A Cure for Euthanasia?

A nonsurgical sterilant could reduce the global population of homeless dogs and cats, but there hasn't been money to develop one—until now

NINETY KILOMETERS SOUTHWEST OF Montgomery and a few decades shy of the modern world lies Oak Hill, Alabama, the smallest town in one of the poorest counties in the state. There are 23 homes, one gas station (which doubles as a general store), and a post office staffed by a single employee.

Oak Hill doesn't have much—but it does have cats. Cats that congregate in barns and under sheds. Kittens born in long-vacant restaurants and antique shops. Pregnant queens abandoned in the woods. Tomcats that fight raccoons for food.

There are no animal-control services in Oak Hill, so the cats keep breeding. And dying. Cars mow them down on the state highway; locals shoot them on site; and those that do make it to overcrowded, faraway shelters are euthanized within days.

A few fortunate felines find their way to the back porch of David Fuller, a retired electronics engineer who, as a contractor for NASA, spent years ensuring that rocket components destined for space survived their environment. These days, Fuller and his wife do the same for Oak Hill's cats. They trap the ones they can and try to find homes for them. They bottle-feed kittens whose eyes have been glued shut by dust. And they drive an hour each week to the nearest Wal-Mart, where they load their pickup truck with 8-kilogram bags of dry cat food.

Thirty-five feral cats call Fuller's property home, and he takes care of another 30 at his mother's farm in a nearby town. Despite Fuller's best intentions, however, he can't possibly keep up. He's running out of people to give the cats to, and the overflowing shelters will no longer take them. He's spayed and neutered a few, but he can no longer afford the $100 surgeries. And so the cats keep breeding.

The problem isn't confined to Oak Hill. Humane organizations throughout the United States can't surgically sterilize homeless cats and dogs fast enough to control their numbers, and developing countries with dangerous feral dog populations—such as China and India—fare even worse. As a result, millions of dogs and cats are euthanized in U.S. shelters each year, and millions more are shot and poisoned around the globe. "There's almost no hope of making any kind of dent in the problem with surgery," says Joyce Briggs, the president of the Portland, Oregon–based Alliance for Contraception in Cats and Dogs (ACC&D).

For the past decade, ACC&D and other humane organizations have pushed for a nonsurgical alternative to traditional spay/neuter surgery—something cheaper and faster, such as a vaccine or a pill. "Something," Briggs says, "that would let us reach far more animals with the same resources." Researchers have developed similar products for wildlife, but they have turned out to be ineffective or impractical for use in companion animals. Lack of funding and interest has slowed further progress.

That may be about to change, thanks to a U.S. billionaire named Gary Michelson, who has announced $75 million in

Vagabonds. About 30 million feral cats roam the streets of the United States.

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Death row. Overcrowded U.S. shelters euthanize nearly 4 million dogs and cats each year.

grants and prize money for the development of a single-use, nonsurgical sterilant for dogs and cats. Suddenly, researchers who had abandoned this work are ramping up their efforts again. And those who had never considered the problem are starting to brainstorm novel approaches, such as genetically silencing brain pathways critical for fertility and developing toxins that specifically target sperm and eggs. This summer, Michelson's foundation announced its first grantee, with more to follow. The scientific challenges are daunting, however, and some question whether such a product could actually solve the global dilemma of cat and dog overpopulation.

A walk on the wild side

The story of nonhuman contraception traces back to Billings, Montana, in 1971, when two cowboys walked into the office of a young Montana State University assistant professor named Jay Kirkpatrick. The U.S. Congress had just passed the Wild Free-Roaming Horses and Burros Act, which sought to prevent the often-brutal hunting of feral horses in the American West for pet food.

Although the cowboys applauded the principle of the legislation, they knew that without some sort of population control, wild horse numbers would soon explode. "They saw the train wreck coming years before it got here," says Kirkpatrick, now the director of the Science and Conservation Center, a Billings-based nonprofit dedicated to managing wildlife. "They came into my office—hats, boots, the whole 9 yards—and said, 'Can you make horses stop reproducing?'" Kirkpatrick was dumbfounded but intrigued. "The concept of contracepting large wildlife was really off the screen," he says. "It hadn't been tried before."

Kirkpatrick first turned to human contraception—specifically, "the pill," a hormone-based approach introduced a decade earlier. Colleagues gave him a hard time. "I got laughed at a lot in the early days," he says. "I couldn't convince anybody that this was more than a harebrained idea."

Things started to change in 1977, when the Bureau of Land Management granted Kirkpatrick $300,000 to test his hormone idea in western horses. "All these people who had been snickering before were suddenly interested in wildlife contraception," he says. Over the next 10 years, Kirkpatrick showed that he could contracept wild horses with steroid shots that lasted through the breeding season. But catching the horses was expensive, and the hormones caused cancer in zoo animals. "The practicality wasn't there," he says.

So in 1988, Kirkpatrick says he "chucked everything out the window" and tried a new approach called immunocontraception. Originally developed for women, the idea was to administer a vaccine that would stimulate the production of antibodies against zona pellucida—the membrane that covers eggs—thereby preventing sperm from entering.

In humans, the approach proved less effective than the pill, but Kirkpatrick had great success in horses. He traveled to Assateague Island off the coast of Maryland and Virginia, which was dealing with its own impending horse overpopulation problem, and spent months wading through marshes and forests, darting mares with the zona pellucida vaccine. "A year later, not a single foal was born," he says, and the vaccine showed no side effects. "The Assateague work changed everything."

That's when Kirkpatrick's phone started ringing off the hook. For the past 2 decades, he and colleagues have used the zona pellucida vaccine to contracept everything from urban deer to sea lions. The vaccine was so effective in so many species that when researchers asked to try it in cats and dogs, Kirkpatrick was sure it would work. It didn't.

Down and out. Feral dogs are a huge problem in developing countries, where they cause thousands of rabies cases.

CREDIT: LOIJE PSIHOYOS/CORBIS

Online
sciencemag.org
Podcast interview and reporter's notebook.

Man's best friends?

About the time that Kirkpatrick hit upon the immunocontraception approach, Julie Levy was witnessing the homeless pet problem for the first time. As a veterinary student at the University of California, Davis, in the late 1980s, she walked past sickly feral cats every day on her way to class. Occasionally, the campus's public health and safety department would round them up and euthanize them. "As veterinary students who were trained to save animals, killing all of these cats seemed very contradictory to what we were on campus to do," says Levy, now the director of a shelter medicine program at the University of Florida, Gainesville. So, with the faculty's permission, Levy and a group of students began trapping and surgically sterilizing the cats. "By the time we graduated," she says, "most of the cats on campus were neutered."

Levy's small program was part of a larger surgical sterilization movement begun in the 1970s. Estimates suggest that, by the beginning of that decade, U.S. shelters were euthanizing more than 20 million cats and dogs each year. At the time, most vets considered spay/neuter surgery "unwarranted mutilation" and performed it on only about 10% of dogs and cats, says Andrew Rowan, the chief scientific officer of the Humane Society of the United States. But as feral dogs posed an increasing public health risk, animal-welfare groups began pushing for surgical sterilization. Today, most U.S. shelters spay or neuter every animal that leaves their doors.

The surgical sterilization movement has had a dramatic impact. "Feral dogs are now, in large part, a thing of the past in the U.S.," says Rowan, and rates of euthanasia have dropped precipitously. Yet U.S. shelters still euthanize nearly 4 million healthy dogs and cats every year, he says, and about 30 million feral cats still roam the streets. Feral cats are also a huge problem in Australia, where some environmentalists claim they have hunted endangered species to extinction.

Feral dogs, on the other hand, tend to dominate in developing nations. Rowan says India alone is home to up to 35 million "street dogs," which in 2004 caused the vast majority of the country's 20,000

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human rabies cases. There's little funding for sterilization programs, he says, so "there's no way to take these dogs off the streets." China has also seen a spike in rabies cases and has responded with massive culling campaigns: City workers fan through towns, says Rowan, clubbing dogs to death by the thousands.

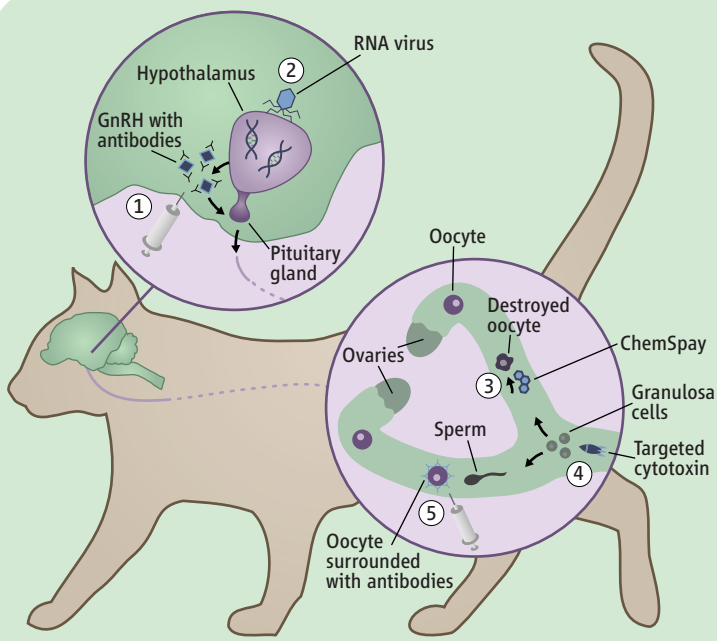
"We need to stop the carnage," says Rowan. "That's where the whole idea of a better contraceptive comes into play."

A decade after leaving vet school, Levy began looking into such a contraceptive. She had founded a few high-volume spay/neuter clinics for feral cats—called Operation Catnip—but "the cats were reproducing faster than we could sterilize them," she says. So Levy asked Kirkpatrick for some of his zona pellucida vaccine. She ran a small clinical trial in cats. But "it had zero efficacy," she says. Trials in dogs showed similar results. Levy says the antibodies the females produced did not bind to their eggs—and thus did not block sperm entry.

Undaunted, Levy turned to another approach that had proven successful in wildlife: a vaccine called GonaCon. Developed in 1994 by immunologist Lowell Miller at the U.S. Department of Agriculture's National Wildlife Research Center in Fort Collins, Colorado, the vaccine induces the body to make antibodies against the brain's gonadotropin-releasing hormone, which signals the production of various sex hormones. In field trials, Miller and colleagues contracepted deer, prairie dogs, and even kangaroos. Levy found that the vaccine also worked well in cats: A single injection contracepted males and females for up to 5 years, although the effect diminished over time. Other groups tried the vaccine in dogs but stopped trials after the injection caused a painful reaction.

In 2004, Levy also began working with a sterilant called ChemSpay. Loretta Mayer, an ovarian physiologist at Northern Arizona University in Flagstaff, had helped develop the product—a chemical that destroys female eggs—and had used it to sterilize feral dogs on a Navajo reservation. Levy saw results in cats, too, but the product required multiple injections over several days, making it impractical for hard-to-catch feral animals.

Levy and Mayer worked to improve the efficacy of GonaCon and ChemSpay, respectively, but both soon ran short of money. "Animal work is horrendously expensive," says Levy. Each research cat costs her $800—and $5 a day to feed and house. She and Mayer scraped together small grants, but neither could find a large funding agency to support the research. "There were times between grants when I was paying for the cats myself for a year," says Levy.



Sterilization strategies. Researchers are looking into a number of ways to permanently sterilize cats and dogs without surgery, including: (1) a vaccine that would block the release of sex hormones, (2) a virus that would genetically silence fertility pathways, (3) a chemical that would destroy eggs, (4) a targeted cytotoxin that would destroy cells necessary for the production of sperm and eggs, and (5) a vaccine that would block sperm from entering eggs.

Nonsurgical sterilization research stuttered and slowed. An Australian group working on cat contraception abandoned its studies entirely when funding ran out. And then Gary Michelson entered the picture.

A shot in the arm

In November of 2008, postdoc William Ja was taking a break from his lab work at the California Institute of Technology in Pasadena when an ad in a scientific journal caught his eye. Seeking to minimize shelter euthanasia, a Los Angeles–based nonprofit called Found Animals was announcing $75 million toward the development of a nonsurgical sterilant that would work in male and female cats and dogs—$50 million in grants and a $25 million prize for the first team to develop a viable product. "I had never thought about this problem before," says Ja, "but I was inspired by the challenge." He brainstormed with some colleagues over dinner and came up with an idea that he thought might work.

The awards are the brainchild of Michelson, a retired spinal surgeon and one of the richest people in the United States, thanks in part to a $1.35 billion settlement over surgical devices he invented. An animal lover who has also donated millions to humanitarian causes, Michelson says he was saddened and frustrated by current animal-control efforts. "The amount that municipalities in the U.S. spend to catch, house, and kill our pet cats and dogs is staggering," he says. "Surely we should be able to come up with a more cost-effective and humane approach."

Last year, Michelson's Found Animals foundation created a review board of scientific advisers and started seeking proposals. The response has been overwhelming. To date, the foundation has received more than 80 pitches—from academics, physicians, and industry scientists, many of whom have no background in companion-animal research. "There's a lot of very bright people out there who haven't applied their research direction to dogs and cats, in part because there's been no money," says Found Animals scientific director Shirley Johnston, a former veterinarian with a Ph.D. in clinical reproduction. "We've seen some very impressive ideas." (And some that were not so impressive. One proposal described a kitty chastity belt, complete with blueprints.)

Ja sent in his proposal, and he was one of nearly 30 scientists asked to submit a full grant application. His idea draws heavily on his work in fruit flies, for which he has designed proteins that target specific receptors involved in aging. For his Michelson project, Ja wants to target Sertoli cells and granulosa cells instead. In mammals, these gonad-specific cells foster the development of sperm and eggs, respectively. Ja hopes that by attaching a cytotoxin to his targeting proteins, he could essentially create a missile that would seek out and

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destroy these cells and cause permanent sterilization. "The basic idea is to treat cells that are critical for reproduction as cancerous," he says.

The first applicant to actually receive Michelson grant money is Beverly Davidson, a neuroscientist and the associate director of a gene-therapy center at the University of Iowa in Iowa City. Davidson's project builds on her lab's use of RNA interference to treat neurogenetic diseases like Huntington's. Like Ja, she's pursuing a targeted approach—but her weapon is genetic: Davidson's lab plans to design a virus that would deliver an RNA interference payload to regions of the brain involved in fertility, genetically silencing critical pathways. The virus would hang out in these brain cells indefinitely, resulting in permanent sterilization. "It would be like a switch we turn off," she says.

Levy and Mayer have also applied for Michelson grants, hoping that the cash infusion will help them optimize GonaCon and ChemSpay for dogs and cats. "Our excuse for not having a product after 30 years of research into contraception is that there's never been enough money or enough people with interest in this field," says Levy. "All of that has now been wiped away with the stroke of a pen."

Michelson says he hopes to see a product on the market within 10 years. But is such a product realistic?

Pitfalls in the past

Any research team embarking on the path of companion-animal sterilization would do well to heed the lessons of Neutersol. A formulation of zinc gluconate—the same compound often found in anti–cold and flu lozenges—the product was designed to be injected directly into the testicles of dogs, where it causes testicular atrophy. Briggs says ACC&D's lack of funding slowed U.S. Food and Drug Administration approval, and veterinarians were hesitant to use the product when it finally came on the market in 2003. What's more, Neutersol was not much cheaper than traditional spay/neuter surgery, so shelters had little incentive to adopt it. Disagreements over how to market the product forced it off U.S. shelves in 2005, although some Latin American countries still use it.

Michelson says he has designed his awards to avoid these pitfalls. To ensure that a promising technology makes it to market quickly, his foundation will "finance and support commercialization of the prize-winning product," including funding clinical trials and helping with regulatory approval. Ja says that's been a huge incentive for him: "As a basic researcher, it's very appealing to think that if my work gets somewhere, I don't have to build a team all by myself and push this out."

Zero efficacy. Julie Levy gave the zona pellucida vaccine to these research cats, but it didn't work.

Michelson also says he'll work to make the product cheap, subsidizing its cost if necessary. "If it's going to get widespread traction in the developing world—and even in cash-strapped U.S. shelters—it's going to need to be a few dollars a dose," says Levy.

Still, some question whether Michelson's scientific criteria are too rigorous. The prizewinning product must cause permanent sterilization, for example, but Levy says even a temporary contraceptive could dramatically reduce the number of feral cats, because most don't live more than 3 to 4 years. What's more, Cassandra James, a viral immunologist who has researched nonsurgical sterilants at Murdoch University in Western Australia, says she doubts any single product will work in both males and females, dogs and cats: "I think it's a Holy Grail that will probably never be achieved." Michelson says his foundation is "willing to consider applications for grant funding that may not address all criteria but have the potential to significantly impact the problem."

Big spender. Gary Michelson is offering $75 million toward the development of a nonsurgical sterilant for cats and dogs.

Levy and others also caution that even a perfect product will not eliminate cat and dog overpopulation. People still need to be responsible pet owners and spay/neuter their animals, for example. "There isn't one intervention that's going to solve this problem," says Levy. Michelson is optimistic, however. Citing data from high-volume spay/neuter programs, he says that if the prizewinning product could lower the number of animals coming into shelters by half, the euthanasia rate would drop by more than 90%.

Ja will find out in November if he'll be receiving Michelson funding for his cytotoxin-targeting project. Even if he doesn't, he says he's been so inspired by the problem that he may dedicate some of his start-up money to the idea once he heads his own fruit fly lab in a few months.

Back in Oak Hill, David Fuller is doing some anxious waiting of his own. "When I first heard about the Michelson Prize," he says, "I said, 'Bingo! This is just what we need.'" He's even volunteered his feral cats for clinical trials. "If we could put a sterilant in the feed that we put out for these cats, we could control the population," he says. "It would be a lifesaver."

–DAVID GRIMM

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