lithium ratio, the two-way analysis of variance was repeated excluding the five relatives with a diagnosis of alcoholism. Significant differences among the mean lithium ratios of the three diagnostic groups remained [$F(2, 29) = 3.89$, $P < .04$)]. The significant differences among groups therefore cannot be attributed to elevations in the lithium ratio in affected relatives with alcoholism.
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Bitter Taste of Saccharin Related to the Genetic Ability to Taste the Bitter Substance 6-*n*-Propylthiouracil

Abstract. *Bitter taste thresholds for* 6-n-*propylthiouracil are bimodally distributed, dividing subjects into tasters and nontasters. Their taste worlds differ with regard to the sweetness of sucrose and saccharin and to the bitterness of saccharin. These differences suggest that nontasters tend to perceive less bitterness in saccharin at concentrations used in beverages.*

Saccharin tastes bitter as well as sweet to many individuals. The data reported here suggest that the intensity of the bitter taste of saccharin is related to the genetically determined ability to taste 6-*n*-propylthiouracil (PROP).

Taste thresholds for the bitter substances PROP, phenylthiocarbamide or phenylthiourea (PTC), and other compounds containing the -N-C=S group show a bimodal distribution (*1*). Family studies have generally concluded that those least sensitive to PROP (nontasters) carry two recessive genes for taste blindness to PROP; the most sensitive (tasters) are either heterozygous or homozygous for the dominant gene (*2*).

In the present study 20 tasters and 20 nontasters of PROP (*3, 4*) scaled the intensities of the sweet, salty, sour, and bitter taste qualities of sodium saccharin, sodium chloride (NaCl), quinine hydrochloride (QHCl), and sucrose (*5*) according to Stevens's (*6*) method of magnitude estimation as modified by Smith and McBurney (*7*). Figure 1 shows the bitterness and sweetness of sodium saccharin. As a means of averaging the magnitude estimates of different subjects, each subject's estimates are expressed relative to that subject's estimate of the intensity of 0.32*M* NaCl (*8*). Saccharin tastes significantly less bitter (relative to 0.32*M* NaCl) to nontasters than to tasters at the two lowest concentrations (*9*). The concentration of sodium saccharin used in many diet beverages is about 0.0010 to 0.0015*M* (*10*). Note that at these concentrations the average bitterness attributed to sodium saccharin by PROP nontasters is one-third to one-half that of PROP tasters.

The distribution of bitter responses in the two groups is of special interest. There is considerable overlap, so that some tasters produce low estimates of the magnitude of the bitterness of saccharin that are similar to those of nontasters. However, one group of tasters gave estimates of the bitterness of the weakest saccharin that were higher than those of any nontaster. One nontaster reported essentially no bitterness at any concentration of saccharin tested. This overlap is much greater than that seen in the bimodal distribution for PROP itself.

Previous work indicated that tasters and nontasters did not differ with regard to sensitivity to saccharin (*11*). However, the thresholds measured were for the sweetness of saccharin, not its bitterness. In general, a molecule could contain the -N-C=S group but fail to show a bimodal threshold distribution if some other features of the molecular configuration produced taste sensations at lower concentrations. In such a case, scaling the perceived intensity of suprathreshold concentrations could reveal differences between tasters and nontasters because the -N-C=S group would add to the perceived intensity at concentrations above its threshold.

Saccharin does not contain the -N-C=S group originally believed to be necessary for the bimodal bitter threshold distribution. Two other compounds without this group, anethole trithione and caffeine, also have bitter tastes related to that of PROP (*12, 13*). Fischer (*4*) and Beets (*14*) suggested that the original -N-C=S structure may be too restrictive. For example, Fischer (*4*) proposed

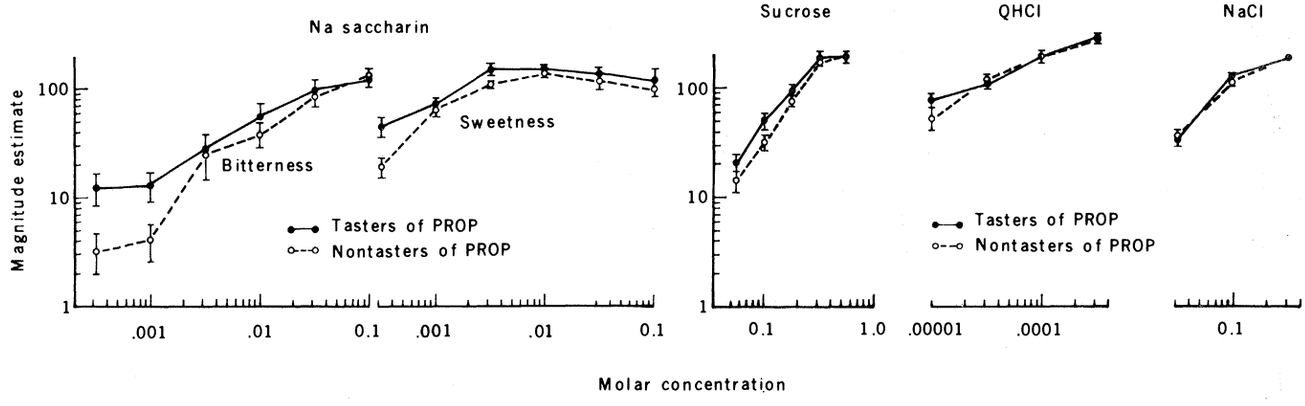

Fig. 1 (left). Magnitude estimates ±1 standard error (S.E.) of the sweetness and bitterness of sodium saccharin for tasters and nontasters of PROP. Fig. 2 (right). Magnitude estimates ±1 S.E. of the sweetness of sucrose, bitterness of QHCl, and saltiness of NaCl for tasters and nontasters of PROP.

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a generalization of this structure that would encompass anethole trithione, caffeine, and saccharin.

Figures 1 and 2 show that differences between tasters and nontasters of PROP were not limited to the bitterness of saccharin. The judgments of sweetness of both saccharin and sucrose show differences similar to those for the bitterness of saccharin and similar to those shown previously for the bitterness of caffeine (*13*): the nontaster functions are lower at the lowest concentrations but have higher slopes and so ultimately reach the taster functions (*15*). These steepened slopes resemble the recruitment of loudness in typical nerve deafness (*16*) and the effects of adaptation in taste (*17*). These differences between tasters and nontasters cannot be explained on the basis of structural similarities to the -N-C=S group. However, they may be related to the nature of subgroups of tasters and nontasters identified by Fischer and Griffin (*18*). Individuals in one subgroup were particularly insensitive to both quinine and PROP, and those in another subgroup were particularly sensitive to both. Sensitive individuals produced lower thresholds for a variety of compounds not chemically related to PROP, including sucrose, NaCl, and quinine sulfate. Extrapolation of the lower portion of the sucrose, saccharin, and possibly QHCl functions in Figs. 1 and 2 suggests lower thresholds for tasters, which would be consistent with the observations of Fischer and Griffin (*18*).

The observation of reduced saccharin bitterness for PROP nontasters is of practical importance. It not only explains some of the variations in hedonic response to saccharin but also suggests that considerable caution should be exercised in the future evaluation of potential nonnutritive sweeteners.

The relation between the bitterness of saccharin and PROP status is also of importance for research with other species because genetically mediated sensitivity to PROP is not limited to human subjects (*1, 19, 20*). For example, some early data suggest that rats may show a bimodally distributed sensitivity to PTC (*20*). Other data suggest that saccharin has a complex taste to rats (that is, bittersweet), as it does to human subjects (*21*). Nachman (*22*) showed that saccharin preference can be inherited in rats. He selectively bred rats that preferred 0.01*M* saccharin to water and those that preferred water to 0.01*M* saccharin. Most saccharin-bred rat pups in the next two generations strongly preferred the saccharin. The water-bred rat pups were more variable; most preferred water but some preferred saccharin. These results are consistent with a relation between the bitter tastes of saccharin and PTC; the rats that were nontasters of PTC (the rats that preferred saccharin) would have been homozygous for nontasting while the rats that were tasters of PTC (the rats that preferred water) would have been heterozygous and so could have produced nontasting offspring. The possibility of variation in the bitterness of saccharin in different rats has important consequences for studies of the hedonic value of saccharin to rats as well as for generalization studies (for example, conditioned aversion) using saccharin as a cue.

The shapes of the psychophysical functions for saccharin suggest a strategy to reduce intake of saccharin. Note that the functions for the sweetness of saccharin are relatively flat for both tasters and nontasters. This means that if the concentration of saccharin in a product were reduced by a particular factor, the perceived sweetness would be reduced by less than that factor (*23*).

The present analysis of saccharin taste suggests a possible strategy for the development of nonnutritive sweeteners that would be palatable to most users. The bitterness of saccharin begins to rise rapidly with concentration at about 0.001*M* sodium saccharin for nontasters. Careful study of how sweetness and bitterness add in mixtures of nonnutritive sweeteners should reveal a way to construct a mixture sweetener by combining several compounds at concentrations below the onset of bitterness.

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References and Notes

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3. Subjects (18 female and 22 male; 18 to 39 years of age) were paid volunteers. Thresholds for PROP were measured by the Harris-Kalmus technique as modified by Fischer (*4*) and met Fischer's criteria for tasters and nontasters. It was decided to use PROP rather than the PTC that was used in earlier studies because PTC has an odor.
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8. Each concentration was presented three times to each subject during a session lasting about 45 minutes. The arithmetic means for each concentration were determined for each subject. A subject's responses were transformed by multiplication by 200 divided by that subject's mean response to 0.32*M* NaCl. This arbitrarily sets each subject's response to 0.32*M* NaCl at 200 and expresses all other responses relative to that value. Such a multiplicative transformation does not change the slopes of individual functions plotted in log-log coordinates (as in Figs. 1 and 2) but merely moves those functions up and down on the ordinate.
9. Analysis of variance and *t*-tests cannot be used to analyze judgments of the bitterness of saccharin because the distribution of responses violates some of the assumptions required by these parametric tests (in particular, distributions for low concentrations were markedly skewed away from normal because of the relatively large number of zero responses found, especially among nontasters). Therefore, bitterness judgments were tested with the Fisher exact probability test [S. Siegel, *Nonparametric Statistics* (McGraw-Hill, New York, 1956)]. To apply this test, taster and nontaster responses at each concentration were classified as greater or less than one-half of the highest bitter response from a taster. Probabilities of obtaining the exact result observed by chance were: for 0.00032*M* sodium saccharin, $P = .01$, and for 0.001*M* sodium saccharin, $P = .05$. For higher concentrations, the *t*-test is valid. No differences between bitter judgments of sodium saccharin from tasters and nontasters are significant at these concentrations.
10. Saccharin concentrations in diet sodas are on the labels. Examples are Diet 7-Up, 0.0010*M*; Diet Pepsi, 0.0015*M*; Tab, 0.0014*M*; and Sugar-Free Dr. Pepper, 0.0012*M*.
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24. I thank R. Fischer, R. S. Shallenberger, I. J. Miller, T. V. Getchell, and M. L. Getchell for helpful advice. A pilot version of this experiment was supported by General Foods Corp. The experiment reported here was supported by PHS grant ES00880.

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