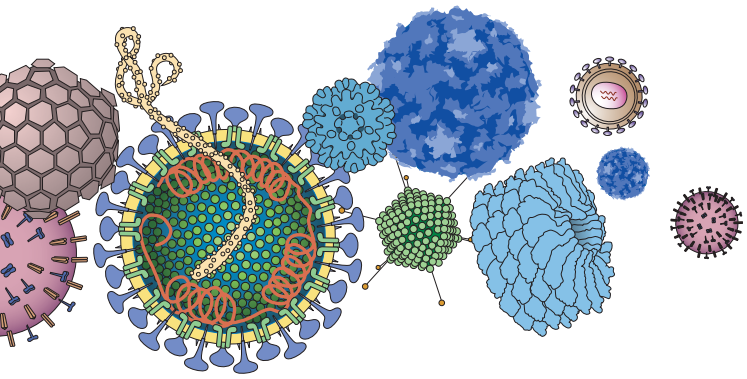
Almost every day some virus or other makes news—HIV, SARS, smallpox as a bioweapon, last fall's new flu, and, most recently, the avian flu in Southeast Asia. But it's my impression that most people don't know what a virus *is*. So, since viruses have played a critical role in my professional career, I felt that I was in a good position to be useful and explain a bit about them.

Viruses exist in uncountable variety, since every animal, plant, and bacterial species has its own set of them. It's not sufficiently interesting for anyone to bother to find out how many different viruses exist on every obscure species, so I think we'll never really know the extent of these tiny devils. But scientists have already isolated tens of thousands of them. You can observe them in an electron microscope, get an idea what their shape is, do a little molecular biology, put them in their place relative to other viruses, and thus classify them. We now recognize more than 1,500 species of viruses, each one of which can be broken down into subspecies and further.

The notion of a virus goes back only to 1892, when Ivanovski in Russia showed that a filter that would hold back bacteria would pass the agent that caused mosaic disease in tobacco. That agent, he realized, is much smaller than a bacterium. Bacteria were at the limit of a light microscope's resolution, so no one could see these objects then; all they knew was that they were very small.

In 1911 Peyton Rous discovered that one agent that passed through bacterial filters could cause cancer. This was one of the seminal experiments in cancer research, but because such tiny agents were difficult to conceive of, the work wasn't immediately appreciated. Rous finally won the Nobel Prize in 1966, 55 years later; it took that long to realize how critical his discovery was to unraveling the problem of cancer.

When the electron microscope was invented around World War II, the first pictures could be taken of viruses. Then scientists could see that the



We now recognize more than 1,500 species of viruses, each of which can be broken down into subspecies and further.

particles were indeed very small, in the range of 25 to 100 nanometers ($10^{-9}$ meters; by comparison, the wavelengths of visible light are 380–780 nanometers). From chemical analysis, we learned pretty quickly that viruses consisted mostly of protein and that they contained either RNA or DNA. Of course, by the 1950s, it was clear that DNA was the hereditary material of higher organisms, bacteria, and many viruses, so it was a bit of an anomaly that some viruses didn't have DNA. But it was demonstrated in 1957 that the RNA isolated from a plant virus was infectious, showing that RNA could be hereditary material just like DNA.

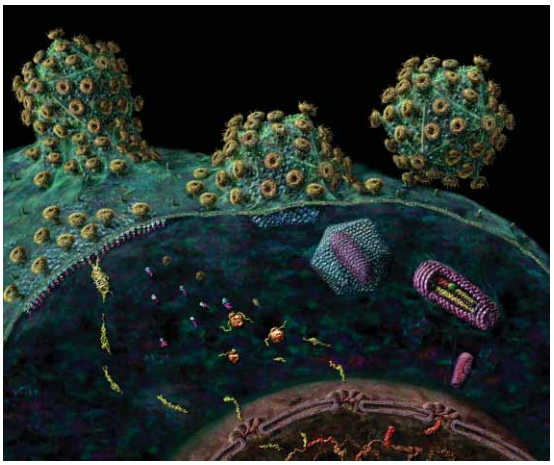
Hermann Muller, a great drosophila geneticist, wrote a paper in 1927 saying that because viruses are so small, there's just no space in there for anything other than the hereditary material of life. That insight, which took many years, and the advent of molecular biology, to prove, was actually the key to understanding viruses. Viruses are, in fact, protein shells packed full of genetic information. They have no cellular machinery (or at most, very little) of their own.

Viruses can grow only inside of cells. They can't multiply in the environment and are to some extent dead objects there. There's a running debate about whether viruses are alive or dead because, when you crystallize them and they behave like crystalline proteins, they're like dead chemical objects. (Bacteria, on the other hand, are definitely living organisms.) And yet, when allowed into a cell, they can hijack the total metabolism of the cell (in minutes in a bacterium, hours in a mammalian cell) and completely reprogram that cell so that the only thing it can do effectively anymore is make more viruses.

To that extent I think they're about as alive as anything. In a cell they can multiply extremely rapidly, a thousandfold in six hours. But to stay alive, since they have to grow inside cells (and cells exist only as parts of living beings), they have to spread from host to host. That's a tough way to earn a living, especially when the host has an immune system, as we do, and can fight off the virus. Usually, when we get a virus infection, our immune system is activated and within days is making antibodies and T-lymphocytes that can attack viruses and virus-infected cells and clear the virus from the body within a week. That, for instance, is the course of the common cold.

So, the virus has to pass to another host before the immune system revs up and inactivates it. If it doesn't pass to at least one other individual before the immune system clears it, it dies out. If at each instance of infection it is able to infect one more person, it effectively lives forever. Measles virus, for instance, passed continually from person to person, used to spread very widely before we had a vaccine. Young children usually got it, and when they got over it, they were immune thereafter; the immune system has a wonderful memory of what it has seen before. But when some isolated populations who had never seen measles were exposed, it was devastating to them because they had to fight it off as adults. For one reason or another, young people usually fight off viruses much better than older people do.

When viruses pass from one organism to another, they adapt to that host; viruses of humans adapt to the specific ways that humans interact. We shake hands; that's one of the best ways to pass viruses. I think the Japanese learned to bow because they realized they stayed healthier if they bowed to one another rather than shaking hands. When I feel as if I have a virus disease, I just don't shake hands with people. (I have to explain so they don't get insulted.) Sneezing and coughing, obviously, are good ways, but mostly just in the immediate local area, because a sneeze dries up very rapidly in dry air. And then there are other wonderful things we do, such as kissing and sex, which provide the opportunity to pass viruses as well as sentiments.



**To escape a cell and venture out to find new hosts, the human immunodeficiency virus sends out its viral proteins (the yellow squiggles at left) and implants them in the cell's outer membrane. When the virus buds off the cell, it carries with it a piece of the cell membrane, now studded with proteins that can recognize and infect new cells. (Copyright Russell Kightley Media, rkm.com.au)**

Over many, many years, viruses have adapted to our way of life. If you put one of our viruses in a mouse, it won't survive because mice don't kiss or shake hands, and they don't raise their kids in communal kindergartens. The fact that viruses have become attuned to our lifestyle is wonderful in one way: it means that if you eradicate a particular human virus, it will never come back, because it can exist only in humans. That is, in fact, what happened when a worldwide vaccination campaign got rid of smallpox. Lots of other species have related pox viruses, but they're not adapted to us.

Stopping the spread of smallpox faced the world with a difficult decision: whether or not to get rid of all the smallpox stocks that exist in the world's laboratories. An edict came down from the World Health Organization: yes, we should make smallpox extinct, but an exception was made for two laboratories, one in the United States and one in the Soviet Union.

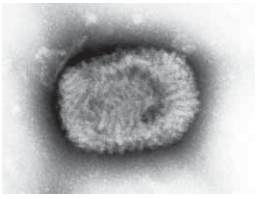
Why do we keep it at all? I am one of those who believe that we should totally get rid of it. It only continues to exist because some people got sentimental over smallpox. Environmentalists, in particular, feel that we should never eradicate a living species. Of course it happens all the time, but this would have been conscious, and some people felt bad about it. To be fair, the environmentalists were joined by a large number of virologists who did not want to see an object of their potential inquiry taken from them.

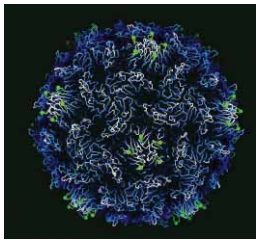
The question also arose as to whether some countries lied. We're still worried that there are caches of smallpox held by rogue governments or terrorists that could be developed as bioweapons. Since vaccination ended when the virus was eradicated, we are defenseless against it now.

Polio is another virus that has been virtually eliminated by vaccination and very conscious activity on the part of the World Health Organization. A few places in the developing world (India, in particular) still have outbreaks of polio, but there hasn't been any polio virus in the Western hemisphere for a couple of decades.

Because viruses multiply inside cells, they are faced with the problem of exiting from the cell. They have found two solutions: they can either break the cell open, or they can bud off the cell's surface, carrying the outer membrane of the cell with them. In the second mode, the virus modifies the cell's outer membrane by insertion of one or more viral proteins. This protein is picked up by the budding virus and endows the virus with the ability to recognize new host cells and infect them. Both of these ways of escaping the cell are pretty efficient, but the budding process is the most insidious because it doesn't kill the cell and can continue for the life of the cell.

**Top: Electron micrograph of the smallpox virus. (Courtesy of F. A. Murphy, School of Veterinary Medicine, UC Davis.) Bottom: Computer model of the polio virus. (Courtesy of James Hogle, Harvard Medical School.)**





### Molecular biology of viruses

We know an enormous amount about many viruses today, but it was only when molecular biology was born that they began to make sense. So let me give you a very brief course in molecular biology. The nucleus of a cell has chromosomes in it; the number varies from species to species. If you unravel those chromosomes far enough, you see that they contain supercoiled molecules of DNA. When you uncoil the DNA, you see that it's a double helix, held together by cross bridges of complementary chemical bases, which are paired up. That's almost all the molecular biology you really need to know. When Watson and Crick published their famous paper in 1953 describing this structure, it became obvious what was going on at the basic level: the DNA was encoding the structure of proteins. And it also became clear (although it took some time to prove it) that the way to duplicate this molecule took advantage of the fact that the two strands are redundant; they carry the same information, because a pairing rule determines their structure. The duplication of DNA, therefore, involved unwinding the duplex

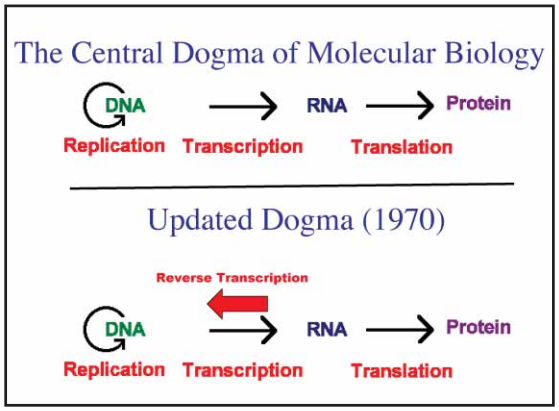
and duplicating each strand individually.

The one other thing you need to know about molecular biology is that it has a central dogma. That dogma says that DNA duplicates itself (replication); that RNA is made from it (transcription); and that RNA is the key material that directs which proteins are in the cell (translation). The proteins do the work of the cell; they're the muscles in the structure of the cell itself. That *was* the central dogma until 1970, when Howard Temin (PhD '60) and I did an experiment that showed that you can also reverse-transcribe RNA back into DNA. At the time, that looked like a particular characteristic just of viruses, but we now know that it happens a lot in the life of cells, especially over evolutionary time. In fact, about 50 percent of the genetic material that we carry around in each of our cells arose by reverse transcription.

Many of the discoveries in molecular biology depended on working with viruses, particularly bacteriophage, a virus adapted to bacteria. The great gods of bacteriophage research were Max Delbrück, here at Caltech, and Salvador Luria, first at Indiana University and then at MIT, where he was my mentor. It was with bacteriophage that A. D. Hershey and Martha Chase at Cold Spring Harbor demonstrated that DNA was the hereditary material, and that Seymour Benzer (now the Boswell Professor of Neuroscience, Emeritus, at Caltech) showed that genes had a fine structure that corresponds to the individual nucleotides in the DNA. It was also at Caltech that experiments using bacterial viruses showed that RNA carried the information from DNA to protein.

Mammalian viruses also played their role. Our discovery of reverse transcriptase came from mammalian viruses, as did splicing, a process by which the transcript RNA is cut up and certain sections are removed. And plant viruses showed us that RNA is able to act as a genetic material. We thought this was an oddity at the time; it doesn't happen in any other class of organisms. But it was the first clue to what was probably a very important stage in evolution, when there was an RNA world in which DNA had not yet evolved. Life back then depended on the genetic abilities of RNA, as well as on its protein-like catalytic capability.

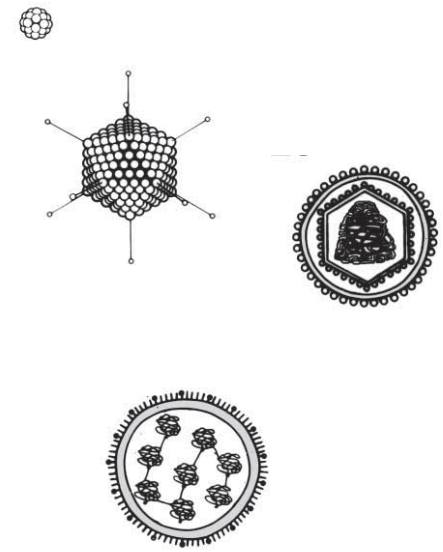
**Ever since DNA's double-helical structure was discovered in 1953 and its role in encoding proteins became clear, it was assumed that DNA copies itself, that RNA is made from it, and that RNA directs the making of proteins. In 1970, the discovery of reverse transcriptase proved that the process can work backwards—that RNA can transcribe itself back into DNA. It was work with viruses that led to this discovery and to the Nobel Prize.**




**Below: Max Delbrück (left) and Salvador Luria, shown here at Cold Spring Harbor in 1953, worked with the bacteriophage virus in making many of the early discoveries in molecular biology.**

## Equilibrium and Nonequilibrium Viruses

Let's get back to how viruses are adapted to individual species—to us, in particular. These I call equilibrium viruses, because they live in equilibrium with us. They know how to keep passing from person to person, but they're not terribly lethal. They may kill a few people (smallpox killed more than a few), but, in general, the equilibrium viruses that occasionally give us colds are not a very big danger to us. Many people, including me, think that part of a virus's



**Viruses come in all shapes and sizes. From top: the tiny picornavirus, the larger adenovirus, the reverse-transcribing retrovirus, an orthomyxovirus, a coronavirus (the cause of SARS), the bullet-shaped rhabdovirus (rabies), and a poxvirus, showing exterior and interior. (Courtesy of F. A. Murphy, UC Davis.)**

evolution is that it adapts to its host species in ways that keep its host alive so that it can continue to infect the host's children.

But when an equilibrium virus in one species jumps into another species, it becomes a non-equilibrium virus. Such a virus will rarely spread well in a population because it's not well adapted to the new species' lifestyle. A few people may get it from an infected monkey or rodent; it can be highly lethal, but it's not likely to cause an epidemic in the overall population. It *could* become an equilibrium virus in the new species, but only over a long time.

We guess that HIV first jumped into the human population in the 1930s and certainly no later than the 1950s. Yet it's clearly not an equilibrium virus. It is highly lethal, but only over a long time; it is spread among people, but not efficiently, requiring either injection or sexual contact. It and flu, which are the two nonequilibrium viruses that most bother us, do not follow the rule of poor spreading as a guest in the population, because they are able to pass well enough from person to person that they can be a serious problem.

Equilibrium viruses include polio, smallpox, measles, mumps, herpes, most of the common cold viruses, and lots of others. Among the non-equilibrium viruses are the influenza, HIV, SARS, Ebola, and Hantaan viruses. Flu is the oddest, because it clearly passes around among us as if it were an equilibrium virus. But one of the reasons it can be so devastating is that it is constantly regenerating from a reservoir in wild birds. We believe the birds infect domesticated ducks, they in turn infect pigs, and the pigs infect people. This all generally happens in China—until it finally breaks out of China by finding a ship or an airplane or some other conveyance, and becomes a part of our circulating pool of viruses. It's the only virus I know of that can jump out of another species and adapt itself rapidly enough to the human species that we pass it around as if it were one of our own.

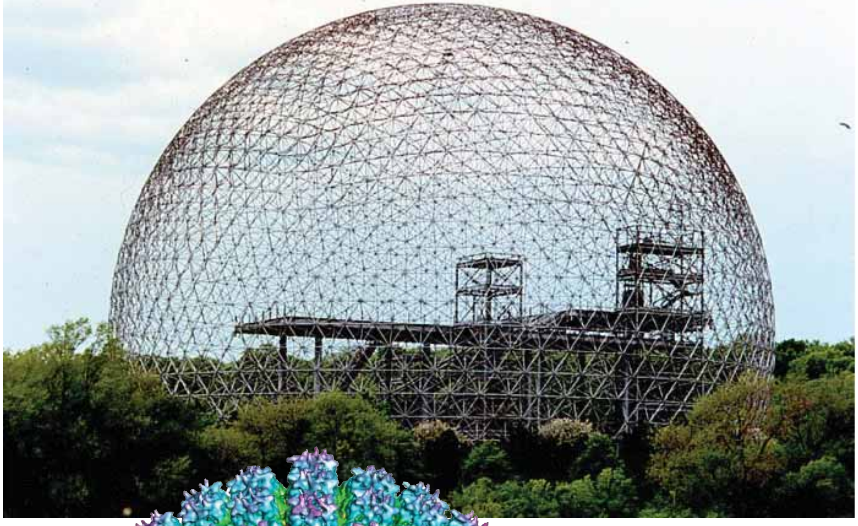
SARS came from an as yet unknown animal, maybe a civet cat. It originated in China and was carried out of that country by people traveling to Canada and other places, where local epidemics then began. The virus never started a serious epidemic in the general population. Most cases occurred in hospitals or in medical personnel; a couple of cases spread in an apartment house. But there was never a real epidemic.

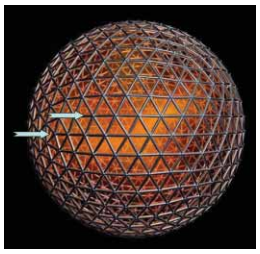
## The amazing variety of viruses

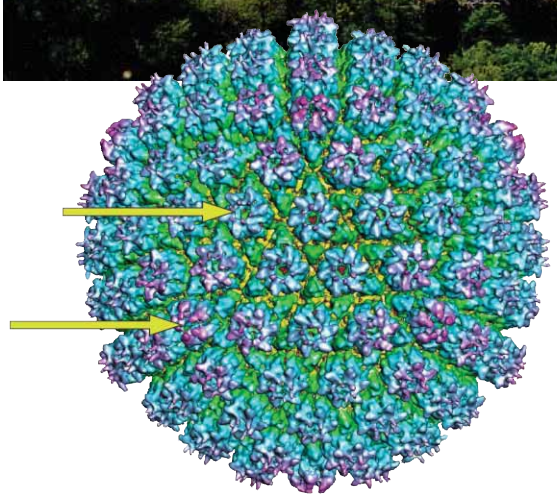
Viruses come in an astonishing assortment of shapes and sizes and have evolved some quite remarkable features. What I'd like to do now is examine some individual viruses and look closely at what's interesting about each of them. Some, like parvoviruses and picornaviruses, are extremely small, only about 25 nanometers across, just big enough to package an RNA or DNA molecule inside. The bigger adenovirus can accommodate a much larger piece of DNA. Particularly large RNA viruses include retroviruses like HIV and coronaviruses, of which SARS is an example. All these are spherical in shape, but then we have things like the bullet-shaped rhabdoviruses and the complicated poxviruses. A poxvirus makes more than a hundred different proteins and is much closer to being an actual organism than most of the others.

Herpes simplex is a large, spherical virus, which I'd like to discuss from the point of view of its structure. Herpes, related to the viruses that cause chicken pox, infectious mononucleosis, and shingles, is the virus of cold sores. (A close relative, herpes simplex type II, causes genital herpes.) It has a way of passing from person to person that most other viruses don't have. Its size enables it to encode some special mechanisms, one of which is the ability to sneak into nerve cells to hide and emerge later. The herpes virus hides in the nerve cells in the brain and comes back out later to cause cold sores on our lips, which can then pass the virus on to a new host. Other kinds of herpes viruses hide in other parts of the nervous system, emerging occasionally to cause problems such as shingles.

The computer model of the inner core of the herpes virus on the next page illustrates the







**The icosahedral symmetry of the herpes virus (right) is the key to encoding the proteins that repeat to form its coat. It's a symmetry made up of fives and sixes. Most of the blue and purple subunits (proteins) are surrounded by six others (top arrow), but some (bottom arrow) have five neighbors. (Courtesy of Z. Hong Zhou, U. of Texas Medical School, Houston.) The same symmetry is the basis for Buckminster Fuller's geodesic dome structure (top), which can be seen more clearly in the Fuller globe next to it. The top arrow points to a hexagon, the bottom arrow to a pentagon.**

answer to a very important question, raised years ago by Watson and Crick in another, not-so-famous, paper: Where does all the information come from to make the viral protein that coats the DNA or RNA with a complex protein shell? The answer lies in the virus's symmetry, which allows one protein to be used over and over again. This is the nature of viruses: they encode one or a small number of coat proteins that know how to aggregate themselves into beautiful shapes that enclose space—and the DNA or RNA is in that space.

The nature of this symmetry is quite interesting. Most of the proteins in the model are surrounded by six other proteins (top arrow). But you can see some (bottom arrow) that have five neighbors. So this is a funny kind of symmetry; it's not exactly the same over the whole surface. Actually called quasi symmetry, it's made of fives and sixes.

Buckminster Fuller didn't know anything about viruses when he developed these principles himself. He realized that he could enclose space with an elegant structure, one that is light and simple because it uses the same parts over and over again. It's hard to see on the actual geodesic dome above, but it's easier on the adjacent model of the complete Fuller sphere. The top arrow indicates six units around a point, and the bottom arrow points to one with five. (Most of them are sixes; other fives are hard to find.)

Fuller's design is basically that of an icosahedron. Icosahedra have 20 triangular faces, either fives or sixes at the vertices. If you place hexagons (sixfold symmetric objects) next to one another, they form a flat surface, like old-fashioned bathroom tiles. But if you try to do that with pentagons, it won't work. You have to tilt the pentagons around to make the edges meet, and when you do, you get a classic solid, the dodecahedron. So five is something that leads to curvature, while six is flat. That's what is going on in the Fuller dome: the curvature of the dome, which leads ultimately to a spherical form, comes from the fivefold axes, while the sixfold axes just tile a flat or slightly curved surface. Another well-known example is the buckyball (named for Fuller), a natural chemical form of carbon.

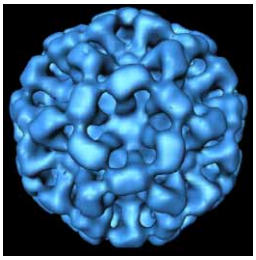
I'm very taken with this quote from Buckminster Fuller:

> When I am working on a problem,
> I never think about beauty.
> I think only of how to solve the problem.
> But when I have finished,
> If the solution is not beautiful,
> I know it is wrong.

That's not exactly a scientific proof, but when Watson and Crick published their structure of DNA, what convinced so many people it was right was its beauty.

Viruses enclose space with this same elegant geometric symmetry. Poliovirus, much smaller than herpes, also encloses its space on the principle of icosahedral symmetry, as does Norwalk agent. But I'd like to discuss Norwalk agent from the point of view of how it's spread. Most viruses are unstable in the environment. If you sneeze out a stream of droplets containing virus particles, and the droplets have a chance to dry, the forces of drying are so great that the virus is ripped apart and is no longer infectious. But this isn't true of Norwalk, which is quite resistant in the environment. That's why it has become known as the

cruise-ship virus. It created a number of mysterious illness outbreaks and headlines last fall, some of them (62 people in a Canadian mounted-police academy, 74 at a wedding) on land, but it's the cruise ships that give us the really impressive statistics, where hundreds can be infected on a single cruise. Norwalk infections are estimated at 23 million cases per year in the United States, and most of these are actually on land. Most of them are probably mistaken for something else, because the illness looks very much like food poisoning. I'm not a physician or an epidemiologist, but I think that a large fraction of people who get what they think is food poisoning have actually come in contact with Norwalk agent. Food poisoning comes from a bacterium, which causes a fever along with the other disagreeable symptoms. Norwalk doesn't cause a fever, and you get over it quickly. So, most of the cases of overnight distress that you blame on the restaurant you just visited may have had nothing to do with food but rather came from some other infected individual you interacted with over the previous few days.

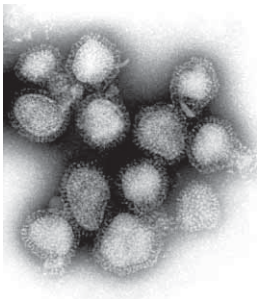


**A computer model of the Norwalk virus. (Courtesy of B. V. V. Prasad, Baylor College of Medicine.)**

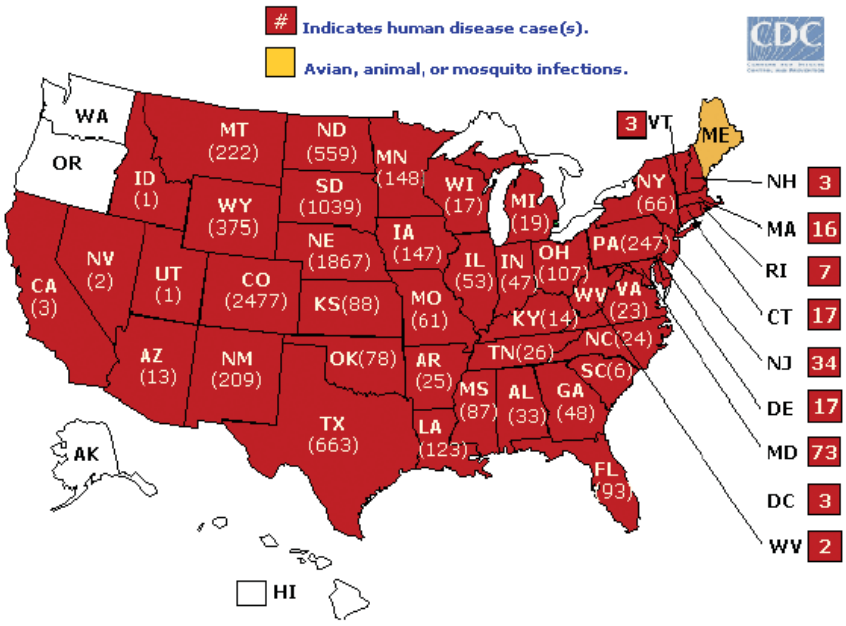
Plants also have a lot of different viruses, as many as animals do, some icosahedrally symmetric, some helically. There are, for example, more than 30 viruses of beets alone. Beet growers know all about these viruses, but the rest of us fortunately are spared having to acquire this knowledge. I don't know of any case of a plant virus infecting a human, but they have been known to infect insects. Plant viruses are, actually, responsible for one of the few *good* things viruses do; they can cause beautiful streaking in flowers. In the 17th century, this led to the first widely known financial bubble, when the Dutch became obsessed with ornamental tulips and were willing to pay enormous sums of money for them. The most expensive tulip bulbs were the virus-infected ones with streaked petals. So the tulipmania bubble, which had many of the same properties and craziness as the recent Internet bubble, was caused by a virus.

Influenza virus, which kills more people annually than any virus besides HIV, has a very particular property. Rather than having one long piece of genetic material, as most viruses do, it has eight separate pieces. This gives it the ability to recombine itself with other influenza viruses. So, human and bird influenza viruses can infect the same animal, say a pig, and reassort their RNAs in that animal. This reassortment is one of the reasons we get so many new flu viruses. Since flu varies all the time, it never really reaches a nice equilibrium, so we can't make a general vaccine that will protect us against it once and for all. But we can make a vaccine that varies from year to year by modifying just one piece of RNA. We can also take advantage of the viruses' reassortment strategy to make a vaccine by inserting a new RNA molecule that will interfere with its multiplication.

**The stripes in tulip petals are caused by a virus, one of the few nice things that viruses do.**



**Electron micrographs of the influenza virus (above) and the Ebola virus (right). (Courtesy of F. A. Murphy, UC Davis.)**

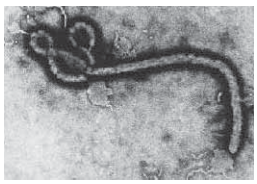



**Starting in 1999, when it first hit New York, West Nile virus has spread across the country, carried by mosquitoes. Although as of February 2004, as illustrated here, it's still quite rare in the West, it's permanently established in the country and unlikely to be eradicated.**

The trick to making a flu vaccine for a particular winter flu season is to be able to guess more than six months in advance the strains that will circulate. In the winter of 2002–03 the Fujian strain that circulated was a surprise, and the vaccine lacked representation of that precise strain. The best guessers in the world simply guessed wrong. The vaccine gave at best partial protection. The flu epidemic started early and promised to be quite severe, but then it suddenly diminished quite dramatically in early winter.

West Nile virus is interesting because, while it naturally infects birds, it's carried by mosquitoes. Mosquitoes, in turn, can infect humans (and horses). More than 99 percent of infected people are asymptomatic and never know they had it, but there's no danger of them passing it on to others, because it's a nonequilibrium virus. Some fraction of people (and we don't know what's different about them) develop a fever, and some cases even progress to infections of the brain, which can be fatal. West Nile does cause a significant number of deaths, and we don't yet know how to vaccinate against it. The only way we know how to protect ourselves is to avoid mosquito bites.

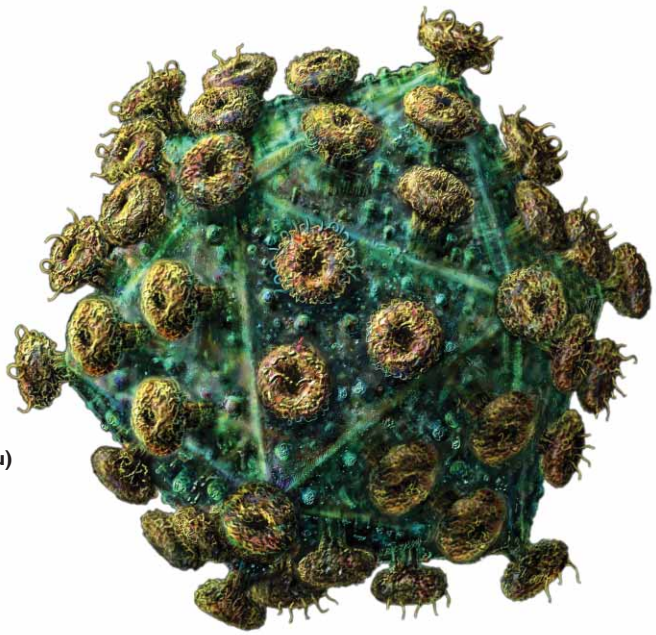
West Nile virus was discovered in 1937 in Uganda and spread widely in Africa and the Middle East over subsequent decades. It's amazing that it didn't reach the United States until 1999, when a few cases were discovered around New York. Then it began to spread. In 2003 there were 9,136 cases and 228 deaths. The year 2002 saw 284 deaths. But the frightening thing about it is that it's now permanently established here. No one believes that we can eradicate it with anything we know about today, because it winters in an animal reservoir, particularly mosquitoes. At least it's good for the mosquito-repellent industry. And even though it has spread widely, there are still very few cases west of the Rocky Mountains. I don't know if that's because the virus finds it difficult to maintain itself in the West, or if it's just a matter of time before we have as big a problem as the East and middle of the country.



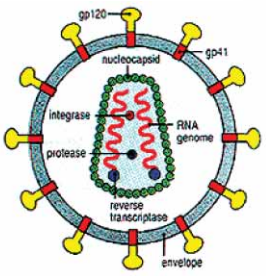
Ebola is a virus of helical symmetry, long and convoluted because it's not rigid. It looks aggressive and is aggressive. Like other viruses, Ebola is not one fixed virus but a complex family of viruses. We can get the complete RNA sequence from each outbreak and construct a tree that shows how closely related they are. For example, the Ebola viruses isolated in Gabon in 1994 and 1996, and in Zaire in 1995 and 1976, are very similar, indicating that there must be an animal reservoir in that part of Africa. No one can find it, although they've looked very hard. It's probably an equilibrium virus in some rodent living in the forest or bat living in a cave, and it may not much bother the animal species that maintains it in equilibrium. It's always the same virus coming out again and again. Other Ebola viruses, slightly different in their RNA, have broken out farther away, in the Ivory Coast and Sudan, where they must reside in other reservoirs—different but related. Then there's a very strange set of Ebola viruses that appeared in Reston, Virginia, and starred in the book and movie *The Hot Zone*. Interestingly, these viruses infected monkeys, not humans, but because of its reputation in Africa, the fear was that it would spread to humans. Still another Ebola-like virus, Marburg agent, very different from all the rest, erupted in Germany in 1980, killing a significant fraction of the people it infected before it was quickly contained.

## HIV, THE WORLD'S MOST SERIOUS HEALTH CHALLENGE

HIV (human immunodeficiency virus) has a beautiful, very unusual internal structure. For unknown reasons, it's asymmetric. HIV is not known for its beauty, however, but for its relentless and lethal effects. The horrifying statistics from the end of 2003 show 40 million people infected with HIV/AIDS worldwide. This past



**The little studs projecting from the surface of the human immunodeficiency virus (HIV) are the proteins that enable the virus to attack and enter a cell. (Copyright Russell Kightly Media, rkm.com.au) HIV has an unusual asymmetric internal structure (below).**




year brought 5 million new cases and 3 million deaths, more deaths than tuberculosis and malaria, which were the two greatest infectious killers in the world until HIV came along. In some African countries, life expectancy has been reduced by more than 20 years. This is an epidemic on a scale that we have not seen in modern times, and we should be doing a lot more about it than we are.

What kind of response can we make? We have been very good at making drugs to combat it. The pharmaceutical industry rose to the occasion and makes a lot of money selling drugs that slow down the infection's development enormously, even if they don't cure it. Many people are living today who would have been dead 10 years ago without these drugs. It's a great success story, but not a perfect one; these drugs are very expensive, and they require a lot of attention from the patient. So they have not been transferred into the developing world with any efficiency. This may be changing now with the money coming from the Gates Foundation, the U.S. government, and elsewhere to make these drugs more available.

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Education has also worked. Educating people about a sexually transmitted disease is a very difficult job, but the programs in Uganda and Thailand have been very effective, reducing transmission by 60 to 80 percent. But education, also employed in the United States, requires constant vigilance. For instance, new cohorts of young men entering a gay lifestyle must continuously be taught to protect themselves.

But the right answer for protection against a virus is a vaccine. A vaccine preprograms your immune system so that the memory protects you forever, without your having to be exposed to the virus. The scientific community has been trying to make a vaccine against HIV since the day the discovery of the virus was announced. Margaret Heckler, then secretary of the Department of Health and Human Services, got up in front of the press in 1984 and said, "We've discovered the virus; we know what it is; we'll have a vaccine in a year or two." She could not have been more wrong, but I can understand why she said it. We had been so successful making vaccines against smallpox, polio, measles, mumps, and lots of other viral diseases. But, while the immune system controls all the other viruses pretty well, it can't control HIV, for a set of complex reasons. That makes a vaccine very difficult. The truth of the matter is that we're not even sure we can make a vaccine. We *can* vaccinate monkeys against a related virus, and we *can* show that in certain cases people can be protected by their immune system, but there has been no successful efficacy trial of any vaccine against HIV.

HIV, oddly enough, may give us a way of doing the only other good thing viruses can do (besides striped flowers). Viruses, as we've seen, are able to bring genes into cells. And if we can splice good genes into a virus, we can get those genes into cells in place of the damaged ones (gene therapy). In my lab and in laboratories around the world, we are trying to use genes to turn the HIV viruses on themselves and actually make them valuable. The idea is to use a stripped-down version of the virus to carry into cells genetic components that can interfere with the growth of the real virus. It works in the lab, but it will be a while before we can know if it works in people.

Last but not least of our headline-making viruses is SARS, a coronavirus, so called because the proteins, strung on a long stalk surrounding the virus, resemble a halo. Thanks to modern molecular biology, the SARS genome was sequenced within weeks after the virus was discov-

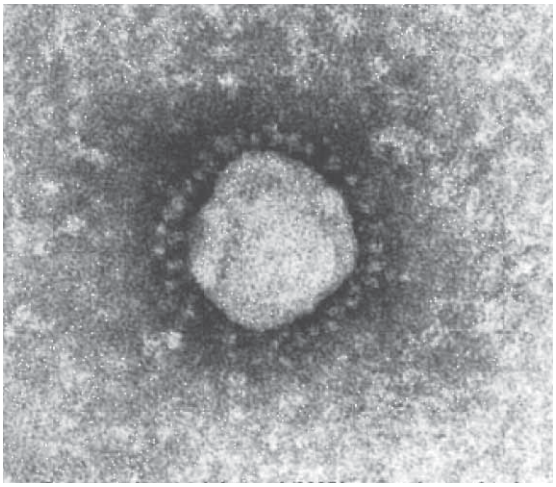
This huge reservoir is not going to just sit there and stay in its species; some of the viruses are going to jump over to our species. We should consider this at least as much of a challenge as bioterrorism.

ered. Comparison to other known coronaviruses showed that it was on its own branch of the genetic tree, which told us instantly that this was a virus we had never seen before. It was something brand new. The sequence also told us about all the proteins the virus makes. Many of them turn out to be quite unusual, and it will take years to figure out what they all do.

SARS (severe acute respiratory syndrome) started in China in November 2002. The last case was found in June 2003 (with the exception of two separate cases in laboratory workers who were infected from lab samples). The number of cases topped out at 8,098, with 774 deaths, none in the United States. There is no evidence that there was a large number who were infected but not symptomatic (as, for instance, with West Nile virus). This is fortunate, because it means that the 8,000 is not really 800,000. Some experts claim there's a reservoir somewhere, probably in humans, and predicted that it would come back again in the fall of 2003. This is the standard thing viruses do—come in November and leave by June, like flu or the common cold. In October my forecast was that SARS would not reappear, that it's gone, and that the only place it exists now is in some unknown animal reservoir in China. Could it come out again? Yes, it could, but the Chinese should be ready for it next time, and it should be quickly contained. So far my prediction has held up.

The bottom line is that it's these non-equilibrium viruses that we need to be concerned about. They emerge from a huge pool in nature to cause havoc among us. Although I don't see SARS in our future, we have to expect that more viruses will emerge. This huge reservoir is not going to just sit there and stay in its species; some of the viruses are going to jump over to our species. We should consider this at least as much of a challenge as bioterrorism. In fact, it's sort of nature's own bioterrorism and, fortunately, similar. We can employ the same public health skills that have been put on alert to deal with bioterrorism to watch out for viruses coming out of nature. SARS was a good rehearsal. □

PICTURE CREDITS: 20-21 – Doug Cummings; 23 – Caltech Archives; 26 – Free Foto



**The SARS virus is a coronavirus, so called because of the garland of proteins that surrounds it. The SARS genome was sequenced only weeks after the virus was discovered.**

*David Baltimore, Caltech's president since 1997, has good reason to appreciate viruses; he's been studying them for a long time. He won the Nobel Prize in 1975 for his discovery of reverse transcriptase, an enzyme that allows a strand of RNA to copy itself back into DNA—work published in 1970 that came out of his research on how cancer-causing RNA viruses manage to infect a healthy cell. The discovery added significantly to scientists' understanding of retroviruses such as HIV. Baltimore earned his BA in chemistry from Swarthmore College in 1960 and his PhD in biology from Rockefeller University in 1964. He was founding director of MIT's Whitehead Institute and spent most of his professional career at MIT (except for a few years at Rockefeller University, as a professor and president) before coming to Caltech. From 1996 to 2002, he has chaired the National Institutes of Health AIDS Vaccine Research Committee. This article was adapted from Baltimore's Watson Lecture last fall.*