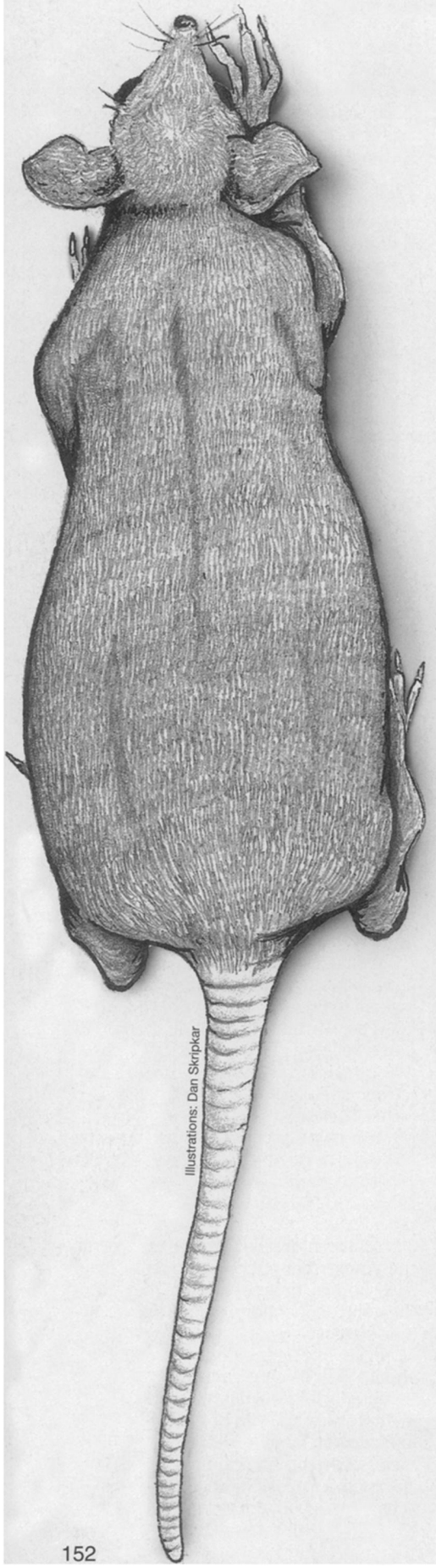


Illustrations: Dan Skripkar

A Rat-and-Mouse Game

Mapping the rat genome opens new paths in biomedical research

By JOCELYN KAISER

The rat, throughout history, has never attracted many admirers, but in the 19th century its image improved. Long reviled for devouring stores of grain, carrying plague, and biting babies, rats found a nobler calling in the late 1800s. They became the favored research animal of scientists.

Soon there emerged the pink-skinned, red-eyed, furry white creature known as the laboratory rat, a humble soul that has yielded new insights into everything from cancer to cocaine addiction.

But when geneticists chose a model mammal for their work, the rat lost out to the smaller, cheaper, faster-breeding mouse. Today, the sequence of genes on the chromosomes of *Mus musculus*, the laboratory mouse, is nearly as well charted as the human genome. As a result, mice have grabbed headlines in such breakthroughs as last fall's discovery of a gene linked to obesity.

The rat genome, in contrast, remains largely unknown. And that frustrates scientists eager to unravel the genetic causes of some major ailments — heart disease, diabetes, psychiatric disorders, and alcoholism, among them. For decades researchers have studied these killers mostly in rats, not mice. But with few clues to the rat's genetic makeup, "the rat can't live up to its full potential," says Stephen Mockrin of the National Heart, Lung, and Blood Institute in Bethesda, Md.

Now, however, researchers have constructed the first genetic map to span the entire genome of the laboratory rat, *Rattus norvegicus*. The map identifies more than 400 "landmarks" — specific, easily identifiable, short stretches of DNA scattered along the rat's chromosomes. They offer a rough framework for helping researchers to pinpoint the locations of genes. Because rats bear many genetic and biological similarities to humans, the map will help find genes that cause human disease, develop drugs and treatments, and answer basic questions about our biology.

"Now we can link powerful genetic techniques with a wealth of physiological data in [rat] models," says Howard J. Jacob of Massachusetts General Hospital in Boston. "That's really why we went after it." Jacob, Eric S. Lander of the Whitehead Institute in Cambridge, Mass., and their colleagues reported the new genetic map in the January NATURE GENETICS.

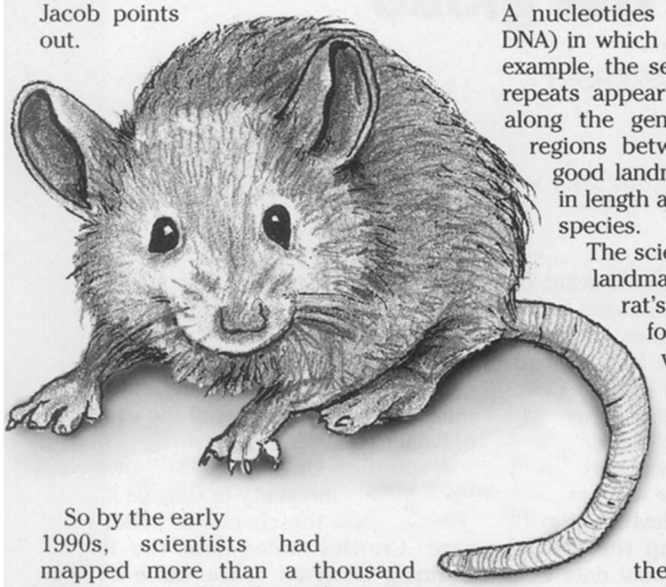
The rat's rise from vermin to valued research model traces back to a French scientist named Philipeaux. In 1856, he published the first known report of an experiment on rats — the effects of removing an albino rat's adrenal glands. By the 1890s, American scientists were feeding albino rats alcohol and experimenting with their diet. Before long, the rat had become entrenched as the research animal of choice.

But when modern genetics got started around 1910, scientists turned to the mouse. "The point of genetics is breeding them, and you can get a lot more mice in a room than rats," Lander explains.

Mice had another advantage, too. To trace genetic patterns in a species, scientists need many different strains. And for centuries, Chinese and Japanese nobility bred mice with weird neurological disorders that made them do unusual things, such as dance in circles. Collecting such mice, and others with odd coat colors, became the rage among some Europeans and Americans in the 19th century. These mouse fanciers gave mouse genetics a jump start.

While geneticists filled their laboratories with mouse cages, most physiologists and behavioral biologists stuck with

the rat. For them, the rat's size offered a big advantage. A lab mouse weighs just 18 grams; a lab rat is a much heftier 300 grams. That makes it a lot easier to put a catheter in a rat's artery to measure its blood pressure, or insert a probe into its brain to study a neurological problem, or assay its liver for changes caused by some toxin, Jacob points out.



So by the early 1990s, scientists had mapped more than a thousand mouse genes, but the rat's genetic map remained *terra incognito*. True, some geneticists had begun tracking down rat genes. But the resulting map held details of only a few small stretches along the genome. For scientists in search of uncharted genes, it was like being dumped somewhere on Interstate 80 — the highway connecting New York and San Francisco — with a handful of city street maps but no road atlas showing the whole route. Unless you were close to one of those cities, you would be lost.

Enter genetic mapper Lander. He and Jacob and another research group working separately had just tracked down a gene linked to hypertension in rats, a tantalizing hint of the rewards of rat genetics. And Lander's team had given a big boost to mouse genome mapping by combining a recently recognized kind of marker with fast, automated techniques. So with colleagues from Belgium, Sweden, Czechoslovakia, Stanford University, and the University of California, San Francisco, Lander's group turned its mapping firepower on the rat.

The scientists set out to make a first, sketchy version of a road atlas — known as a genetic linkage map — of the rat genome. Such a map doesn't necessarily contain the exact locations of genes; instead, it's a series of landmarks along the chromosomes.

"Genomes are very big places," Lander explains. "The rat genome [has about] 3 billion letters of DNA. But if you want to trace the inheritance patterns of the chromosomes, it's enough to look at spelling differences every 3 million letters or so. Once I have a genetic landmark on a chromosome, I can trace its inheritance pattern and it gives me not just the inheritance pattern of that spot, but of the whole region of chromosome around it."

Lander's group used landmarks known as simple-sequence repeats. These are short sections of the genome's C,T,G, and A nucleotides (the building blocks of DNA) in which pairs are repeated — for example, the sequence CACACACA. The repeats appear in thousands of places along the genome, especially in the regions between genes. They make good landmarks because they vary in length among strains of the same species.

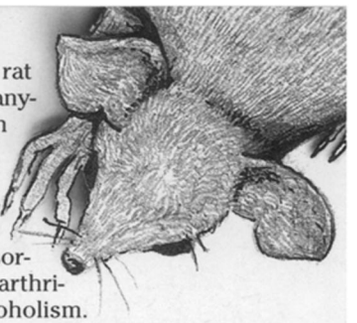
The scientists found 432 of these landmarks dotted all along the rat's 21 chromosomes. Now, for example, if researchers want to find genes involved in diabetes, they'll take a strain of rats that gets diabetes and one that doesn't. They'll breed them, then cross their offspring. That will give them a mixed generation, some with diabetes, some without.

Next, they'll look for what happened to the landmarks in the grandchildren's DNA. As DNA is passed on, bits of it — including the landmarks — get shuffled around on the genome. But sections that lie close together tend to be inherited together. Say the researchers notice this trend: All diabetic rats have an extra CA in a landmark on one end of chromosome 5 and so does the diabetic grandparent. "You'd say, Aha, this is not an accident. The gene must be there," Lander says.

"Now anybody who can do PCR (polymerase chain reaction, a technique used to copy fragments of DNA) can do rat mapping," says mouse geneticist Wayne N. Frankel of the Jackson Laboratory in Bar Harbor, Maine, the world's leading source of research mice. "All they would really need to do is to start from this paper." Frankel wrote a comment accompanying the rat linkage map.

Hunting for rat genes will get easier as the sprinkling of landmarks on the rat genome becomes denser. That shouldn't take long. Last December, the National Institutes of Health requested applications for an $11 million effort aimed at adding 6,000 landmarks to the rat genetic map and building a collection of cloned DNA fragments over the next 5 years. Twelve NIH institutes and centers kicked in funds for the marker hunt, says Mockrin, coordinator of the plan.

NIH's interest points to the vast array of human problems that will benefit from rat genetics. "Almost anything you can think of," Mockrin says. "Cardiovascular disease, hypertension, behavior disorders, drug abuse, arthritis, obesity, alcoholism. Cancer, especially environmentally induced.... Also normal structure and function."



Of course, some of these problems are studied in the mouse. But rats offer a "huge, huge history of research," Mockrin says. For example, scientists have compiled a wealth of information about the anatomy of the rat's brain. "Trying to recreate in the mouse the 100 years of research that's been done in the rat would be very, very difficult and expensive," Mockrin says.

On top of this, the rat often works better as a model than the mouse because it's bigger and because, says Mockrin, "there are diseases that occur in the rat that don't occur in the mouse" — certain arthritic diseases, for example. In all, researchers can draw on 140 inbred strains of rats.

Some of these rats love to swill alcohol, while others won't go near it. Some get cavities easily. Others get breast cancer, or brain cancer, or skin cancer. At least nine strains have various kinds of hypertension, Mockrin says. Jacob thinks rats will be especially useful for studying polygenic diseases, those linked to more than one gene, because most well-studied mice strains develop diseases caused by a mutation in a single gene.

Down the road, researchers would like to perform in rats the genetic manipulations now done in mice, such as inserting a human gene to create a model for a disorder such as sickle-cell disease.

As with mice, understanding the rat may be the immediate goal of this research. But the ultimate beneficiaries will be people.

"You have genes that interact with each other and with the environment," Mockrin says. "It's very, very confusing and difficult to sort them out. If we can begin to understand what genetic influences are responsible for different phenomena . . . that will lead to a whole range of possibilities in terms of diagnosis, prevention, using existing therapeutics, [and] designing new therapeutics." □