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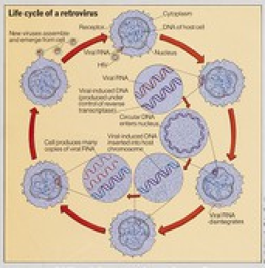
SCIENCE OF AIDS

THE World Health Organization has described the spread of infection with human immunodeficiency virus (HIV) as an unprecedented and urgent challenge to international public health. The numbers of cases of HIV infection and of AIDS are shooting up throughout the world. Yet since doctors first began to recognise cases of AIDS in the US in 1981, scientists have accumulated a huge amount of knowledge about the virus and the sinister disease it causes. The battle to control AIDS is well under way.



Illustrations by Peter Gardiner

What is a retrovirus?

THE VIRUS that causes AIDS is called human immunodeficiency virus, HIV, because it destroys the body's immune system. It does not do this immediately following infection, however. It can take several years between infection with the virus and the appearance of the variety of diseases that typify AIDS. This delay is unusual. Most viruses that infect humans cause symptoms almost immediately.

The long latency of HIV is one reason why it has proved difficult to control the spread of the virus. People can be infected for several years, spreading it to others, before they come down with the symptoms that tell them that they are ill.

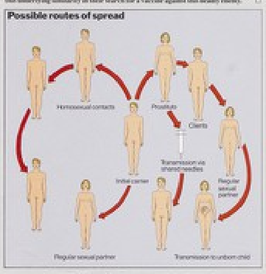
This long latency period is typical of a group of viruses called the lentiviruses. "Lenti" means "slow". It refers to the length of time that these viruses take to cause disease to develop. HIV is the first lentivirus that scientists have discovered in humans, although they have known about them in other animals, such as sheep, for some years. The way in which the genetic material of HIV is organised is similar to that in other lentiviruses. Certain genes in these viruses, serving similar functions, appear in a similar order along the genetic material.

Another unusual feature about HIV is that its genetic material is not DNA, but RNA. After the virus has inserted its strand of RNA into human cells, a special enzyme, reverse transcriptase, makes a DNA copy of the chain of RNA. This viral DNA then becomes part of the cell's DNA. All lentiviruses, and quite a few viruses in other groups, can carry out this step. This is why virologists call them all retroviruses. Retro means backwards, and retroviruses carry out the normal steps of life, from DNA to RNA, in reverse, from RNA to DNA. It was the presence of reverse transcriptase, the enzyme that is unique to this group of viruses, that first alerted virologists to the idea that a retrovirus might be causing the spate of diseases that doctors first called AIDS in 1981.

The nearest relative to HIV seems to be a type of retrovirus that infects African green monkeys. Virologists do not know how HIV has come about, or why it has suddenly spread in the human population around the world. Some have suggested that HIV and the virus infecting African green monkeys may have had a "common ancestor" many years ago — perhaps centuries ago. Other virologists have suggested that humans might have become infected with the virus after being bitten by monkeys. The virus then changed to suit its new host.

What is so unusual about HIV compared to other lentiviruses is that there is remarkable variation between viruses isolated from different people. No two viruses appear to be the same. Scientists have even found strains of HIV that are so different that they can no longer be considered part of the same family. One is called HIV-1 and the other is called HIV-2. The second virus seems to be endemic in parts of West Africa, where it was first found. HIV-2 shares about half of its genetic material with HIV-1 and, surprisingly, about 90 per cent of its genetic material with the African green monkey virus. This similarity has added further evidence to the theory that HIV and the monkey virus share a common ancestor, and that HIV-1 has evolved further from this ancestor than HIV-2.

Virologists cannot dismiss the notion that there may be other AIDS viruses, HIV-3 and so on, or that these may come about as the present viruses evolve. The only hope is that scientists can identify parts of the virus that are common to all strains, and exploit this underlying similarity in their search for a vaccine against this deadly enemy. □



Profile of the epidemic

AS MANY as five or ten million people throughout the world may already be infected with human immunodeficiency virus (HIV). The World Health Organization estimates that by 1991 probably one million cases of AIDS will have occurred worldwide.

HIV can spread from one person to another in three main ways. One is by sexual contact with an infected person. Another is by blood from an infected person getting into someone else's bloodstream. Thirdly, an infected woman can pass the virus on to her baby. There is no evidence that HIV can spread via shared eating and drinking utensils, in swimming pools, by blood-sucking insects, or as a result of normal social contact. Although HIV infection in the West has spread most rapidly among male homosexuals and drug addicts, the pattern of infection elsewhere shows that these groups are not the only ones at risk. In Africa, heterosexual intercourse is the commonest means of spread. Men and women there are affected by AIDS in almost equal numbers.

In the West, the virus shows signs that it will spread more widely to heterosexuals. The World Health Organization estimates that the proportion of cases of AIDS acquired through heterosexual contact has risen from 1 per cent to about 4 per cent. Spread to heterosexuals will occur in several ways: via bisexual men, and via people who inject drugs. Intravenous drug abusers can spread infection as a result of sharing contaminated needles. Many experts believe that this group poses the greatest threat to the heterosexual population, particularly as many drug addicts turn to prostitution in order to finance their need for drugs. □

This false-colour scanning electron micrograph shows many new viruses, in blue, leaving a human T cell. HIV takes over the cell, directing it to make viral proteins and genetic material. The newly assembled viruses then push out part of the cell's membrane and detach themselves. According to one theory, this exodus leaves hundreds of tiny holes in the membrane. The contents of the cell leak out – and it dies

The latest model of the virus

HUMAN immunodeficiency virus is tiny — just a tenth of a micrometre across. A cube of one thousand million such viruses would just be visible to the naked eye. Even such a minute entity as a virus has a specific structure, however. Studies of the virus with an electron microscope by scientists at the Robert Koch Institute in Berlin suggest that there is a regular arrangement of proteins on the viral surface. According to the latest model of HIV (right), the proteins are arranged on the membrane rather like the panels on a soccer ball. There appear to be 12 pentagons and 20 hexagons "stitched" together to make a sphere.

Molecules of the protein called gp120 (the gp stands for glycoprotein) appear at the corners of the hexagons, with an extra molecule of the protein in the centre of each hexagon. So altogether there are 80 molecules of gp120.

Within this outer envelope of protein and lipid (fat) is the "core shell". This layer is also made of protein. Scientists have several theories about the arrangement of this layer. Some researchers believe that it is arranged as an icosahedral structure. (An icosahedron is a solid figure having 20 faces.) Others have suggested that the core shell is in fact organised in a complicated shape called a deltaicosahedron — a polygonal structure composed of 60 triangular elements. These elements form a mixture of alternating hexagonal and pentagonal structures which partly penetrate each other.

At the heart of the virus lies the central core. This contains the genetic material of HIV. The core, which is hollow, is narrower at one end than at the other. At the narrow end, it is open; the wide end has a dimple-like indentation, rather like the bottom of a champagne bottle.

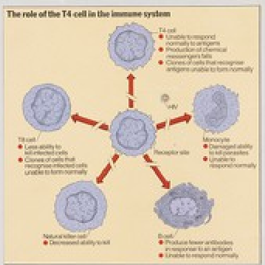
How does HIV make its attack? Once inside the body, the proteins on the surface of the virus bind to receptors (which are also proteins) on the surface of some blood cells. The cells that HIV attacks are a particular type of white blood cell (lymphocyte) known as a T4 cell. Scientists are not sure exactly how the virus enters the cell. The cell's membrane may engulf the virus, or the virus may just merge with the membrane. But once inside the cell, the structure of the virus disintegrates, releasing its genetic material, RNA, and an enzyme called reverse transcriptase.

This enzyme causes the cell to copy the viral RNA into DNA — the type of genetic material that is found in cells. The DNA that results then enters the cell's nucleus, becoming incorporated into the cell's own DNA. This is the crucial act of piracy that makes the virus a permanent part of an infected person's own cells.

The viral genes can remain dormant for some time. They probably become activated when the T4 cells respond to some other infection. The cell begins to make new proteins for growth — including those coded for by the viral DNA. It also makes fresh viral RNA, which will act as the genetic material for new viruses.

Within these activated cells, viral proteins and viral RNA begin to assemble into new viruses. All that these particles lack is the outer membrane. They gain the membrane when they leave the cell, forming buds on its surface which then become detached. In this way, the cell manufactures and releases a whole new generation of viruses before it itself dies. The new viruses attack not only more T4 cells, but several other types of cells in the body. As the person's T4 cells succumb, the immune system weakens, leaving the body vulnerable to the spectrum of infections that characterises the acquired immune deficiency syndrome. □

The material on the structure of the virus first appeared in articles by Michael Koch and Andrew Quick in New Scientist (26 March 1987). Steve Connor, Sharon Kingman and Gail Vines wrote the remaining text. Design by Colin Bowater. © New Scientist



Failure of immunity

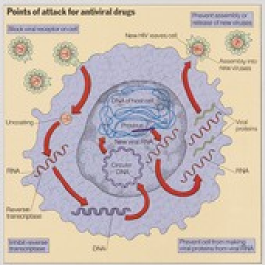
THE immune system is a complex network of defences against foreign substances. Many different kinds of cell help to identify foreign particles, called antigens, and then destroy or neutralise them. Cells of the immune system called macrophages, monocytes and neutrophils, for instance, can engulf bacteria, viruses and cell debris. White blood cells (or lymphocytes) create another line of defence.

There are two types of lymphocyte: B cells and T cells. B cells, when stimulated by an antigen that they recognise, transform themselves into plasma cells. Plasma cells secrete antibodies, special proteins called immunoglobulins. The antibodies bind to the antigen and act in several ways. They may neutralise bacterial toxins, destroy viruses, or prevent them from binding to a cell. Antibodies also make it easier for macrophages to engulf bacteria.

The other class of white blood cells, T cells, also plays a vital role in our immune defences. There are many kinds of T cell, with a variety of functions. Cytotoxic T cells (also called T8 cells), for instance, attack infected cells to prevent microorganisms inside the cells from multiplying and spreading. Suppressor T cells help to prevent B cells from indefinitely producing a particular kind of antibody. T cells also initiate the rejection of foreign skin grafts or transplanted organs.

HIV mainly infects and damages a class of T cells known as T4 cells. These "helper" T cells coordinate the activity of B cells, cytotoxic T cells and macrophages. In addition, it now seems that T4 cells regulate, directly or indirectly, every aspect of the immune system. For instance, helper T cells secrete several chemicals that activate macrophages and B cells, and direct monocytes to a site of infection. The varied symptoms and diseases that typify AIDS probably stem primarily from a defect in this component of the immune system.

T4 cells infected with HIV appear to lose their ability both to recognise antigens and to proliferate normally after meeting them. The virus also seems to make B cells abnormally active: some B cells continue to produce antibodies for no apparent reason. As a result, they may be unable to respond to genuine infections. Finally, monocytes also appear to be abnormal in people with AIDS. These cells become less responsive to certain chemical signals and less able to destroy some parasites.



Plans of attack

INFECTION with HIV poses a peculiarly difficult problem for scientists who hope to develop ways in which to conquer it. The virus affects T4 lymphocytes, cells that normally help the body to fight infection. In addition, HIV incorporates its own genetic material into the DNA of the host cell. The virus also enters the central nervous system. Yet many drugs do not cross into the brain because they cannot pass through the "blood-brain barrier", the membrane that keeps the circulating blood separate from the cells of the central nervous system.

The task of developing a vaccine is even more demanding. In most infectious diseases, the presence of antibodies means that a person has been exposed to the disease and has some degree of immunity to another attack. In the case of HIV, antibodies to the virus indicate that the individual is infected, not that he or she has any immunity to HIV. Researchers will also have to overcome the problem of distinguishing between the antibodies that develop as a result of infection and the protective antibodies produced in response to a vaccine.

Researchers have already had some success in developing antiviral drugs. The drug azidothymidine, or AZT, seems to prolong the life of patients with AIDS. AZT is very similar to one of the four chemical groups called nucleosides that make up the backbone of the DNA molecule. Each nucleoside contains a sugar as well as one of the four bases that carry the genetic information in DNA. AZT is an analogue of the nucleoside thymidine. Both compounds contain the base thymine, but AZT contains a modified sugar. This is why AZT is called a nucleoside analogue. Such nucleoside analogues have already proved effective against other viruses. One example is acyclovir, which doctors use to treat infections with herpes viruses.

When HIV infects the host cell, the viral enzyme reverse transcriptase catalyses the formation of new DNA from viral RNA. The DNA molecule grows as reverse transcriptase adds new nucleosides to it. Unlike thymidine, however, once AZT has attached itself to the growing DNA chain, it prevents the next nucleoside from joining it. In other words, AZT blocks the process of DNA synthesis by terminating the chain.

Work on vaccines is at a relatively elementary stage. Most vaccines already in use against viral diseases make use of an inactivated form of the virus. Another possibility is to use viral antigens, the markers on an organism that stimulate the body's immune system, to produce antibodies. If a real virus subsequently enters the body, the antibodies against it are ready and waiting.

The problem with HIV is that many parts of the two proteins in its envelope frequently mutate, producing different viral strains. Luckily, other parts, called "conserved" sections, do not mutate at all. Presumably, antibodies produced in response to the conserved regions would respond to every strain of the virus. □