Scientists slowly unravel Alzheimer's mystery

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and certainly not just the sticky clumps of proteins called beta-amyloid plaques that have received the most attention.

In the brain, the disease's hallmarks are those plaques, tangles of another protein called tau, and the progressive death of nerve cells, called neurons, that gradually strip a victim of memory, language, reasoning, and, finally, life.

Mutations in three genes cause early-onset Alzheimer's, the rare form of the disease that strikes people in their 30s, 40s, or 50s. Those altered genes trigger production of too much beta-amyloid. But none appears to be involved in the kind of Alzheimer's that strikes after age 60.

So far, researchers have linked two major genetic changes to old-age Alzheimer's and are on the trail of four or five more. These mutations do not cause the disease, but rather increase the risk of developing it. One, ApoE4, increases the risk of getting the disease three- to four-fold. A second potential gene mutation, called UBQLN-1, was identified this month by Rudy Tanzi, a geneticist at Massachusetts General Hospital. Tanzi, founder of TorreyPines Therapeutics, which is working on Alzheimer's drugs, said he believes it may increase the risk one- to two-fold, but its specific role in the disease has not been determined.

The lead suspect in the search for a cause remains the protein beta-amyloid because of its clear involvement in early onset Alzheimer's and its big presence in Alzheimer's brains.

Tests of an amyloid vaccine in people, which might have proved amyloid's leading role, were halted in 2002 when 18 of 300 subjects developed a potentially fatal brain inflammation. Nevertheless, some participants showed inklings of a positive effect, enough to keep researchers pursuing similar experiments. In addition, antibodies to amyloid reversed memory problems in mice, and cleared out amyloid deposits and then tau.

"It's my feeling that all the cases of Alzheimer's are caused by an imbalance in the accumulation versus removal of the beta-amyloid protein," said Dr. Dennis Selkoe, a leading amyloid researcher who is codirector of the Center for Neurologic Diseases at Brigham and Women's Hospital, and who is a director of Elan Corp., which is working on amyloid-based treatments.

Much of the amyloid research is shifting away from the big clumps called plaques to focus on smaller clusters that can still be dissolved by the body. The plaques are problematic for researchers because they also occur in people without symptoms of Alzheimer's and do not correlate well with memory problems. Some scientists are now suggesting that plaques, which develop outside the neuron, may be a defensive response, an effect rather than a cause.

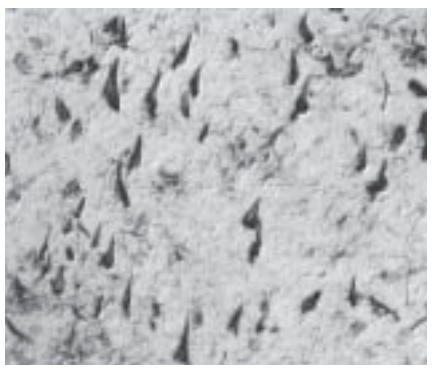

PHOTO COURTESY OF DR. PETER DAVIES

In Alzheimer's, a protein called tau collects in tangles, disrupting nerve impulses.

The small clusters, on the other hand, correlate closely with memory decline, even before plaques and tangles appear, according to research in mice. The clusters occur inside as well as outside neurons, and may interfere with the ability of neurons to signal each other.

One critic of the amyloid focus, Peter Davies, a professor at Albert Einstein College of Medicine in New York, jokes about the new work on "the" cause. "Ten years ago, it was the visible amyloid deposits," he said. "When everybody realized that didn't work, it became the invisible. It's only one more step before they get it right."

A small group of scientists is instead stalking tau as the lead culprit. In healthy people, tau acts like a scaffolding to support a tube inside neurons that allows movement of nerve impulses. In Alzheimer's, the tau is misshapen and collects in tangles, causing the neuron tube to collapse.

Damage to tau correlates better than amyloid with the severity of Alzheimer's. Research shows that people with mild cognitive impairment, often a precursor to Alzheimer's, have tau tangles but not amyloid plaques in their brains. Other research in mice, however, suggests that tau may need beta-amyloid to do its worst damage in Alzheimer's.

Davies, who like Selkoe has been studying Alzheimer's for decades and is a founding scientist at Applied NeuroSolutions, which is working to develop treatments, said he believes that the disease starts well before tau and amyloid problems appear. He traces the illness back to a number of potential insults — such as stroke, head injury or problems with insulin — that he believes trigger nerve cells to try to divide. But unlike other cells, neurons cannot split, and they die in the process of trying, he said. It is this abnormal action of neurons, in this theory, that leads to amyloid plaques and tau tangles.

While the evidence for the cell-cycle theory is still thin, many scientists are investigating possible "insults" to the brain that might trigger abnormal amyloid and tau, or that might spur worsening of the illness. Stroke, serious head trauma, diabetes and a sedentary lifestyle, for example, are all associated with higher risk of getting Alzheimer's.

"Which is likely to be the originator of the disease?'' asks William Thies, vice president of medical and scientific affairs for the national Alzheimer's Association. "My guess is it's in the life stress."

A paper published this month put insulin's role in the spotlight. Insulin's main role in the body is to help control levels of the sugar that fuels cells. The work at Brown Medical School found abnormally low levels of insulin and insulin growth factors in parts of the brain most affected by Alzheimer's, and that the low levels contributed to the "brain rotting," said Dr. Suzanne de la Monte, a pathology professor there. Earlier research indicated that insulin helps regulate amyloid and also prevents formation of destructive forms of tau. Studies have also found that people with Type 2 diabetes, in which cells become insensitive to insulin, have a higher risk of developing Alzheimer's.

Other work is focusing on damage caused by destructive oxygen molecules that the body creates when it turns food into energy. Research suggests that this damage and the inflammation it causes can trigger accumulation of beta-amyloid, which can generates more oxygen-related damage. Studies have also found that people who took anti-inflammatory drugs for other reasons had a lower risk of Alzheimer's. But one experiment testing these drugs as treatment for moderate Alzheimer's found no benefit, and a prevention trial in 2,400 healthy adults was halted late last year when the drugs were linked to increased risk of heart attack.

PHOTO COURTESY OF ALBERT EINSTEIN COLLEGE OF MEDICINE

Dr. Peter Davies said he believes Alzheimer's disease can be traced back to a number of potential insults — stroke, head injury or problems with insulin — that he believes trigger nerve cells to try to divide.

A Seattle researcher, who is testing other possible anti-inflammatory substances, said he isn't sure which comes first, inflammation or accumulation of beta-amyloid and tau. "That's going to be difficult to determine with certainty," said Dr. Tom Montine, a professor of neuropathology at the University of Washington. "I view it as a circle. If it's important to the disease process, which one comes first may not be that meaningful."

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Soft tissue is discovered inside a dinosaur fossil

By Robert Lee Hotz
LOS ANGELES TIMES

In bone blasted from Montana sandstone, fossil hunters for the first time have discovered the microscopic meat of a Tyrannosaurus rex, preserved almost unaltered since the dinosaur died 70 million years ago, scientists announced last week.

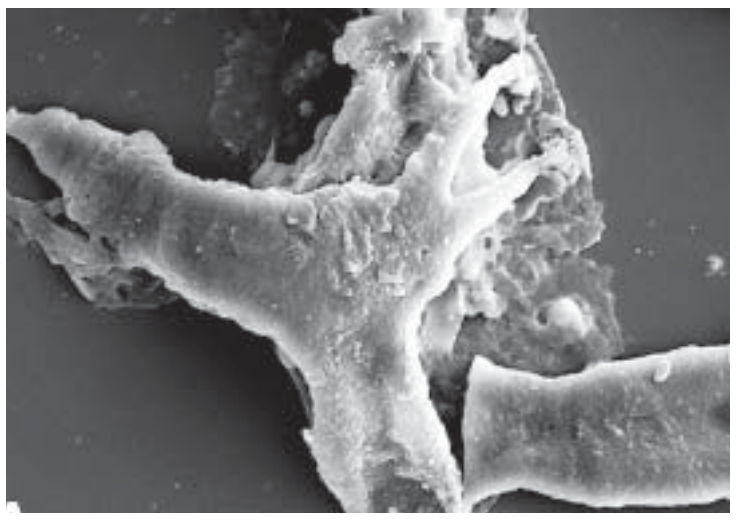
Scientists at North Carolina State University and the Museum of the Rockies in Bozeman, Mont., found brownish oblong cells, elastic threads of veins and pliable dabs of red bone marrow in the core of a stout hind leg, the researchers reported in the journal Science.

The translucent vessels were so elastic that, when one was stretched out and then released, it snapped back like a rubber band.

"To my knowledge, preservation to this extent has not been noted in dinosaurs before," said paleontologist Mary H. Schweitzer at North Carolina State University in Raleigh, who led the research team. "The tissues are still soft. . . . The microstructures that look like cells are preserved in every way."

Under a scanning electron microscope, these dinosaur tissues — minute remains of the mightiest of Earth's ancient carnivores — were "virtually identical" to those of a modern ostrich.

The scientists have not completed their laboratory tests, so they would not say whether they had found any intact genetic material or isolated individual proteins. In the unlikely event that researchers could identify the actual genes of a Tyrannosaurus rex, it might help settle debates about the kinship of dinosaurs and birds, or even prompt cloning experiments aimed at replicating the creatures.



SCIENCE MAGAZINE PHOTO

A photo released by North Carolina State University shows branching blood vessels found in the femur of a 70 million-year-old Tyrannosaurus rex.

Far from a freakish accident of preservation, the researchers said, fragile fresh tissue inside dinosaur bones may turn out to be common. Indeed, a quick examination of three other dinosaur specimens revealed similar microscopic tissues inside the bones, they said.

''It may be that this isn't a unique specimen," said paleontologist Jack Horner at Montana State University's Museum of the Rockies, a coauthor of the study. Horner has pioneered the use of molecular and cellular techniques to probe the growth and behavior of dinosaurs.

If confirmed by other researchers, the find could force scientists to reconsider how fossils are formed.

Until now, scientist believed that bones fossilized when minerals gradually replaced all organic material. Current theories about fossil preservation hold that organic molecules should not preserve beyond 100,000 years.

"Our theories don't allow for this," Schweitzer said.

Other researchers were fascinated but cautious about the announcement.

The field of dinosaur paleontology is still an academic netherworld where trained paleontologists must compete for specimens with amateur rock-hounds and private collectors. It is no stranger to outlandish technical claims, black-market hyperbole, and fraud.

Time and again, however, the truth of these vanished denizens as revealed by reliable fossils — creatures that flew on four wings, snake-necked vegetarians larger than locomotives, and giant fanged predators cloaked in feathers — has proved far stranger than fiction.

Philip Currie, curator of dinosaurs at the Royal Tyrrell Museum in British Columbia, considered the latest discovery plausible and called it "great news."

''Under the right circumstances, incredible things can be preserved in these fossils," Currie said.

But he added: "It is out on the fringes, and consequently you have to be doubly careful."

Microscopic traces of soft tissues may have eluded detection until now, the scientists said, because paleontologists were too squeamish to break open their irreplaceable dinosaur specimens to dissolve the mineral matrix inside the bones.

Horner called the discovery a combination of adept laboratory analysis and an accident of field work.

The tissue specimen was extracted from a fossil femur chiseled from 1,000 cubic yards of rock in the Hell Creek Formation at the Charles M. Russell National Wildlife Refuge in Montana. The bones belonged to a relatively complete skeleton of a 40-foot-tall Tyrannosaurus rex that died when it was about 18 years old.

It took field researchers three years to dig out all the bones. So remote was the site that the fossils could be removed only by helicopter.

The dinosaur remains encased in thick jackets of plaster were so heavy, however, that field workers had to break the massive thigh bone in two places to load it safely aboard the aircraft. They did not treat it with the customary chemical preservatives.

"On that particular specimen, it was serendipitous, because we did have to break it to get it out by helicopter," Horner said. Normally, "people tend not to want their dinosaurs broken, or to have cut holes into the bone, or to cut them in half."

When the broken thigh bone was delivered to Schweitzer's lab in Raleigh, she quickly noticed what appeared to be unusual tissue fragments lining the narrow cavity at the core of the bone.

It took seven days to dissolve the surrounding minerals without contaminating the specimen. For weeks more, the samples were washed in chemical baths, incubated and purified.

In the process, Schweitzer essentially distilled the remains of a 5-ton predator whose step once made the earth tremble to a few milliliters of cloudy solution under a Zeiss dissecting microscope.

Magnifying the purified remains by 63 times, Schweitzer could see tiny branching red and brown structures that looked very much like vessels in bones from the largest of modern flightless birds. She also identified what seemed to be three different sorts of cell.

"Ostriches that died six months ago are producing structures that are similar to dinosaurs that died 70 million years ago."

Strict vegetarians — surprise — have healthy bones

People who adhere strictly to raw food vegetarian diets are thin but have surprisingly robust bones, US researchers reported yesterday.

Although nutritionists and the food industry have warned that a diet without dairy foods can lead to the bone-thinning disease osteoporosis, the team at Washington University School of Medicine in St. Louis found the vegans they studied had many of the signs of strong bones.

"We think it's possible these people don't have increased risk of fracture but that their low bone mass is related to the fact that they are lighter because they take in fewer calories," Dr. Luigi Fontana, who led the study team, stated in a release.

Raw food vegetarians eat only plant-derived foods that have not been cooked or processed. The team, which reported its results in this week's issue of the Archives of Internal medicine, compared 18 average Americans with 18 strict raw food vegans ages 33 to 85. All ate a diet that included unprepared foods such vegetables, fruits, nuts, and sprouted grains. Fontana expected the vegans to have low vitamin D levels because they avoid all animal products including dairy. But their vitamin D levels were ''markedly higher'' than average.

And the vegans had low levels of C-reactive protein, an inflammatory molecule that is becoming linked with the risk of heart disease, diabetes and other chronic diseases.

Furthermore, they had lower levels of IGF-1, a growth factor linked to risk of breast and prostate cancer.

Fontana does not advocate a raw food diet. But he said that to lower the risk of cancer and heart disease people should eat more fruits, vegetables and whole grains.

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