



PROCESS OF ELIMINATION
 Jerome Rafferty was finally diagnosed with Lewy body dementia after previous diagnoses of Alzheimer's and vascular dementia.

The “Other” Dementias

Alzheimer’s disease is not the only cause of dementia. Knowing the others may help you or your loved one get the right diagnosis and treatment. **BY TOM VALEO**

Renata Rafferty first suspected trouble when her late husband Jerome, a bright, curious, and articulate man, couldn’t tell her about an article he had just read.

“He would start to tell me and then say, ‘I’d better go find the article and give it to you,’” she recalls.

Jerome was nearly 70 at the time (he died on Oct. 20, 2009, at the age of 76), so Rafferty attributed such lapses to typical age-related forgetfulness. But that wasn’t the first disturbing change she had noticed in him. For more than two years he had been having terrifying dreams several nights a week.

“They were scary, violent dreams, and he would act them out,” Rafferty remembers. “He would kick, push, and speak angrily, and if I tried to wake him he’d lash out at me. I learned to get out of bed, shake his foot, and call to him so I wouldn’t be close enough to get hurt.” Their doctor attributed the dreams to the pain medication Jerome had been taking for a ruptured disc in his back. But he prescribed the Alzheimer’s drug donepezil when Jerome could no longer follow the plot of *Law and Order*, one of his favorite TV shows. A neurologist added another Alzheimer’s medication, memantine.

COURTESY OF RENATA RAFFERTY

If someone diagnosed with AD doesn't appear to have the right symptoms, **voice skepticism.**

After Jerome went through eight hours of neuropsychiatric testing over two days, the doctor who administered the tests concluded he did not have Alzheimer's disease (AD) but rather vascular dementia, which is caused by the damage that accumulates from several small strokes.

Since strokes can occur in any part of the brain, the symptoms of vascular dementia can vary greatly. But they often cause memory problems, mood disorders, and difficulty with walking and other movements—symptoms found in some Alzheimer's patients as well.

If the strokes accumulate in the front of the brain, they may produce symptoms of frontotemporal dementia (FTD). This group of disorders affects the prefrontal cortex, which modulates mood, judgment, speech, creativity, and other distinctly human functions.

Still, the neuropsychologist who performed the testing insisted Jerome had vascular dementia, and predicted that unlike patients with AD, who decline steadily, Jerome would decline, remain stable for a while, then have another small stroke and decline again, and so on.

"We went for a year or so thinking it was AD, and then we went for another year or so thinking it was vascular dementia," Rafferty says.

Then Jerome went to the Mayo Clinic in Scottsdale, AZ, seeking relief from his persistent back pain. After a thorough exam his doctors concluded that Jerome did not have vascular dementia or AD. They had noticed that the toes on one foot were constantly wiggling, a sign of a very rare condition known as "painful leg moving toe syndrome."

"Everyone was very excited about that," Rafferty says. "They wanted to enroll him in a study, videotape his foot and leg."

But during the exam she heard the senior neurologist on the team mention—in passing—that Jerome did not have vascular dementia, so she followed him into the hall and asked him what he meant.

"I'm so sorry to tell you this, but it's obviously Lewy body dementia," he said, and rushed off.

"That was the first time I heard those words," Renata says.

Now that she knows more about Lewy body dementia (LBD), she can see early symptoms that should have pointed to the diagnosis. Acting out violent dreams, for example, is one poorly understood symptom of the disorder. And when Jerome took olanzapine, one of the newer drugs used to treat psychiatric symptoms, he had a violent reaction that produced high blood pressure and delirium.

"It turns out that this is a sign of LBD too," Rafferty says. "We found out that people with LBD often have a severe re-

action to atypical antipsychotic medications—also, that LBD patients should not be put under general anesthesia because they may proceed rapidly to end-stage disease."

To complicate the diagnosis further, LBD may overlap with other conditions, including AD, Parkinson's disease, FTD, and vascular dementia. Although Jerome did not have vascular dementia, he did have a fourth transient ischemic attack—a temporary interruption of blood flow to a part of the brain. A brain scan revealed signs of a previous stroke, which could have produced symptoms of its own.

Despite his memory problems, and occasional hallucinations, and fleeing bouts with anxiety and aggression, Jerome remained acutely aware of his condition in a way that Alzheimer's patients seldom are. When a hospice nurse recently asked him if he needed anything, he replied with a mordant, "Yeah, a getaway car."

THE BIG FOUR

Everyone knows about AD, which accounts for 65 percent of all dementia in the United States. Alzheimer's begins with degeneration of the hippocampus, a brain structure essential for the creation of new memories, and spreads to other brain areas, producing problems with speech, mood, judgment, motor skills, and other abilities.

But the hippocampus is not the only region subject to degeneration. Other brain structures can develop problems, and although they may produce similar symptoms, the underlying diseases each have a life of their own.

"There are well over 100 causes of dementia, but the big four that make up 94 to 98 percent are Alzheimer's disease, Lewy body dementia, frontotemporal dementia, and vascular dementia," notes James E. Galvin, M.D. M.P.H., assistant professor of neurology, anatomy, and neurobiology at Washington University School of Medicine and director of the Memory Diagnostic Center and the Wolff Neuroscience Laboratory. "If you take 100 people with dementia, 65 will have AD, 10 or 12 will have LBD, 10 or 12 will have vascular, and eight will have FTD."

Because Alzheimer's was identified more than 100 years ago and accounts for the vast majority of dementia, it attracts the largest number of research dollars, and therefore is better understood than the others.

But the other types of dementia tend to strike earlier, consuming many years of productive life.

"These other diseases affect people in their 50s, 60s, and early 70s," observes Dr. Galvin. "Alzheimer's affects people in their late 70s and early 80s."

Although the precise causes of these different dementias (including AD) remain obscure, they all seem to involve the

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—JAMES E. GALVIN, M.D., M.P.H.

faulty production or management of proteins in the brain. In AD, tau protein accumulates within the body of neurons, while amyloid protein forms clumps in between neurons.

In LBD, a protein known as alpha-synuclein aggregates into clumps named after Frederick Lewy, the German-American physician who described them in 1912. (Dr. Lewy worked in the same lab as Dr. Alois Alzheimer, who identified the protein clumps and tangles characteristic of the disease named after him.)

FTD involves the accumulation of a protein known as TDP-43, which also plays a role in amyotrophic lateral sclerosis (ALS), or Lou Gehrig’s disease. Discovered just three years ago, TDP-43 plays such a decisive role in both diseases that some researchers suspect that FTD and ALS may be different manifestations of the same disease process.

One type of FTD known as Pick’s disease, named after Arnold Pick, a professor of psychiatry at the University of Prague who described the disease in 1892, involves the accumulation of tau protein—one of the two proteins associated with Alzheimer’s disease. In Pick’s disease, however, the protein accumulates in the frontal lobes, where it causes erratic behavior and the loss of normal inhibitions. A normally reserved man with Pick’s might make lewd sexual comments to women or become belligerent. Pick’s disease may also produce speech difficulties that eventually leave the patient mute.

Vascular dementia is an imprecise term that refers to dementia caused by brain cells that have been damaged by lack of oxygen from several small strokes. Some research suggests that the most common form of vascular dementia, known as multi-infarct dementia, merely causes or accelerates AD, producing a decline in memory and cognitive function.

“There can be some overlap in pathology, but in vascular dementia you think the primary dementing component is due to vascular disease,” says Dr. Galvin. “If you have AD and then have a stroke, you don’t then have vascular dementia too; you have AD and a stroke. It’s not clear cut, though.”

WHAT IS DEMENTIA?

Understanding dementia, which is a complex and varied dysfunction, requires understanding the complex and varied function of the brain itself.

What we experience as consciousness involves the seamless integration of signals generated by dispersed regions of the brain. To produce accurate perceptions of the environment, appropriate emotions, reliable memories, and good judgment, brain regions must perform efficiently, and the fibers that link those regions must transmit signals smoothly and swiftly.

All this activity depends on the ability of brain cells, known

as neurons, to manufacture, transport, and recycle proteins, a process that requires huge amounts of glucose and oxygen. (The brain accounts for two percent of the body’s weight, but consumes 20 percent of the body’s energy.)

This constant and arduous process provides many opportunities for mistakes. A neuron may start to manufacture defective or misfolded proteins, or fail to manufacture enough to provide the chemical signals that enable neurons to communicate with each other. Proteins may not be broken down or recycled efficiently enough, causing debris to build up within and between the neurons, which can result in harmful inflammation.

This variety of brain functions points to one of the great mysteries of dementia: Why do various regions of the brain degenerate so differently?

“It’s what we call selective vulnerability, and no one understands why it exists,” says Bradley Boeve, M.D., professor of neurology at Mayo Clinic College of Medicine in Rochester, MN. “Why does AD affect the hippocampus, while FTD affects the frontal and temporal lobes and LBD affects the brainstem and neurochemical centers? I’ve never heard a good hypothesis as to why. Even in patients with end-stage FTD, their parietal and occipital regions [other major brain regions] look pretty normal. If dementia is a protein dysfunction, why is it so selective for certain parts of the brain?”

The variety of dementia makes treatment extremely difficult. Antipsychotic drugs, for example, quell the voices and hallucinations of schizophrenia and help some people with AD, but often produce delirium in LBD patients.

And the complexity of the brain—from protein synthesis within the neuron to the dense highways that transmit signals—makes effective treatments difficult to devise, leaving physicians with little to offer but relief for some symptoms. Donepezil, for example, developed to stimulate the memory of AD patients, may help people suffering from another form of dementia that causes memory problems. Patients with LBD who develop rigidity of movement may benefit from drugs used to treat Parkinson’s disease. Such drugs do nothing to treat the underlying cause of the dementia but may provide some relief from the consequences.

WHAT GOES WRONG?

The investigation of Alzheimer’s disease demonstrates how elusive the cause of dementia can be. For nearly a century scientists believed that AD was caused by the plaques and tangles that Alois Alzheimer spotted through his microscope in the brain tissue of a woman who had been severely demented. (The tissue had been taken at autopsy.) Inside of the neurons

Lewy Body Dementia

Affects the entire brain, so symptoms are wide-ranging and unpredictable.

Frontotemporal Dementia

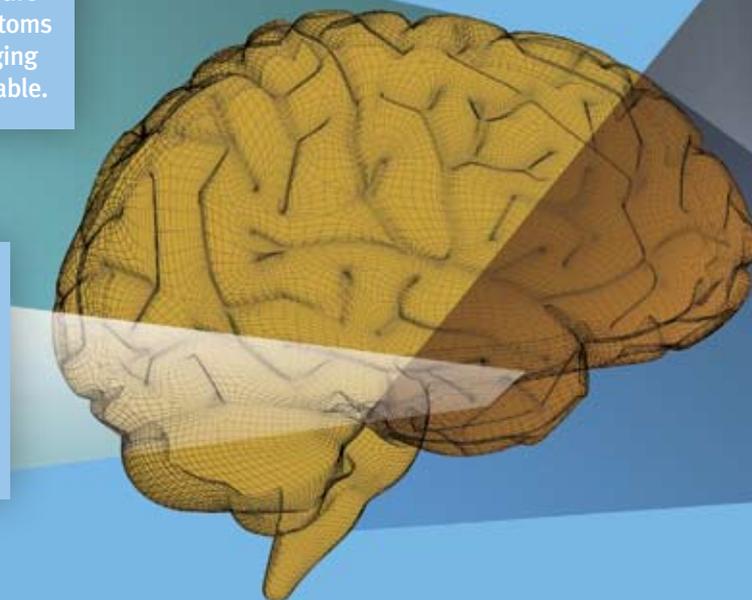
Affects the frontal and temporal lobes in the front and sides of the brain.

Alzheimer's Disease

Affects the hippocampus at the base of the cortex.

Vascular Dementia

Affects the entire brain, so symptoms can vary widely.



The Big Four

More than 100 types of dementia have been found, but four of them account for nearly 98 percent of all cases of dementia in the United States.

ALZHEIMER'S DISEASE (AD)

DESCRIPTION: People with AD develop memory problems, often followed by confusion, apathy, depression, emotional volatility, and other problems.

CAUSE: People with AD develop two types of dysfunctional protein in the hippocampus, the part of the brain essential for creating new memories. Tau protein accumulates within neurons in that region, while clumps of amyloid protein develop between neurons in that region. Some researchers, however, suspect that the toxic proteins may be the result of the disease rather than the cause.

TYPICAL CASE: The first symptom of AD almost always involves memory problems, such as forgetting familiar names and misplacing items. As the disease progresses people may have trouble finding their way home or keeping up with routine obligations such as doctor appointments, paying bills, and preparing meals. Later stages may affect the frontal lobes, resulting in erratic emotions, loss of normal inhibition, and hallucinations.

TREATMENT: Since AD results in decreased levels of acetylcholine, a neurotransmitter essential for memory and learning, drugs that boost acetylcholine, such as donepezil and memantine, often help, at least for a while. Other treatments are available for specific symptoms such as depression, hallucinations, and movement disorders, but nothing seems to slow development of the disease.

ON THE HORIZON: Several drugs and vaccines designed to inhibit the production of toxic tau and amyloid protein, or remove it once it appears, are in development. However, people who have tried the drug experimentally failed to improve significantly, even though protein levels declined, sometimes dramatically.

LEWY BODY DEMENTIA (LBD)

DESCRIPTION: Like Alzheimer's, LBD produces cognitive decline, but with three additional traits. Instead of declining continuously, people with LBD tend to fluctuate in terms of attention, alertness, ability to speak coherently, and other symptoms. They also tend to have visual hallucinations, often benign. Finally, they tend to develop symptoms of Parkinson's disease, including rigidity, tremor, and slowness of movement.

CAUSE: A type of protein known as alpha-synuclein clumps into "Lewy bodies," which appear inside of cells, or neurons. Lewy bodies may result from the inability of the cell to break down and recycle alpha-synuclein efficiently. As the protein accumulates, it sticks together, as though the cell is trying to gather its own debris to keep it out of the way.

TYPICAL CASE: People with LBD often act out violent dreams that involve being pursued or attacked. They may develop benign hallucinations involving, for example, children or animals running around the house. Attention and concentration may fluctuate, and patients may start to have trouble with visual-spatial abilities—they may misjudge the height of a step or miss a cup when they reach for it. Some people with LBD experience an overwhelming urge to sleep during the day. Their movements also may become rigid and slow, like the symptoms of Parkinson's disease, and they may develop problems with memory, judgment, and mood, like the symptoms of AD.

TREATMENT: No treatment specifically for LBD exists. However, since LBD affects nearly every neurochemical system in the brain, specific aspects of the disease can be treated. Memory problems can be treated with donepezil and other drugs for AD. Movement disorders may respond to L-dopa and other medications for Parkinson's disease. Modafinil may alleviate daytime sleepiness.

ON THE HORIZON: No drug yet exists that affects the synuclein protein, although some drugs exist for daytime sleepiness, and another, which resembles methylphenidate, is in development.

FRONTOTEMPORAL DEMENTIA (FTD)

DESCRIPTION: FTD includes several disorders that cause the frontal lobes behind the forehead, and the temporal lobes at the sides of the brain, to atrophy and shrink. Patients either develop speech difficulties, known as aphasia, or they display inappropriate social behavior. Aphasia may involve halting, effortful speech with the patient struggling to produce the right word. Behavioral changes may involve indifference to the concerns of others. Some patients developing FTD may start shoplifting or become attracted to shiny objects or fire.

CAUSE: In FTD, a protein known as TDP-43 accumulates within cells at the front of the brain. In one form of FTD known as Pick's disease, tau protein, found in the hippocampus of people with AD, accumulates within cells in the frontal lobes.

TYPICAL CASE: A person developing FTD generally exhibits personality or mood changes. An outgoing person may become withdrawn and depressed, while an introverted person may become loud and outgoing. Socially inappropriate behavior may also become more common. Later, FTD patients may develop speech difficulties as they lose the ability to recall the meaning of words, or they may start to speak with great fluency while making no sense.

TREATMENT: Only symptomatic treatments are available with medications developed for other disorders, such as psychiatric medications for behavioral problems or mood disorders. There are no treatments for language problems.

ON THE HORIZON: Methylene blue, a drug in development for AD, inhibits the aggregation of tau protein, so it may help patients with Pick's disease. Another tau aggregation inhibitor known as AL-108, or davunetide, is in clinical trials, and may soon become the first tau-active drug available in the U.S. TDP-43, the offending protein in other forms of FTD, was discovered only three years ago, leaving little time for the development of effective treatments.

VASCULAR DEMENTIA

DESCRIPTION: Since this dementia results from several small strokes, and strokes can affect any part of the brain, the symptoms of vascular can vary widely. However, they usually include declines in problem-solving ability, memory, and socially appropriate behavior.

CAUSE: Vascular dementia is believed to result from damage to brain cells caused by lack of oxygen when the blood supply is cut during a series of mild strokes. However, one study of 1,000 brains from demented patients who had died found only six that had pure vascular dementia, with the slow progression typical of the disorder. The rest also had another form of dementia.

TYPICAL CASE: To be diagnosed with vascular dementia, a patient must show evidence of a stroke in a location that could affect cognition, and cognitive problems must develop within three to six months of the stroke. A patient who meets these criteria may develop memory problems and have trouble speaking coherently or understanding the speech of others. They may also develop motor difficulties that prevent them from dressing themselves.

TREATMENT: The first goal is to reduce stroke risk by improving cardiovascular health. Statins may be prescribed to lower cholesterol, anti-hypertensives to lower blood pressure, and omega-3 pills to improve triglyceride levels. Low-dose aspirin may be prescribed to inhibit the clotting of the blood, and patients may be urged to give up smoking and drinking and reduce stress.

ON THE HORIZON: Damage from strokes cannot be reversed, but the brain can compensate for some deficits. Physical therapy designed to stimulate brain plasticity may provide some help.



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Alzheimer's attracts the largest number of **research dollars**, but the other types of dementia tend to strike earlier in life.

he found neurofibrillary tangles—strands of tau protein that looked like a length of thread crammed into a ball. Between the neurons he found clumps of amyloid protein, which he dubbed amyloid plaques.

The solution seemed obvious: Get rid of the plaques and tangles. But treatments that clear the brain of these toxic proteins have failed to cure the disease, suggesting that tangles and plaques develop relatively late in the disease process.

The same may be true of other dementias. The toxic proteins they produce probably are not the cause of the problem but the consequence, and an understanding of the cause may be many years away.

In the meantime, is there anything we can do to reduce the risk of dementia?

"Pick your parents well," says Dr. Galvin, noting that genes seem to predispose some people to dementia. In addition, exercise that promotes cardiovascular health will help deliver a generous supply of blood to the brain, providing neurons with the nutrients they need. Keeping the brain active also helps, according to Dr. Galvin.

"But that's not absolute," he adds. "There are astrophysicists who are also vegetarian marathoners who get dementia, and couch potatoes who don't. But from a population perspective, those behaviors seem to afford some protection."

Other advice: If someone diagnosed with AD doesn't appear to have the right symptoms, voice skepticism.

"If you suspect that it's not AD but one of these other dementias, see a neurologist, preferably a cognitive neurologist well versed in these disorders," says Dr. Boeve. "A lot of primary care physicians haven't been as well educated in these less common disorders, so they may not recognize them. I hear this from families all the time: My doctor diagnosed AD, but I read about AD and it doesn't sound like AD. And they're usually right."

That's why Renata Rafferty spoke to *Neurology Now* about her husband's long and arduous illness: to encourage others to be skeptical of a diagnosis of Alzheimer's disease when the symptoms don't seem right, and to educate themselves about other dementias that the doctor may not be considering.

"I have made it my personal mission to talk to people about Lewy body dementia," she says. "I have my little elevator speech ready in which I describe symptoms that are not typical of Alzheimer's, and I don't hesitate to suggest that people with those symptoms be evaluated for one of the other dementias."

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For more information on dementia, see **RESOURCE CENTRAL** on page 37.