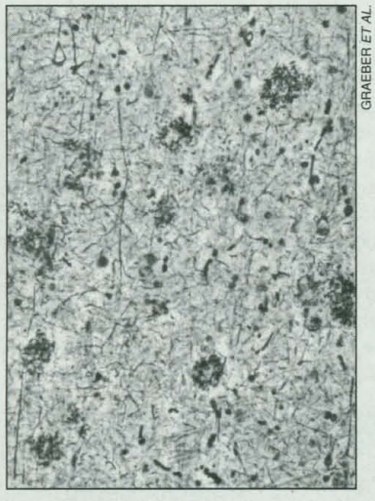
NEURODEGENERATIVE DISEASE

First Alzheimer's Diagnosis Confirmed

Ending a 2-year-long search, German scientists have uncovered a piece of science history: brain samples from Auguste D., the first Alzheimer's patient ever to be described in medical literature. The finding, published this week in *Neurogenetics*, is likely to put an end to lingering doubts about the cause of Auguste's dementia. Some scientists had argued that she may have suffered not from Alzheimer's, but from another, rarer brain disease.



GRAEBER *ET AL.*

Case closed. Plaques and tangles in the brain of Auguste D.

Researchers have been hunting for Auguste's brain since psychiatrist Konrad Maurer and two colleagues from the University of Frankfurt found her original hospital file at an institute of the university (*Science*, 5 July 1996, p. 28). When they published their findings last year, the trio still nursed hopes of also finding her brain somewhere in Frankfurt. But they were looking in the wrong place. Last September, a rival team led by neuropathologist Manuel Graeber of the Max Planck Institute for Neurobiology in Martinsried, near Munich, discovered more than 250 slides of Auguste's brain in a basement of the University of Munich. Graeber's team had also found the brain of Johann F., the second case described by Alzheimer, just a few months earlier.

In searching for Auguste D.'s brain, both teams had studied the history of her case and the movements of Alois Alzheimer himself in the early years of this century. Auguste D. was admitted to the Hospital for the Mentally Ill and Epileptics in Frankfurt in 1901. Then only 51 years old, she did not understand the world around her, had hallucinations, and was disoriented, paranoid, and hardly able to speak. Alzheimer, who had been a doctor at the hospital since 1888, studied her intensively and continued to follow her progress from a distance after his research career took him to the Royal Psychiatric Clinic in Munich in 1903. After Auguste's death in April 1906, the hospital's director sent her brain to Alzheimer in Munich for investigation. He presented her case at a psychiatry meeting in Tübingen 7 months later and published it in 1907, thus assuring Auguste a place in medical history.

Nobody knew what happened to the brain slices after Alzheimer died. Graeber says he was convinced they had remained somewhere in Munich, but Maurer hoped at least part of the samples might have been returned to Frankfurt. "It would have been nice to have found [them] here, of course," he says. "But that's life." There is no doubt about the brain's authenticity, says Graeber: The arrival of the brain at Alzheimer's clinic was recorded in the hospital's autopsy book, and every single slide is labeled with Auguste's last name—a very rare one in Germany.

A fresh look at Auguste's brain dispels allegations that she may have suffered from something other than Alzheimer's, Graeber says. Some neurologists have speculated that she was ailing from a rare metabolic disorder called metachromatic leukodystrophy. But Graeber says the rediscovered slides show no evidence of this, although her cortex does display the two classic pathological signs of Alzheimer's disease: amyloid plaques and neurofibrillary tangles. "It's exactly what you would expect" in a classical case, Maurer says.

The Max Planck researchers were even able to extract and test Auguste's DNA from a few of the slides. They discovered that she did not carry the ε4 allele of the *APOE* gene, which would have predisposed her to Alzheimer's. They would also like to screen for mutations in other genes involved in Alzheimer's, but these tests would require lots of tissue. Rather than destroy many of Alzheimer's meticulously conserved slides, Graeber prefers to await a new generation of tests that can do the job as economically as possible.

To Graeber, there is more to these analyses than just science history. As a neuropathologist, he is interested in the genetics of brain disease. And with fewer and fewer autopsies being carried out worldwide, he says, archived, well-studied brain tissue will become an important resource in studying the relationship between known genetic defects and disease symptoms. If a brain as old as Auguste's can relinquish its secrets, so can many others. "We have to run genetic tests on the best diagnosed cases there are. And many of them are old."

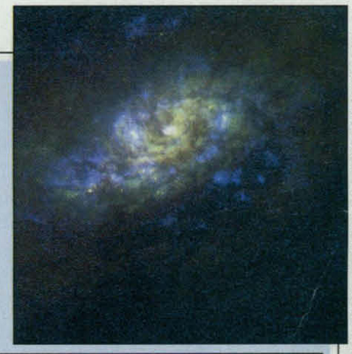
The discovery also has a bearing on the definition of Alzheimer's disease. According to neuropathologist Dennis Dickson of the Mayo Clinic in Jacksonville, Florida, there is still a debate about what it takes to confirm a case of Alzheimer's in a post-mortem: just amyloid plaques, or both plaques and neurofibrillary tangles. The finding stresses that "Alzheimer originally described it as having tangles as well," Dickson says. "So it's an important paper in terms of ... understanding the historic base of the term Alzheimer's disease."

–Martin Enserink

Martin Enserink is a writer in Amsterdam.

Star Birth, Star Death

The Hubble Space Telescope captures knots of star birth at the heart of the galaxy NGC 1808, about 40 million light-years away (*top right*). In this false-color image, blue indicates glowing hydrogen, a sign of newborn stars. It highlights the compact clusters just tens of light-years across in which the stars are forming. At bottom right, a medium-sized star like the sun experiences death throes after shining uneventfully for billions of years. The star, NGC 7027, some 3000 light-years away, has used up its hydrogen and helium fuel and puffed off its outer layers, creating a so-called planetary nebula. The star's hot white core sets the inner region of the nebula glowing brightly. This false-color composite of visible and infrared images from the Hubble also reveals outer layers of gas—thousands of times farther from the core than Earth is from the sun—which are cooler and can be seen only in the infrared.



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