THE FICKLE VIRUS

The AIDS virus is a master of disguise, capable of making subtle changes in its outer appearance that probably help it give the immune system the slip. Now studies show that it's a quick-change artist as well. The virus—technically known as the human immunodeficiency virus, or HIV—mutates at great speed, and researchers fear that this ability increases its chances of thwarting not only the immune system but any future vaccines also. "Variability," says virologist Dani Bolognesi of Duke University, "is probably the trickiest property that HIV has."

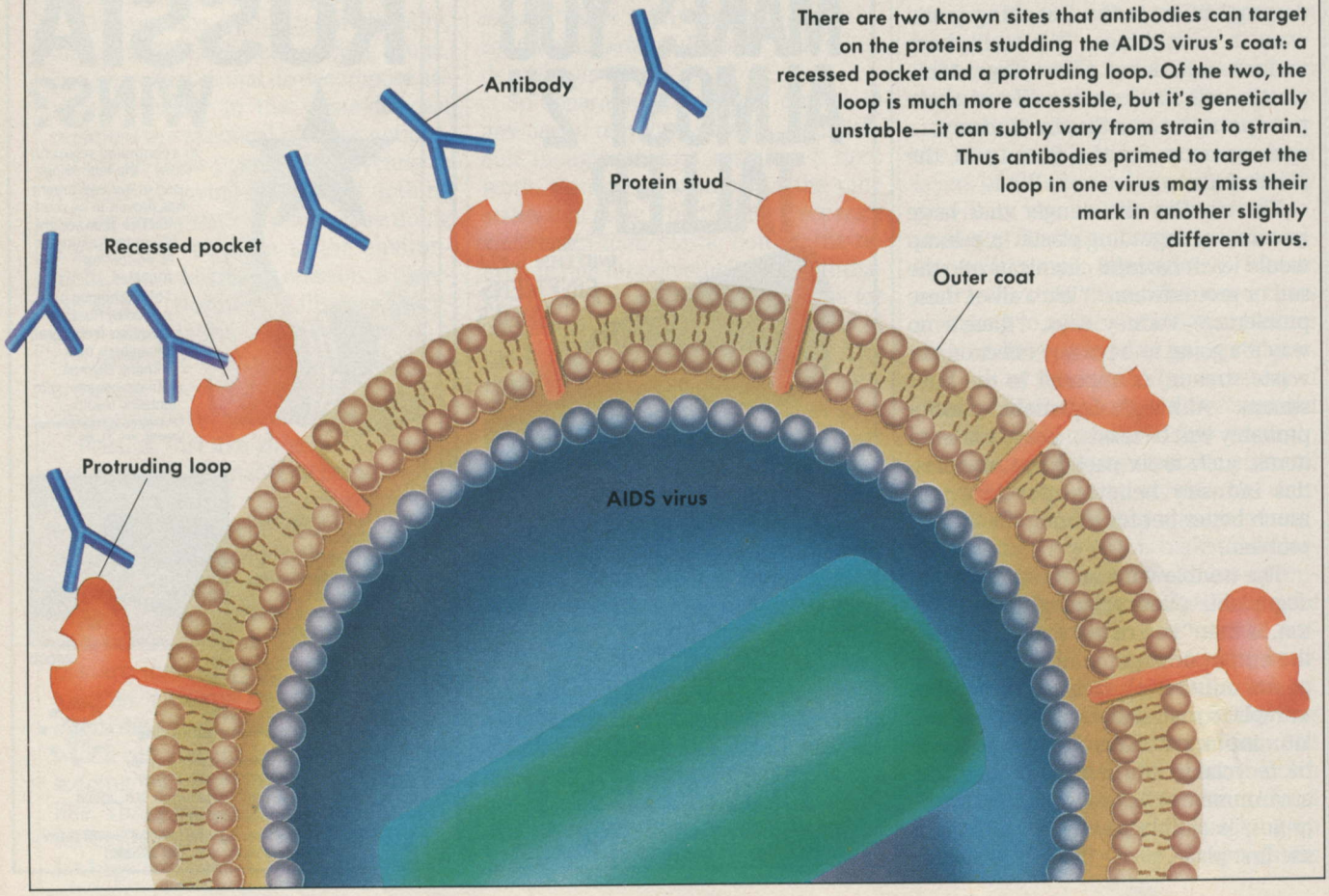
It didn't take long for researchers to realize they were dealing with not just one unchanging AIDS virus but many variations on a theme. By the end of 1985, two years after the virus was first discovered, more than 200 different strains had been isolated, each with a slightly different genetic makeup. Most of these genetic changes showed up as modifications in the sugar-coated proteins, or glycoproteins, that stick out like studs from HIV's outer surface: a strain isolated from an AIDS patient in San Francisco, it appeared, could vary by more than 25 percent from one found in a New York patient. In 1986 an entirely new member of the AIDS virus family was reported in West Africa; named HIV-2, it differed from other known strains by more than 50 percent.

And it turns out that virus strains differ not just from one patient to another but also within a single patient. Evidently, even after HIV has invaded a body, it continues to churn out a wide variety of new, subtly different versions of itself.

"The more we've looked for variation," says Wade Parks of the University of Miami, "the more we've found it." Last year he and his colleagues reported that they had identified 17 different strains of HIV in one AIDS patient and 9 strains in another. Sixteen months later the researchers found an additional 13 HIV strains in the second patient. Given that these strains were isolated from just a syringeful of blood, the number of strains coexisting in a patient's body may number in the thousands, says Parks.

HIV's propensity for change seems to be inherent and more the result of sloppiness than anything else. It apparently results from the virus's tendency to make errors when it reproduces itself. The virus, researchers believe, may not have the capacity to proofread and correct the many mistakes it evidently makes. According to Flossie Wong-Staal of the National Cancer Institute, a new HIV mutant can arise every few days.

Some of these mutations—for example, those that hamper the virus's ability to infect cells or reproduce—are probably doomed to die out fast. The



There are two known sites that antibodies can target on the proteins studding the AIDS virus's coat: a recessed pocket and a protruding loop. Of the two, the loop is much more accessible, but it's genetically unstable—it can subtly vary from strain to strain. Thus antibodies primed to target the loop in one virus may miss their mark in another slightly different virus.

ILLUSTRATION BY IAN WORPOLE

ones that persist, says Wong-Staal, are most likely the ones that are advantageous to the virus. A recent study at the University of California at San Francisco suggests that this kind of viral Darwinism is indeed at work: researchers there have found that as time goes by and HIV mutates, the virus becomes more versatile, broadening the range of cells it might attack in the body.

The research team, headed by Cecilia Cheng-Mayer, isolated HIV strains from four patients at various stages of their infection. When the researchers squirted these virus strains into petri dishes, each lined with a different type of white blood cell, they found that the later strains invaded more cell types than their predecessors. Strains isolated from one patient before he developed AIDS symptoms, for example, only infected the T cells. But seven months later, when the patient had full-blown AIDS, offshoots of these strains invaded not only T cells but B cells, the body's antibody producers, as well as the scavenger cells called monocytes and macrophages. Two months later the patient died.

HIV's capricious nature may enable it to dodge the attacks of these immune system cells as well as invade the cells directly. Normally, when the immune system meets a new virus it launches antibodies custom-designed to latch on to the proteins decorating the virus's outer coat. But in the case of HIV, chances are that each time these specialized antibodies disable the most prominent strain found in a person's body, several more strains with slightly different characteristics emerge to take its place. A study by Wong-Staal and her colleagues has shown that a change in just one amino acid—one protein building block—in the virus's coat enables HIV to escape the grasp of antibodies. This finding may help explain one of the great oddities of AIDS: although patients often make plenty of antibodies to HIV, the antibodies don't appear to be effective. Somehow they fail to stop the virus in its tracks.

This doesn't augur well for researchers trying to develop an effective AIDS vaccine. Most vaccines, after all, also work by stimulating antibodies designed to target a specific portion of the microbe's protein coat. That HIV keeps rearranging some of these key proteins is an added complication in a task that's already difficult enough.

Consider, for example, the formidable problems faced by researchers trying to make a vaccine that stimulates antibodies that attach to the knoblike end of the virus's protein studs. Most researchers have been hoping to target one of two areas on the knob (see illustration). Target one, as it happens, is a genetically stable site: it stays nearly the same in most, if not all, HIV strains. The problem is that this site is hidden inside a pocket within the protein, making it difficult for a relatively bulky compound such as an antibody to squeeze in and bind to it.

Target two, on the other hand, is a loop that sticks out next to the pocket on the protein stud. This portion is easily accessible to antibodies. But—here's the catch—this area is genetically very variable. It's one of the areas that is most likely to change from one HIV strain to another.

Fortunately the virus's variability poses less of a threat to researchers developing AIDS drugs. Although it's conceivable that HIV could mutate into drug-resistant forms, most researchers think it's not likely. "It's a concern that requires monitoring," says Samuel Broder, head of the National Cancer Institute's clinical oncology program, "but we don't see any evidence of it yet in AIDS patients." Nor do most researchers foresee problems with current AIDS screening tests. These tests detect antibodies to the stable parts of the virus that are shared among all strains.

In fact, some researchers are hoping that the variability of the virus may one day turn out to be an ace up their sleeve. At St. Luke's–Roosevelt Hospital Center in New York, for example, researchers recently identified an HIV-1 strain that doesn't kill cells in culture; they are now comparing it with more typical lethal varieties. "Finding the difference between a killing and a nonkilling strain," says team leader David Volsky, "may just turn out to be the key to understanding HIV's modus operandi." —*Margie Patlak*