tion might speed up the patients' deterioration.

Should the toxicology studies pan out, another problem would have to be addressed—how to administer the NGF. It is a protein and proteins are not supposed to cross the blood-brain barrier. The current thinking is that NGF would be delivered through a fine tube inserted directly into a patient's brain and connected to a small pump that could infuse a solution containing the protein.

But the invasiveness of this procedure might well make it difficult to perform a standard controlled study with some patients getting NGF and others an inert material. Hefti points out that it would probably be unethical to outfit a patient with a pump and then not give him or her an active drug. Some clinical trials have gotten around this type of problem by letting patients serve as their own controls, alternately giving them the active agent and placebo control. This might be done with NGF. The animal studies have indicated, however, that the growth factor's effects may persist for days or weeks after administration is stopped, and this persistence could be another complicating factor if the protein were to be alternated with a placebo control.

The researchers are also looking for alternatives to direct brain injection. Mobley's group, for example, is beginning to identify the segments of the NGF protein that are required for its activity. Eventually, this kind of information might be used to design nonprotein drugs that could cross the blood-brain barrier on their own. Another approach, Khachaturian says, would be to encapsulate the protein or active peptides in a membrane that could also penetrate the blood-brain barrier.

And then there is the prospect of genetic engineering. In one set of experiments, for example, Gage and his colleagues introduced an active NGF gene into rat fibroblasts, a type of cell that would not normally make NGF. They then implanted the cells into the brains of rats that contained their standard lesion in the cholinergic nerve tract running between the basal forebrain and hippocampus. The NGF-secreting cells prevented the cholinergic nerves from degenerating, just as the NGF injections did.

But for now, researchers are concentrating on direct NGF infusion, not genetic engineering. Next month, Khachaturian will convene another study group at NIA to assess the situation again. Despite the great need for an Alzheimer's treatment, no one wants to make a mistake now. "It's more than ordinary drug development," Hefti says. "We are dealing with an entire new concept." ■ JEAN MARX

Shooting at a New HIV Target

The first reports are trickling in from a new front in the war against AIDS, and the news is promising. Two teams, one at Smith Kline & French Laboratories in King of Prussia, Pennsylvania,* and another at the Upjohn Company in Kalamazoo, Michigan (see page 454, this issue), have identified compounds that inactivate a crucial enzyme that the AIDS virus, HIV, needs to reproduce itself. Although the work has not yet gone beyond the test tube, these companies, as well as numerous others around the world, are now working feverishly to find even more potent compounds that may ultimately be used therapeutically to limit HIV infection in humans.

The targeted enzyme—called HIV protease—breaks two large viral polyproteins into smaller units. Some of these are assembled together to form the virus's core; others form molecules that permit HIV's genetic material to insinuate itself into a healthy cell's nucleus.

Efforts to design compounds to attack HIV protease rely on knowledge gained from the explosion of research on the basic biology of the virus. But they have also benefited from a bit of luck—the fact that pharmaceutical companies have been struggling for a decade to find a way to block renin, an enzyme with some similar properties that plays a critical role in raising blood pressure.

Although the precise three-dimensional structure of HIV protease has only recently been accurately determined (*Science*, 11 August 1989, p. 616), it has been known for some time that, like renin, it is an aspartic protease—so called because two aspartic acid residues flank the active site of the enzyme. As Alexander Wlodawer, a crystallographer at the National Cancer Institute who has been studying the three-dimensional structure of HIV protease, puts it, "If it weren't for [the work on] renin inhibitors, we wouldn't be anywhere right now with HIV protease inhibitors."

"We had molecules that were potent inhibitors of renin," says W. Gary Tarpley who directed the Upjohn effort. "We systematically modified various regions of some of our renin inhibitors so that we could optimize the protease activity."

It was clear from assays that the new compounds had a direct effect on the protease, but would they enter cells and seek out the enzyme? For both groups, the answer was yes. Both groups have also shown that in the presence of the antiprotease compounds, the virus can form new viral particles, but the newly created viruses are incapable of infecting other cells.

Promising though these preliminary tests are, several hurdles must still be overcome to develop a candidate compound for human therapy. Tarpley says Upjohn's compound can be washed out of infected cells and its effect mitigated. He says compounds with longer half-lives will have to be found.

Then there is the question of specificity. Any effective drug will have to work only on HIV protease and not other aspartic proteases. According to John Kay, a protein chemist at the University of Cardiff, five human aspartic proteases (or proteinases, as he insists they are more properly called) have been identified: renin, two digestive enzymes called pepsin and gastricsin, and two proteolytic enzymes called cathepsin E and cathepsin D. Part of the difficulty pharmaceutical companies encountered in developing oral anti-renin compounds is that they also attacked pepsin and gastricsin, which are found in the stomach. More problematic for AIDS therapy may be the fact that cathepsin E plays a role in normal immune functioning.

"If you start giving [AIDS patients] a drug which interferes in its side effects with another enzyme that's an aspartic proteinase that's involved in immune surveillance and antigen processing, then that's really bad news," says Kay.

A British company may, however, have cracked the specificity problem. Roche Products, the British subsidiary of Hoffmann–La Roche, has discovered a group of compounds that they say are much more selective for the HIV protease than for any of the human aspartic proteases.

The Upjohn and Smith Kline teams have taken the first step in showing that targeting HIV protease may be an effective AIDS therapy. "Now it's a question of taking something which works in tissue culture and making it into a drug," says Wlodawer. "That's a big step, but without these results, there would be no step to take." ■ JOSEPH PALCA

* T. D. Meek *et.al.*, *Nature* **343**, 90 (1990).