Viruses: New Light on an Old Enemy

by Roger Lewin

CANTERBURY, ENGLAND

A virus's ultimate ambition is to live forever. And judging by what researchers are discovering about these minute molecular entities, it seems that many of them have learned how to achieve this Methuselan goal.

The trick, it appears, is for the virus to inveigle itself deep into its host's genetic material so that it gets passed from generation to generation without any effort of its own. Scientists at the Sixth Harden Conference of the Biological Society, held in Kent, England, were forced to admit that many more viruses can perform this trick than they ever thought likely, even as little as a year ago.

Research on the relationship between viruses and their hosts has taken giant strides recently: Using brilliant new techniques, researchers can now detect small fragments of viruses that lurk within the host's genetic material (DNA). It is principally through this technique that researchers have discovered that many viruses do not—as was once thought—simply enter a cell, multiply themselves by using the host's molecular machinery, and then vacate the cell. They now know that viruses can make permanent bases inside cells by integrating themselves into the host's DNA. That remarkable discovery has major implications for cancer virology, for the conquest of persistent virus infections, and for our understanding of how the viruses themselves evolve.

First, what do we mean by persistent infections, and how do viruses cause them? Perhaps the best example is herpes simplex infection, in which tiny, itchy blisters form on the skin or mucous membranes. Typically, the affliction begins as a simple skin sore that soon disappears, only to return many, many times. UCLA researcher Jack Stevens has been trying to discover how the virus brings off this reappearing act. Now Stevens and his associates think they have a working explanation. They believe the first stage of the disease occurs when the virus infects the skin. Later, the infective particles locate a nerve ending, into which they insinuate themselves. They then begin a journey through the nerve fiber, finally finishing up at the sensory ganglion, a way station just beside the spinal cord. Here the viruses just sit quietly in place, often for many years.

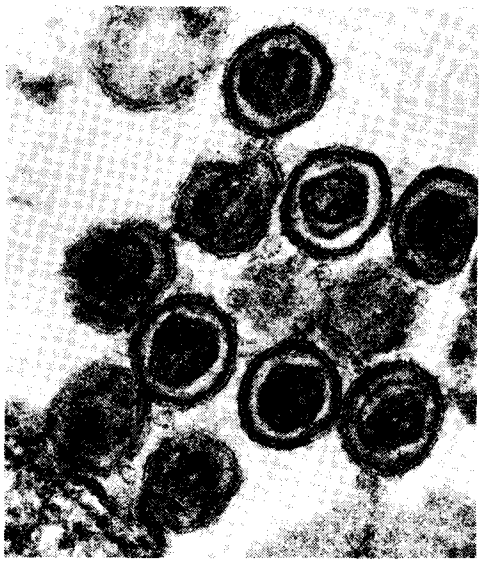
Meanwhile, the skin sore disappears and all seems well—that is, until some kind of stress triggers the infection. Then the viruses come teeming down the nerve, and the skin sore breaks out once again.

The fact that herpes simplex sequesters itself in the nerve cells explains the neurological symptoms often associated with this infection. But how do the viruses lie quiescent for so long? Stevens has seen the viruses in the sensory ganglion's nerve tissue (though he's not sure yet exactly where it is in the cells). He's even followed the progress of viruses along a nerve fiber. But so far he remains baffled about why—and how—the viruses maintain long periods of inactivity. Very probably it will turn out, as it has with many other viruses, that herpes simplex gets into some very intimate association with its host's genes.

To sit there among a cell's genes and occasionally to make a few copies of itself seems an admirably secure existence for a virus. But how does it get there in the first place? John Paul of Glasgow, Scotland, points out that the genes in the chromosomes of animal cells are anything but easy to get at, even for something as small as a virus, which may be no more than one ten-thousandth of a millimeter long. As part of their control systems, the genes, which are long chains of DNA, are covered by a forest of protein molecules. This protective forest, Paul suggests, must make access difficult, at least to some parts of the genes.

Nevertheless, equipped as they are with the necessary enzymes, many viruses appear able to penetrate this undergrowth of protein and finally to integrate themselves in the genetic material.

This integration process is best thought of if we imagine the virus as a short piece of string and the host genes as a long piece. The long piece is cut (by the virus's snipping enzymes), the short piece is slipped into place, and the loose ends are tied (again, by special enzymes). In her experiments at the Imperial Cancer Research Fund in London, Natalie Teich has found that in certain strains of mice this process happens at least four times in every infected cell. The virus involved actually causes leukemia.



Courtesy of Dr. E. de Harven, Sloan-Kettering Institute for Cancer Research, New York

Virus Particles—Electron photomicrograph of virus particles known to cause leukemia in mice.

In addition to the four whole viruses in these mouse genes, a number of viral fragments are also integrated—a fact that might be important in the virus's ability to cause leukemia.

Most people at the Kent conference work with semi-artificial situations in which laboratory strains of virus cause tumors, either in tissue cultures or in animals. Most of them find that in those cases in which virus infection causes tumors, at least some of the viruses that integrate into host genes are incomplete and fragmented. In these cases the integrated virus fragments do not multiply (presumably because they lack some essential element), but they do so disturb the host's metabolism as to cause cancer.

By contrast, cells that have so-called lytic infections—in which the viruses multiply prolifically, eventually killing the host cells—have whole viruses integrated into their genes. But that pattern is almost certainly not a universal law.

The question of a link between viruses and human cancer still presents many thorny problems, of course. Certainly, many natural animal tumors are virally induced—mammary tumors in mice and leukemia in cats, for example. And the cat-leukemia virus is now known to be integrated into the animal's genes so that it is passed from parent to offspring. But the situation in humans is still clouded

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by conjecture and uncertainty. George Todaro and Robert Huebuer, of the National Cancer Institute, Bethesda, Maryland, have proposed that a special gene —the oncogene—which may be associated with an integrated virus in all animal cells, including man's, is responsible for triggering tumor formation.

That notion, known as the oncogene theory, is now losing support in the form in which it was originally proposed. Most participants at Kent favored the idea that cancer formation is linked to some kind of defective virus. University of Wisconsin researcher Howard Temin, whose presence was a great highlight of the meeting, suggested that such tumor viruses may even arise from the cell's own components. His team is now producing evidence to support his suggestion, first made a decade ago, that viruses evolved from a natural cellular control system that produces short strands of nucleic acid. The race to determine the origin of tumor viruses will likely be one of the main features of virology for some time to come.

ALTHOUGH VIRUSES are often thought of as being only on the borderline of life, it now seems there are particles that are even cruder—the viroids. These tiny structures are made up of nucleic acid—just as viruses are—but they are almost a thousand times smaller, and they aren't covered by protein coats as viruses are. Biologist H. Sanger tells of his disbelief when he realized just how small the viroids are. Like everyone else, Sanger had thought that, to be infective, even the smallest virus had to be at least ten times bigger than the viroids turned out to be. It is amazing that so short a piece of nucleic acid, carrying only a limited quantity of "information," can cause so much mischief.

Viroids cause infectious diseases in plants, but Sanger suggests that similar particles may also affect animals, including man. There are many curious diseases known as slow-virus infections (Kuru and Creutzfeldt-Jakob disease, for example), but no one has ever caught sight of a virus that might be responsible for them. Could viroids be the culprits? asks Sanger. There is certainly a growing body of evidence to support the idea. Bearing that in mind, we are chastened to realize that molecular biologists can already manufacture "harmless" strands of nucleic acid of a size very similar to that of the pathogenic viroids that are now being discovered. □

(**Report:** *continued from page 12.*)
Joy Car. After the war it was renamed Wolfsburg.

When World War II began, the plant had been only partially completed, and the town consisted principally of barracks and muddy streets. Almost immediately the Volkswagenwerk went over to war production. Not one passenger car came off the assembly line during the Nazi years. Instead the plant helped produce a jeeplike vehicle called the Kübelwagen and an amphibious offshoot known as the Schwimmkübel. The factory never worked anywhere near capacity. In 1945 the U.S. Strategic Bombing Survey estimated total production for the five-year period 1940–45 at under 50,000 vehicles. Today the Volkswagen Company around the world turns out that many cars in five days.

When the U.S. Army arrived on April 11, 1945, they found a factory severely crippled by air raids and a population of mainly slave labor living in appallingly crowded conditions. Soon the zones of occupation were laid out, and the British forces took over, Wolfsburg just narrowly missing the Russian net. With a town full of unemployed workers, the British decided to get the plant tidied up—and, if possible, back in operation —until its fate could be determined. It says much for human resilience and ingenuity that the first production models of the Beetle began coming out of Wolfsburg that same summer. Luck played a part, too. Though the factory structure itself was appreciably damaged, much of the essential machinery for producing the Beetle had been dispersed throughout the surrounding countryside by the canny Dr. Porsche before the worst of the air raids. This equipment was now brought back, and by the end of 1945 the plant had managed to put together 1785 cars.

For three years the plant at Wolfsburg just about managed to stay alive, producing fewer cars in twelve months than it now does in two days. But in 1948 two events took place that thrust Volkswagen into its spectacular trajectory. One was the German currency reform, which put an end to the country's post-war "cigarette economy" and established the credibility of the deutsche mark at home and abroad. The other was the advent of Heinz Nordhoff as the company's managing director. Nordhoff came to Volkswagen from Opel, the General Motors subsidiary in Germany. He was an experienced automobile man, a tireless worker, and a persuasive motivator. But what turned out to be his strongest asset for Volkswagen was an unswerving faith in Porsche's original vision. The improvements he sought in the Beetle were organic—better materials, comforts, performance—rather than conceptual; the basic design of the car remained inviolate. When Ferdinand Porsche drove to Wolfsburg a few months before his death in January 1951, he had the satisfaction of seeing the Autobahn filled with Beetles.

Year by year the car improved and with it the fortunes of the company. This was much, much more, however, than a mere commercial success story. The Volkswagen revolutionized world attitudes toward the motorcar. It demonstrated that the equation for small-plus-cheap need not necessarily equal tinny. In America particularly, the Volkswagen had dramatic and far-reaching effects. Aided by Doyle Dane Bernbach's witty and honest advertising campaign (as revolutionary an influence as the car itself), the Volkswagen almost singlehandedly upset the cherished American belief that in automobiles bigger is *ipso facto* better. And to the growing consternation of the industry's Big Three, it destroyed forever the myth of Detroit's automotive infallibility.

Wolfsburg today has changed almost beyond recognition from the barracks town that Nordhoff saw when he took charge of Volkswagen a quarter-century ago. It is in many respects more American than European in character: wide streets, supermarkets, high-rise apartment buildings, even a Holiday Inn. The place is blatantly up-to-date; its oldest houses were built in 1938, and there are precious few of those. Only the market stalls in front of the Town Hall, presided over by round and ruddy women hawking bratwurst, smoked eels, and cabbages, delineate the scene as belonging to Mittel Europa rather than Middle America. It's a pleasant environment—open, unpolluted, with plenty of parks for the nature-loving German temperament—but it's also more than a little dull.

Three times a day Wolfsburg comes momentarily alive: just before 5:30 A.M. when the first shift begins, at 2:00 P.M. when the shifts change, and at 10:30 P.M. when the second shift ends. Then the town turns into a maelstrom of traffic, for VW factory hands get a whopping discount on company cars, and most of them drive to work. Parking lots around the plant present a mosaic of brightly

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Light Refractions

by Thomas H. Middleton

Yay, Team?

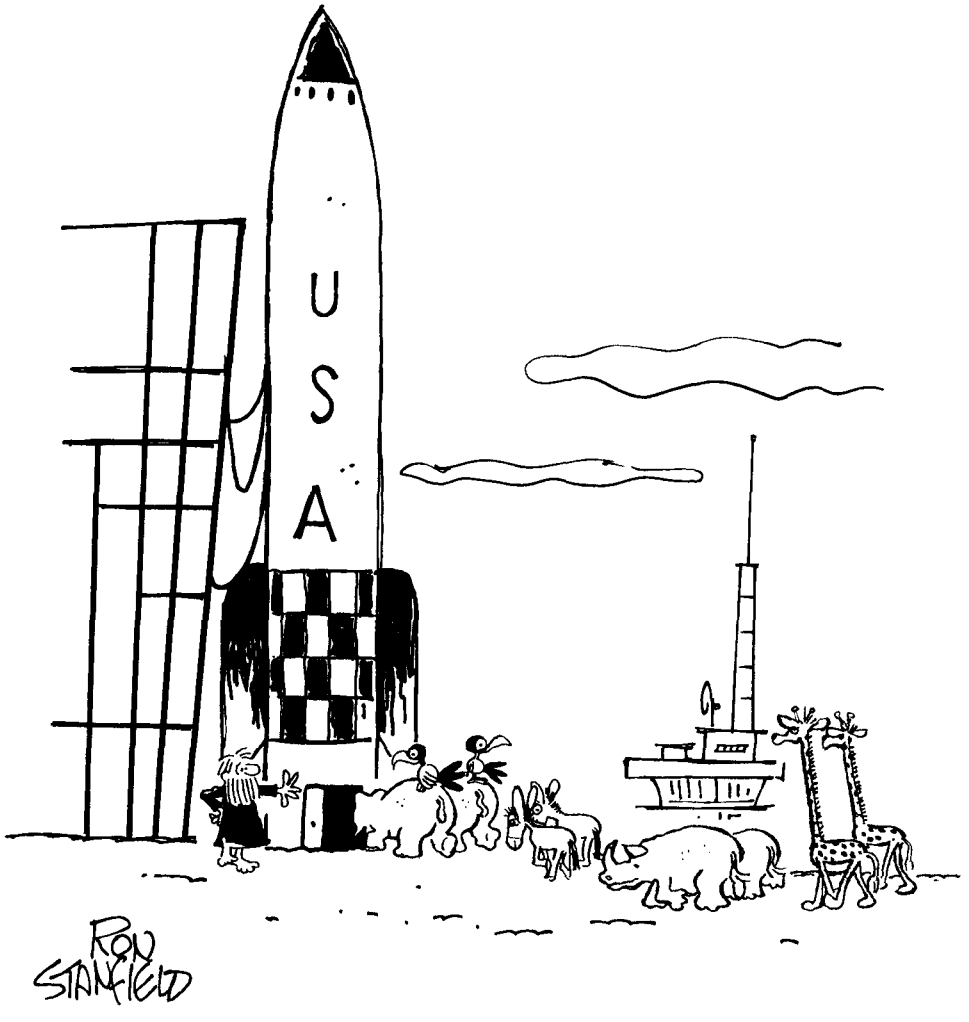
During the hearings concerning the confirmation of Rep. Gerald Ford as Vice President, Ford commented, "You don't go out and tackle your quarterback once he has called the play," to which Sen. Harrison A. Williams, Jr., countered, "If your quarterback was running toward the wrong goal line, wouldn't you tackle him?"

"Yes," said Ford, "but that would be the exception rather than the rule."

The football metaphor has become an accepted commonplace in recent years. In my opinion, it's a bad one. It's simply inept.

Literate people are sensitive to jumbled metaphors. "The arms of the American Minuteman will be the scourge that stems the rising tide of vermin swooping down on the sleeping giant of outraged citizenry" collapses of its own disharmony, but "You don't go out and tackle your quarterback" may sound okay but it doesn't do the job.

The trouble is that football, though it's big business, is still basically a game. It is not comparable to government. To use football as a metaphor for government—and particularly for war—is to oversimplify, perhaps with deadly results. It's easy to see why football terminology is seized upon by politicians. It has a simple, pragmatic, virile ring to it. And I suppose everyone who makes money from football, with the exception of some of the players, has in one way or another fostered the idea that football is contained warfare. "He hasn't used the bomb yet" means merely that the quarterback or the coach or whoever really calls the plays has not yet called for a long forward pass. And have you ever watched those films of the glorious moments from the preceding week's games?



—slow-motion pictures of enormous bodies hurtling high in the air and landing on their heads to the accompaniment of tympani and Götterdämmerung-oriented music. The narrator, with a deeply resonant voice, sounds like the same one who used to say, "But France's military might crumbled rapidly before the invincible onslaught of Hitler's Wehrmacht" over shots of thundering panzer divisions. During the Vietnam war, there were constant references to "our team" and "our quarterback," and I once heard a man urging a hawkish policy say, "When you're on your opponent's five-yard line, you don't punt!" He didn't mention that, in football, neither do you saturate your opponent's city with high explosives from five miles in the air. Killing is equated with a game in this metaphor, and now there are a lot of people who deal with the fortunes of the American political system in the same terms.

The hackneyed, timeworn old Ship of State works much better. There is a real matter of life and death in the fortunes of a ship. I'd feel more comfortable with a man who said, "You don't get rid of your captain once he's set his course" than with one who used quarterbacks calling plays. If it's discovered that the captain's chosen course leads to Suicide Shoals, or that he and some of his fellow officers have been hacking holes in the hull below the waterline, it will occasion a greater sense of urgency than if the quarterback chooses to try for a field goal instead of a first down.

I HOPE THE NEW Vice President will get over that "quarterback" business.

I think we have a tendency to think of the world in terms of winning, losing, happy endings, unhappy endings, and that sort of thing, as though the world were a game or a stage and all the men and women merely players. I'm a frequent listener to listener-response radio, as well as an ardent Letters-to-the-Editor fan. The other day I heard a woman who called in to one of the local talk stations say she'd like to live to be at least 100 "because I want to see how it all turns out."

World without end is a tough conception, but it doesn't help to picture the world in terms of opening kickoffs and final guns. In fact, thinking in terms of final guns, we just might *get* final guns.