NSF isn't the only one looking for alternatives: Officials at the National Institutes of Health (NIH) would like to adopt similar qualitative measures and are waiting anxiously to see if OMB grants NSF a waiver to use them. "If we can't use that approach, then OMB may end up with gobbledygook," says NIH budget chief Francine Little. Rather than invent new metrics, NIH officials say they would be more comfortable using tried-and-true methods such as getting input from peer panels and advisory bodies to evaluate their research programs. "GPRA isn't rocket science, after all," says Cherie Nichols, planning officer for the National Cancer Institute (NCI). "It's just good planning and evaluation."

Still, NCI is already experimenting with quantitative measures. Last month, it issued its annual budget request to Congress in a format that closely resembled GPRA: It set five goals for additional spending and spelled out quantifiable criteria that Congress could use to measure its success, such as identifying every major cancer gene within 5 years.

But NCI's document was developed independently of GPRA, says Lana Skirboll, head of NIH's policy office, and that made it easier for the institute to propose quantifiable targets. "If Rick [Klausner, NCI's director] falls short, then it's a lesson learned with little pain because it's his goal," says Skirboll. "But if that happens to NIH [under GPRA], then OMB and Congress will hold us accountable. And that could be a lot more painful."

Painful or not, GPRA has become a fact of life for all federal agencies. It is part of a mandate for change that is sweeping the federal research establishment and, like a tornado, it's a force that cannot be ignored.

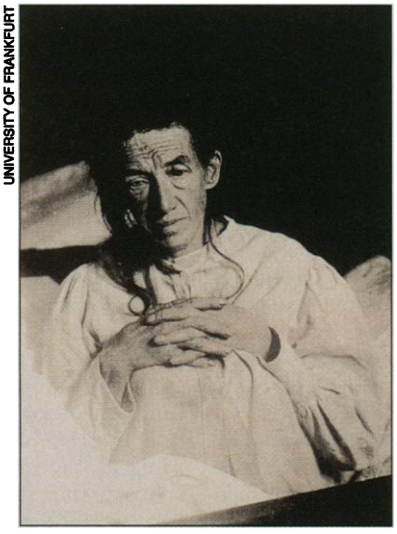
–Jeffrey Mervis

SCIENCE HISTORY

Auguste D. and Alzheimer's Disease

New diseases do not suddenly present themselves, ready labeled, in a new patient. They emerge slowly from the collection and interpretation of clinical observations and physiological measurements. Think of AIDS, the many symptoms of which baffled the medical establishment for years before it was recognized as a distinct disease. Now the discovery of a long-lost file is providing medical historians with the original observations that led to the recognition of another modern plague, certain to worsen as the population ages (see special section on Aging starting on p. 41): Alzheimer's disease. Ironically, it appears that the original patient might now be classified as having a different dementia.

The file, which has been missing since 1910, is that of a 51-year-old female patient, called Auguste D., who in 1901 came under the care of the German physician Alois Alzheimer at a Frankfurt hospital. Last December, psychiatrists Konrad Maurer, Stephan Volk, and Hector Gerbaldo of the University of Frankfurt, Germany, were surprised to find the hospital file in the archives of their university psychiatric clinic. The blue-colored cardboard pocket, still in pristine condition, contains photographs of Auguste D. and samples of her attempts at a signature. There are also several pages of Alzheimer's handwritten notes, in a now-outdated German script, documenting in detail his patient's behavior during the first 5 days of her hospitalization, and other pages by two colleagues describing subsequent changes in her condition.



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Dr. Azheimer's patient. A 1902 photograph shows Auguste D.'s helplessness.

"It's fantastic," says neuropathologist Bengt Winblad of the Karolinska Institute in Stockholm, Sweden; "it will clarify the symptoms of the patient." And they are not quite the same as the textbook symptoms of Alzheimer's. "Here we've got the real thing, in Alzheimer's hand, and this confirms that the clinical symptoms were more complex [than what we now call Alzheimer's disease]," says neuropsychiatrist German Berrios of the University of Cambridge, U.K.

Auguste D. was admitted to what was then Frankfurt's Hospital for the Mentally Ill and Epileptics in 1901 and stayed there until her death in 1906. Her answers to Alzheimer's simple questions reveal her confusion. The first page of the file begins as follows:

(She sat on her bed with a helpless expression)
"What is your name?"
"Auguste."
"Last name?"
"Auguste."
"What is your husband's name?"
"Auguste, I think."

Samples of handwriting show that she was also unable to write her own name without being reminded what she was doing. After 5 days of conversations and tests, Alzheimer concluded that Auguste D. suffered from progressive cognitive impairment, speech and perception problems, hallucinations, delusions, and psychosocial incompetence—symptoms of senile dementia, but occurring at an early age. She continued to deteriorate until her death, four-and-a-half years later, from septicemia arising from bed sores.

At that time, an autopsy revealed that her brain was atrophied, and staining the brain tissue with a silver-containing dye showed that it was studded with abnormal structures called neurofibrillary tangles and plaques, now considered the most characteristic symptoms of Alzheimer's disease. But the autopsy findings also included one that today is a criterion for exclusion from a diagnosis of Alzheimer's: arteriosclerosis, which was prevalent in the smaller cerebral blood vessels.

Although Alzheimer described Auguste D.'s symptoms and pathology at a 1906 meeting of psychiatrists in Tübingen, Germany, and in a brief paper published in 1907, it was another psychiatrist who put Alzheimer—and Auguste D.—into the history books. In the early 1900s, other psychiatrists, including Gaetano Perusini, E. Sarteschi, and F. Bonfiglio, had documented patients with similar symptoms. But historians trace the naming of the condition marked by those symptoms to Emil Kraepelin, director of the Royal Psychiatric Clinic in Munich, where Alzheimer moved in 1903. It was his colleague's description of Auguste D. that Kraepelin chose to mention as "this Alzheimer's disease" in his influential psychiatry textbook published in 1910.

From then on, the eponym stuck—even though part of Auguste D.'s dementia might have been caused by multiple blockages in small blood vessels due to arteriosclerosis. Neurologist Luigi Amaducci of the University of Florence, Italy, is just one of the clinicians eager to make a new diagnosis by examining Auguste D.'s file: "To have the original ... would make more interesting the hypothesis I'm putting forward, that [Auguste D.'s] clinical symptoms are still open to interpretation." Maurer, meanwhile, is trying to track down Auguste D.'s brain in hopes of finding a more definitive answer.

–Claire O'Brien

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