mean? Why do cardiovascular events tend to occur in the morning and what does the observation mean for the prevention and treatment of heart attacks and strokes?

The most exciting aspect of the findings, says Robertson, is that they may provide clues to understanding "why chronic cardiovascular disease suddenly converts to acute disease," why a person who has had atherosclerosis for years suddenly has a heart attack or stroke.

Investigators are looking with interest at studies of circadian rhythms that show changes in hormones and other biochemical parameters in the morning hours. It is known, says Rocco, that heart rate response and blood pressure change in the morning. There are also circadian rhythms in platelet aggregation and in response to heparin, which prevents clotting. Any of these could be clues to the phenomenon. Muller, who is now working with the much studied population of Framingham, Massachusetts, finds that platelets are much stickier in the morning, indicating that they are more likely to form clots. Ischemia, on the other hand, is more likely to be caused by spasms of the coronary vessels, so the clotting evidence does not explain why ischemia occurs in the morning. One possibility, says Rocco, is that a surge of plasma catecholamines, which occurs in the morning, could make the coronary vessels contract. This, in combination with the heart's increased demand for blood upon rising in the morning, could lead to ischemia.

Strokes, says Marler, are more difficult to explain. The timing data indicate that "there may be more to strokes than random blood clots, but it's so prone to speculation. We just don't know what causes strokes to happen, period, let alone why they happen at a particular time of day."

Still, there could be therapeutic implications even before the reasons for the morning phenomena are understood. Patients, says Rocco, "generally wake up and take their medications. It then takes 30 to 60 minutes for the drugs to act. Perhaps they should take quick-acting drugs when they wake up or longer acting substances when they go to bed at night." Nitroglycerin and calcium channel blockers, for example, can be taken under the tongue, and they act quickly to relax coronary arteries. These drugs "may be preferential in the early morning hours," Rocco remarks.

The investigators are unanimous in their feeling that the timing of cardiovascular events may be a valuable clue to why and how they occur. "It's a puzzle and now we can begin to put the pieces together. I think the implications can be very important," says Robertson. ■ GINA KOLATA

Rallying Against AIDS

Paris. *Most of the world's experts on AIDS gathered here at the end of June for the second International Conference on AIDS (acquired immune deficiency syndrome). Although no one can yet report a cure or a vaccine for the disease that has killed more than 12,000 people in the United States alone, many teams of scientists are collaborating on the problem. Critical to the development of drugs and vaccines is continuing progress in understanding the biology of the virus that causes AIDS and how it affects man. Research News' first report from the conference appeared in the 18 July issue.*

Brain Endothelial Cells Infected by AIDS Virus

That the AIDS virus infects the brain is no longer a question. But what cell types it infects is an issue that is only partly resolved. Clayton Wiley of the University of California at San Diego and his colleagues have reported that, in addition to macrophages and monocytes, the AIDS virus infects endothelial cells that line brain capillaries.

"The AIDS virus is rather selective for endothelial cells in the brain," says Wiley. "Endothelial cells elsewhere in the body are not infected." Wiley and Peter Lampert, also of San Diego, and Michael Oldstone, Rachel Schrier, and Jay Nelson, of the Scripps Clinic and Research Foundation, studied the postmortem brains of 12 AIDS patients, all of which showed mild inflammatory changes (*Proc. Natl. Acad. Sci. U.S.A.*, in press).

The California group found that nine of the brains contained the AIDS virus, with multinucleated giant cells, monocytes, and endothelial cells most commonly infected. Only one brain showed evidence of neuronal or glial infection, a case Wiley describes as "rather unique." He stresses that in this brain, the AIDS virus had infected many more macrophages and giant cells than cells which appeared to be neurons or glia.

Two striking features emerge from these data and from studies by other investigators. The first is that many AIDS patients have severe neurological problems, including varying degrees of dementia and sometimes motor disturbances, with surprisingly mild abnormalities in brain tissue, and only rare (if any) direct infection of nerve cells. The second is that there is a poor correlation between the severity of a patient's neurological symptoms and the degree to which his brain appears abnormal upon histological examination.

Although there are still no data that resolve these issues definitively, Wiley thinks that the AIDS virus may cause brain damage indirectly, and that this damage could result in clinical symptoms. For instance, "there is a precedent for global dementia without specific neuronal damage in patients who receive radiation treatment," says Wiley. Like AIDS patients, their brains show signs of edema, tissue swelling due to fluid accumulation. Edema can result in generalized damage to the brain, which is especially evident in the white matter fiber tracts that interconnect different brain regions. This in turn can disrupt normal communication within the brain and produce many neurological problems, including dementia.

Syndrome d'Immunodéficience Acquise: *AIDS graffiti on a Paris building.*

Thus, "nonspecific damage to white matter can lead to dementia," says Wiley. "Something elicits the migration of macrophages into the brain and in deep white matter there is swelling." Perhaps macrophages infected with the AIDS virus secrete soluble factors that produce edema or even other forms of tissue damage. Infection of brain endothelial cells could make capillaries abnormally leaky, contributing further to the edema and altering ion and electrolyte concentrations in the brain.

What all this means is that it may not be necessary for the AIDS virus to infect large numbers of neurons in order to disrupt

brain function. As yet, the mechanisms by which the AIDS virus causes neurological problems are still hypothetical, but cells in the brain now known to be infected by the virus—macrophages, giant cells, monocytes, and now, endothelial cells—are likely to play a role.

In Search of the Best Drugs Against AIDS

Sometimes a drug that looks promising in preliminary tests turns out to be both ineffective against disease and harmful to patients. In the war against AIDS, scientists thought that suramin, which successfully inhibits replication of the AIDS virus in cultured cells, might benefit patients. But in early tests, researchers quickly discovered that not only is suramin a poor blocker of viral replication in vivo, it is simply too toxic to use in AIDS patients.

In addition to suramin, several other drugs have been tested to varying extents for their ability to combat the AIDS virus in patients who are already infected. Two of them, 3′-azido-3′-deoxythymidine (AZT) and ribavirin, are still viable candidates against AIDS. Both resemble the natural building blocks of DNA and RNA, and both were developed prior to the AIDS epidemic. Both inhibit viral replication in vitro, can be taken orally, and can penetrate the blood-brain barrier, which is an important consideration because the AIDS virus infects cells in the brain.

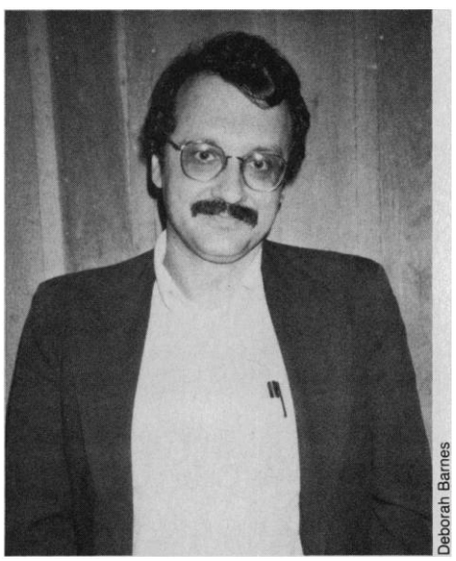
Last year, AZT made its debut in humans as an experimental treatment for AIDS, and to date, over 100 AIDS patients have received the drug. Ribavirin was used for other viral infections in humans and has recently been tested in patients with AIDS-related complex, or ARC. Although both drugs are doing well enough to warrant further testing, scientists describe their potential benefits to AIDS patients in very cautious terms because the data are so preliminary.

"Even if something looks good in an early study, we urgently need to do carefully controlled long-term clinical studies," says Samuel Broder of the National Cancer Institute. In collaboration with Wellcome Research Laboratories in Triangle Park, North Carolina, Broder oversees the testing of AZT and other potential drugs against the AIDS virus.

Most of the anti-AIDS drugs that are now being tested work by a similar mechanism—they interfere with the normal action of reverse transcriptase. This viral enzyme catalyzes DNA chain formation from its RNA genome, a process that is required for viral replication inside a host cell. Ribavirin, on the other hand, seems to interfere in some way with protein synthesis directed by the AIDS virus.

Like suramin and AZT, HPA23 is another drug that seems to work by blocking reverse transcriptase activity. Although HPA23 has yet to undergo rigorous clinical trials in the United States, D. Dormont, Jean-Claude Chermann, and their colleagues of the Pasteur Institute in Paris report that the drug seems to reduce transiently the amount of virus that can be cultured from a patient's circulating blood lymphocytes, but the patient does not get better. HPA23 also has some toxic side effects.

Other chemical compounds, yet to be produced and tested, will probably be designed to attack different protein products of the AIDS virus. "We now know that there are at least seven genes in the AIDS virus," says Broder. "What that means is that there are at least seven gene products that are potential targets for drug therapy."



Samuel Broder: *Working to find safe and effective drugs for AIDS patients.*

Anthony Fauci of the National Institute for Allergy and Infectious Diseases thinks that the most effective approach to combating the AIDS virus in someone who is already infected may be a two-pronged attack. "We feel that the optimal therapy will be using an antiviral drug in combination with immune reconstitution," he says. Because the AIDS virus destroys a person's ability to mount normal immune responses, Fauci recommends combining an antiviral drug with a soluble substance such as interleukin-2, a natural compound that may restore immune function in AIDS patients.

Measuring Antibodies May Predict Disease

It has been difficult to predict whether a person infected with the AIDS virus will become sick very rapidly or will remain free of clinical symptoms for a long time. Researchers now find that having antibodies that block viral replication may be a good sign for an individual infected with the AIDS virus.

People who are free of clinical symptoms often have stronger neutralizing antibodies than people who develop the infections and secondary cancers associated with full AIDS. "We are seeing diverging antibody patterns between those individuals who remain asymptomatic and those who develop symptoms," says Johnathan Weber, of the Institute of Cancer Research in London.

Weber, Robin Weiss, and their colleagues measured the strength of neutralizing antibodies in 32 men infected with the AIDS virus over a 4-year period. Their results indicate that people who remained free of symptoms generally had higher antibody titers than people who developed symptoms of AIDS. Whether or not there is a direct cause-and-effect relationship between having strong neutralizing antibodies against the AIDS virus and remaining free of clinical symptoms for a long time, remains to be determined.

Not only do symptom-free individuals have strong neutralizing antibodies, but some of them also tend to have increasing titers over time, a trend not seen in the individuals who become sick. In contrast, patients who develop AIDS or AIDS-related complex typically show a "gradual reduction of neutralizing antibodies before the onset of symptoms," says Weiss.

The British researchers also find that patients differ in the kinds of antibodies they make to the AIDS virus. Symptom-free individuals make antibodies against the inner core proteins more often than sick patients, but both groups make antibodies against the envelope proteins that surround AIDS virus particles. Weiss says, "We know that some of the anti-envelope antibodies cause neutralization, but there is no direct evidence at this time to indicate that anti-core proteins are important in neutralizing the virus."

The obvious thing to do next is to clarify whether the strongest neutralizing antibodies are directed against envelope or core proteins, something Weber, Weiss, and their colleagues are trying to sort out. Knowing which proteins generate the best immune response could help researchers determine which part or parts of the AIDS virus should be targeted by a vaccine. ■

DEBORAH M. BARNES