

A photograph of a dog, possibly a pit bull mix, lying in a field of tall green grass. The dog has a white face with dark patches around its eyes and ears, and a dark body with white speckles. It is looking directly at the camera.

Dogs and Cats in Their Dotage

Do aged pets get their own type of Alzheimer's, and will a new drug help them?

By SUSAN MILIUS

appa made a big impression on Bill Ruehl when he was a student.

That's not the rock icon of the 1960s but one of his lesser-known contemporaries, a much-loved, mixed-breed dog belonging to Ruehl's roommate.

Zappa (the dog) did not age gracefully. Despite having for years competently differentiated outdoors from in, Zappa lost his house-training. He also stopped sleeping normally and paced during the night. He got stuck in familiar rooms as if he couldn't work out the route past a chair or sofa. At least once a day, Ruehl or his roommate had to rescue the dog because he'd wandered to a neighbor's and been unable to find his way home.

Today, veterinarian William W. Ruehl is vice president of scientific affairs for Deprenyl Animal Health in Overland Park, Kan. The company has applied to the Food and Drug Administration to market what would be the first drug in the United States approved to treat behavior troubles of older dogs like Zappa.

Just the possibility that something could perk up doddering pets is stirring discussion of the mental problems of aged animals. The drug application has called attention to years of research exploring whether canine troubles resemble Alzheimer's disease in humans and whether drugs that affect human brain chemistry can help old animals.

Pets, like people, live longer now, thanks to advances in medicine and nutrition. The American Veterinary Medical Association estimates that the United States alone has more than 7.3 million dogs aged 11 or older, representing some 14 percent of the canine pets in the country. As the number of four-legged senior citizens grows, Ruehl and other veterinarians predict more age-related brain problems in pets, much like the rise in Alzheimer's disease in people.



The drug proposed for doddering pets is already prescribed for some of their owners. It routinely helps those with Parkinson's disease, and one trial found some benefit for Alzheimer's disease patients.

oday, Zappa's diagnosis would be "cognitive dysfunction," but veterinarian Katherine A. Houpt remem-

bers when such complaints were described as "fear of dying" in old pets. As director of Cornell University's Animal Behavior Clinic, she has seen a number of dogs whose behavior changed sadly in old age. Like Zappa, they soiled floors, paced at night, and got lost in their yards. Many eventually failed to recognize their owners.

These animals' personalities changed, too. One malamute-size dog refused to eat from a bowl anymore and hid under furniture. Formerly stouthearted sorts developed terrible thunder phobias. Another patient slept all day in the shower stall and spent the night digging around in closets and tearing at the furniture, acting like a dog left alone even though the whole family occupied their usual beds.

"It's really heartbreaking," Houpt says.

Like Alzheimer's disease in people, the diagnosis for cognitive dysfunction in dogs and cats comes after excluding other medical causes. Ruehl describes a hypothetical schnauzer who seems frequently disoriented and has started to circle in one spot for no apparent reason. Is its brain giving way?

It's a tempting diagnosis, Ruehl admits, but suppose the alert owner realizes the dog seems worst after meals. The schnau-

zer could easily have not a cognitive problem but a liver disorder that allows buildup of toxic by-products that cloud its brain.

David S. Bruyette of VCA/West Los Angeles Veterinary Medical Group has run across the opposite problem, people blaming what are cognitive problems in their pets on physical maladies. When owners tell him that old dogs are going deaf because they fail to respond to commands, Bruyette suggests an easy hearing test: Turn on the electric can opener. That's one of the last sounds a pet's dysfunctional brain fails to process, he says.

To estimate how many dogs develop cognitive dysfunction, Ruehl and Benjamin L. Hart of the University of California, Davis surveyed owners of nearly 140 dogs between the ages of 11 and 16 that had no known ailments. Sixty-two percent of the dogs showed at least one sign of cognitive decline, the researchers reported in *Psychopharmacology of Animal Behavior Disorders* (1998, Nicholas H. Dodman and Louis Shuster, eds., Blackwell Science). The survey probed four categories of complaints: failures in house-training, changes in sleep patterns, disorientation, and changes in sociability.

Such a breakdown in brainpower can be just as life-threatening as failures in other organs, Bruyette points out. He made a presentation on cognitive dysfunction to the American Animal Hospital Association at this year's annual meeting in Chicago, and he has conducted clinical trials for Deprenyl Animal Health.

"Most commonly in veterinary medicine, [cognitive dysfunction] becomes a fatal disorder because the bond between the client and the pet has been broken," he says. "It's not the same pet anymore. The owner just gets frustrated." And the pet gets euthanized.

Are these symptoms inevitable on the last lap of normal aging in dogs, or does cognitive dysfunction mean the dog has an injured or diseased brain? "Nobody has the data to answer that question," says Gary M. Landsberg of Doncaster Ani-

mal Clinic in Thornhill, Ontario. Senility does not strike all dogs, he points out. "We have graceful agers—whether people or animals."

he search for physical signs of aging, or of age-related disorders, in dog brains dates back as far as 1914. In recent years, some of the most-discussed work has come from Brian J. Cummings, Carl W. Cotman, and their colleagues at the University of California, Irvine (UCI). After examining preserved dog brains, the researchers in 1993 described plaques of a nerve-harming protein called beta-amyloid often appearing in old brain tissue. The protein gobs in dogs resemble the denser plaques of beta-amyloid that are characteristic of the brains of Alzheimer's patients. However, dogs fail to develop the second major kind of brain deposit seen in Alzheimer's, knots of material called neurofibrillary tangles.

Even without tangles, plaques may correlate with behavior changes in dogs. Research by Elizabeth Head, also at UCI, and others shows that dogs whose brains hold lots of plaques are more likely to flub certain learning tests. Ability to remember locations declines, as do scores on tests that require dogs to associate a food reward with one stimulus but not another. Also, dogs with more plaques make more mistakes in so-called reversal learning, in which the animal learns that an action will earn a food reward and then must learn to perform the opposite action to get the reward.

Cummings has suggested that these older dogs could be useful for researchers studying the early stages of a human brain sinking into Alzheimer's.

Lary C. Walker of Parke-Davis Pharmaceutical Research in Ann Arbor, Mich., notes that dogs may have been the first animal known to develop brain plaques with age, but researchers have found similar deposits in monkeys and even polar bears. They have also genetically

engineered mice that build up brain plaques.

"I hate to throw cold water on these things," Walker says, "but there is no animal that completely models Alzheimer's disease." None of the animals examined seem to develop tangles in their brains. As far as animal behavior goes, "there's nothing that reaches the degree of decline in humans."

However, Walker argues, canine senior citizens can help researchers study another condition inter-

Dogs on Meds

Alzheimer's disease isn't the only case of a human brain disorder that has an echo in the dog world. Dogs that rampage and whine when their owners leave them get diagnosed with separation anxiety and dosed with canine anti-anxiety drugs. Dogs that scratch or lick their skin raw take a drug prescribed for people with obsessive-compulsive disorder.

Veterinarians also recognize a canine disorder similar to attention deficit disorder, and, yes, they treat it with Ritalin, the drug widely prescribed for hyperactive children.

So-called hyperkinetic pets "are very rare dogs," veterinarian Lyn Johnson emphasizes. During her 2 years of residency in veterinary behavioral medicine at Texas A&M University's College of Veterinary Medicine in College Station, she has diagnosed the disorder only once, in a female terrier.

At 18 months old, the dog showed no signs of losing her rambunctious puppy ways. Her longest naps lasted 15 minutes. She raced around the house and leaped over furniture, so much so that her owners took to keeping her on a leash indoors. They couldn't leave her alone outside because of her barking and digging. During an entire 2-hour session at the clinic, "she just never sat down," Johnson remembers.

Dogs who romp too much are a common story. "The majority are just over-active dogs who are not getting enough exercise," Johnson says. —S.M.

twined with Alzheimer's. Beta-amyloid also accumulates within blood vessels in the brain, boosting the risk of strokes. Dogs, he notes, make great laboratory models for this buildup.

So far, no evidence shows one breed more at risk than another for plaque buildup, Ruehl says. Yet researchers aren't ready to dismiss genetics as contributing to cognitive dysfunction. Michael Russell of the University of California, Davis found that laboratory beagles whose brains built up a lot of plaque were likely to have littermates with the same trait. And beagles with cleaner brains had similar littermates.

at geriatrics has lagged behind dog studies, but Landsberg presented informal survey results about cats at this year's annual meeting of the American Veterinary Medical Association in Baltimore. He conducted clinical trials of Deprenyl Animal Health's new drug for cognitive dysfunction in dogs and then asked owners of 32 older cats if they had noticed similar declines.

"Many of the behavior changes of cog-



nitive dysfunction seen in dogs also occur in elderly cats, but at perhaps an older age of onset," he concluded. Most people didn't bother to talk to the vet about these symptoms because they assumed there was nothing they could do.

And is there anything? The two drugs approved in the United States for Alzheimer's in people are not in veterinary use. The United Kingdom has approved a drug called nicergoline for old dogs' behavior, and pet owners everywhere have been experimenting with other medications, such as extracts of the ginkgo tree.

"Anything you hear on the news, people are going to put into a pet," Bruyette remarks.

In early 1997, Canada approved Deprenyl Animal Health's version of a Parkinson's disease medication for humans called L-deprenyl, or selegiline, for use in addled, elderly dogs. The dog drug goes by the trade name Anipryl. It had earlier won approval for use in canine Cushing's disease, a hormonal imbalance, in both Canada and the United States.

In a controlled clinical trial of L-deprenyl involving nearly 200 dogs, owners reported improvements in behavior in 70 percent of the pets, Ruehl told the American College of Veterinary Internal Medicine meeting this May in San Diego. Behavior changes started showing up within a week to a month of the start of drug treatment.

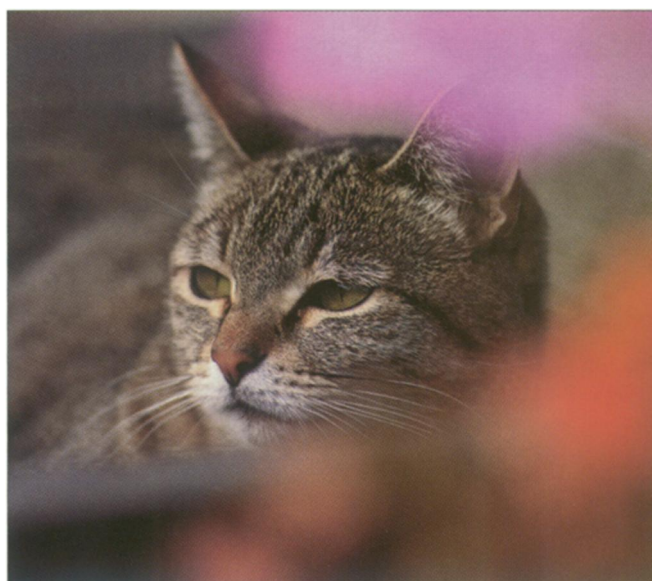
As for cats, Landsberg knows of no

published study on L-deprenyl use. He has prescribed it for 13 cats, aged 14 or older, and he says that 10 of the owners reported improved behavior in their pets.

The L-deprenyl bandwagon is rolling through the veterinary community, building interest in the treatment, observes Nicholas H. Dodman, a behavioral specialist at Tufts University School of Veterinary Medicine in North Grafton, Mass. "I remain probably the most skeptical of my group," he says.

The proposed explanation of how the drug works leaves Dodman with questions. L-deprenyl keeps the enzyme monoamine oxidase B from playing its normal role in breaking down dopamine in the brain, and Ruehl has suggested that the drug perks up old pets largely by increasing dopamine levels and activity.

Dodman, however, points out that one of the drug's breakdown products is an amphetamine, a stimulant. He asks if enough is produced to explain the increased alertness of an ailing pet receiv-



ing the drug. Ruehl responds that "at the relatively low, recommended doses, [breakdown products'] contribution is likely minimal."

Whatever the mechanism by which L-deprenyl acts in pets, "there does appear to be some therapeutic efficacy," Dodman acknowledges. "I understand it's only temporary—you can allow their candle to burn for a little longer."

As canine and feline America continues to gray, more pet owners will confront the question of just what that candle stub of animal companionship is worth. □

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