VIROLOGY

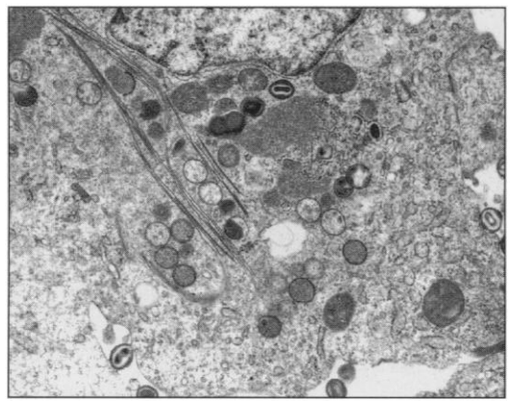
Viruses Have Many Ways to Be Unwelcome Guests

LYONS, FRANCE—It's not easy being a virus. Unwanted and uninvited, these tiny microbes are totally dependent on their hosts for survival. They usually show up with little baggage of their own, often wearing just a thin protein coat wrapped around a small cluster of genes. But if it seems that these lowly visitors hardly merit respect, they are nonetheless taken very seriously for the disease and misery they can cause. And despite their apparent molecular simplicity, viruses have evolved sophisticated strategies to survive and propagate within their hosts.

At a recent meeting* in this city straddling the Rhône and Saône rivers, some 150 virologists gathered to review current research on the lifestyles of more than 40 viruses that infect organisms from bacteria to humans. "This is the first time in my memory that there has been a meeting that set out to look at as many viruses as possible," said Timothy Greenland of the Louis Pradel Hospital in Lyons. During the 3-day meeting, researchers reviewed recent work on the many different schemes viruses use to pursue their unwelcome cohabitation with host cells, including slavish dependency, blatant molecular thievery, and occasionally haughty independence.

Borrowers and lenders. Although viruses form very intimate bonds with their hosts, many contribute only the bare minimum to the relationship. This is particularly true of the RNA-containing retroviruses, which reverse the normal flow of genetic information by using an enzyme called reverse transcriptase to transcribe their single-stranded RNA into double-stranded DNA. Retroviruses, whose genomes are rarely longer than 10,000 nucleotides—the building blocks of RNA and DNA—can produce very few proteins of their own and must beg, borrow, and steal whatever host proteins they need to carry out their life cycle. Stephen Goff of Columbia University in New York City reviewed work that he and his collaborators, including Jeremy Luban of Columbia, have done over the past few years on the hijacking of host proteins by HIV-1, the retrovirus that causes most cases of AIDS.

Goff's group hunted for specific interactions between virus and host proteins using a technique called the yeast two-hybrid system, in which "bait" and "prey" proteins are fused to separate genetic factors that turn on detectable "reporter" genes when the proteins bind. The team demonstrated that the human enzyme cyclophilin A—which is thought to help cellular proteins fold properly—binds tightly to a specific site on an HIV-1 structural protein called Gag. Goff and other researchers went on to show that the enzyme actually becomes incorporated into the virus structure and that each virus particle contains some 200 molecules of cyclophilin A. Just why HIV-1 needs this host protein is still unclear, although some researchers have speculated that cyclophilin A may help the virus assemble itself properly. But Luban and other investigators have shown that without cyclophilin A, HIV-1 cannot infect its target cells, making the protein's interaction with Gag a possible target for therapies.



M. A. SKINNER/ANIMAL HEALTH

Making themselves at home. Fowlpox virus particles dot a cell from a chick embryo.

Rather than just borrowing host proteins, as retroviruses do, many larger viruses have pirated host genes and made them a permanent part of their own genetic repertoire, thus acquiring the ability to produce their own versions of proteins that originally came from cells. "Viruses with large genomes have the capacity to incorporate host genes," says Robin Weiss of the Institute for Cancer Research in London. "They already have 50 or 60 genes, so they can borrow a few more." One such pilferer, described by Weiss in a talk at the meeting, is Kaposi's sarcoma–associated herpesvirus (KSHV), which was identified 3 years ago by scientists at Columbia University and which many researchers believe is responsible for a type of skin tumor often found in older European men and HIV-infected patients. KSHV's DNA-based genome, which contains at least 140,000 nucleotide base pairs, includes genes coding for myriad humanlike proteins, among them homologs of molecules that regulate cell proliferation, intercellular signaling, and immune functions.

Exactly what use the virus makes of these proteins is still under investigation, although Weiss points out that another member of the herpesvirus family, cytomegalovirus, is known to produce its own versions of cellular proteins that modulate the immune response (see Article on p. 248). "We are sure these genes do something for the survival of the virus, although they may not be necessary for basic replication." Weiss adds that various combinations of these pirated genes "may be necessary for viral growth in particular cell types under certain conditions."

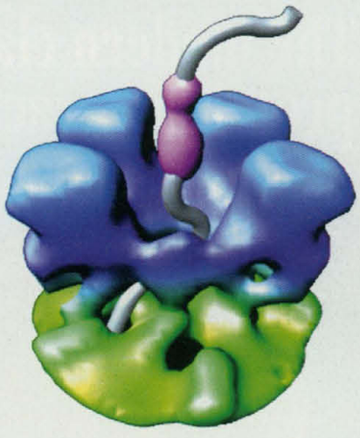
Another intriguing case of gene piracy was reported at the meeting by Michael Skinner of the Institute for Animal Health in Compton, U.K. In as-yet-unpublished work, Skinner's group has identified several genes in the fowlpox virus, which infects chickens, that are homologous with genes found in a wide variety of other organisms, including yeast, roundworms, and mammals. The pirated genes include some that resemble genes coding for so-called SNAP proteins in mammals and squid, proteins involved in shuttling large molecules around within the cell in bodies called vesicles. Others look like genes that code for proteins of unknown function in the roundworms *Caenorhabditis elegans* and *Trichinella spiralis*.

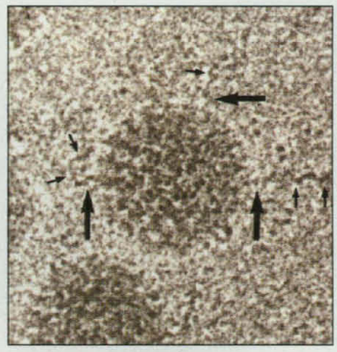
Skinner told the meeting attendees that because these homologous genes are found in all strains of fowlpox so far studied, they must play an important role in the virus's interactions with its host. For example, he speculated that the viral SNAP proteins might subvert normal cellular transport processes to allow viral assembly. Alternatively, he said, they could interfere with antigen presentation, the process by which infected cells ferry proteins from a foreign invader to the cell surface to alert the immune system.

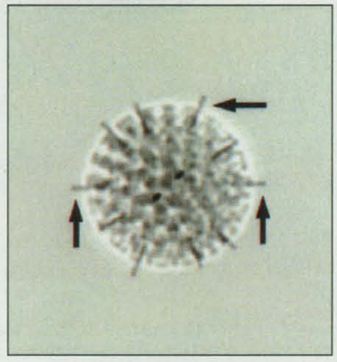
But how did all these diverse genes find their way into the fowlpox virus? Skinner hypothesized that retroviruses may have served as go-betweens. At some point in evolution, he suggested, the reverse transcriptase of retroviruses may have copied messenger RNA—an intermediary molecule between DNA and proteins—from a host organism back into the complementary DNA form. This DNA could then have been picked up by the fowlpox virus and incorporated into its genome.

* Strategies in Virus-Host Relationships, Lyons, France, 16–18 February.

Going it alone. Most viruses depend heavily on the host cell machinery to get their genomes replicated. Retroviruses can use cellular replication enzymes once they have created DNA copies of their genomes via reverse transcriptase, and DNA-containing viruses such as herpesviruses can use the cellular machine directly. But one group of viruses, those containing double-stranded RNA molecules, have to be more self-sufficient, bringing most of their own replication enzymes into the cell with them. The reason is simple: Host cells do not have the enzymes necessary to replicate double-stranded RNA.







LAWTON *ET AL., NATURE STRUCT. BIOL.* **4**, 118 (1997)

Self-sufficiency. A rotavirus particle *(top right)* produces its own messenger RNA strands, visible in a computer-enhanced image *(bottom)*. A computer model of part of the virus shell shows a possible path for the strand.

A talk by B. V. Venkataram Prasad of Baylor College of Medicine in Houston illustrated the lengths to which these viruses must go to reproduce. Over the past few years, Prasad's group has been exploring the replication machinery of the rotavirus, one of the most important causes of severe diarrhea in children, causing more than a million deaths around the world each year. Earlier work by Prasad's team and other researchers had shown that rotaviruses wear three protein coats: an outer garment that is shed when they enter their target cells in the intestinal lining, and two inner layers that shelter 11 separate segments of double-stranded RNA.

Last year, using a technique called electron cryomicroscopy, which gives a high-resolution picture of frozen, well-preserved viral particles, Prasad and his co-workers demonstrated that the RNA segments are actually embedded in the innermost protein layer, which also contains the enzymes necessary for replication. Unlike most viruses, which come apart after infecting a cell and then go in search of molecular building blocks, double-stranded RNA viruses "stay intact and suck in the nutrients they need to replicate their RNA," says David Bishop of the Pasteur Institute in Paris. And remarkably, once rotavirus has replicated its double-stranded RNA, Prasad saw single-stranded messenger RNA molecules exiting from the virus via narrow channels through the protein layers. They were presumably on their way to the cell's protein-making machinery, where they would direct the production of proteins needed by new virus particles.

Given the wide range of strategies viruses have evolved to adapt to life within their hosts, it is no wonder researchers have faced such daunting challenges in coming up with therapies against these unwelcome guests. Says Bishop: "The meeting gave lots of illustrations that, as far as our health and welfare are concerned, viruses are a moving target."

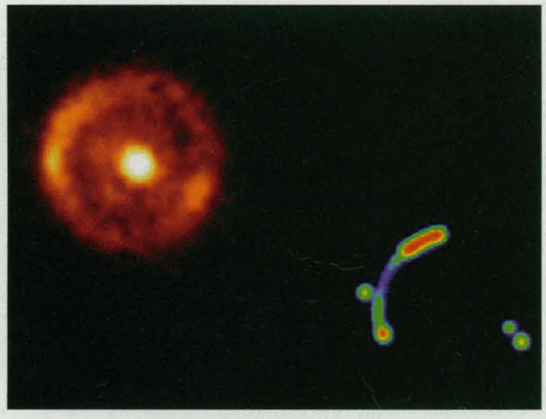
–Michael Balter

ASTRONOMY

Einstein's Theory Rings True

The ancients knew that glass could bend light, but it took the genius of Albert Einstein centuries later to realize that gravity can perform the same trick. In much the same way as a glass lens can focus light, a sufficiently huge mass—say a galaxy—can focus the light from some source far beyond it. "Gravitational lensing" usually takes the form of multiple images of a single distant source. But a team of U.S. and European astronomers has now used three telescopes to pin down an "Einstein ring," the complete circular image formed when source, gravitational lens, and telescope are in perfect alignment.

The finding, announced at the U.K. National Astronomy Meeting in St. Andrews last week and published in the 1 April *Monthly Notices of the Royal Astronomical Society*, "is a clear, textbook example of gravitational lensing at work," says team member Roger Blandford of the California Institute of Technology in Pasadena. Although Einstein rings have been seen in radio observations, this is "the first time a really complete, unambiguous Einstein ring has been seen in the optical and infrared wavebands," says team member Neal Jackson, of Britain's Jodrell Bank radio telescope, near Manchester.



MERLIN/HST

Full circle. Gravity bends radio waves from a distant galaxy into an arc, infrared light into a complete ring.

The group, which also includes Dutch and French astronomers, has been finding and counting gravitational lenses as a way of gauging the "geometry" of space, which depends on its density of mass and background energy (*Science*, 21 November 1997, p. 1402, and 13 February 1998, p. 981). As a first pass in their lens survey, the team uses the Very Large Array in New Mexico, a system of linked radio telescopes, to spot distant radio-emitting objects that seem to be more than simple bright spots. MERLIN, a six-telescope network centered on Jodrell Bank and spanning 250 kilometers across England to Cambridge, then zooms in for a closer look.

At radio wavelengths, the new system, dubbed B1938+666, looked like an arc rather than a complete ring, because the radio emissions come from two off-center regions in the source galaxy. But when the researchers took another look with an infrared camera aboard the Hubble Space Telescope, the complete ring was revealed—a dazzling demonstration of Einstein's theory at work.

–Andrew Watson

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