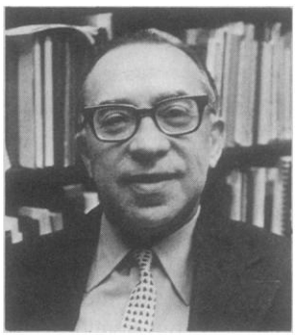
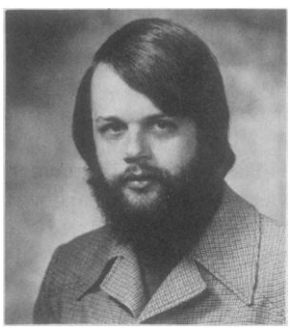
Latest Saccharin Tests Kill FDA Proposal

The debate over saccharin is an excellent example of how a difficult scientific concept might founder in the political and public arena

The public was informed by the press last month that saccharin does not cause cancer in people, news which only confirmed the widespread public reluctance to believe that the popular dietetic sweetener is a carcinogen. Newspapers reported that three new epidemiological studies of bladder cancer patients, had refuted the rat tests by which saccharin had been condemned. The diet food and beverage industry took up this refrain, claiming that the safety of saccharin had been affirmed. Congress took new pride in its 1977 decision to overrule the Food and Drug Administration's (FDA) determination that saccharin should be removed from the general diet.



Emmanuel Farber of the NAS panel



Robert Hoover of NCI

Unfortunately all these reactions are based on an incorrect premise. The three new epidemiological studies do not refute the animal tests, but rather are generally compatible with them. The studies were performed by scientists at the National Cancer Institute (NCI), the Harvard School of Public Health, and the American Health Foundation in New York City.* The consensus reached in the scientific community, that saccharin poses a risk of cancer to humans, albeit a low risk, has not been changed by the new data. "The studies do not prove that saccharin is safe, and anyone who says that is giving us a snow job," says Emmanuel Farber, a University of Toronto pathologist and chairman of the National Academy of Sciences' most recent panel on saccharin.

The press, the public, and Congress have misinterpreted the inherently complex and often conflicting evidence of a weak carcinogen. One reason is the general misunderstanding of toxicological methodology and the nature of animal testing. Another reason is the aggressive effort of the diet food industry to foster this misunderstanding, and its ability to bring its views forcefully to the attention of Congress. Contributing to the public befuddlement was the FDA's presentation of the issue, which in several aspects played into the hands of its opponents. And most recently, there has been a general misunderstanding of the inherent shortcomings of epidemiology, which preclude it from establishing the absence of a risk. Thus last month's misrepresentation was only the most recent miscarriage of facts in a running scientific-political imbroglio.

The saga began in March 1977, when Canadian scientists reported that saccharin caused cancer when fed in high doses to laboratory animals. FDA Acting Commissioner Sherwin Gardner told the press that "science and law dictate that saccharin be removed from our food supply," but that the evidence against it did not "indicate an immediate hazard to human health." The public was thus presented with a spectacle of sweeping action proposed against a risk of low magnitude, which led some to call the proposal absurd.

Donald Kennedy, who arrived as the new FDA commissioner within weeks of Gardner's announcements, often said his agency's proposal had been misunderstood—that the FDA intended only to remove saccharin from processed foods, while permitting its use as a tabletop sweetener if the industry could prove any benefits. But FDA officials neglected to emphasize the possibility of saccharin's continued use until a month after the initial news of the ban. Instead of projecting their decision positively, as the best choice made on the basis of difficult scientific evidence, the agency's spokesmen presented it as a requirement of the Delaney clause of the food law. Unfortunately, the FDA's initial press release also noted that the rats used in the Canadian tests had been fed doses of saccharin "in excess of the amount that a consumer would receive from drinking 800 diet sodas daily."

This was an open invitation to the diet food industry to hold up to ridicule what was in fact a standard part of toxicological methodology made necessary by the difficulty of picking up a low level effect in a small group of animals. The Calorie Control Council, an organization of Japanese and American makers of saccharin, soft drink companies, and pharmaceutical firms, spent $890,000 for lobbying, advertising, and public relations during the first 3 months following the FDA's proposal and has invested a total of $1.14 million on congressional lobbying to date. "The industry confused the public, perhaps permanently, on the value of animal tests," FDA spokesman Wayne Pines remarks of the Calorie Control Council's campaign.

Faced with considerable public pressure, Congress blocked the FDA's proposed action against the sweetener pending an independent analysis by the National Academy of Sciences (NAS). Some members of Congress with expertise in food and health issues hoped that the Academy report would provide a specific endorsement of the FDA's decision. Although the chairman of the NAS panel on saccharin did so in oral testimony to a congressional committee, the panel's report, in the manner of Academy committees, stopped short of direct comment on the FDA's proposals.

Although the NAS panel report stated clearly that, on the basis of the Canadian animal tests, saccharin should be considered to be a carcinogen, Congress chose instead to look for more incriminating

*R. Hoover *et al.*, National Cancer Institute, Bethesda, Md., 1979; A. S. Morrison and J. E. Buring, *N. Eng. J. Med.*, 6 March 1980; E. L. Wynder and S. D. Stellman, *Science*, 14 March 1980.

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evidence, such as that which might be produced by an epidemiological study. Existing studies for the most part showed no positive evidence that saccharin might be a carcinogen, but it was thought that larger or more carefully conducted studies would produce more conclusive results. What Congress apparently neglected to observe was that, because of the inherent limitations of these studies, none would be sufficiently sensitive to detect whether or not saccharin is a weak carcinogen.

Congress has chosen to take the three new epidemiological studies as confirming the previous negative results, but here it parts company from the weight of scientific opinion on the issue. The generally unappreciated fact is that the new studies must be interpreted in conjunction with the results of the best available animal tests. These suggest that exposure to saccharin increases the risk of bladder cancer in man by a range centering around 4 percent. But the most elaborate of the three new studies, that conducted by the National Cancer Institute, would detect no change in cancer incidence smaller than 15 percent. Officials at the FDA and NCI thus knew in advance that detection of a positive effect of saccharin on bladder cancer was highly unlikely. The chief purpose of the study was to determine if the cancer rate was much higher than expected, as had been suggested by a single questionable epidemiological survey. The answer was that it was not, which is a far cry from being proof of no effect.

The NCI study, conducted by Robert Hoover and colleagues, surveyed 3000 bladder cancer patients and 6000 control subjects. No significant correlation between cancer and exposure to saccharin was detected as far as the total patient population was concerned. But the study did pick up a correlation in particular small subgroups, such as heavy smokers and heavy users of saccharin (two or more diet sodas daily or six packets of sweetener daily) which might have been only random fluctuations in the data. Despite this uncertainty, the authors say the results "can all be interpreted as consistent with the results of animal experimentation." Hoover observes that "Nothing in this study, or the other two, is inconsistent with saccharin being a weak carcinogen."

The other two studies, by Ernst Wynder and Alan Morrison, included fewer patients than the NCI's, and were thus even less likely to detect evidence of saccharin's carcinogenicity. Neither did.

Hoover concludes that few if any cases of bladder cancer to date have been caused by saccharin, but that does not mean that continued widespread usage might not cause such cases in the future. "The evidence is that little, if any, current bladder cancer is due to the consumption of artificial sweeteners, at the doses and in the manner in which sweeteners were commonly used in the past," he wrote recently in the *New England Journal of Medicine*. He and others have noted that the three new studies failed to address the maximum risk situation pointed to by the animal studies, that of exposure to saccharin in the womb and childhood, which is now common. Hoover concludes that when all the evidence of toxicity is weighed against the lack of any evidence that saccharin actually helps people lose weight, "any use by nondiabetic children or pregnant women . . . and excessive use by anyone is ill-advised and should be actively discouraged by the medical community."

Others in the scientific community also urge caution in the interpretation of the studies' negative results. Jere Goyan, Kennedy's successor as commissioner of the FDA, notes that "none of the studies is sufficiently robust to pick up the cancer rates predicted by the animal studies, which were, in fact, too

MX on Land or Sea?

Another chapter in the saga of mankind's greatest construction project played itself out on 25 March before a House defense appropriations subcommittee, which was trying to decide what to do with America's newest and biggest missile, the MX. The subcommittee, chaired by Representative Gunn McKay (D-Utah), wanted to know whether there was any alternative to the basing plan chosen by the Administration known as the racetrack. It will require spending 10 years and $34 billion to build a garage and road network in the valleys of Nevada and Utah. Couldn't the missile be put out to sea on small submarines instead, as suggested by defense analysts Sidney Drell and Richard Garwin? (*Science*, 12 October 1979)

The Pentagon's answer: No. William Perry, under secretary of defense for research and engineering, reportedly told the congressmen that this option had been considered and rejected because it was vulnerable to the van Dorn effect. If the Soviets were to blanket the coastal waters with a barrage of nuclear warheads, the reasoning goes, the concussion would create a tsunami wave 50 feet high, neutralizing the submarines.

There is "nothing new" in this, says Garwin; there have been all kinds of studies in the last 10 to 15 years showing that a tsunami would have a devastating effect on ships in shallow water on the continental shelf. That is precisely why his plan would keep the submarines beyond the shelf where the water is 800 feet deep, and where a Soviet attack would not have a lethal effect. The van Dorn criticism is "totally irrelevant" and a "phony issue," according to Drell. He is "damned angry" that this sort of criticism is being used against the submarine basing concept. He planned to come to Washington to talk to congressmen and set the record straight. Perry is not the source of the misinformation, Drell says.

Garwin, too, has been trying to set the record straight on this point for several months. For example, he wrote to the under secretary of the air force, Antonia Chayes, on 12 February in evident frustration at his inability to get the air force to state its position clearly. He asked Chayes to initial his letter and return it, indicating that she agreed or disagreed that the official position was that the small submarines were not threatened by the van Dorn effect. There was no reply. Some people in the Pentagon, according to Garwin, would prefer to obfuscate than come to grips with the substantive merits and faults of the submarine alternative.

Meanwhile, as the dust from that skirmish clears, the Pentagon is preparing to release a new paper on the Drell-Garwin proposal, undertaken in response to a request by Senator Mark Hatfield (R-Oregon). According to a defense spokesman, it finds the submarines inadequate because they are not fit to withstand the stresses of high seas, too small to hold the necessary strategic missile equipment, and too costly if major modifications are required. This salvo in the antisubmarine war will be fired within days, the Pentagon says.—ELIOT MARSHALL

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small to be picked up by any reasonable project." Goyan says he tried to explain this to a few of his nonscientist friends, without any great success. "Most of them are 'Tab' drinkers," he says.

Emmanuel Farber, who chaired the NAS panel, is even less convinced that the results are important or surprising. There have been negative epidemiological studies of cancer and smoking, he notes. Farber still recommends that saccharin be taken out of processed food and drink, as it has been in his native Canada. Frederick Robbins, who was chairman of the Institute of Medicine's food safety panel that also studied the saccharin question, says that the new studies are "in general, consistent with what we said all along."

But this is not how the new studies were generally reported in the press. "Saccharin Scare Debunked," proclaimed the Washington *Post* last month. "The evidence contrasts sharply with results from studies that have shown increased risk of cancer from animals," reported the *New York Times*. "Whatever saccharin does to rats, it does not after all appear to cause bladder cancer in humans," ran the verdict of the *New Scientist* of London.

Reports of this ilk shaped Congress's comprehension of the issue. The new epidemiological studies, says a staff member of the Senate subcommittee on health, "suggest that saccharin is not as strong a hazard as we originally thought." According to a staff member of the House subcommittee on health, the press accounts of the studies "confirmed the view of most members that they made the right decision" in imposing the 1977 2-year moratorium on the FDA's actions against the sweetener; "Frankly I don't think the members understand the results of these studies. They simply don't want to deal with saccharin any more, and not many will read past the headlines," this staff aide remarks.

At the FDA the attitude toward the saccharin affair is one almost of resignation. According to FDA Commissioner Goyan, "There is a 100-to-1 chance that the Senate will extend its moratorium on our proposal. So I don't intend to expend a great deal of effort explaining the latest studies to the American people." "Our credibility on this subject is diminished anyway—people wouldn't believe us," remarks FDA public affairs officer Wayne Pines. Goyan states that the FDA will prepare the ground more carefully next time it takes action to regulate a weak but popular carcinogen.

—R. JEFFREY SMITH

Controversial Scientist Considers Leaving NCI

Gio Gori, the government scientist who angered his superiors in 1978 by hinting publicly that it was tolerable to smoke low tar and nicotine cigarettes, is saying that he wants to leave government service because the directors of his agency, the National Cancer Institute (NCI), have made life difficult for him. He is actively considering a post as director of a new center to study health policy that will be endowed in part by the Brown and Williamson Tobacco Company.

The center will be affiliated with the Franklin Research Center, a nonprofit organization based in Philadelphia that does $20 million worth of contract research for private clients and the federal government. The organization runs the federal Solar Heating and Cooling Center, for example, and is performing studies for the National Institute for Occupational Safety and Health on the appropriate exposure levels for seven dangerous workplace conditions or chemical classes.

W. B. Ligett, director of the parent Franklin Institute, says the new health program will study "government and private health policies, particularly the cost-benefit ratio of these things—to see if federal money could be spent better some other way, or if it could be spent more efficiently." He says that contributions for the program's estimated $3 million endowment are being solicited from the chemical, pharmaceutical, and petroleum industries, in addition to the tobacco firm. "The program will be 100 percent within the control of the Franklin Institute," he says, however.

In response to a reporter's call, Gori says he is considering three options at present, including two offers from the food industry. He says that things might also work out at NCI. "Left to my own devices, I would prefer to stay. But I have been forced to look around, so to speak. Life has been difficult for me here at NCI, since the smoking matter. I've had things taken away from me with no explanation. They just put you in a broom closet; it's a time-honored technique." But he also says, "The NCI has been good to me, and some of my best years have been spent here. I don't want to go out slamming any doors, although the provocation is there. I have no resentment, and I'm not bitter."

Gori, who is presently NCI's deputy director of cancer cause and prevention, says that if he takes the post as director of the health center, he will push it to look at the costs of health prevention programs. He says that not enough people realize that prevention programs can impose indirect costs, a point of view that "many of my colleagues here are unhappy with."

Proxmire Reenters the Ring After Scientist Lands a Hit

Senator William Proxmire (D–Wis.) ate some crow at the behest of one research scientist on 24 March and 4 days later zinged another with one of his monthly "Golden Fleece" awards for the most ridiculous waste of the taxpayer's money.

The senator announced that he had settled a libel suit brought against him by Michigan research psychologist Ronald Hutchinson, by paying the scientist $10,000 in addition to $5,400 in court costs. Hutchinson filed his $8 million lawsuit in 1976 after he received Proxmire's Golden Fleece and found his sources of research funds beginning to dry up. Proxmire gave Hutchinson the award for research on signs of aggressive behavior, which included studies of teeth-clenching in monkeys.

Proxmire did not flatly apologize in his statement on the Senate floor, but said that some of his statements about Hutchinson may be subject to an unintended interpretation. After correcting several factual errors, he said "my conclusions about Hutchinson's work are solely my own," noting that others had judged it meritorious. "My policy is not, nor will it be, to prejudge or censor any application for a federal grant," Proxmire said. Earlier, in a significant decision against Proxmire, the Supreme Court had decided that the senator's statements in press releases were not exempt from libel law, and that Hutchinson could sue under an easier standard of proof than Proxmire's attorneys had claimed. Proxmire's defense cost the Senate $124,351.

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