Plaque hemorrhage linked to stroke

Stroke, the third most frequent cause of death in the United States, can result from the buildup of fatty plaque, which narrows the arteries and induces blood to form clots that block blood flow to the brain.

In recent years, some physicians have also come to suspect that small hemorrhages in the plaque's own capillary networks may further increase the risk of stroke or prestroke symptoms. The results of a new study support this link and, at the same time, demonstrate the usefulness of computer tomography (CT) scanning for pinpointing the cause of blood flow blockage.

At the 12th International Joint Conference on Stroke and Cerebral Circulation held recently in Tampa, Fla., Antonio Culebras of the State University of New York at Syracuse described his use of CT scanning in identifying plaque features in the neck's carotid arteries, which may lead to stroke. CT scanning is used for imaging the brain, but Culebras and his co-workers were the first to develop the technique for arterial studies in the neck. They have found that a plaque hemorrhage shows up on a CT scan as a small dot called a "lucent defect."

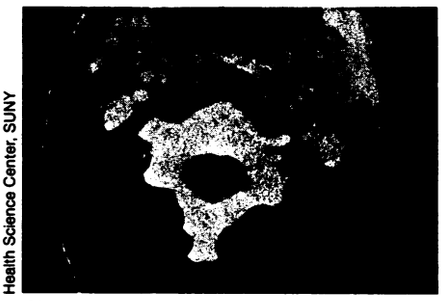
The researchers looked for lucent defects in the CT neck scans of 95 patients who, in the previous three months, had suffered a stroke or a transient ischemic attack (TIA), a temporary blockage of blood vessels that is often followed by a major stroke within days to months. For those patients who had plaque hemorrhages, Culebras's group found a high correlation between the side of the neck in which the plaque hemorrhage was discovered and the side of the body that experienced stroke or TIA. He says his group is now conducting a larger prospective study to further test the link between stroke and plaque hemorrhages.

Lucent defects were not correlated with every stroke or TIA case, but Culebras says that plaque hemorrhages make "a convincing contribution to the development of symptoms." He and others think that the hemorrhage causes the plaque to grow, which further narrows the artery and may cause the plaque to burst open into the vessel, producing stroke- or TIA-triggering clots.

Louis R. Caplan at Tufts University School of Medicine in Boston cautions that there have been other studies indicating that plaque hemorrhages do not play much of a part in strokes. He thinks that the importance of both CT neck scanning and an ultrasound technique being developed in Germany is that, unlike conventional methods, they show detailed cross sections of arteries: "They have real potential for letting people know what's happening with the arterial wall . . . and the more you know about [that], the more intelligently you can pick appropriate treatment," such as what kind of anticoagulant to administer.

He also notes the importance of imaging carotid arteries in particular, because his research has shown that strokes in some groups, particularly white males, are initiated predominantly in the neck.

Culebras says that CT scanning reveals all the stroke-related features of plaque seen by conventional imaging techniques, but it is the only "tool that can show us the microhemorrhage of the plaque." Moreover, he says that CT scanning is safer than the commonly used arteriography, in which X-rays are taken of vessels that have been injected with an X-ray opaque dye. "This allows us to follow up on those patients at short intervals — such as every four to six months — with very little risk to the patient," he notes. "By knowing how the plaque is behaving over time, it permits us to plan more reasonable treatment strategies." In particular, he hopes the identification of lucent defects will lead to better-informed decisions about whether or not to resort to carotid endarterectomy surgery—which he says currently is overused — to clean out carotid arteries (SN: 2/8/86, p.89). — *S. Weisburd*



Health Science Center, SUNY

CT scanning of a carotid artery produces a cross section that shows much more detail — such as the plaque hemorrhage marked by the arrow — than do other imaging techniques.

Gene defect located for Gaucher's disease

Using recently developed methods for genetic analysis, scientists have located a rare gene defect that often leads to a potentially fatal enzyme deficiency in infants. Shoji Tsuji of the National Institute of Mental Health (NIMH) and his colleagues tracked the mutation to a site on chromosome 1.

The finding will improve genetic counseling for victims of the the most serious forms of Gaucher's disease, which is caused by the enzyme deficiency, report the researchers in the March 5 NEW ENGLAND JOURNAL OF MEDICINE.

The enzyme in question, glucocerebrosidase, breaks down a critical fat in certain body tissues. When the undegraded fat builds up, it can cause several types of Gaucher's disease. Type 1, the most common form, is characterized by an enlarged spleen and liver, and bone deterioration. The genetic mutation for type 1 is carried by one in 600 Jews of Eastern European ancestry. Type 2 kills infants by about 2½ years of age, often because motor and respiratory control is severely hindered. In type 3, nonfatal neurological symptoms, including epilepsy, dementia and difficulty in controlling eye movements, begin during adolescence. Most of the estimated 10,000 to 20,000 people in the United States with Gaucher's disease have relatively mild cases of type 1. About 2 percent have types 2 or 3.

All three types are known to result from mutations in the gene that codes for glucocerebrosidase. The investigators cloned the sequence of chemical subunits that determine protein production for a normal glucocerebrosidase gene and compared it with a sequence cloned from a patient with type 2 Gaucher's disease. An alteration at just one location was identified in the latter sequence. This chemical substitution leads to the synthesis of an abnormal enzyme that fails to break down the key fat in body tissues.

The genetic-code change was then checked in a larger sample using an enzyme that slices DNA at points signaling either the presence of a normal glucocerebrosidase gene sequence or the Gaucher's disease mutation. Four of 5 patients with type 2 disease and all 11 patients with type 3 disease had the mutation on at least one of two chromosome strands, or alleles, that were isolated from blood samples. One strand is inherited from the mother, the other from the father. Two of 5 patients with type 2 disease and 7 of 11 with type 3 had the mutation on both alleles. The mutation showed up on a single allele for 4 of 20 patients with type 1 disease. None of 29 healthy controls had the mutant allele.

"Clearly, this mutation is not responsible for all cases of type 2 and 3," says project director Edward I. Ginns of NIMH. "But we can now predict whether neurological problems are likely to occur later in life for children with symptoms of Gaucher's disease." There may be another mutation, he contends, that will distinguish between type 2 and type 3.

Work is under way on the development of gene therapy to treat Gaucher's disease. NIMH investigators, working with scientists at the Whitehead Institute in Boston, have transferred the normal gene into Gaucher's cells with a type 2 mutation and corrected the enzyme deficiency in tissue culture. The next step, says Ginns, is to transfer the normal human

gene into the bone marrow of mice to see if the critical enzyme is then produced. Undegraded fat in Gaucher's disease is stored predominantly in cells derived from bone marrow.

There are indications, notes Ginns, that a "pseudogene" missing parts necessary to code glucocerebrosidase moves into the region of the functional gene and creates the mutation. — *B. Bower*

New plan drafted to save the panda

Despite extensive efforts to protect the giant panda, over the past 10 years its population in China appears to have been more than decimated, according to a study conducted by the Chinese Ministry of Forestry and the Swiss-based World Wildlife Fund (WWF) International. The decline results from sustained human encroachment on the animal's habitat. To counter this threat, WWF consultant John McKinnon and Qiu Minjiang, a Chinese environment official, have drafted a management strategy calling for an immediate strengthening of measures by the Chinese government to protect that habitat. WWF expects the joint plan, currently under study by the Chinese government, to win the government's formal approval within a few months.

It calls not only for greater enforcement of regulations in China's existing 12 panda reserves, but also for establishing a new class of forests called "panda management ranges." As at the reserves, the plan would prohibit hunting, grazing, human settlement, agriculture and burning in the ranges. Logged areas would be reforested with indigenous species and bamboo. On panda habitats outside ranges and reserves, the strategy recommends halting all new human settlement, maintaining forest cover and strictly enforcing panda protection laws.

Another key recommendation is the reestablishment and protection of panda migration corridors to link small, now-isolated subpopulations. Satellite photos indicate that most pandas — shy, solitary inhabitants of China's mountainous bamboo forests — live in groups of fewer than 50, many in groups of as few as 10. Once a group falls to 20 pandas, its members "can be expected to become extinct within a few generations," WWF says.

England's Prince Philip, president of WWF International, announced the strategy last week at the press conference launching a fund-raising campaign to help finance China's efforts to save the remaining 800 to 1,000 wild pandas. Said Prince Philip, "Without this joint effort by the Chinese and WWF we would be condemning the panda to extinction as surely as if we were to go out and deliberately exterminate them."

— *J. Raloff*

Future 'patchwork' cure for hemophilia?

Researchers at the Fred Hutchinson Cancer Research Center and the University of Washington, both in Seattle, are giving a genetic-engineering twist to basic procedures used in skin grafting. Using fibroblast cells infected with viruses carrying specific genes inserted in the laboratory, they hope to cure genetic disease with cell grafts.

Some genetic diseases are characterized by a lack of certain substances, such as a particular enzyme. According to the scientists, patches of fibroblasts that contain genes coding for the missing components may be induced to supply them, thereby reversing the disease.

Unpublished data presented by the scientists at last week's DNA/Hybridoma Congresses in San Francisco suggest this gene-therapy technique may have the potential to someday cure hemophilia, the genetic disease characterized by lack of a blood component essential to normal clotting. Because of this deficiency, hemophiliacs are susceptible to serious blood loss following minor cuts or tooth extraction.

While others are looking at tumor-derived fibroblasts as gene carriers, the Seattle group uses fibroblasts taken from normal individuals or from patients with the deficiency being treated. *In vivo* work has begun in rats and will later move to dogs. Also, because substances produced by the added gene may not effectively reach the plasma from a skin patch, other routes of fibroblast introduction are being studied.

On March 2, the Food and Drug Administration announced the approval of a new drug called tranexamic acid, which protects the weak blood clots formed in hemophiliacs undergoing surgery. Although the drug is an important step for hemophiliacs, its efficacy is affected by severity of the disease. Gene-therapy techniques like that being studied in Seattle may offer a better solution.

In addition, a report from the Seattle scientists in the February PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES (Vol.84, No.4) describes a similar system that restored production of adenosine deaminase (ADA) in fibroblast cells from a patient with severe combined immunodeficiency syndrome. Without the ADA enzyme to destroy them, certain substances accumulate in the blood of ADA-deficient patients and cause immune system malfunction. Transfer of ADA-coding genetic material made the patient's fibroblasts produce 12 times as much ADA enzyme as was produced by cells from normal individuals. — *D.D. Edwards*

Keys to help unlock photosynthesis

"If we fully understood photosynthesis, it might be possible to build solar chemical factories to make food and fuel faster and with higher overall quality than nature can," says James Norris, a chemist at Argonne (Ill.) National Laboratory. Though scientists are a long way from understanding photosynthesis that well, they are making important inroads. Among the most recent is the discovery of two key photosynthetic structures.

Argonne scientists have just revealed the three-dimensional structure of a molecule known as the photosynthetic reaction center. "It's responsible for converting sunlight into chemical energy — the first step in photosynthesis," explains Marianne Schiffer, a crystallographer in the group.

They worked with *Rhodopseudomonas sphaeroides*, a purple bacterium, for which the constituent subunits of its photosynthetic reaction center were already known. By crystallizing the molecule and studying it with X-ray diffraction techniques, "we now know where they [the subunits] are and how they're related to each other," Schiffer says. This should help others interpret spectroscopic information for related molecules whose structures have not been characterized, she says, such as the more complicated photosynthetic reaction centers in green plants.

Also using X-ray crystallographic techniques, researchers from three West German institutes report in the Feb. 19 NATURE that they have found the structure of the enzyme (RuBPCase) that initiates the reduction of atmospheric carbon dioxide into organic molecules during photosynthesis. (Reduction can involve either the removal of oxygen or the addition of electrons or hydrogen.)

Writing in the same issue of NATURE, plant physiologist Jim Barber from the Imperial College of Science and Technology in London points out that every molecule of carbon incorporated into some compound in the biosphere originates from the catalytic activity of this enzyme. However, he explains, because the enzyme "does not work at maximum efficiency," it constrains the productivity of photosynthesis. Many scientists believe it will be necessary to genetically alter this enzyme or its activities if the efficiency of photosynthesis is to be improved, he says. First, however, its structure had to be determined.

— *J. Raloff*