ARE RATS RELEVANT?

Most scientists agree that animal experiments, properly qualified, are valid to predict which chemicals will cause cancer in humans

BY JULIE ANN MILLER

If news events were categorized pictorially, the recent move by the Food and Drug Administration to ban saccharin (SN: 3/19/77, p. 182) would certainly be represented by a bloated rat feeling unwell after drinking hundreds of cans of diet soda. Almost every news report of the Canadian experiment that triggered the FDA action mentioned that the amount of saccharin fed the rats was more than a consumer would receive from drinking 800 12-ounce diet sodas daily.

Yet, according to Umberto Saffiotti, the director of experimental pathology at the National Cancer Institute, the Canadian study followed accepted scientific practice. Congress's Office of Technology Assessment agreed after a panel of 11 scientists reviewed all available data on saccharin. A prepublication draft of their report says evidence from the Canadian experiment and two 1973 American research projects, one by the FDA and the other by the Wisconsin Alumni Research Foundation, "demonstrates that saccharin is a carcinogen."

Public hearings held by the FDA and by Congress on the proposed saccharin ban have included diabetics who depend on saccharin, drug manufacturers who sweeten medicines with saccharin and parents who fear the ban will make their diabetic children social cripples. The testimony has also included scientists trying to justify a generally accepted scientific practice to congressmen and to the public. Representatives of the FDA and the National Cancer Institute have been called on to explain why the results of the animal experiments using high doses of a chemical are relevant to human disease and why the FDA action is not just the agency acting, as Rep. James G. Martin (R-N.C.) charged, "at the drop of a rat."

The importance of reasonable animal testing goes far beyond the saccharin issue, even beyond the underlying 1958 Delaney amendment, which states that no food additive may be deemed safe if it is found to induce cancer in man or animals. Animal testing of chemicals also underlies decisions on chemicals inadvertently in food, such as pesticides and antibiotics, and air and water pollutants as well as drug approval or banning.

The crucial question troubling those who must make decisions based on animal experiments is how well do the results predict what would happen to people. Scientists vary in their opinions of the detailed applicability of the tests, but at the moment most agree that there is no better approach. Recent techniques using bacteria or cells grown in a laboratory are useful for cheap and rapid screening of chemicals, and studies of human populations can sometimes indicate potent cancer-causing agents after people have been exposed 5 to 50 years, but animal tests are still considered most relevant and practical for routine evaluation.

Why do scientists think that the reactions of animals to large amounts of a food additive have any relationship at all to what will happen in humans? The answer is twofold. First there are basic similarities in how cancer is initiated in man and in animals. Second, there is no good evidence that a safe low dose exists for chemicals that cause cancer at high doses.

"Effects in animals, properly qualified, are applicable to man," states the recent report of the National Research Council on drinking water and health, a study that examined, among other water contaminants, chemicals suspected of causing cancer (SN: 6/11/77, p. 374). The report continues: "This premise underlies all of experimental biology and medicine; but, because it is continually questioned with regard to human cancer, it is desirable to point out that cancer in men and animals is strikingly similar. Virtually every form of human cancer has an experimental counterpart, and every form of multicellular organism is subject to cancer, including insects, fish, and plants."

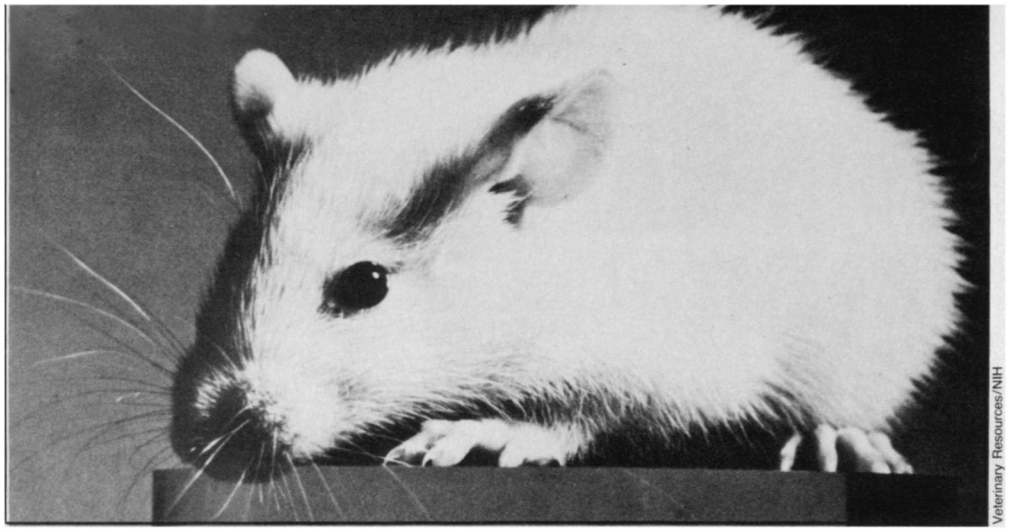
Still, toxicologists have long recognized that, no matter how useful in experiments, mice and rats are not scaled-down people. This dilemma is called the "mouse-to-man" problem. A chemical's effect may vary among types of animals or even among individuals. Unfortunately, the details of how most chemicals are processed in the body are not yet known. Therefore, it is not possible to choose rationally an experimental animal that treats the chemical being tested the same way that the human body does.

Nevertheless, Joseph K. Wagonner of the National Institute of Occupational Safety and Health told a press briefing sponsored by four congressmen, "There is a high concordance between carcinogens in humans and in animals." He points out that in almost all cases where agents known to cause cancer in humans were tested in laboratory animals, they gave positive results. The cancers that developed, however, were not always in the same organ as in the people, nor did they develop in all the experimental animals tested. "Although there are differences in susceptibility between different animal species, between different strains of the same species, and between individuals of the same strain, carcinogenic chemicals will affect most test species," the NRC report agrees.

In several cases, animal data have predicted that certain substances will be carcinogenic in humans. "If people had taken the evidence seriously, human suffering could have been diverted," Wagonner says. One of these examples is diethylstilbestrol (DES). In 1941, studies in laboratory animals showed that DES was associated with cancers of the reproductive organs. Then in 1970 it became clear that there was a sharp increase in cancer of the vagina among daughters of women who had taken DES during pregnancy. Similarly in 1962 researchers found that cadmium induces testicular cancer in laboratory animals, but it wasn't until 1975 that people recognized that the metal increased by three to five times the rate of prostatic cancer in cadmium workers in the United States.

Because using people in experiments on cancer-causing chemicals is practically and morally out of the question, and epidemiological techniques are usually too insensitive and take too long, a choice of experimental animal must be made. Primates may be closer to people in their biochemistry and physiology, but practical considerations usually lead researchers to rats and mice and occasionally to dogs, rabbits and guinea pigs. As a safeguard against being misled by the differences between mice and men, the National Cancer Institute recommends that tests be conducted in two species, raising the odds that a chemical's observed effect in at least one species will resemble the effect on humans. The OTA report on saccharin warns, "It is prudent to take the results of experiments in the most sensitive species to determine carcinogenicity." Others, however, believe that identification of a chemical as a carcinogen in at least two species, rather than just one as the Delaney clause requires, would be a far more solid indication that the chemical is likely to be carcinogenic in humans.

Although finding a chemical carcinogenic in animals does not guarantee that it will prove so in humans, that information certainly increases the odds. Of all the compounds that have been tested



Rats, although they are not scaled-down people, are used in safety tests.

extensively, only about 5 percent cause cancer when fed to animals in high doses, according to William Lijinsky of the National Cancer Institute.

Besides the "mouse-to-man" problem, a popular objection to animal studies is the high doses of chemicals used in the tests. In 1970, the Food Protection Committee of the National Academy of Sciences recommended a dose for such experiments ten to a thousand times greater than a person might be expected to consume.

Researchers cite three major reasons for testing chemicals in large doses. First, high doses compensate for shorter life spans and faster metabolisms of the test animals relative to humans. Rats live about 2 years, people live about 70 years. Therefore people ingest a chemical for a longer period. Small mammals also usually break down and excrete chemicals more rapidly than humans do. Ralph Nader told the congressional press briefing that the much-cited figure of 800 cans of diet soda is inaccurate as the human equivalent to the amount of saccharin in the Canadian study. When the rats' higher metabolic rate and shorter lifespan is taken into account, Nader said, the proper equivalent is about two cans per day.

Practical necessity is the second reason scientists give for using high doses. A test with low doses would require thousands of animals to demonstrate that an increased incidence of tumors is due to the chemical tested rather than just to chance. The OTA study points out that in the Canadian experiment, which used 100 rats, only 8.9 percent of the animals exposed to saccharin as 5 percent of their diet developed tumors. A tenfold reduction in dose would be expected to result in a tenfold reduction in tumor frequency. Therefore, less than one animal in the group they examined should develop cancer, an effect impossible to detect.

This problem is even more obvious in epidemiological studies. Since a 30 percent increase in cancer incidence is the smallest effect such studies have detected, Robert Hoover of the National Cancer Institute calculates that epidemiologists would need to follow 15 million people, each drinking one diet soft drink per day, for their entire lives, to demonstrate the small increase in cancer rate predicted by the Canadian animal experiment.

Although there have been some studies of human use of saccharin, they only rule out a relatively rapid, intermediate or high-level risk among adults consuming saccharin, Hoover explains. "Because of the small numbers involved," he says "the observation of no excess risk could be consistent with an observation of a 50 to 70 percent excess risk, on the basis of chance itself." Even more worrisome, according to Hoover, is the likelihood that there are pertinent differences between saccharin users (diabetics in the case of these studies) and the control group. "There is some evidence diabetics smoke fewer cigarettes, which would decrease their risk of bladder cancer," Hoover says. "A difference of three cigarettes a day would cancel out the calculated saccharin effect."

Use of high doses raises the question of whether there is any level below which a cancer-causing substance will do no harm. Typically, poisons show no ill effects below a measurable threshold level. The body's reaction to two aspirin, for example, is totally unlike its reaction to two bottles of aspirin. On the other hand, damage inflicted by radiation appears to be proportional to the amount of radiation, even at the lowest levels measured. The probability of a normal cell becoming transformed into a cancer cell in a person varies directly with dose for the incidence of leukemia among survivors of nuclear blasts and of various tumors following occupational and therapeutic radiation, the OTA report notes. The incidence of lung cancers in men also appears to be proportional to the number of cigarettes they smoke.

For estimating risks of chemicals to human populations, it is important to know whether there is a threshold. After reviewing the data of 151 experiments, Paul N. Craig and Gene Miller of the Franklin Institute in Philadelphia found no evidence that there is a threshold dose below which a carcinogen will not cause cancer. If a threshold exists, it has not yet been measured, and thus, cannot serve as a practical tool in making extrapolations, the OTA report points out. Differences in methods of converting animal data to predictions for humans have led to estimates of the human risk of saccharin consumption ranging from 15 to 15,000 additional cases of bladder cancer per year in the United States, with most researchers citing numbers around 1,000. "There are no reliable quantitative estimates of the risk of saccharin to humans," the OTA report concludes.

Natural variability among people is the third argument for using high doses of chemicals in safety tests. Some people may react to a chemical more acutely than will others. Laboratory animals are inbred and are much more uniform in their sensitivity to carcinogens. Human populations may vary in the activity of the enzymes involved in activating carcinogens (SN: 6/4/77, p. 362) and will certainly differ in their exposure to other substances that may stimulate cancer initiation. Barry Commoner, director of the Center for the Biology of Natural Systems in St. Louis, says, "Because the human population is so variable, it will contain some individuals who react like one species, some who react like the other, and many who occupy the range inbetween."

Even people who accept the validity of animal testing become confused when scientists change their recommendations, seemingly capriciously. In the case of saccharin, the OTA report responds that some of the previous experiments, which showed no effect of the sweetener, were not sensitive enough to detect the carcinogenic effect and none were as well-designed as the three experiments that gave positive results. ". . . cancer testing is rapidly evolving and many older experiments are not now considered to be satisfactory. The positive two-generation studies come the closest of all that have been conducted to meeting the current testing standards," the report says.

Any decision on what experimental data are required before the use of a chemical will be restricted depends on how cautious people want to be. Is it worse to occasionally permit use of a product that causes cancer or to forbid a product that does not? "Unfortunately, the saccharin data are not so good as to eliminate all misgivings about using them for quantitative estimates of human risk. The data are good enough, however, to allow the qualitative judgment that saccharin presents a potential risk to human health," the OTA report decides. The hope is that improved methods of both experimentation and extrapolation to people will make evaluations easier in the future. However, even now most scientists believe that the animal experiments are more relevant to human risk than Rep. Andrew Jacob's (D-Ind.) proposed warning: "The Canadians have determined that saccharin is dangerous to your rat's health." □