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## SACCHARIN — BITTER AFTERTASTE?

The use of saccharin in food was conceived by cupidity, born of avarice, suffered for a time by the lawmakers, stigmatized by the Referee Board, condemned by the three Secretaries, forbidden by the laws of enlightened nations and States, is dead and buried beyond the hope of resurrection, and it only remains for the honorable Secretaries and the courts now to pronounce its obituary.<sup>1</sup>

*G. P. McCabe, Dept. of Agriculture*

To permit it [a decision to remove saccharin as a food additive] to stand would be to commit as great a scientific error as that which condemned Bruno and Galileo as heretics because of their belief in the Copernican theory. Considering the boon to humanity which saccharin is, to prohibit its use would be a crime against nature.<sup>1</sup>

*W. M. Hough, Monsanto Chemical Works*

AFTER 69 years of scientific study and debate, the issues may be different and the words may be less vivid, but the relative positions in the controversy over saccharin as a food additive seem remarkably similar. This leads the media, the legislators, the medical community, and the general public to despair that modern science has assisted us little in difficult decisions of national importance. This despair is unwarranted; it fails to differentiate the issues that science can resolve clearly and unequivocally from those that can only be addressed indirectly, and it fails to take into account recent advances toward understanding the toxicity of saccharin.

Measurement of small differences in biologic systems is difficult. Biologic end points, particularly such general ones as toxicity or benefit, result from the complex interactions of millions of separate events. Long-term toxic effects commonly occur in only a few of the very many who are exposed and often can be identified only indirectly. For example, assessment of cancer risk often involves testing animals of susceptible strains with very high doses of a substance. After that one draws inferences about the likely effects on human beings exposed at lower doses, relying on several untestable assumptions about extrapolations between species and between high and low doses.

If epidemiologic studies avoid the problems of extrapolation that are part of animal testing, they have their own weaknesses. Human beings generally have not been exposed to the extreme doses possible in animal experiments, and often the doses can only be crudely measured. In addition, the genetic homogeneity, randomization of subjects, and ability to control all other aspects of life that are regular features of animal experimentation are obviously not possible in human observational studies. In other words, the pinpointing of relatively small but potentially important increases in human risk (up to 30 per cent) is practically impossible because of the influence of both known and unknown background factors.

Thus, decisions concerning saccharin and other low-level exposures to potentially hazardous substances can seldom be based on unequivocal scientific evidence. Those who make these decisions must reach beyond the available scientific base to what appears to be most prudent. Opinions on what is prudent are more numerous than opinions on what is good

science; it is this fact, not the quality of the scientific base, that explains much of the seemingly endless controversies over these issues.

The scientific base on saccharin's toxicity has recently been broadened and promises to be improved further in the near future.<sup>2</sup> It is unfortunate that the weakest portion of our scientific base is in the area of potential benefits of saccharin. There is essentially no scientific evidence of any health benefits of saccharin, although many physicians believe that it is important in the management of diabetes, obesity, hypertriglyceridemia, and tooth decay. Potential psychologic benefits are even more difficult to assess, particularly in terms that would allow some comparison with toxic health effects. We can hope that research into these areas will become available soon and will receive the same careful critical review applied to the research on toxicity.

A generation of conflicting laboratory studies raised suspicions of carcinogenicity but were heavily criticized on methodologic grounds. A second generation of better studies, designed to eliminate these concerns, has confirmed the capacity of saccharin itself to initiate cancer, although with less potency than most other carcinogens. In rats saccharin is most effective as an initiator of bladder cancer when the mother is exposed to high doses before pregnancy and the offspring are exposed in utero and throughout their lives. It also appears that high doses of saccharin can markedly promote or enhance the potential of other carcinogens in rats..

Recent advances have also been made in epidemiology. In the past, a number of studies found no association between the use of artificial sweeteners and bladder cancer in human beings, but one study did report a 60 per cent excess risk among male subjects who had used sugar substitutes. Like the laboratory studies, all these studies were heavily criticized on methodologic grounds. Results of two studies whose designs avoided many of these criticisms have been reported recently, one by Morrison and Buring in this issue of the *Journal*, and the other by the National Cancer Institute.<sup>3</sup> The major finding of both studies is that there is no saccharin-induced epidemic of bladder cancer in this country. 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 consumed in the past. There is also general agreement that these studies did not address the carcinogenicity of artificial sweeteners for organs other than the bladder, the effect of very heavy use of artificial sweeteners many decades ago, the effect of heavy use of artificial sweeteners by the young, or the effect of in utero exposure to artificial sweeteners.

Is there any evidence of human carcinogenicity in these two studies? The answer is unclear. In the report from the large NCI study submitted to the Food and Drug Administration, some excess risks were noted among very heavy users (those drinking the

equivalent of more than four dietetic beverages per day). Elevated risks appeared at lower dose levels, and there was more consistent evidence of a dose-response relation in a subgroup whose background risk of bladder cancer was very low (women who had never smoked cigarettes or had a hazardous occupation). Some excess risk was also noted among heavy users of artificial sweeteners who were also heavy cigarette smokers, when their risk was compared with that in heavy smokers who did not use artificial sweeteners. In the study by Morrison and Buring no excess risk was seen in heavy users of artificial sweeteners either in the total study group or among heavy cigarette smokers. However, an excess risk was noted among the small group with a low background risk of bladder cancer (women who had never smoked cigarettes). The findings of these studies can be interpreted as being consistent with the laboratory evidence suggesting that saccharin is a weak carcinogen. On the other hand, the findings can also be interpreted as showing no evidence of carcinogenicity, with the positive associations being dismissed as mere random fluctuations in small subgroups of studies that, overall, show no effect. The correct or more prudent interpretation will probably be a matter for conjecture and debate for some time. Given the inability of our science to address issues of low-level risk directly, it could hardly be otherwise.

Fortunately, this controversy does not have to be resolved for us to make prudent decisions rooted in a now much-improved scientific base. Numerous other editorials have been and will be written about the proper regulatory decisions. There are, however, decisions that individual physicians must face frequently. The diabetic whose perception of the quality of life is markedly improved by the availability of a sweet drink and the middle-aged man whose use of one packet of artificial sweetener per day in his morning coffee is important to his self-image can be assured that the excess risk of bladder cancer from such practices, if present at all, is quite small and little cause for concern. On the other hand, the general patterns of use of artificial sweeteners in this country are troublesome.<sup>2</sup> The heaviest use is by women in the childbearing years. There has also been an increase in use among children, who are receiving much higher doses (per kilogram of body weight) than adults. In addition, although very few people at the age when bladder cancer is likely to occur drink two or more dietetic drinks daily, many young adults drink four or more. When all the evidence of toxicity is weighed against the lack of objective evidence of benefit, any use by nondiabetic children or pregnant women, heavy use by young women of childbearing age, and excessive use by anyone are ill-advised and should be actively discouraged by the medical community.

**REFERENCES**

1. United States Department of Agriculture. Saccharin; under the Food and Drugs Act of June, 1906; before the Secretary of the Treasury, the Secretary of Agriculture, and the Secretary of Commerce and Labor. Washington, D.C.: Government Printing Office, 1911:87, 97.
2. Committee for the Study of Saccharin and Food Safety Policy. Saccharin; technical assessment of risks and benefits (report no. 1). Washington, D.C.: National Academy of Sciences, 1978.
3. Hoover R, Strasser PH, et al. Progress report to the Food and Drug Administration (FDA) from the National Cancer Institute (NCI) concerning the National Bladder Cancer Study. Bethesda, Md.: National Cancer Institute, 1979.