Scientist Sues Over Genetically Impure Mice

Unusual suit raises questions about whether animal breeder is liable for "thwarted research" if stocks are contaminated

Brenda C. Kahan, a cancer researcher at the University of Wisconsin, Madison, filed an unusual lawsuit in late June against Charles River Breeding Laboratories, the largest commercial producer of animals for research. Kahan is claiming that Charles River supplied her with genetically impure mice, and as a result several experiments were wrecked.

Other lawsuits, including one being planned by the University of Wisconsin itself, are expected to follow. At issue is whether the company knowingly or negligently shipped mice other than the inbred strains ordered, and what responsibility the company bears for the problems that followed.

Officials at Charles River, which is based in Wilmington, Massachusetts, decline to discuss the substance of Kahan's suit, but plan to "vigorously defend" the company, says James F. Foster, vice president and general counsel at Charles River. "There is not a lot of merit to Kahan's action," he says, and adds that the company has improved its genetics monitoring since the period when Kahan claims to have had problems with impure strains.

Kahan contends that the mishap, which involved a strain of mice known as BALB/c, cost her and others considerably in lost research time and money, and that her career has been set back (*Science*, 22 July, p. 345). Moreover, she says the company has not been open with researchers about what happened, and thus failed to prevent some of their wasted research efforts.

Kahan is not the only researcher who claims to have had difficulties with genetically impure animals supplied by Charles River during a period that began in 1979 and lasted until 1982. Researchers at the National Institutes of Health (NIH), for example, also received mice purported to be BALB/c but which were so genetically contaminated that NIH banned receipt of such mice from Charles River for several months beginning in August 1981. And, before these mouse problems came to light, researchers who used inbred rat strains for transplant experiments were reporting genetic contamination in animals supplied by Charles River (see box, p. 627). Although Kahan is the first scientist to go to court against the company, others have contemplated such action.

During the period when Kahan and other scientists say they were having difficulties with animals supplied by Charles River, the company was expanding substantially. Considered the world's largest supplier of laboratory animals, Charles River's net sales in 1982 were almost $41 million, producing a gross profit of just under $14 million, up modestly from 1981. At the end of 1980, the company successfully raised $9.4 million in a public stock offering, and early in 1981 acquired subsidiaries in West Germany and Japan. Also, during this period, the company expanded its facility in Portage, Michigan, by 30 percent, according to documents on file with the U.S. Securities and Exchange Commission.

> Losses in time and research were "incalculable," one affected researcher claims.

Kahan and her colleague Robert Auerbach in the zoology department at the University of Wisconsin, Madison, used BALB/c mice from Charles River in 1980 and early 1981. Their research involved transplanting tumor cells from one type of mouse into embryos of another to "see if we could get the cell line to participate in embryogenesis when it's reinjected," Kahan says. The experiments involved looking at newborn mice to see whether tissues maintained cells (and characteristic enzyme markers) from the two different kinds of mouse cells being mixed. Instead of seeing patterns indicating exclusively one type of cell or the other, "We saw an F-1 pattern," she says, meaning a hybrid enzyme pattern that ought not to have been possible at that stage.

"This was either a phenomenal breakthrough or something was wrong," says Auerbach. "Either the tumor combined with the new cells or something was wrong with the mice." Testing of the mice showed them not to be pure BALB/c's. At first, the Wisconsin scientists considered the possibility that a mix-up in mice occurred at their end, but when subsequent orders of BALB/c mice arrived and also proved to be genetically impure, the Wisconsin researchers became convinced that the problem lay with the supplier.

Kahan and Auerbach say they called Charles River to ask about the BALB/c mice that then were being shipped. In one phone conversation, they were told that a set of male and of female mice from different facilities were en route but that, due to some mistake, those two sets of mice were "incompatible." Yet, they did arrive soon thereafter, marked "BALB/c." "I thought, 'what do you mean not genetically compatible,' " Auerbach recalls. "That was a war cry." Whatever might have been unusual about different shipments of BALB/c mice, there's no straightforward way that they could have been genetically incompatible.

To double-check their own findings, the Wisconsin researchers asked Barbara J. Alter and Fritz H. Bach of the University of Minnesota, Minneapolis, independently to test BALB/c mice from Charles River. The results indicating genetic contamination confirmed those of the Madison team. A report was drafted and sent simultaneously to Charles River and to *Science* in early 1982. Published midyear (*Science*, 23 July 1982, p. 379), the report, signed by the four scientists, concludes that mice from several Charles River facilities were "incorrectly identified" and differed "significantly from the standard phenotype. . . . The seriousness of our findings cannot be overemphasized."

In an accompanying reply, company officials Henry L. Foster and Melvin W. Balk noted: "Charles River breeds BALB/c mice at nine different locations throughout the world, in 13 separate rooms, and suspicion of a problem in one room at one site represents a small percentage of the production animals available. . . ." That reply does not directly address the Wisconsin and Minnesota scientists' findings, which pertained to mice from several—not one—Charles River facilities. Moreover, the reply

does not say whether Charles River ever detected a problem of genetic contamination in mice anywhere in its facilities and thus says nothing about the extent of the problem uncovered by Kahan and her collaborators.

Kahan is seeking to recover from Charles River compensatory and also punitive damages of at least $100,000 in each category. In her formal complaint, she claims that the company either failed to perform necessary tests on mice, and thus breached its contract with her, or performed the tests and then "deliberately did not notify its customers . . ." or alternatively, "performed the tests in a negligent manner." Kahan and her lawyers say they do not yet know which, if any, of these allegations is correct but that the discovery process leading to a trial ought to help determine the correctness of their "hypotheses."

"There is a twofold purpose to the lawsuit," Kahan says, "to settle damages and to bring to public attention what might be done. My concern is that a problem existed for some time, involving the company that claims to be the largest shipper of animals for research, and [that problem] involved a number of researchers besides myself." Though the company promised to share information about the genetic quality of its animals with researchers who purchased them, that promise was not met, according to Kahan. "I couldn't see any alternative to filing suit; I could sit and do nothing but that's not acceptable to me."

Assessing the magnitude of the genetic contamination problem is not easy. But there is little doubt that it extended beyond Kahan and her immediate collaborators. Estimating the scope of the problem is made all the more difficult by Charles River's refusal to talk about the subject at earlier times with many of the affected scientists and now because the matter is under litigation.

Even threat of litigation can affect how openly these matters are discussed. "If a commercial breeder supplies genetically contaminated stock that results in the loss of research data, he may be liable to a claim for substantial compensation," observed Michael F. W. Festing of the Medical Research Council Laboratory Animals Centre, Carshalton, United Kingdom, in a commentary in the *Institute of Laboratory Animal Resources News*—published coincidentally in the summer of 1982 when Kahan and her collaborators were reporting their analysis of Charles River mice in *Science*. Frequently, according to Festing, instances involving genetically impure animals simply never are reported. "The majority of cases result in loss of research data and nonrepeatable results. However, because this type of loss is not recorded in the scientific literature, it does not come to the attention of most research scientists," he noted.

Brent Nicastro

Brenda Kahan

Contends her career was set back

"In some sense the possibility of claiming compensation works against the interest of the scientist, because a commercial breeder . . . will not generally be in a position to inform his customers lest he incriminate himself," Festing also pointed out.

Nevertheless, several suits similar to Kahan's are being planned. Currently, for example, the attorney general's office of the state of Wisconsin is planning a suit on behalf of the University. "For all practical purposes, it agrees with the pleadings of the [Kahan] suit, with slight twists because we represent a state institution," says Assistant Attorney General Robert Repasky. "Lots and lots of work went down the tubes. The University had some correspondence with Charles River to see if they'd make some accommodation. But it was unsuccessful."

Though separate from Kahan's legal action, this university-based suit in effect would represent Auerbach's lab where much of the affected research was conducted. Largely because Kahan is seeking compensation for alleged personal damages, her suit has not been consolidated into the university's contemplated action, one of her attorneys explains.

At least one other scientist, Alvin Warfel, who was associated with Memorial Sloan-Kettering Cancer Center in New York but now is without a research position, is seriously considering bringing suit against Charles River for allegedly supplying him with genetically contaminated BALB/c mice. "It's incumbent on the company to sell the product they're advertising," he asserts. "In a certain sense, to me there's no difference between sodium chloride and BALB/c mice. That's why these companies exist, because they supposedly sell things of a certain quality. If researchers had to check all the reagents they purchased, they'd never get any research done. "If they can't guarantee they're selling BALB/c mice when they say they are, why are they in business?" Warfel asks.

Several other researchers also found they had genetically contaminated BALB/c mice during about the same period that Kahan, Auerbach, and Warfel were having such problems. Some of those mice were obtained by researchers at the NIH as part of a National Cancer Institute (NCI) production contract, held by Charles River. Others came from commercial production colonies, separately maintained by the company in various locations.

Some of the genetic mix-ups identified independently by researchers at universities and at NIH also affected at least one other commercial breeder besides Charles River—the Laboratory Supply Co. of Indianapolis—inadvertently causing it to produce genetically contaminated mice. However, Laboratory Supply reported back promptly to NCI in the spring of 1980 that purported BALB/c mice "not typical by appearance" were being sent to the company from Charles River. Later, the NIH project officer was notified the litter size from these animals was also larger than that expected from BALB/c mice. Tests subsequently proved that the mice were genetically contaminated, according to Eldon Cox, president of the Indianapolis-based company. The contamination was consistent with crossbreeding of BALB/c with Swiss-Webster mice, which also are albino.

Problems with genetically contaminated mice began to affect research at NIH at least as early as the summer of 1981. Harold A. Hoffman, who then was in charge of genetic testing of animals in the division of research services at NIH but has since left to start a consulting firm to monitor animals genetically, reported to NIH investigator Gerald Quinnen that animals he received after 17 June that year were genetically impure. "The degree of genetic contamination is so great that in a study in the blind I never would have determined that these mice were supposed to be BALB/c's," Hoffman wrote in a memorandum to Quinnen dated 8 September.*

A week earlier, however, NIH's Richard L. Pierson, who was dealing directly with Charles River, filed a memo summarizing a conversation on 21 August with Melvin Balk of Charles River: "He informed me that they just finished testing the mice at the Portage facility and there were no problems," the memo says. The Portage facility referred to in Pierson's memo is one of several from which the Wisconsin scientists say they received genetically contaminated mice during the autumn of 1981—shortly after NIH scientists were reporting difficulties to one another and to the company.

Balk's statement, as Pierson recalls it, seems to contradict Hoffman's findings, although Hoffman did not mention specifically what Charles River facilities Quinnen's contaminated mice came from. Those mice tested by Hoffman also appeared to be contaminated with genes from Swiss-Webster mice.

Hoffman's findings of genetic impurity were confined to two of the 13 commercial breeding colonies of Charles River that then handled BALB/c mice, according to NIH documents. NIH instituted a ban on purchases of this mouse strain from Charles River between August 1981 and January 1982, lifting it when the company said that the contaminated colonies no longer were in production and that a genetic monitoring program was in place. During the same period, Auerbach and Kahan received several shipments of supposedly BALB/c mice from Charles River. They were not notified of the NIH ban.

What occurred with the NCI contract program with Charles River is, if anything, less clear. At least two investigations took place, the first in November 1980 and the second beginning April 1981. Here again, the genetic contamination pointed to probable crossbreeding of BALB/c mice with outbred mice of Swiss-Webster origin.

Investigators outside NIH also were affected directly by genetic mix-ups involving mice in the NCI contract program. For example, Marion Zatz of the biochemistry department at George Washington University Medical Center in Washington, D.C., traces difficulties with genetically impure BALB/c mice back to September 1980.

At first, not realizing what the problem was, "we continued doing experiments [with them] until May 1981 when we knew we had serious problems," she recalls. During that time, "NCI assured us the mice were okay." But tests, done in conjunction with NCI scientists, proved otherwise. NCI credited the GWU program for the cost of the mice, but the losses in time and research are "incalculable." Zatz and her collaborators eventually dropped one whole phase of their work that had been affected. "We were never able to reestablish that tumor system, for whatever reason," she says. "We decided it was not worth pursuing. This certainly hurt a segment of our research program, but didn't wipe it out."

NIH's role in these genetic mix-ups adds complexity to an already complicated situation. NIH is the source of the breeding stock for animals in contract programs, such as the one in which Charles River was awarded a contract to expand and maintain lines of BALB/c mice. A few years ago, according to Joseph Mayo, chief of NCI's animal and breeding protection branch, "NIH was sending out 'starts' without them being checked," which means that when contamination occurred, there was uncertainty whether the contamination originated with the breeding stock sent out by NIH or with the contractor's handling of

*This and several other documents were shared with *Science* by National Public Radio reporter Bruce Gellerman who obtained them through Freedom of Information requests.

Purity of Rats Also Questioned

Several former Charles River customers who had problems with genetically impure, though supposedly inbred, Wistar/Lewis rats still are angry over their dealings with the company. The rat incidents date back at least to mid-1979 and thus began before the genetically impure mice episodes occurred.

In 1980 and 1981 several reports about the rat problems were published in the journal *Transplantation*. Various scientists, including Hinrich Bitter-Suermann, now at Dalhousie University in Canada but who was then at Georgetown University in Washington, D.C., and David W. Scharp of Washington University in St. Louis, reported difficulties in transplanting islets of Langerhans between rats as part of research on diabetes. They, and Marshall Orloff of the University of California, San Diego, independently traced this difficulty to the rat strains they were receiving from Charles River. In one issue of *Transplantation*, several animal breeding companies were invited to comment on this problem, but only Charles River chose not to.

Several of these scientists say that they came very close to filing legal suits against Charles River because of these difficulties. Bitter-Suermann, for example, points to a frustrating exchange of letters between him and Charles River that, he says, shows the company was "trying to sweep the problem under the rug."

In a letter to him in early 1980, Sumner J. Foster, executive vice president of the company, wrote that skin graft and other tests were under way "to reestablish whether or not these animals are inbred to the degree that we assumed they were." It is unusual, if not impossible, to establish a "degree" of inbrededness; more usually it is referred to in absolute terms. The letter goes on: "Again, I wish to express my sympathy to you that the Charles River Wistar/Lewis was not the appropriate animal for your study, but obviously, again we cannot guarantee successful results to any research investigator. We will certainly keep you informed . . . regarding this problem."

It has taken "many years for me to swallow my anger," Bitter-Suermann says. "We wanted them to guarantee the rats, not our research." Both Orloff of UCSD and Scharp of Washington University had experiences similar to those of Bitter-Suermann. Moreover, they claim that efforts to inform the company about these difficulties were met with rebuffs and a lack of cooperation.

Of the three, Bitter-Suermann through attorneys representing Georgetown University came closest to taking legal action against Charles River. But all three scientists say that plans were dropped largely because lawsuits can be time-consuming and otherwise burdensome. In several instances, attempts to recover damages out of court from Charles River met with considerable resistance, the company making it a policy only to replace animals or the direct cost for animals.—**J.L.F.**

the colonies. "Now we have a piece of paper verifying the source. We didn't have the paperwork before and were not in a position to come down on the contractor."

Mayo is circumspect about where genetic contamination arose. "There's no way to trace it out," he says. An NIH document, dated 1 October 1982, summarizing these incidents is considerably less ambivalent: Mice from NIH's foundation stocks "have been shown to be homogeneous and typical for the BALB/c strain. . . . There has never been any evidence of genetic contamination involving the pedigreed colonies of [these] mice," it says, thus attributing the responsibility to the contractor, Charles River, without spelling that conclusion out.

Mayo, other NIH officials, and lab animal users elsewhere praise Charles River for its quality breeding programs, especially for its reputation for supplying healthy animals. Partly because of this reputation, Charles River not only is considered the giant of the lab animal–breeding industry in general, but also holds a lion's share of government contract work in this arena. About 18 percent of the company's business is done under federal contract, including annual contracts with NCI for $2.5 million and with the National Institute on Aging for $2 million. (There has been no problem of genetic contamination in the colonies maintained by Charles River for NIA, according to an institute official.)

Charles River has recently taken steps to preserve its reputation for quality by instituting a major new genetic monitoring program with the help of consultants, including geneticists from Texas A&M University and the University of Pittsburgh. One outgrowth of this program was a "Genetic Monitoring Bulletin" issued a year ago reporting another instance of genetic variation in BALB/c mice "sometime between May 1, 1982 and August 16, 1982. . . . The incidence of this finding is very low (approximately 5%), however, we have discontinued the colony much as we would for a microbiological contamination," says the report dated 20 August 1982. Charles River's efforts to make sophisticated genetic monitoring a routine service have been applauded widely by those who do business with the company and also by its competitors.

Nonetheless, company practices in the period before such programs were instituted are what Kahan and others are challenging. And her argument that "career and publication opportunities were lost" could strike a chord in the research community, particularly among those scientists who had to do considerable sleuthing before they realized that genetic contamination could explain difficulties they had with experiments.

It is scientists in the basic research community, and not other users of inbred animal strains, such as toxicologists or researchers in drug development programs, who have felt the main impact of genetic contamination problems. For example, a spokesman for the Food and Drug Administration (FDA) says: "Toxicology is not sophisticated enough so that a difference in strains will affect the safety of our determinations. Such differences wouldn't affect anything because experiments are internally controlled." Thus, even if a protocol called for an inbred strain, the presence of genetically impure animals would likely be distributed randomly among control and test animals.

By contrast, in experiments like those done by Kahan, difficult transplant procedures precede extended animal growth periods. Hence, all sorts of reasons why a procedure failed might be invoked and checked before genetic contamination would be considered. Other scientists who have had difficulties with genetic contamination of animals, including several representatives of pharmaceutical companies, paint more or less the same picture.

"Where Charles River is *today* is what's relevant," says vice president Foster. The company has implemented increasingly sophisticated genetic monitoring programs but, all along, has used "proper methods at relevant times," he says. Those capabilities are becoming "more and more refined."

Foster suggests that scientists bear a responsibility to notify the vendor when problems arise. "It's incumbent on both parties to work together, to provide as much information as they can," he says. Says Kahan, "They told me what they did to check genetic integrity but never told me their results."

Information promises to be a key issue in the case Kahan has brought against Charles River: How is information properly and amicably shared between animal supplier and user; how quickly can and should either party alert the other over potential problems; and by what means? By establishing monitoring programs, Charles River has lessened the likelihood of genetic contamination in the future. But establishing how problems arose in the past and whether the company is responsible for them now is a matter for the courts to decide.

—JEFFREY L. FOX

Redemption for Social Science Tomes

The social and behavioral sciences have enjoyed a modest stroke of good fortune in the form of a decision by the publishers of *American Men and Women of Science* not to cancel issuance of a new directory of U.S. social scientists.

Editor-in-chief Gary Ink says that, because of poor sales of the last couple of editions, it was decided to postpone the planned 1982 edition indefinitely. Biographies of physical and biological scientists, now occupying seven volumes, are issued every 3 years.

Ink says the decision was reconsidered following a market research survey and a meeting with the Consortium of Social Science Associations (COSSA) in Washington, which persuaded the publishers there was a strong, indeed "desperate," demand for a new edition. Ink says this was manifested despite the fact that reductions in federal social science spending have forced libraries to reduce purchases, and despite the proliferation of online information services.

He adds that help in contacting relevant buyers has been pledged by COSSA, a lobby group set up 2 years ago in reaction to the budget cuts. The plan now is to issue the two-volume set on the social and behavioral sciences in September for $150, and to update it every 5 years.

—CONSTANCE HOLDEN

Stone Age Sites Saved from Flooding

A recent decision by the High Court of Australia has effectively halted a massive hydroelectric power project that would have flooded significant ecological and archeological resources in southwest Tasmania. The decision, by a vote of four to three, appears to resolve a long and often bitter wrangle over the separate powers of the state and federal governments (*Science*, 3 December 1982, p. 988).

The discovery in the past several