Heart Attacks at 9:00 a.m.

Researchers are finding, to their surprise, that heart attacks and strokes tend to occur in the morning, which may lead them to an understanding of why they occur at all

It began by accident. In the spring of 1984, James Muller of Harvard Medical School was presenting data from a clinical trial on heart disease. Someone in the audience commented that from Muller's data it looked as though heart attacks were more likely in winter than in summer. Muller thought that sounded plausible—it certainly fit the image of the middle-aged man who has a heart attack while he shovels snow. So he decided to review the data to see if the observation was correct.

The observation could not be substantiated—heart attacks were equally likely to occur at all times of the year. But there was something peculiar about the timing of heart attacks. Muller noticed that, in this clinical trial at least, heart attacks tended to occur around 9:00 a.m. "I thought it was an artifact," he recalls. But the more he and others looked, the more the finding held up. Now there is evidence that not just heart attacks but strokes, angina, and sudden death all tend to occur close to 9:00 a.m.

Moreover, this phenomenon seems to be specific for cardiovascular diseases. Deaths from other causes show no particular tendency to occur in the morning. The investigators now are examining why so many cardiovascular events occur in the morning, with the hope that this study may lead them to an understanding of why they occur at all.

The original study that led Muller to the finding that nonfatal heart attacks tend to occur near to 9:00 a.m. was the Multicenter Investigation for the Limitation of Infarct Size, sponsored by the National Heart, Lung, and Blood Institute. Designed to determine whether propranolol or hyaluronidase could reduce the damage from a heart attack, the study called for participants to receive one of the two drugs up to 18 hours after an attack began. For this reason, the computerized data from the trial included the time of the heart attacks.

Muller first looked at data from 847 patients and saw the 9:00 a.m. clustering. He also had data from over 2000 other patients who had had heart attacks but had been ruled ineligible to participate in the study. They, too, tended to have their attacks around 9:00 a.m. The likelihood of a nonfatal heart attack occurring at 9:00 a.m. is three times greater than at 11:00 p.m., when the attacks are least frequent.

Muller wondered whether the patients only reported their heart attacks when they woke up. The attacks might actually have begun in the night when they were asleep. But there was one objective measure of the timing of the heart attacks. The study included data on blood concentrations of creatine kinase, an enzyme that is released into the bloodstream 4 hours after an attack begins. Creatine kinase concentrations were available for 703 of the 847 patients in the study, and when Muller looked at those data, he found that 9:00 a.m. still held up. By this time, it was May 1985, and Muller had spent a year working with the study data, "trying to prove the timing was an artifact." Finally, he was convinced that, for this study at least, the finding was real.

"We just don't know what causes strokes to happen, period, let alone why they happen at a particular time of day."

But then he had another concern. There are so many possible associations that can be checked in computerized data from a large clinical trial that it is quite easy to find strong correlations between various parameters that turn out to have occurred by chance. So Muller began looking for other reports that heart attacks may occur in the morning. He found 14 studies all published "in obscure journals," each of which confirmed the finding.

"Once I found those studies, I began to believe the finding was real, and I reasoned that if heart attacks are caused by blood clots that occur in the morning, perhaps strokes are too." To check, he called Thomas Robertson of the heart institute to see if the institute had any databases giving times that strokes occur. The National Institutes of Health do have a stroke data bank with information on 1200 patients, but no one had ever looked for the time when strokes occurred. "You couldn't ask for a better data set," says Robertson.

Robertson called John Marler of the National Institute of Neurological and Communicative Disorders and Stroke and asked him to run a computer search for stroke timing. "Within a few minutes, John came into my office with an excited look on his face," Robertson says. The stroke data were even stronger than the heart attack data—there was a much greater likelihood that a stroke would occur between 8:00 a.m. and 9:00 a.m. than between 3:00 a.m. and 4:00 a.m., when stroke incidence is lowest.

But the stroke data lacked the objectiveness of the heart attack data. There is no enzyme test to pinpoint the onset of a stroke, so the time the strokes began was determined from careful interviews with patients and their families. Marler, who is, he says, "my own worst skeptic," did a small study of data from patients who were hospitalized and under constant monitoring. The stroke timing held up.

Encouraged by the stroke and heart attack findings, Paul Ludmer, who until recently worked with Muller but is now with Cardiovascular Consultants in Oakland, California, looked at the time of death as noted on death certificates for all persons who died of sudden death in Massachusetts in 1983. Once again, there were twice as many sudden deaths at 9:00 a.m. as at 5:00 a.m., when they were least likely.

Michael Rocco of Harvard Medical School looked at the timing of transient ischemic attacks—times when the heart muscle is deprived of blood. Most of these attacks are symptomless—only about 20% are accompanied by chest pains. Rocco studied 32 patients at Brigham and Women's Hospital who had verified heart disease, monitoring these patients for 24-hour periods to detect ischemia. "Most of the attacks occurred in the morning within 1 to 2 hours after awakening," he reports. Both the frequency and the duration of the attacks were greatest in the late morning hours.

Now the question is, what does it all

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

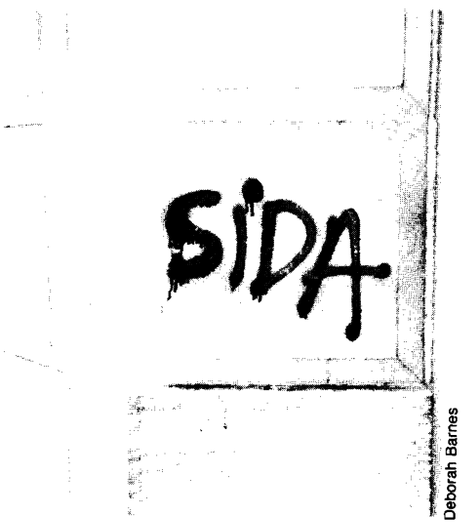
That the AIDS virus infects the brain is no longer a question. But what cell types it infects is an issue that is only partly resolved. Clayton Wiley of the University of California at San Diego and his colleagues have reported that, in addition to macrophages and monocytes, the AIDS virus infects endothelial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



Deborah Barnes

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