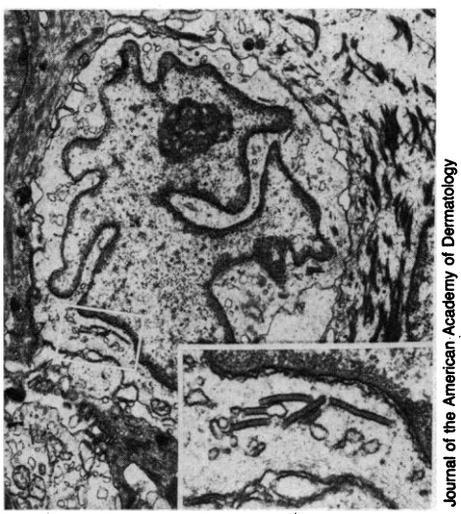
Where Is the AIDS Virus Harbored?

Nobody knows where in the body the AIDS virus is harbored. The virus has been found only rarely in circulating T cells, probably because it kills the cells so quickly. But researchers reason that the virus must be sequestered somewhere. A group of investigators from the University of Vienna and the National Cancer Institute have preliminary evidence that Langerhans cells, which are immune system cells that nestle in the skin, particularly in the epidermis, may serve as a reservoir for the virus. Georg Stingl of the University of Vienna presented that evidence recently at the annual meeting of the Society for Investigative Dermatology.

Langerhans cells are best known for their role in presenting antigens to T cells. They take up a foreign antigen and then present it



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Langerhans cells

on their surface to T cells, which then can start responding to the antigen.

Both T cells and Langerhans cells carry the T4 antigen on the cell surface; it is this antigen that the AIDS virus appears to recognize and bind when it enters T cells. So Stingl, Erwin Tschauchler, Veronika Groh, and Klaus Konrad of the University of Vienna and Mica Popovik and Dean Mann of the NCI decided to see if they could find the AIDS virus in Langerhans cells.

Skin biopsies from 25 individuals with AIDS or AIDS-related complex, the syndrome that often precedes full-blown AIDS, showed that five of these people had AIDS viruses in Langerhans cells. The skin, Mann notes, is the largest organ of the body and these biopsies were extremely small—just 4 millimeters. Because they found AIDS virus in these small samples from one-fifth of the patients, "just think of the tremendous virus load these persons have." Since they took only a small skin sample from each patient, the researchers cannot say whether those who had no detectable virus in Langerhans cells actually have infected cells elsewhere in their skin, Stingl points out.

Since the finding is so recent, the investigators can only speculate on what it means. But the prime possibility, says Stingl, is that Langerhans cells are more resistant than T cells to the lethal effects of the AIDS virus, enabling the infected Langerhans cells to serve as a reservoir for the virus. ■

A Perspective on Degenerative Brain Disease

"What happens," asks Stanley Pruisner of the University of California School of Medicine, "when the structure of the brain crumbles and degenerates?" One person in a million, for example, develops Creutzfeldt-Jakob disease, a progressive dementia that causes death within a year. Natives of the New Guinea highlands developed kuru, a similar disease. Sheep get scrapie—once again characterized by a pervasive destruction of the brain. Researchers suspect that an understanding of these and similar diseases might reveal new basic mechanisms of degenerative pathology.

Speaking at a symposium at the annual meeting of the American Federation for Clinical Research, Pruisner reviewed what is known about prions, small proteins, formerly known as slow viruses, that cause certain degenerative brain disorders.

Creutzfeldt-Jakob disease, kuru, and scrapie are all caused by prions, according to Pruisner. The name, which Pruisner coined, stands for proteinaceous infectious particles, and, as the name implies, prions are largely or entirely made up of protein. Prions are smaller than even the smallest virus and, unlike viruses or bacteria, they have no detectable DNA or RNA. Among their other properties, they somehow evade their host's immune system, which ordinarily attacks foreign proteins.

Where prions originate and how they bypass the defenses of the immune system to destroy the brain remains to be uncovered. Pruisner's own speculation is only general: "prions arise within individuals from their own genes." These "new" particles, he proposes, are actually modified versions of normal proteins, which means that the immune system does not see them as foreign.

Working with mice and hamsters that were infected with scrapie prions, Pruisner and his many colleagues at the California Institute of Technology and the University of California in San Francisco isolated a prion protein and made molecular probes to locate the gene. It is on chromosome 2 in the mouse and on chromosome 20 in humans. The mouse and human genes are nearly identical, differing in only 10% of their DNA bases. Finally, Pruisner reports that mice and, presumably, humans normally make a protein that is almost exactly like the prion protein. The function of this newly discovered mouse protein, called PrP^c, for cellular prion protein, is unknown. The prion protein, however, seems to be slightly altered by the cell after it is made.

These findings still leave open the questions of how prions replicate and how the diseases originate. Although many cases occur sporadically, for no known reason, it is clear that prion diseases can be transmitted through direct contact with infected tissue. For example, Creutzfeldt-Jakob disease has been transmitted in patients through corneal transplants.

Another unanswered question is what determines the incubation time for scrapie and other prion diseases. In mice, for example, the incubation time can vary by nearly 100%—from 120 to 200 days. Using inbred mice, Pruisner and his associates determined that, with scrapie, incubation times are controlled by a gene that is at least close to, if not identical with, the prion protein gene.

Although the diseases known to be caused by prions are few in number and are rare, Pruisner suggests that prions may tell us about other, more common diseases. "The molecular mechanisms of brain degeneration in Alzheimer's disease, amyotrophic lateral sclerosis, and Parkinson's disease may share many features with prion diseases," he says. And there is no reason to assume that prions cause only brain diseases. "We now need to consider prions to explain other degenerative diseases outside the brain." ■

Depression, Anorexia, Cushing's Link Revealed

Patients with depression, anorexia nervosa, and Cushing's disease all tend to produce excessive amounts of the stress hormone cortisol. And they frequently share psychological symptoms including sleep disturbances, loss of libido, and loss of appetite. Yet these are clinically distinct diseases.

Reporting in May at the American Psy-

chiatric Society meetings in Washington, D.C., and in the 22 May issue of the *New England Journal of Medicine*, Philip Gold of the National Institute of Mental Health, George Chrousos of the National Institute of Child Health and Human Development, and their colleagues describe a series of experiments that pinpoint the neurochemical defects in these three diseases and explain how the defects lead to excess cortisol production. The results also provide the first biochemical test for the early diagnosis of Cushing's disease.

Although cortisol is produced by the adrenal glands just above the kidneys, the signal to make it originates in the hypothalamus in the base of the brain. The hypothalamus makes corticotropin-releasing hormone, or CRH, which travels to the pituitary gland just below the brain. Upon receiving the CRH signal, the pituitary makes adrenocorticotrophic hormone, or ACTH, which signals the adrenals to make cortisol. Excess cortisol production could be due to an overproduction of CRH by the hypothalamus or to an overproduction of ACTH by the pituitary or to an overresponse to ACTH by the adrenals.

Until fairly recently, researchers could not distinguish among these alternatives. All the relevant hormones are hard to measure. Even excessive cortisol production can be difficult to document because the hormone is secreted in spurts, mostly during the night, and even patients who make too much of it do not overproduce it all the time.

It was two developments during the past few years that enabled Gold, Chrousos, and their colleagues to tease apart the biochemical pathways that lead to Cushing's disease, depression, and anorexia nervosa. First, the NIH researchers developed a reliable radioimmunoassay for ACTH. Then CRH was isolated and made available for research. Thus the investigators could administer CRH to patients and to normal volunteers and could measure CRH, ACTH, and cortisol responses to determine whether the patients respond normally to CRH and, if not, why.

Their conclusion is that both anorexia nervosa and depression patients oversecrete CRH. Patients with Cushing's disease, in contrast, produce normal amounts of CRH but overrespond to the hormone with an excessive production of ACTH by the pituitary. This finding resolves 30 years of debate over whether Cushing's disease is a disease of the pituitary, according to Gold.

An immediate consequence of this work is that it is now possible to distinguish between Cushing's disease and depression. Patients can be given CRH. If they respond normally to it, they are depressed. If they over-produce ACTH in response, they have Cushing's disease.

This diagnostic test is of clinical importance because physicians have found it impossible to distinguish Cushing's disease in its early stages from depression.

As many as 75% of Cushing's disease patients are depressed and often depression is the first symptom of the disease. As Cushing's disease progresses, patients develop physical features that clearly mark them. They develop a round, moon-shaped face, they become hirsute, their fat is redistributed so that they have fat pads on their back and fat around their waists, they have high blood pressure, and they have severe osteoporosis. The usual treatment is removal of the adrenal glands or removal of the pituitary.

Just as early Cushing's disease is frequently misdiagnosed as depression, some patients with depression are misdiagnosed as having Cushing's disease, particularly if they happen to be overweight and hirsute, according to Gold. As a consequence, depressed patients have had their adrenals or pituitaries removed.

Although patients with anorexia nervosa have essentially the same biochemical abnormality as those with depression, they are, says Gold, "even more hypercortisolemic than depressed patients." Some anorectics, in addition to not eating, are clearly depressed. Others do not have classical depression, but Gold and others propose that they may have an atypical form of the disease. "They are so obsessed with their weight that they are distracted from the other symptoms of depression," Gold remarks. Even the anorectic patients in the NIH study who did not meet the research diagnostic criteria for depression "felt lousy," Gold says. In fact, he continues, "I defy you to find an anorectic patient who does not feel lousy." When the anorectic patients gain weight, their cortisol levels drop to normal.

This still leaves the question of which came first—the obsessive dieting or the excess cortisol production. Gold suggests that in some cases it may be the weight loss. "We know that weight loss in animals can precipitate hyperactivity of the CRH-releasing neurons. It may be that anorectics begin by losing weight, then they become hypercortisolemic and get locked in."

So far, the findings of the NIH group do not immediately suggest new therapies nor do they suggest new explanations for the etiologies of depression, anorexia nervosa, and Cushing's disease. But knowing the biochemical bases of these disorders can only help in further research on the diseases. ■

Limiting Heart Attack Injury

For the past few years, cardiologists have tried to treat heart attack patients by resupplying the heart with blood as soon as possible. Reasoning that the damage of a heart attack occurs because the heart is deprived of blood when a vessel is completely blocked, innovative ways to get blood flowing again were devised. The enzyme streptokinase breaks up blood clots blocking vessels; plaques on artery walls are squashed with inflated balloons within a few hours of the time a patient's heart attack begins.

However, recent experiments suggest that this therapeutic approach is not without problems. Speaking at the recent meeting of the American Federation for Clinical Research meeting, cardiologist Myron Weisfeldt of Johns Hopkins University School of Medicine reviewed data indicating that much of the heart attack damage actually takes place when the blocked vessel is opened up and blood flows into the heart again.

Reperfusion injury, says Weisfeldt, is a controversial concept in cardiology. Thousands of experiments with dogs and other laboratory animals demonstrated that the amount of damage from a heart attack depends on how long the coronary arteries are blocked and that after 6 hours or so, it does not even pay to open the arteries. The damage is already done. The heart muscle fed by the blocked arteries is dead. So it sounds paradoxical to say that much of the heart damage occurs not from the blockage but from the reopening of the arteries.

Yet what Weisfeldt and others are finding is that a series of biochemical changes occur in the heart when it is deprived of blood and thus of oxygen. They result in a massive production of free radicals—molecules with an odd number of electrons—when blood flows back into the heart and unlimited oxygen is suddenly available. These free radicals peroxidize membrane lipids and inactivate key enzymes. The reperfusion of blood causes cell damage and death.

Several groups of investigators, including Weisfeldt's group, find that in animal experiments if the enzyme superoxide dismutase (SOD) is given at the time blood begins flowing into the heart again, the damage from a heart attack can be limited. SOD mops up free radicals. The next step is to give patients human SOD, which is available through recombinant DNA technology. Weisfeldt is confident that human recombinant SOD will be useful. "As drugs go, it's *extremely* benign," he says. "It could easily be utilized. We intend to give it to humans as soon as possible." ■