have to spend so much on a space station," says Hans Mark. "You can spend as much or as little as you want. It just depends on the time scale and the degree of urgency."

Meanwhile, Beggs has been sounding out the Europeans about cooperative financing of the station, with some success. And Major General James A. Abrahamson, head of NASA's Office of Space Flight, says that two groups have already been in contact with him about private financing of a platform for zero-gravity materials work.

Still another question is whether the station should be manned. NASA's belief in "Man in Space" often takes on a mystical quality: "I won't believe it's really a space station unless it's got a man on it," says associate deputy administrator Phillip E. Culbertson. On the other hand, as Wilfred Mellors of the European Space Agency points out, "You don't want the man to be there just to take care of the life support system." The presence of humans on a space station would add greatly to its flexibility, but also to its cost and complexity. NASA needs to do some hard thinking about when humans will really be needed in space and when machines can do just as well.

Then there is the question of the military's role on a space station. NASA, which needs all the support it can get on the project, has been courting the Pentagon actively. "It would be inappropriate to say they're highly enthusiastic," says NASA's Mark T. Nolan, a member of the space station task force. It is a very new idea, after all. "But the Air Force has formed a working group in the Space Division and interest is rapidly picking up."

Nobody is planning for the initial station to carry weapons, he adds. The details are classified, but in the near term the military missions on a station would tend to look a lot like the civilian applications: development of large antennas, for example, or satellite repair. So doing both on the same station should not be difficult.

In the longer term, however, the Air Force is very interested in such things as space-based lasers and particle beam weapons. Should they prove workable, and should the Air Force want to deploy them on a space station—and it is not at all clear that such a thing would be sensible—the compatibility problem would become severe, Nolan says. For one thing, private companies such as McDonnell Douglas and Ortho would hardly want to put their production module on a military target. For another, the Pentagon would hardly want to allow visits by foreign nationals, which would seem to preclude international participation in the station. One obvious solution, if the money were available, would be to build separate stations for military and civilian uses.

Does the United States really need a space station? In the last analysis the question is not technical, but political. As political scientist and space historian John Logsdon of George Washington University points out, "The only reason to build a space station is if there is a national decision that space is worthwhile—and that the space station is the best way to do the things you want to do."—M. MITCHELL WALDROP

Is Hepatitis B Virus a Retrovirus in Disguise?

Among the many features shared by the hepatitis B viruses and the retroviruses is a reverse transcription step in the viral life cycles

Until recently, reverse transcription, the copying of RNA into DNA, was thought to be an exclusive property of the RNA-containing retroviruses. Within the past year or so that view has changed. The discovery of processed genes (*Science*, 28 May, p. 969) strongly suggests that mammalian genes may also be copied from RNA. And now, there is evidence for a reverse transcription step in the life cycle of human hepatitis B and related animal viruses, which have DNA as their genetic material.

In the June issue of *Cell*, Jesse Summers and William Mason of the Institute for Cancer Research in the Philadelphia suburb of Fox Chase reported that during the replication of the genome of duck hepatitis B virus (DHBV) the first of the two DNA strands to be synthesized is copied from an RNA template, not a DNA template. The second strand is then copied from the first.

Although this is the first direct demonstration of reverse transcription in the life cycle of a DNA-containing virus, the finding was not unexpected. Several parallels between the hepatitis B viruses and the retroviruses have emerged during the past few years. In fact, Summers and Mason propose that the hepatitis viruses, despite their DNA genomes, are very similar to the retroviruses. This raises the possibility that the hepatitis B viruses, which have been linked to an increased incidence of liver cancer both in man and animals, may be carcinogenic in the same way as the retroviruses, which are known to cause animal cancers.

> The hepatitis B viruses . . . may be carcinogenic in the same way as the retroviruses.

The resemblance of the hepatitis virus genome to the DNA formed during retroviral infections was one of the reasons that Summers and Mason began looking for evidence of reverse transcription in the hepatitis life cycle. "There is a clear analogy between the genome structure of the hepatitis viruses and the provirus of a retrovirus," Summers says. "It made us wonder if the hepatitis viruses were synthesized in the same way."

When a retrovirus infects a cell, its RNA genome is copied by the viral enzyme reverse transcriptase to form a single strand of DNA, the minus strand as it is called. (The single-stranded RNA of the viral genome is designated "plus.") The minus strand is then copied to form the complementary plus DNA strand, thus producing a double-stranded DNA molecule, the provirus. This is linear and is flanked on each end by long terminal repeats (LTR's), a repeated sequence a few hundred base pairs in length.

Synthesis of the provirus may involve the formation of a circular DNA intermediate consisting of a complete minus strand and a growing plus strand. Although this molecule has not been isolated, its existence is predicted on the basis of what is known about proviral synthe-

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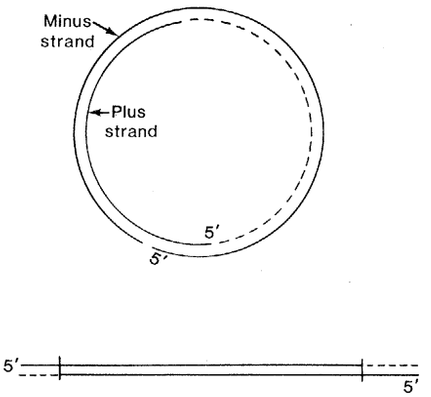
sis and structure. Hepatitis virus DNA closely resembles the postulated structure of the intermediate. "If you packaged this intermediate in a viral particle, it would look like a hepatitis B virus," Summers says.

Work from William Robinson's laboratory at Stanford University School of Medicine and by the Summers group has shown that hepatitis virus DNA consists of two single strands of DNA held in a circular configuration by an overlap of 250 to 300 nucleotides at their 5′ ends. In many of the viral particles one strand is incomplete, leaving single-stranded regions of varying lengths. The viral particle contains a polymerase that may fill in the gaps, thus producing a double-stranded circle containing some 3200 base pairs.

The complete nucleotide sequences of the DNA's of human hepatitis B virus (HBV) and its woodchuck counterpart (WHV) have been determined, with major contributions from the laboratories of Francis Galibert at the Hôpital St. Louis in Paris, Pierre Tiollais at the Institut Pasteur in Paris, Howard Goodman and William Rutter at the University of California at San Francisco, and Kenneth Murray at the University of Edinburgh. These analyses show that the complete strand is the minus strand, whereas the growing one is the plus strand, just as they are in the postulated proviral intermediate. Moreover, all the proteins of both the retroviruses and the hepatitis viruses are encoded in one DNA strand. Finally, the regions of overlap in the hepatitis DNA could give rise to LTR's if the circular molecule were to open up. The retroviral LTR's contain the promoter region, which is the signal for turning on viral genes, and the supposition is that the 5′ overlapping segments might have a similar function for hepatitis virus DNA.

Prompted by these analogies, Summers and Mason decided to look for evidence of reverse transcription during the replication of DHBV. Their results indicated that minus strands were synthesized first on an RNA template. About half of the minus strands were bound to RNA, for example. Moreover, minus strand synthesis was not inhibited by the antibiotic actinomycin D, which binds to DNA and prevents it from being used as a template for synthesizing the complementary strand. In contrast, synthesis of the plus DNA strand was inhibited by actinomycin D.

Summers and Mason propose that a complete RNA transcript of the hepatitis DNA is made in infected liver cells. This RNA, which they call the "pre-genome," is packaged with viral core protein, reverse-transcribed into the DNA minus strand, and degraded. The plus DNA strand is than copied from the minus strand during viral maturation and eventually, with the addition of envelope proteins, a complete viral particle is formed, ready to begin a new round of infection.



Circular hepatitis virus DNA

The complete minus strand contains about 3200 nucleotides. The plus strand is found in the virus particle in varying degrees of completion. The dotted line indicates the incomplete region. If the circle were to open up, a linear molecule with repeated segments on the ends could be generated.

Chronic hepatitis B infections, which affect perhaps 200 million people worldwide, have been associated with an increased risk of such serious liver diseases as cirrhosis and cancer. The question then arises as to whether these viruses might cause cancer the same way the retroviruses do, by integrating their DNA into that of the cell. (In the case of the retroviruses, it is the provirus that integrates.)

Several investigators have shown that hepatitis DNA is integrated in the DNA of hepatoma (liver cancer) cells and of cultured cell lines derived from hepatomas, but this does not necessarily prove that the integration actually caused the cancerous transformation of the cells. As Summers points out, "Integration of viral DNA is not sufficient to make a tumor."

There is a good circumstantial case that WHV causes liver cancers of woodchucks, however. Summers explains, "We haven't seen a single animal that has a hepatoma and doesn't have the virus. And virtually all the infected animals get hepatomas." Almost all—14 out of 15—of the hepatomas examined thus far by the Fox Chase investigators have integrated WHV DNA in the tumor cells.

Integration of proviral DNA can cause transformation in at least two ways, by directly inserting a viral oncogene (cancer gene) that is either expressed in abnormal quantities or at an inappropriate time, or by inserting the LTR promoter region of the virus near a cellular oncogene and turning it on.

The Summers group, in collaboration with that of Susan Astrin, also at the Institute for Cancer Research, cloned segments of DNA from two woodchuck hepatomas that contained integrated hepatitis DNA sequences. They hoped to obtain clues to the mechanism by which the virus infection might lead to cancer. "But we didn't really solve that problem," Summers remarks.

They found that the WHV DNA undergoes extensive rearrangements with loss of sequences when it integrates. This is in marked contrast to what happens when proviral DNA integrates; the complete, unaltered provirus is inserted into the cellular DNA.

The two integrated hepatitis virus DNA's contained some common segments, however. These included the overlap regions at the 5′ ends, which may be analogous to the LTR promoter regions of the provirus. This result raises the possibility that promoter insertion may play a role in transformation by hepatitis viruses, as it does for some retroviruses. Nonetheless, the experiment did not prove that promoter insertion by WHV causes cancer, nor did it rule out other possible mechanisms of transformation.

Despite the many similarities between the hepatitis B viruses and the retroviruses, there are some significant differences. Both the retroviral genome and the complete particle are some two to three times larger than the hepatitis genome and viral particle. Moreover, the replicative strategies of the two types of viruses are not entirely the same. The reverse transcription step occurs early in the retrovirus life cycle, during virus disassembly, but later in the hepatitis life cycle, during virus maturation. There are also differences in the way the two types of viruses initiate reverse transcription and the copying of minus strand DNA. Summers and Mason propose then that the hepatitis viruses constitute a group of reverse-transcribing viruses, but do not belong to the same family as the retroviruses.—JEAN L. MARX

Additional Readings

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