Chapter 4: The Perils of Animal Testing

> *Cancer has been cured a thousand times.*
> **Christopher Austin**, National Center for Advancing Translational Sciences

Hurray! Cancer has been cured a thousand times…*in mice*. You and I will need to wait our turn.

Two decades ago a class of cancer-fighting drugs called MMP inhibitors showed great promise in mouse versions of metastatic cancer. The catch? They failed miserably in human clinical trials.[1]

It is commonly accepted that new drugs should be tested in the laboratory first, on cell cultures and such, and then, before they are tested on humans, tested on animals. The two implicit assumptions, which are somewhat contradictory, are that humans are different—and more valuable—than animals, and yet animals are good proxies ("models") for humans. Using logic from George Orwell's *Animal Farm*, we're equal, but so much more than equal.

Scientists believe that mice and humans descended from a common ancestor about the size of a small rat and, while each possesses about 30,000 genes, only a limited number of genes are unique to either organism. If we shared 100 percent of our DNA with mice, then mice biology would be a flawless "model" for our own, but we could no longer argue that humans are different and more valuable. So, for animals to work as a model for human physiology, they must be close enough but not too close. Sharing 97.5 percent of our genes seems to fit the bill and, from

an ethical standpoint, it helps that mice don't look like us and can't tell us their feelings.[2] When was the last time you saw mice stage a protest rally?

In addition to mice, studies use rats, rabbits, guinea pigs, hamsters, gerbils, cats, dogs, and non-human primates. Ugh. My dislike for animal testing has remained constant throughout my three decades in the industry.

Does Safety in Animals Equate to Safety in Humans?

Animal testing got a big boost in 1921, when a pancreatic extract was successfully tested in diabetic dogs, helping to elucidate how insulin would help humans with the same disease.

Assume for a moment that animal testing of new drugs is a good idea and that dogs are appropriate test subjects. Given this, and buoyed by the success of the pancreatic extract, imagine that scientists start testing new compounds on man's best friend. They find that the first new compound that they put into dogs causes kidney failure, which, understandably, slams the brakes on all further development. Is this a triumph for science and drug safety? No. We later discover that this new "drug" contained some amount of plain old raisins and currants, innocuous to people but harmful to dogs.

The purpose of animal testing is to find drugs that are safe for humans, but it is burdened by two types of errors: dangerous drugs could incorrectly pass animal testing and end up in humans; and safe drugs could incorrectly fail during the animal testing phase, with humans missing out on beneficial therapies. Here are more examples of the latter type based on our hypothetical testing in dogs:[3]

- Dark chocolate? Safe in humans but toxic to the hearts and nervous systems of dogs.
- Anemia from blood cell damage results from the third compound. Later, we find that it is derived from onions and garlic.

- An experimental compound causes kidney failure in dogs. What is it? Something toxic to humans? Nope. Just grapes.
- Alcohol? It can cause coma and death in dogs.
- Avocados? Vomiting and diarrhea in dogs.
- Many varieties of mushrooms? Shock death in dogs.
- Caffeine? Vomiting and diarrhea in dogs.
- Xylitol, which is an ingredient in some gums and candies, produces yummy goodies for humans but liver failure, hypoglycemia, and death for dogs.

Based on this "logical" process for testing new drugs in dogs and the "scientific" evidence that comes from it, the FDA could have potentially prevented us from consuming raisins, currants, grapes, onions, garlic, chocolate, alcohol, coffee, tea, avocados, nuts, mushrooms, caffeine, milk, cheese, chives, yeast dough, and xylitol, had researchers tested these compounds in dogs before humans had ever had the chance to consume them. While the foods listed above can cause adverse reactions in dogs, other foods (bleu cheese, carbonated drinks, dried corn, green bananas, licorice, mango, orange juice, poppy seeds, rhubarb, and spinach) can harm mice, rats, guinea pigs, monkeys, or rabbits. And the list of foods

that would be eliminated from our diets due to this "scientific approach"—foods that are nutritious and delicious and enjoyed by billions of humans daily—grows. I, for one, am drinking a delicious glass of iced tea as I write this, appreciating the fact that tea was well established as safe before the FDA was formed.

Maybe this scientific approach isn't so scientific, and maybe animals aren't perfect substitutes for us.

While researching this topic, I came across a website that listed "people foods" that can be harmful to pets. One category was medicine, and it called out acetaminophen and ibuprofen, saying that they are extremely toxic to dogs and cats. This is sadly ironic. The FDA's thinking is that medicines should be tested in animals to see if they are safe for us. Yet that implies that medicines that are fine for us are also fine for animals. But if some of the most widely used medicines can't be given to animals, lest they lead to gastric ulcers, liver damage, and kidney failure, then we can be certain that the process of testing drugs in animals as a precondition for testing them in humans is logically flawed. This can go forwards and backwards. If drugs are supposed to work in animals first and humans second, then logically, we should be able to take drugs that have been approved by the FDA for human consumption and give them to animals. We should, but we can't. The FDA's approach is seriously flawed.

To recap, there are two types of problems with animal testing: first, drugs that would be beneficial in humans are rejected due to adverse results in animals; second, drugs that pass animal testing are later found to be dangerous or useless in humans. The first mistake potentially reduces the number of new drugs that are available to humans. Not only does the second mistake waste time and money, it raises false hopes in humans and exposes countless animals to needless suffering. Is this a serious problem? Yes, it is. *Ninety percent of drugs that pass animal testing subsequently fail when tested in humans*.[4] While many of these failures aren't for reasons of safety, success in animal studies clearly does not translate into success in

human studies. The numbers are so extreme that we can fundamentally question the value of animal testing.

A comparison that's more relevant is the probability that a drug that passed safety tests in animals then passed safety tests in humans. That number is more like 75 percent, with three drugs passing for each drug that falls short.

Animals are clearly hurt. Are there real examples of people being hurt by this "test in animals first" approach? Yes.

In 2006, six men in the U.K. were made seriously ill by the use of an experimental drug in a clinical trial. Observers were alarmed at the violent reaction, called a "cytokine storm" and involving multi-organ failure, caused by the drug, TGN1412, which is a CD28 superagonist antibody.[5] [6] What is noteworthy about TGN1412 is that it stimulates a protein found *only in humans*. What use is animal testing if the animals lack the required hardware? The scientists admitted that the animal testing might have caused "falsely reassuring results."

You might think that the discussion above is hyperbole and that, in real life, the FDA would never disallow something like tea or chocolate just because of animal testing. The truth is even worse than that. There have been examples of drugs that have been successfully marketed—meaning that they have worked in humans for decades with good safety and efficacy. And then, based on subsequent animal testing results, these drugs were almost recalled for problems that showed up only in test animals but not in humans. We'll explore some real examples.

Which Species Does the FDA Care About?

One can reasonably ask: which species does the FDA care about more, humans or rats? This is a serious question that deserves a serious answer.

Rats

In 2010, the FDA rejected XenoPort's new drug, Horizant (gabapentin enacarbil), a next-generation version of gabapentin.[7] It was just like the original gabapentin except that it was more easily transported through the intestinal wall. That is the crucial fact to know to understand how strange and destructive was the FDA's rejection of Horizant.

In 1993, Pfizer had launched Neurontin (gabapentin) for treating seizures, postherpetic neuralgia, neuropathy, and other nerve pain. The FDA approved Neurontin, even though, in animal testing, some male rats given ten times the highest human dose got a certain type of pancreatic cancer. Yet the rats still did fine. The tumors did not metastasize, were not locally invasive, and did not affect the rats' survival. Interestingly, neither mice nor female rats given gabapentin developed the tumors. And, most important, neither did humans. In 2010, after 17 years of experience with Neurontin, no increase was seen in pancreatic cancer among humans. The FDA even acknowledged this fact.

So, when Horizant came along, the Neurontin results should have been enough to assuage any alarm if Horizant showed the same tumors in some male rats, right?

Not for the FDA.

As could be expected, Horizant showed the same tumors in male rats given up to twenty-five times the highest human dose. Because of this, the FDA put the brakes on Horizant. Said the FDA: "[P]reclinical finding of pancreatic acinar cell tumors in rats was of sufficient concern to preclude approval of Horizant for RLS [restless legs syndrome] at this time."

It gets worse. The FDA had already determined that Horizant was effective and associated with no clinical (human) safety problems. Ronald Barrett, XenoPort's CEO at the time, said, "This one came out of left field."[8] Indeed,

XenoPort's stock dropped a whopping 66 percent the next day. The FDA

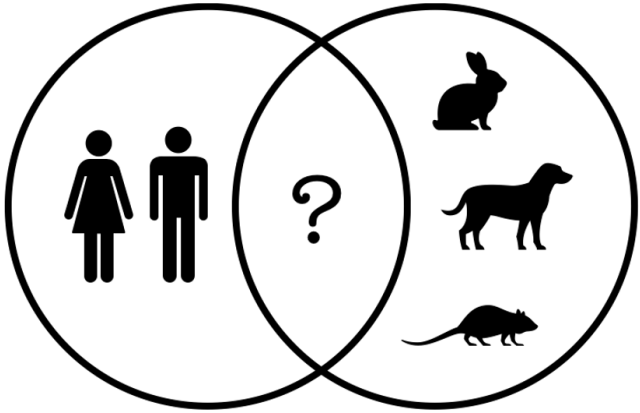


Figure 1: A Venn diagram of the overlap between the "hardware" for humans and animals. The problem is we don't know how much overlap there is.

acknowledged that this safety "signal" occurred only in rats, not humans Researchers had previously shown that the pancreatic exocrine tumors induced by gabapentin in rats do not correspond to human tumors. These are tumors that humans typically aren't susceptible to; acinar cell carcinoma was very uncommon in humans before Neurontin launched, and it was still uncommon 17 years later. Again, our hardware is different from rats'.

Now, you might say that with Neurontin already on the market, rejecting Horizant was no big deal. But it *was* a big deal. Horizant is more convenient and effective because it can be dosed twice a day with fewer milligrams than Neurontin's three-times-per-day regimen and still provide more stable levels in the blood. Ask most doctors what their biggest frustration is with patients and their medicines, and they will likely tell you that it's hard to get patients to keep taking their pills. Easier dosing causes patients to better adhere to their therapy.

Prior to Horizant, there were only two approved medications for restless legs syndrome. Unfortunately, they were associated with significant side effects and could cause the symptoms of RLS to *worsen*. According to the National Institute of Neurological Disorders and Stroke, RLS is a neurological disorder characterized by unpleasant sensations in the legs and an uncontrollable urge to move them for relief. People with RLS report feelings of burning, creeping, or tugging, and they sometimes feel as if they have insects crawling inside their legs. The sensations range in severity from uncomfortable to painful. RLS is generally a life-long condition for which there is no cure. Should these sufferers thank the FDA for trying to make them suffer for a lifetime?

Beyond the damage inflicted on people with RLS is the damage inflicted on drug companies. Yes, drug companies. Biopharmaceutical companies are in business to make money by curing or ameliorating disease. When the FDA gives them the green light to go beyond animal studies and do the more-expensive studies on humans, drug companies believe that they have some assurance that if the drug works on humans without untoward side effects, the FDA will approve the drug. But now the FDA has established a bad precedent. It can say, in effect, "We know we approved this next phase of testing, but we've changed our minds. We're worried about the effect on male rats that we ignored earlier." This creates enormous uncertainty for drug companies. If they see this decision on Horizant as a precedent, they will be less likely to invest in new medicines. And that will hurt all of us.

Remember that one of the primary purposes of testing new drugs in clinical trials of humans is to look for possible dangers to humans. That is exactly why Horizant was tested in clinical trials, where it passed. Is the FDA going to admit that human clinical trials aren't that useful? And if they aren't useful, why does it persist in requiring them?

Seventeen years of human data from millions of patients showing that gabapentin doesn't cause pancreatic cancer in humans were trumped by a

two-year study in 200 rats given extremely high doses. The FDA needs to be reminded that it should be reviewing drugs for humans, not for rats.

As explained above, the FDA did reject Horizant in 2010. Thankfully, a little more than one year later, the FDA finally saw the light and approved Horizant, which is still on the market today.

Mice

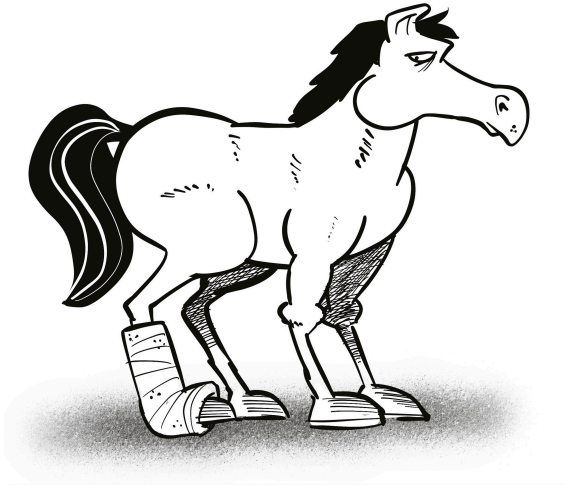
In a similar story, the popular sleep drug Lunesta (eszopiclone) was almost derailed by the FDA because of tumors that developed in rat and mice test subjects. As with Horizant, scientists later determined that the incidence of cancer in rodents didn't apply to humans.[9]

Monkeys

Diabetes drug Galvus (vildagliptin) was delayed at the FDA because some monkeys who had been given high doses developed skin lesions. The agency took this action even though this problem hadn't arisen in the 5,500 patients exposed to Galvus in (human) clinical trials.[10] While caution is often warranted with such safety signals, we are left to wonder what would have happened to Galvus if the monkeys had developed these problems *before* the new drug ever had a chance to be tested on thousands of humans. It, too, might have ended up in the scrapheap of failed drugs.

Horses

In 2011, after Peyton Manning, the star quarterback for the Indianapolis Colts, had his third neck surgery in 19 months, he was still not healthy enough to play professional football. Willing to try something else and frustrated that nothing had worked, he agreed to try stem cell therapy to further his recovery. Unfortunately, this procedure came with a mandatory trip to Europe. Why? Because the FDA had not reviewed and therefore not approved such a treatment for humans, Manning couldn't stay in



Indianapolis or a nearby city, close to his family and friends; he had to go overseas.

The FDA doesn't regulate therapies for animals, and so racehorses, which are valuable and prone to injuries, have been the lucky recipients of stem cell therapies for years. "Orthopedically, the horse is a disaster waiting to happen," says veterinarian Bob Harman. "They're so big—a 1,000-pound animal on little toothpick legs—and they're working at high capacity." Harman has more than a passing interest in racehorses—he is the CEO of Vet-Stem, a California company that treats racehorses with stem cell therapy. As of 2011, Vet-Stem had treated 4,141 horses for soft-tissue injuries such as tendinitis and muscle contusions. He claimed that 70 to 80 percent had healed completely.

The clinical benefits of stem cell therapy in horses are impressive. In a study of 170 horses, researchers found that nearly 80 percent of them could return to racing, compared with previously published data showing a 30-percent success rate for horses given traditional therapies. After three years, the re-injury rate was 23 percent versus 56 percent.

Stem cell therapy has produced some exciting results in humans, too. A trial conducted at Stanford University and the University of Pittsburgh