Mouse mix-up may alter research results

Researchers from the University of Wisconsin have charged that for nearly a year the world's largest supplier of laboratory animals, Charles River Breeding Laboratories in Wilmington, Mass., made shipments of an inbred strain of mouse, called BALB-c, that were not the pure genetic strain they were supposed to be. Brenda Kahan and Robert Auerbach write in the July 23 SCIENCE that "the seriousness of our findings cannot be overemphasized" because, they say, the results of "possibly hundreds" of published experiments where research relied upon genetic purity of these mice may be wrong.

While Charles River's executive vice president, Henry Foster, does not dispute Kahan and Auerbach's charges, he calls their actions "unorthodox" because they did not inform the company when they suspected something was wrong with the mice. He says that by the time he heard there was a problem — when the paper was submitted to SCIENCE in January — the company had already destroyed the questionable colonies of mice as a result of their own genetic monitoring efforts.

Because BALB-c mice have been inbred since 1913, all individuals should be "as identical as identical twins," says Auerbach. Genetically identical mice are important, he says, because they "lead to uniformity" in experimental results and, when more than one mouse strain is used, the clear genetic individuality of each is essential to telling their cells apart. In addition, says Auerbach, much modern cancer research relies on tumor transplantation. Unless transplants and their hosts are genetically identical, a tumor will be rejected by the host's body.

Last year, when Kahan was studying tumor cell differentiation, she began to get results that were "either very spectacular or a mistake," says Auerbach. "She was sufficiently cautious to doubt her results" and they reviewed the experiment, tracing the problem to the BALB-c mice she was using. Two genetic biochemical markers, the equivalent of footprints for a particular genotype, were analyzed. If the mice had been genetically identical, these markers would have been identical in all of the mice as well. They were not, however, meaning that many of the animals were not pure BALB-c mice.

"By no means were we convinced, even then, that anything was wrong with the mice at Charles River," says Auerbach. On the "off chance" that there was, he and Kahan ordered more mice from three separate Charles River breeding units, repeated the tests, and, according to Auerbach, found that "at least three-quarters" of the mice from two of the three units were not purely BALB-c. Similar tests conducted by Barbara Alter and Fritz Bach at the University of Minnesota (at Auerbach's request) further confirmed these findings.

Because random mutations can happen without visible changes in a population, this kind of error "has happened before," says Foster. But, when it does, "the normal practice" is to alert the company involved, which he says the Wisconsin researchers neglected to do until January. Harold Hoffman, program director for the genetics quality control program at the National Institutes of Health, however, says that, in response to a similar complaint from an NIH immunologist, he tested Charles River mice last summer, with the same results, and that his agency informed the company in the fall.

Whether company officials found out last fall or last winter, it is "unfortunate that Charles River did not notify their users," says Auerbach. The contamination "has put a lot of research in jeopardy," agrees Hoffman. "One Sloan-Kettering investigator lost one whole year of work as a result of this." Worse, many researchers do not know if their published results are valid because the mice are dead and cannot be tested.

Foster says that his company did inform a few of their customers in the fall when results of their own genetic monitoring program cast doubt on the two now controversial breeding colonies. The colonies were immediately destroyed, he says. No general alert was issued because they were not positive the mice were contaminated and "had not heard any complaints" from researchers using them. Because mice in each of 13 breeding units are now tested with nine different genetic markers, this kind of error "should not happen again," says Foster. —*L. Tangley*

Hopp/Univ of Wis.

Kahan holds a genetically pure (left hand) and impure (right hand) BALB-c mouse. The two animals appear to be identical.

Winding up work of antibiotic watchdogs

A chapter in the history of antibiotics is due to close Oct. 1. That is when the Food and Drug Administration is scheduled to shut down the National Center for Antibiotics Analysis — a federal institution that monitors quality, strength and purity of such drugs before they are sold. FDA officials say work at the laboratory now is being phased out because it is no longer necessary; but a public interest group charges that industry pressure is the reason antibiotic drugs will no longer be subjected to batch-by-batch testing.

Such testing began with 1945 amendments to the Federal Food, Drug and Cosmetic Act that required batch certification for penicillin. In their report in the May 7, 1982 FEDERAL REGISTER, FDA officials note that the original requirement was instituted "...because of the newness of the drug and the heightened concern for its quality. ... In enacting these requirements, however, Congress was aware that the need for the special type of control offered by certification might subsequently be rendered unnecessary." Therefore, it also included in the Act sections that would permit the exemption of penicillin and other antibiotics from batch-by-batch testing should "developments [occur] in manufacturing technology or otherwise that may render the need for these special types of control unnecessary."

FDA believes that that time has come. Of 18,819 antibiotic batches tested in fiscal 1981, fewer than 1 percent failed to meet government standards of purity and strength, FDA spokesperson Christopher Smith says. The antibiotic laboratory now "is considered a waste of industry's money [most of the costs to operate it are covered by drug manufacturers' fees]," he says, "and consumers end up paying for this."

Smith stresses that antibiotics manufacturers still must continue to meet the Good Manufacturing Practice regulations that govern the manufacture of all drugs. These regulations "spell out what kind of records a drug manufacturer must keep, how often machines have to be cleaned, what type of personnel should be running those machines and so on," Smith says. By eliminating the final product testing of antibiotics, Smith says, FDA is simply "making all drugs equal."

But Sidney M. Wolfe of the Public Citizens Health Research Group says Smith's explanation is "ridiculous." He says, "It's like saying that if you don't have enough police to watch all neighborhoods, then you don't watch any so that all neighborhoods are equal." Ideally, says Wolfe, "there are other categories of drugs that need this kind of final product testing, but the most important types now are antibiotics." FDA's move to end this testing, Wolfe says, paints an ominous consumer health picture. —*L. Garmon*