Viruses and Their Lifestyles

Few can have escaped learning that once again a deadly virus is loose among humans. But what are viruses, and how do they subsist and reproduce?

Viruses are freeloaders, parasites that carry out their only function—multiplication-only by making free use of the metabolic and biosynthetic machinery of "host" cells, particularly their machinery for protein synthesis. The parasitism of some viruses is fatal to host cells; that of others is benign. Many kinds of viruses have evolved, each adapted to some bacterial, plant, or animal host. Of course defenses aginst viruses have also evolved, ranging from the restriction enzymes of bacteria to the immune systems of vertebrates. And, in the case of some animal viruses, such as poliovirus and rabies virus, research has provided vaccines that greatly strengthen the natural immune response to viral attack.

The complete extracellular form of a virus is called a virion. Its components are few: a genome of nucleic acid, a proteinaceous housing for the genome, and, in certain instances, a few molecules of a virus-specific enzyme. Multiplication of a virus requires replication of its genome and synthesis of the proteins the genome encodes. The host cell provides all of the energy and many of the biochemical needed to carry out those processes.

The genome of a virus may consist of either one of the two nucleic acids, DNA and RNA. The nucleic acid polymer may be single- or double-stranded, linear or circular. Viruses with genomes of RNA **are** unique: in all other organisms RNA is involved only in synthesis of proteins and not also in storage of genetic information. The smaller viral genomes encode as few as four proteins; the larger, which approach the size of small bacterial genomes, encode several hundred. (The human genome is thought to encode about 100,000 proteins.)

The housing enclosing a viral genome consists of a coat (capsid) made up of many copies of a very few types of virus-specific proteins. The architecture of the capsid is geometric; in fact, all simple viruses exhibit helical or icosahedral symmetry (that of a twenty-sided regular polyhedron) or a combination of the two. The housing of many of the more complex viruses includes an "envelope" surrounding the capsid. The envelope is very similar in structure and composition to the plasma membrane of the host cell, containing lipids derived from the cell and virus-specific glycoproteins.

The processes involved in the life cycle of a virus (more properly, its multiplicative, or reproductive, cycle, since viruses are not "living" organisms) include delivery of the viral genome to the interior of a host cell, replication of the viral genome, synthesis of the proteins encoded by the viral genome, assembly of the newly produced viral components into new virions, and exit of the virions from the host cell. Since the details of those processes are complex and vary from one kind of virus to another, only their general features are sketched here.

Delivery of the viral genome to the interior of a host cell ("infection" of a cell) is accomplished through site-specific and often cell-type-specific interaction of the capsid or its envelope with the cellular membrane. The site- and cell-specificities are the result of selective interaction between viral housing and receptors on the surface of the cellular membrane. The mechanisms of infection are varied. For example, the T4 phage infects *Escherichia coli* by injection, the Semliki Forest virus infects mosquito cells by receptor-mediated endocytosis (a normal cellular process by which proteins enter cells), and the human immunodeficiency virus infects T4 lymphocytes by fusion of the viral envelope and the lymphocyte membrane.

Infection of a cell is followed by replication of the viral genome and synthesis of the proteins it encodes. Since the features of those processes depend foremost on whether DNA or RNA composes the viral genome, that property is the basis for dividing viruses into two major classes.

The genome of a DNA virus is processed (transcribed and replicated) by an infected cell in much the same way that the cell processes its own DNA. That is, the viral DNA is used as the template for synthesis of viral messenger RNAs (which in turn serve as templates for synthesis of viral proteins) and as the template for synthesis of new viral DNA. However, only the simplest of viruses (whether DNA or RNA) entrust the production of new viral components entirely to the normal workings of a host cell. Instead, the genomes of most viruses include genes for enzymes that "reprogram" the cellular machinery toward preferential (sometimes exclusive) processing of the viral genome. Such reprogramming is necessary, for example, to achieve rapid replication of the genome of a DNA virus, since a cell normally synthesizes DNA only in preparation for cell division. In addition, the genomes of most viruses include sequences that regulate the timing and extent of gene expression.

Processing of the genomes of some DNA viruses does not always immediately follow infection. Instead the viral genome can become incorporated into that of the host cell. There it lies latent, its gene expression repressed, being passed silently through (typically) many generations of daughter cells. Ultimately, some stimulus triggers the exit of the viral DNA from that of the host, and its processing then begins.

Three types of RNA viruses are recognized. Two are distinguished on the basis of whether the genomic RNA or its complement serves as messenger RNA, that is, as the template for synthesis of

REPRODUCTIVE PATHWAYS OF VIRUSES

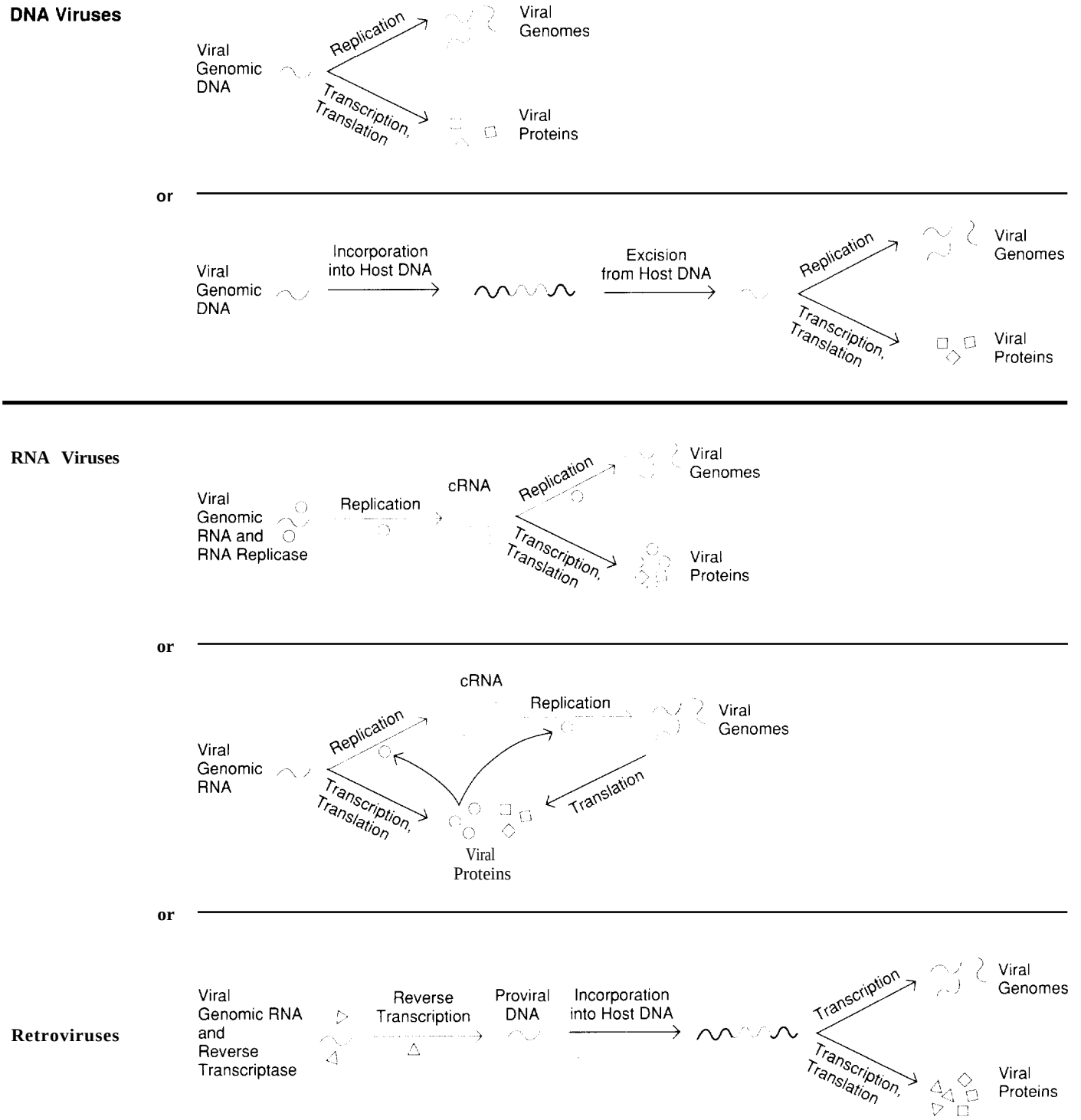

Fig. 1. Reproduction of a virus involves replication of its genome and synthesis of the proteins encoded therein. Shown here schematically are general features of the pathways by which those processes are carried out, Each biochemical reaction is catalyzed by an enzyme; however, only the virus-specific enzymes (those not supplied by the host cell) are listed. The squares represent all viral proteins other than RNA replicase and reverse transcriptase. For simplicity the viral and cellular genomes are assumed to be single-stranded.

viral proteins. (We assume here that the genomic RNA is single-stranded; double-stranded genomic RNA adds only minor complications.) Encoded in the genomes of both those types of RNA viruses is an enzyme, an RNA replicase, that catalyzes the synthesis of RNA from an RNA template. (Host cells cannot supply such an enzyme because they never replicate RNA.)

In the case of an RNA virus whose genomic RNA serves as messenger RNA, its RNA replicase is the first of the viral proteins to be synthesized from the template of the genomic RNA. The replicase catalyzes the synthesis first of RNA Complement to the genomic RNA and then of RNA complementary to the complement of the genomic RNA, that is, of RNA identical to the genomic RNA. Some of the replicas of the genomic RNA serve as genomes for daughter virions, and some serve as messenger RNA for further synthesis of viral proteins.

In the case of the second type of RNA virus, the complement of the genomic RNA, and not the genomic RNA itself, serves as messenger RNA. Therefore some RNA replicase is needed initially to synthesize the complement and allow synthesis of viral proteins, including the RNA replicase. The cycle is started by entry into the cell, along with the viral genome, of a few molecules of RNA replicase produced during the previous reproductive cycle. Those molecules catalyze the synthesis of the complement of the genomic RNA (which then serves as the template for synthesis of viral proteins) and as the template for synthesis of replicas of the viral genome.

The third type of RNA virus follows an entirely different reproductive pathway in which neither the genomic RNA nor its complement serves as the template for protein synthesis. Instead, the genomic RNA serves as the template for synthesis of DNA. Viruses of that type, known as retroviruses, are the only known exception to the "central dogma" of molecular genetics, which asserts that genetic information flows from DNA to RNA. The synthesized DNA, known as proviral DNA, is incorporated into that of the host cell and processed by the cellular machinery under control of viral regulatory mechanisms. Unlike the incorporated DNA of DNA viruses, the incorporated DNA of retroviruses is not excised from that of the host cell before processing.

HIV STRUCTURE

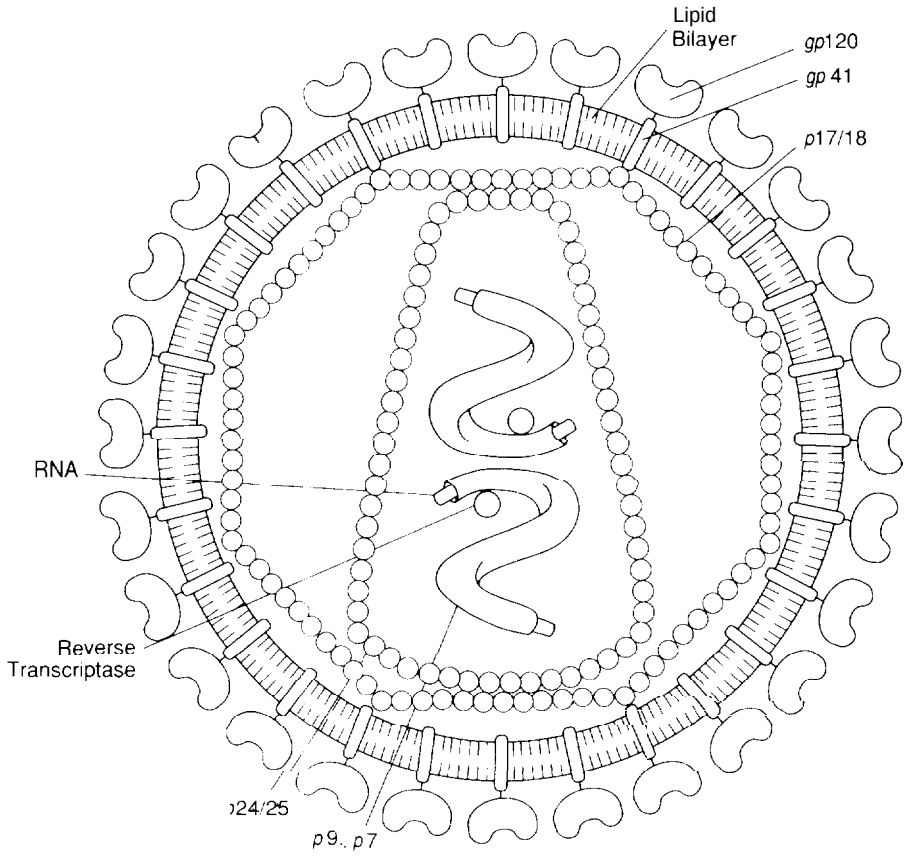

Fig. 2. The diplold genome of HIV, together with two molecules of reverse transcriptase, is housed within a capsid made up of many copies of the protein *p24/25.* The capsid itself is encased within an envelope made up of the glycoproteins *gp120* and *gp41* and a lipid bilayer derived from the membrane of the host cell. (Adapted, with permission, from a figure in the article "AIDS in 1988" by Robert C. Gailo and Luc Montagnier. *Scientific American,* October 1988.)

Since cells never synthesize DNA from an RNA template (the reverse of transcription), a retrovirus must have encoded in its genome an enzyme, a reverse transcriptase, for catalysis of that reaction. Furthermore, since the genomic RNA of a retrovirus is not translated into proteins, it must be accompanied into the cell by a few molecules of reverse transcriptase.

The various pathways for synthesis of viral proteins and replication of viral

GENETIC MAP OF HIV

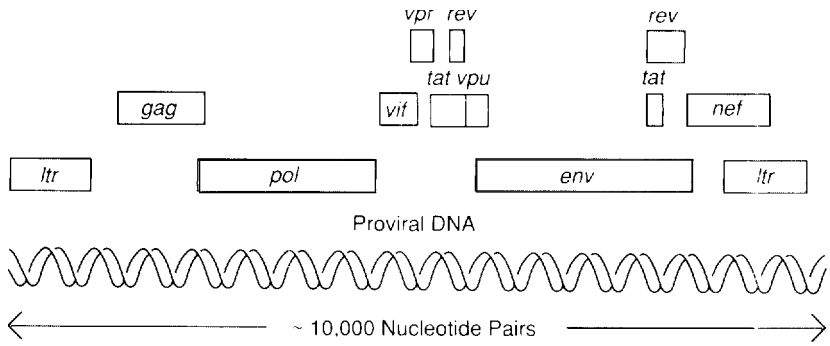

Fig. 3. The DNA of the HIV provirus includes two noncoding long terminal repeats *(ltrs)* that flank at least nine genes. Three are genes for viral components: *gag,* which encodes the proteins *p24/25* end *p9,p7; pol,* which encodes the enzyme reverse transcriptase; and *env,* which encodes the proteins *gp120* and *gp41.* The genes called *tat, rev, vif,* and *nef* encode biochemicals that regulate expression of the viral-component genes. Note that both the fat and rev genes consist of two seperate segments. The functions of *vpr* and *vpu* are not known. (Adapted, with permission, from a figure in "The Molecular Biology of the AIDS Virus" by William A. Haseltine and Flossie Wong-Staal. *Scientific American,* October 1988.

genomes are illustrated in Fig. 1.

The next step in the reproductive cycle of a virus is assembly of the newly synthesized components into daughter virions. That occurs by sequential stages of spontaneous aggregation involving formation of weak bonds, such as hydrogen bonds. Details of viral morphogenesis have provided insight into the development of more complex organisms.

The final step is escape of the new virions from the host cell. Some naked (non-enveloped) viruses escape by natural protein-secretion mechanisms of the cell, others by destroying the cell membrane with virus-specific proteins. Enveloped viruses escape—and become enveloped—by "budding," a process akin to the reverse of receptor-mediated endocytosis.

To conclude this primer on viruses, we present a few more details about retroviruses, particularly the human immunodeficiency virus (HIV), the cause of AIDS.

The unusual nature of retroviruses was not recognized until 1970, although some of the diseases they cause, such as the "swamp fever" that afflicts horses, had been known for many years. Some retroviruses cause cancers, others slowly degrade various physiological systems, and others apparently cause no disease. Only four human retroviruses have been identified, all within the past decade. Two cause rare and fatal cancers; the others are the two recognized types of HIV.

Like all retroviruses, HIV is enveloped and diploid (that is, its genome consists of two copies of its RNA "chromosome"). Figure 2 shows its structure and constituents. The reproductive cycle of HIV is basically that of any retrovirus, but its ability to regulate that cycle, through both positive and negative feedback mechanisms, is much greater than that of any other known retrovirus. The very rapid reproductive tempo that HIV can achieve is the basis for one mechanism by which HIV may kill infected T4 lymphocytes. (Reproduction of most retroviruses is not lethal to host cells.)

HIV has been, and continues to be, the object of intensive research. The nucleotide sequence of its proviral DNA (and hence of its genome) has been determined, and so have the locations of its genes along that sequence (Fig. 3). Numerous details about the biosynthetic pathways involved in HIV replication have been ascertained, and many more will be. Not only are such details necessary to develop drugs and vaccines to combat AIDS; they also exemplify the awesome complexity of even those not quite living organisms we call viruses. ■