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POSTINGESTIVE MODULATION OF THE SWEETNESS PREFERENCE GRADIENT IN THE RAT[1]

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Preference for a solution of a particular sweetness is increased by its previous association with postingestive effects of 10% glucose or polysaccharide solutions. Sweetness acceptance is decreased by previous association with 25%–50% glucose solutions. Conditioning in these two directions simultaneously by continuous access to a choice of solutions can reverse the usual gradient of preference for the sweeter of two solutions. This reversal is initially facilitated, but after some days attenuated, by a high proportion of carbohydrate in the diet. The reversal extinguishes over a few days without reinforcement. Expression of the relative aversion to the sweeter solution is not dependent on immediately prior carbohydrate ingestion (unlike sickly taste in man). Such conditioned attractions and aversions may assist normal caloric regulation.

Much of the experimental analysis of mechanisms which control nutrient intake has been concerned with separating oral from postingestive factors. For example, it has been shown that rats can learn to regulate nutrient intake purely by intragastric self-administration, although it now seems that some concurrent oral facilitation or rapid gastric filling is generally necessary to enable such learning (Snowdon, 1969). It may one day even prove possible to bypass the gut as well as the mouth and develop adequate feeding by parenteral self-administration, but this will be irrelevant to the question of the role of oral factors (and noninstrumental behavior) in normal feeding. In so far as postingestive factors relate to the normal operation of the feeding control system rather than to its limiting capacities, the fundamental effects of ingested food must be on the acceptability of the sensory qualities of the available nutrients. Thus oral and postingestive effects must be studied in interaction and not merely each in isolation.

Furthermore, those factors affecting feeding which are apparently purely oral may well not simply add to or subtract from postingestive effects but may also be modulated by them. Such modulation of the acceptability of oral qualities might be learned or conditioned via the reinforcing action of associated nutritional effects. On the basis of the negative reinforcing effects he observed glucose and insulin injections to have, Le Magnen (1956, 1959) argued for the existence of such a mechanism in caloric regulation. It has been demonstrated in thiamine deficiency (Garcia, Ervin,

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Yorke, & Koelling, 1967) and during limited amino acid availability (Booth & Simson, 1971). Alternatively, a change in internal state might, without learning, induce changes in preference or in satiating power. An established example is the shift in the sodium–salt preference–aversion function during sodium deficiency (Handal, 1965; Krieckhaus, 1970; Krieckhaus & Wolf, 1968; Young & Chaplin, 1949). There may prove to be another case in the change from pleasantness to unpleasantness which is induced in sweet taste by sugar ingestion in man (Cabanac, Minaire, & Adair, 1968).

By means of such interactions food could be selected, and the size of a meal determined appropriately to nutrient needs, long before the full nutritional value of that meal would be seen in the organism's metabolism. Thus nutrient exchange regulation could be approached more rapidly and hence, on the average, be maintained more precisely.

On the basis of such considerations we were looking for phenomena which involved oral and internal effects in nonadditive interaction. We had begun a study of insulin-induced "glucose appetite" because we had found that a single injection of insulin in the rat failed to alter the preference for a saccharin-adulterated glucose solution (Booth & Brookover, 1968). This had made us wonder whether the changes in glucose intake or preference in human or rodent subjects repeatedly injected with insulin (Jacobs, 1958; Le Magnen, 1953; Mayer-Gross & Walker, 1946; Richter, 1942; Soulairac, 1944) were acquired, rather than being an innate behavioral consequence of hypoglycemia. The suggestion that feeding can become a learned means for avoiding hypoglycemia in the rat, as in man (Marks & Rose, 1965), has recently been advanced by Seigel and Nettleton (1970). To assess the effects of chronic insulin treatment, Jacobs (1958) used long-term presentation of glucose solutions. We repeated one of his experiments with a view to using the paradigm to detect conditioned or learned components of the insulin-induced intakes. Rats on ad-lib food and water were given a continuous choice of 10% and 35% glucose and were injected with either insulin or saline. It was immediately evident that the preference of the saline-injected rats for 35% glucose over 10% glucose was decreasing very markedly over the first few days of choice. We therefore postponed further investigation of the changes which insulin induced in glucose intake until we were able to understand changes occurring even without insulin treatment. Furthermore, we considered that the loss of preference for the more concentrated of two sweet solutions in saline-treated rats was extremely surprising and an indication that there existed some previously unknown or little appreciated mechanism capable of controlling caloric intake.

Initially the rats took a very low proportion of their total glucose intake from the more dilute solution. The proportion taken as 10% increased daily until, after some days, the rats were taking considerably more glucose as dilute solution than as concentrated solution—that is, they were drinking a volume of 10% glucose more than four times the volume of 35% glucose. The preference shift is evident from Jacobs' (1958) report, although not to the extent of the preference reversal we observed. Such an effect had not been reported in previous studies of choice between two concentrations of a sweet solute, although Young and Greene (1953a) mentioned that unexplained anomalies of preference occasionally appeared with repeated presentation of sucrose choices. Valenstein (1967) has since described a reversal of preference from .25% saccharin solution to 3%–10% glucose solution. He offered an explanation in terms of a bitter component in the taste of saccharin. It did not seem that such an account could apply to a choice between two concentrations of glucose or of sucrose, even if it was true of saccharin–glucose choice. The most obvious sort of explanation for the reversal of glucose preferences—and perhaps, then, the observations of Valenstein (1967)—was that the ingested sugar somehow altered the relative acceptability of the two levels of sweetness. We have, therefore, established the existence of a complete reversal of long-term preference (Experiment 1),

characterized some of the primary conditions for its occurrence (Experiments 2–4), and differentiated between various classes of mechanism by which postingestive modulation of the sweetness preference gradient might occur (Experiments 5–18).

General Method

Albino rats with no previous experience of sugar or saccharin solutions were used, being (except as stated) males weighing 300–450 gm. They were given free access in the home cage to water, rock salt, and chow pellets (either Rank's Diet 41B or Spillers' Autoclaved Small Animals Diet). Test solutions were presented on the cage front in inverted polypropylene or glass measuring cylinders (generally 100 ml.) closed by a rubber bung and stainless-steel drinking tube. Solutions were changed and the cylinders cleaned frequently to avoid contamination. The positions of two solutions of a pair were generally reversed once every 24 hr. Volumes remaining were read to the nearest 1 ml.

Anhydrous D-glucose (British Drug Houses) was dissolved in tap water at least 16 hr. before use to allow mutarotation to equilibrium. The maltodextrin MD05 was supplied by Manbré Sugars, London. Saccharin was used as the sodium-salt (British Drug Houses). Concentrations are expressed as grams of solute per 100 ml. of solution (%).

Preference Reversal during Simultaneous Access to 10% and 35% Glucose

Experiments 1 and 2

The first experiment was an attempt to replicate Jacobs' (1958) finding that normal rats tend to lose their initially greater intake of the more concentrated glucose solution when given a continuous choice of two solutions. The second experiment involved alternating presentations of 10% or 35% glucose, to show that the change in relative intake was dependent on simultaneous access.

Method

The general method already given above followed Jacobs' (1958) procedures in using male albino rats with concurrent free access to water, chow, lump salt, and glucose solutions. Computation from Jacobs' graphs indicates an average body weight of 470 gm. So for these first two experiments we used rats that weighed 400–500 gm. at the start of access to glucose. Glucose concentrations were 10% and 35% as in Jacobs' (1958) two-solution experiment, and our Experiment 1 had 18 rats to compare with Jacobs' saline-injected group of 11. Experiment 2 had six rats per alternation schedule, and six rats each on 10% only or 35% only. Two alternation schedules involved continuous access to glucose, the solution being changed every 12 hr. in one case and every 24 hr. in the other. The third alternation schedule involved presenting one solution for 24 hr., none for 24 hr., then the other solution for 24 hr., followed by a 24-hr. break and so on. Half the rats in each group received 10% first.

Results

Experiment 1. The pattern of intake volumes (Figure 1) was virtually identical to that shown by the rats given continuous choice of 10% and 35% glucose by Jacobs (1958), as far as can be determined from his data presentation. His saline-injected

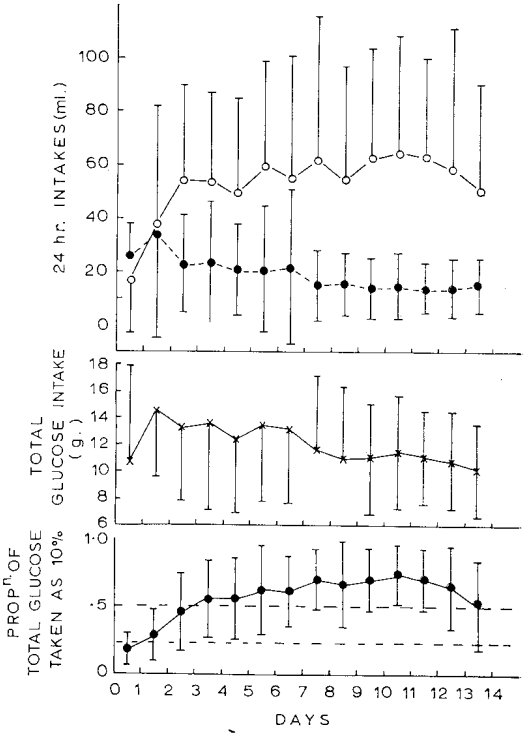

Fig. 1. Daily intakes of 10% and 35% glucose solutions during continuous access ($n = 18$). (The vertical bars on one or both sides of the data points represent standard deviations. Upper graph: mean volume intakes—open circles 10%, filled circle 35% solution; middle graph: mean daily weight of solute taken; bottom graph: the ratio between weight of glucose taken as 10% solution and the total weight of glucose ingested from both solutions.)

group drank a volume of 35% glucose nearly twice that of 10% over the first 12- and 24-hr. periods of choice. Intake volumes were equal for his first 3-day block. In the second 3-day block his rats drank nearly three times as much 10% as 35%, and about twice as much in the third and final 3 days. In our rats the slight drop back of 10% volume did not appear until a few days later.

An individual rat's daily intake in a glucose choice presentation can be represented by the total grams of glucose ingested and the proportion of glucose weight which was taken as the more dilute solution (Figure 1, lower two graphs). Such a pair of measures contains all the information in the raw volume measures and provides a preference ratio of broader application than the simple volume ratio or difference. It can be seen that the average total glucose intake varied over a range of only 45%, initially rising rapidly and then very slowly declining. Yet the proportion of glucose taken dilute increased by a factor of more than 3. This proportion on the fourth and subsequent days of continuous choice was reliably greater than on the first day ($ps < .05$, two-tailed correlated t tests). The proportion was reliably less than .5 on the first 2 days and reliably greater than .5 on the eighth and tenth through twelfth days ($ps < .05$, correlated t).

Figure 1 shows that the variation between individuals in intake of either solution on a given day was large. In this respect the use of albino rats may be unfortunate, as Nachman (1959) has reported that they are highly variable in saccharin preference. However, the variability in intakes and proportions is not merely differences between rats. Especially during the first several days of choice, a majority of rats showed an abrupt change of preference ratio by .3–.6 from 1 day to the next, generally an increase but sometimes a decrease. Oscillation of preference ratio for a given rat over a range of .2–.4 persisted throughout choice. However, in all but 3 of the 18 rats in this experiment, runs of 7 days or more were observed with preference ratios greater than .5 ($ps < .04$; Grant, 1947).

Experiment 2. The pattern of relative intakes was very different when the same two glucose solutions were only presented to a rat one at a time. When each solution in turn was presented for 24 hr. in every 48 hr., or when one solution immediately succeeded the other at 24-hr. or 12-hr. intervals, the proportion of glucose taken as 10% was equal to the proportion seen between separate groups of rats (Figure 2). The proportion was initially equal to or only very slightly less than .5, in contrast to less than .2 initially in two-stimulus tests. It remained constant at this level for the 3–4 wk. of presentation.

Discussion

One of the simplest interpretations of these results is that ingestion of glucose is followed by a reversal of initial preferences and the appearance of a relative aversion to the sweeter solution. Cabanac et al. (1968) reported, after we began this work, an effect in man which encouraged us to take this possibility seriously. They found that intragastric administration of glucose induced with a latency of 20 min. a long-lasting decrease in the pleasantness of samples of sucrose or saccharin solution. The samples began to be rated as neutral and eventually as unpleasant. Thus sugar ingestion, in man at least, is capable of inducing an aversive quality in the taste of sweet solutions. Possibly this aversiveness increases with increasing concentration and hence can also be expressed as a reversal of the normal sweetness preference gradient.

On this basis, we initially hypothesized that glucose remaining from a previous drinking bout, or less probably glucose ingested early in a bout, induced an aversive reaction to strong sweetness in the rat and, hence, selection of the more dilute solution. This might have no more than a marginal effect on relative intakes in long-term single-solution tests, because an increase in bout frequency could compensate for any decrease in bout size induced by aversive reactions to sweetness. The hypothesis implies that pretreatment with glucose might facilitate the preference switch. Also the preference switch itself might be self-limit-

ing if the aversion reaction intensity was dependent on the concentration of glucose in the gut. This concentration would decrease with greater intake of dilute solution or with smaller drinking bouts, and so a continued slow oscillation of preference could be generated. The remaining experiments presented here were carried out in an attempt to define the generality of the preference switch beyond 10% and 35% solutions of glucose and to determine whether the above or some other type of mechanism was involved.

Effect of Varying Concentrations of Glucose Solutions

Experiment 3

We surveyed a range of solution pairs to determine whether the relative or absolute concentrations of 10% and 35% glucose were at all critical in generating the preference reversal.

Method

Groups of six rats were given continuous access to pairs of glucose solutions according to the General Method section, with the ratio of concentrations varying from 1:2 to 1:5, the lower concentrations varying 5%–20% and the higher concentrations varying 20%–50% (Figure 3).

Results and Discussion

Each panel of Figure 3 represents the results for a group of six rats, except for the 10% vs. 35% panel which is taken from Figure 1. It appeared that there might be a threshold level of the average of the two glucose concentrations above which the preference switch was induced and below which a trend toward indifference at most was all that developed. Alternatively, for a given concentration of the more dilute solution, the change in preference to the weaker solution generally occurred more rapidly and went to a greater extreme the higher the strength of the more concentrated solution, even though the initial preference for the more concentrated solution might be expected to have increased along the same dimension. With a constant ratio of concentrations, and hence presumably approximate equivalence in discriminability, doubling the concentration of both solutions intensified the eventual preference for the dilute solution. With a constant 50% solution, doubling the concentration of the weaker solution made no obvious difference to the eventual preference. Thus it seemed possible that the phenomenon was most sensitive to high concentrations of the stronger solution and that it was not particularly sensitive to variations in discriminability, at least down to a concentration ratio of 2.

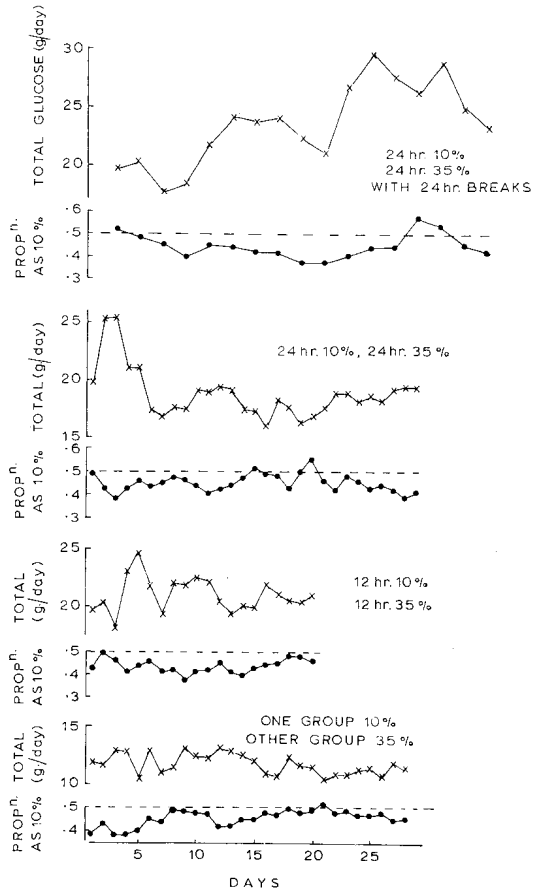

FIG. 2. Mean total glucose intake and proportion of total taken as 10% during single-solution access. (The top three pairs of graphs are each a group of rats receiving 10% and 35% solutions alternately, and the bottom pair of graphs combines data from two groups, one continuously on 10% and the other on 35%.)

The solution pair originally used by Jacobs (1958, 10% and 35%) provided one of the more clear-cut effects. The choice between 10% and 50% also gave a good prefer-

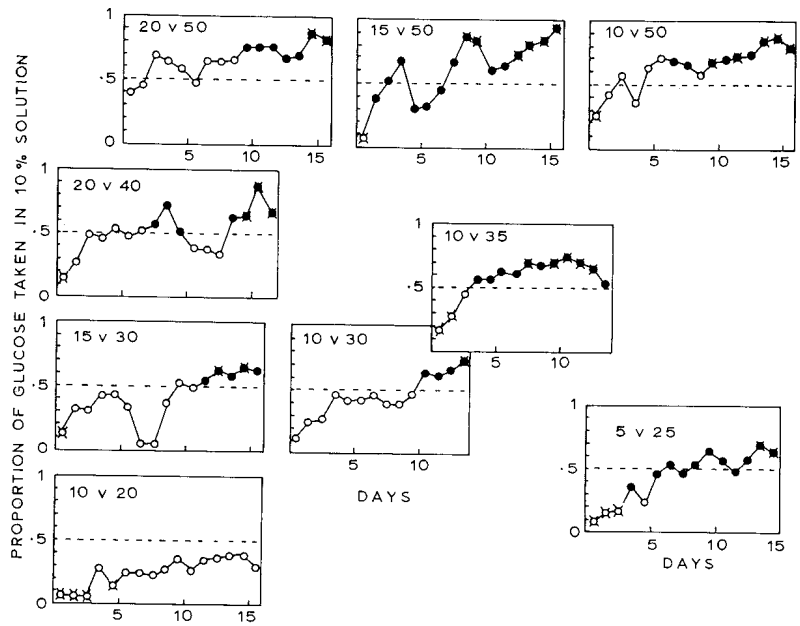

FIG. 3. Preference ratios during continuous access to pairs of glucose solutions for 14–17 days. (Groups of 6 rats, except 10% vs. 35% which is the group of 18 from Figure 1. Solid points: days reliably different from Day 1; open or solid points with superimposed crosses: reliably different from .5; $ps < .05$, two-tailed correlated t tests.)

ence switch and was therefore extensively used in later experiments.

EFFECT OF SEX DIFFERENCES

Experiment 4

Ovarian hormone-dependent sex differences in saccharin preference have been found in the albino rat (Valenstein, Cox, & Kakolewski, 1967a; Valenstein, Kakolewski, & Cox, 1967; Zucker, 1969). Female rats might be expected to take longer than males to switch to dilute glucose, simply because they preferred concentrated glucose initially to a greater extent. However, there might in addition be sex differences in susceptibility to the factors reversing preference: Valenstein, Kakolewski, and Cox (1967) found that, although males shifted from saccharin to 3% glucose in a few days, females never did.

Method

Four groups of nine rats were presented with continuous choice of 10% and either 35% or 50% glucose for about 1 mo. according to the General Method section. The two groups of female albino rats ranged 270–330 gm. in body weight.

Results and Discussion

Males showed a faster reversal on 10% vs. 50% than on 10% vs. 35% (Figure 4). The initial preferences of the female rats were slightly more extreme and the shift in preference was much slower, not even going beyond indifference within 1 mo. on a choice of 10% and 35% glucose. It seemed likely, therefore, that the preference-modulating mechanism was less effective in females and so we have mostly confined our attention to the male.

EFFECTS OF PRIOR ACCESS TO CARBOHYDRATE SOLUTION

Experiment 5

If, as we had initially hypothesized, a greater preference for the more concentrated glucose solution was directly reversed by some change in internal state induced by glucose ingestion, then one concentration of glucose might be better than

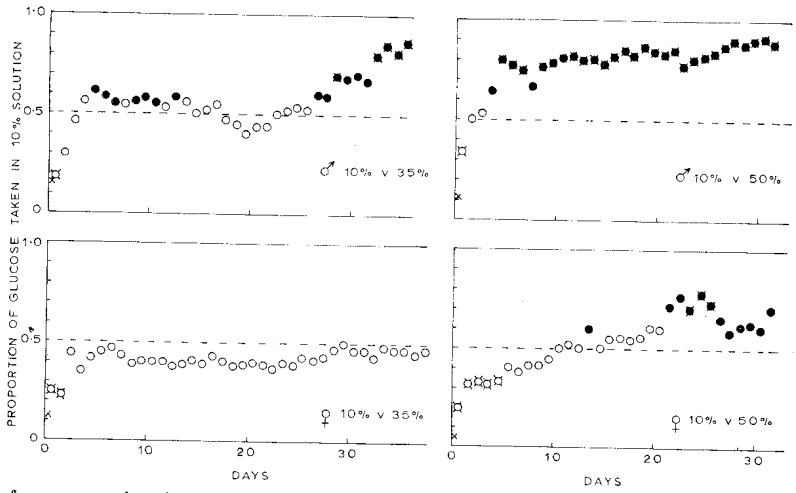

FIG. 4. Preference ratios for groups (ns = 9) of male or female rats on continuous choice between 10% and either 35% or 50% glucose. (Cross near origin: preference over first 2 hr. of access; solid points: reliably different from Day 1; crossed points: reliably different from .5; $ps < .05$.)

another at inducing the behavioral adaptation. That is, prior access to one concentration might induce a faster preference shift than prior access to the other concentration, and alternate access to the two concentrations could produce an intermediate effect. If, on the other hand, conditioning or learning were involved, possibly prior access to glucose at either concentration would facilitate the preference shift when choice was given, by positive transfer of acquired stimulus control. Furthermore, access to each concentration in turn before giving the choice might facilitate the shift more than prior access to either concentration alone.

Method

Groups of eight rats had access to one solution at a time for 9–10 days before being presented with ad-lib choice. One group had 10% glucose for 9 days, another 35%, and a third group had each solution on alternate days for 10 days. A fourth group had no pretreatment.

Results

There were no obvious differences among the groups in total glucose intake, either during single-stimulus access or during choice (Figure 5, top). Yet prior access to 35% glucose, either alone or alternately with 10%, completely eliminated any preference shift. Pretreatment with 10% solution prevented preference from shifting away from the concentrated solution further than to indifference level. Thus pretreatment with glucose inhibited preference change, rather than facilitating it as predicted.

Discussion

While puzzling over how the results could contradict predictions based on both adaptation and conditioning hypotheses, we came to paying fuller attention to a feature of Experiments 1 and 3. There was a fairly consistent tendency for the initial switch to preference for the dilute solution to begin to lapse somewhere between 5 and 20 days after choice began. It often relapsed to indifference, although there developed again after some days a definite preference for glucose from the dilute solution. One explanation for this temporary lapse could be that, under certain conditions, effects of prolonged glucose intake interfered with the state in which adaptation occurred or with the reinforcement process maintaining an acquired response. Indeed state dependency, either of the reactions to sweetness or of the strength of the reinforcement modulating the preferences under test, could produce a protracted slow oscillation of preference. This might explain why Jacobs' (1958)

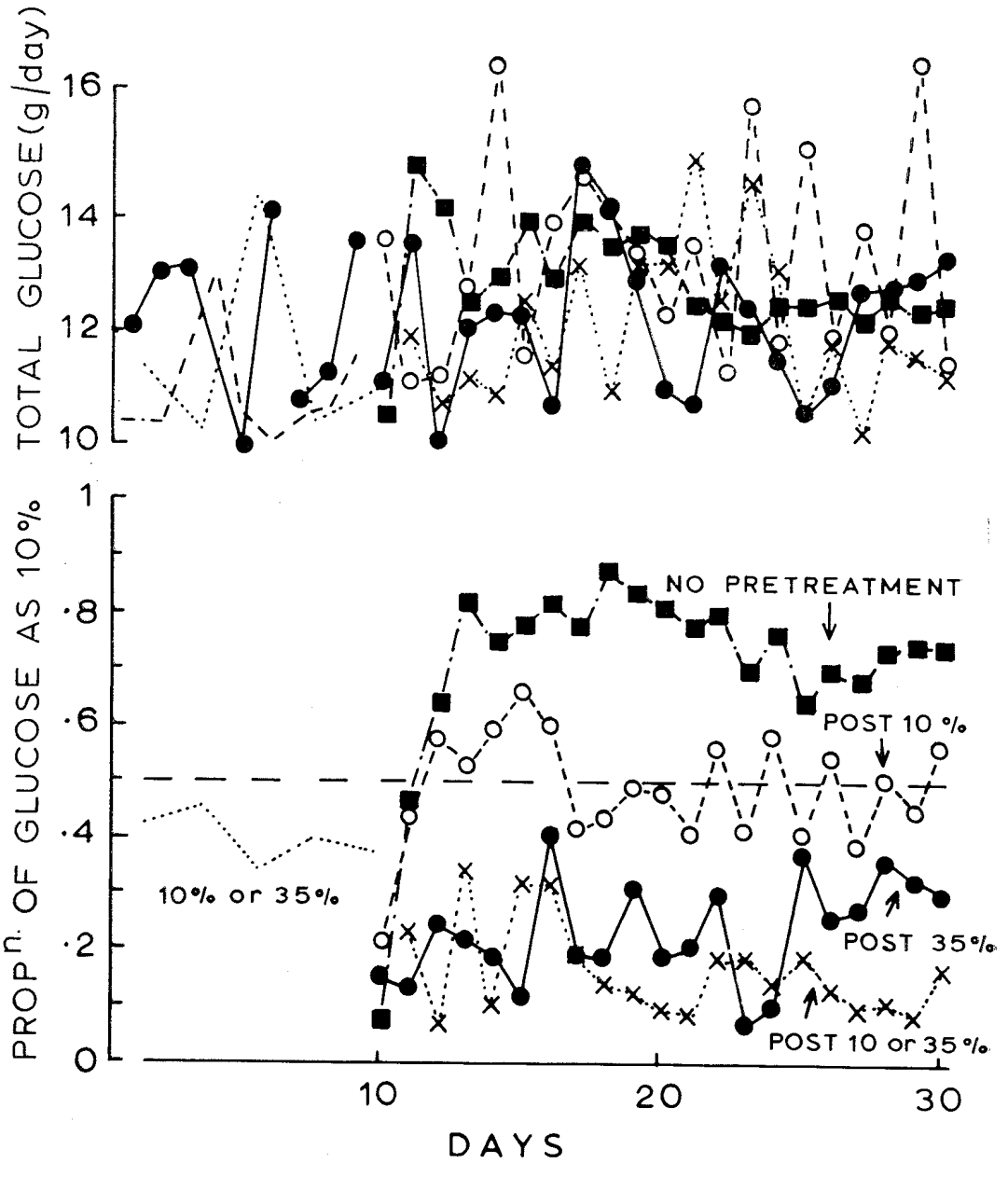

FIG. 5. Total glucose intake and preference ratio with prior access to single solutions. (Solid line and solid circles: prior access to 35%; dashes and open circles: prior access to 10%; dotted line and crosses: prior access to 10% and 35% alternately; solid squares: no prior access to glucose. Standard deviations of preference ratio lay in the range .3–.5.)

data, which was averaged over 3-day periods, and covered 9 days from the start of continuous choice, failed to show a period in which preference moved through indifference to greater intake of glucose as dilute solution, unlike the results of our Experiment 1 which was averaged over 24-hr. periods.

Authors' Note

Experiments 6 to 14 were pursuing the proposal by Cabanac (1970-1) of an innate carbohydrate-specific activation of the preference for sweetness (misnamed "alli-aesthesia" — no sensation changes, only the effect on ingestion). There was no support for such a mechanism and so this paper returned to the initial hypothesis of learnt aversion to the stronger sweetness, and Experiments 15-18 confirm the associative conditioning also of a preference for the weaker sweetness if it is paired with postingestional effects of glucosaccharides (since investigated in depth by Sclafani & colleagues).

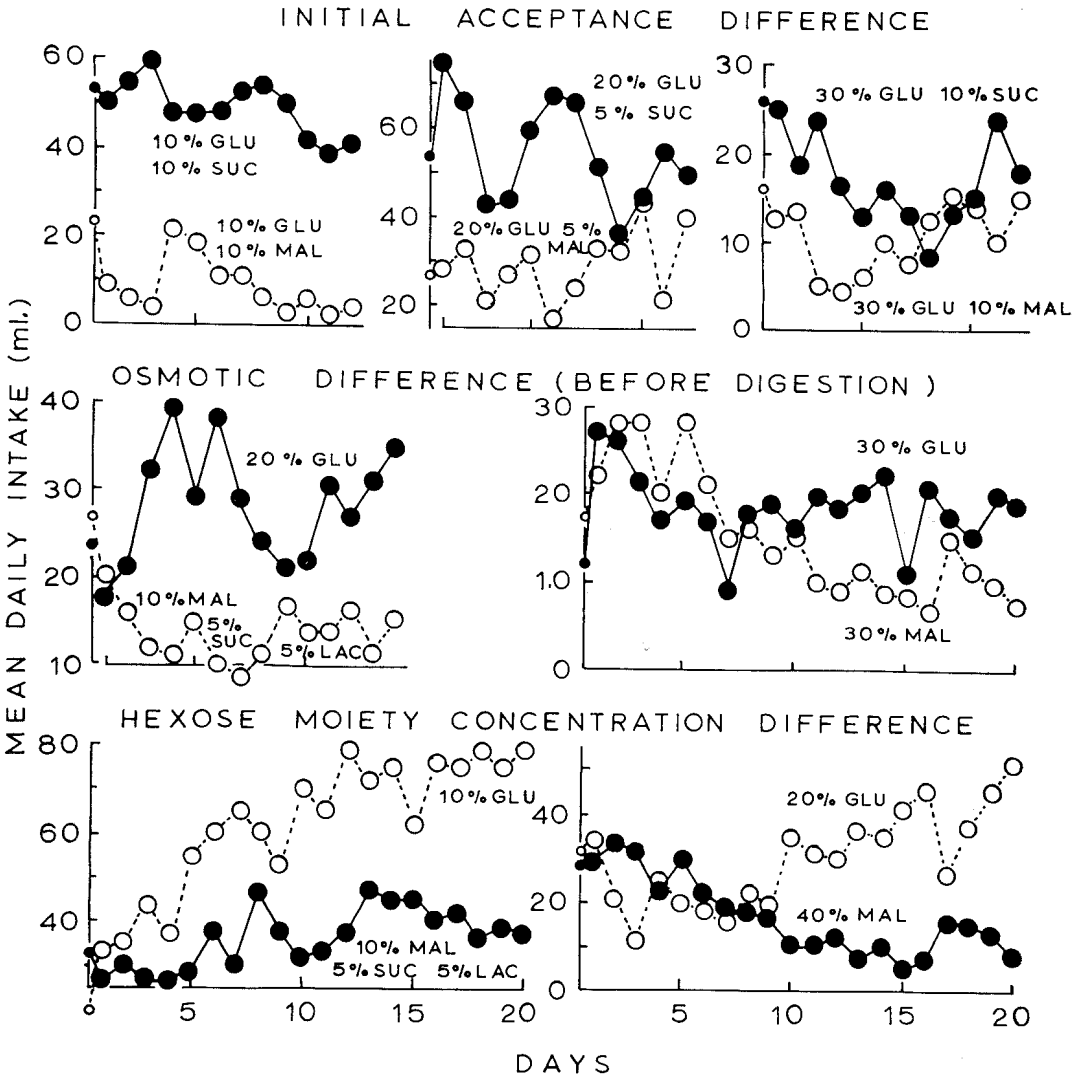

FIG. 11. Daily intake volumes on continuous choice. (Data points on the ordinates represent volume intakes over the first 6 hr. of choice. The open symbols represent the solution for which a preference should have appeared if the difference between that pair of solutions was the main factor producing preference reversal during continuous choice between pure glucose solutions. Abbreviated: GLU—glucose; SUC—sucrose; MAL—maltose; LAC—lactose.)

that a preference appeared when there had been none initially (because we had eliminated marked sweetness differences) suggested that the phenomenon should not be attributed to an unconditioned reversal of the usual sweetness preference under these conditions, but rather to a change in reactions to initially equally preferred cues, acquired by association with differential reinforcement.

Effects of Normal or Reversed Association of Carbohydrate Concentration with Degree of Sweetness

Experiment 15

With the results gained thus far, we were encouraged to perform direct tests of the hypothesis that the preference switch was based on postingestive reinforcement of

TABLE 4

REINFORCEMENT OF SWEETNESS PREFERENCE SHIFT BY INTUBATED CARBOHYDRATE SOLUTIONS

Group	Solution stomach tubed (% glucose)		Ratio of .02% intake volume to total saccharin volume in brief preference tests		
	After .07% saccharin	After .02% saccharin	Screening test	After pretreatment	After conditioning
1	5	50	.362 ± .237	.285 ± .131	.165 ± .061**
2	50	5	.330 ± .172	.247 ± .103	.313 ± .129*
3	27.5	27.5	.444 ± .244	.286 ± .136	.240 ± .043
p between groups			>.1	>.1	<.02[a]

Note.—n = 12 per group.

[a] Group 1 differs from both Groups 2 and 3 according to t tests ($ps < .05$).

* $p < .05$ by correlated t test, for difference from the same group's preference immediately after pretreatment (before conditioning).

** $p < .01$ by correlated t test, for difference from the same group's preference immediately after pretreatment (before conditioning).

changes in acceptability of the particular level of sweetness experienced close in time to generation of the reinforcement. If this hypothesis were true, it should be possible both to diminish the usual sweetness preference gradient in one group and, with reversed cue-reinforcement contingencies in another group, to steepen it. As sweetness cues, we used moderate concentrations of saccharin at a ratio of 3.5, to mimic the sweetness differential between 10% and 35% glucose solutions. The differential reinforcement was intragastrically administered as dilute or concentrated glucose.

Method

Rats were screened on a 1-hr. choice between .07% and .02% sodium-saccharin solutions and distributed into three groups of 12 of approximately equal mean preference ratios. They were allowed 30% maltodextrin to drink overnight and were then rescreened for brief saccharin preference. This may have accentuated slightly, perhaps because of improved discrimination (Table 4). They were then given 30-min. periods of access to each of the saccharin solutions in turn according to CDDC or DCCD (C = concentrated, D = dilute) sequences. A sequence of four access periods 2 hr. apart was given each day for 4 days. Immediately following each access, a volume of glucose equal to the volume of saccharin drunk spontaneously was gastrically intubated. One group received 50% glucose after the dilute saccharin and 5% glucose after the more concentrated saccharin: This was expected to accentuate the initial preference. Another group received the reverse contingency and the third group was given 27.5% glucose after both saccharin solutions, to control for adaptation effects.

Results and Discussion

The control group showed no effect of tubing. The differentially reinforced groups changed preferences in the expected opposite directions (Table 4). The preference changes were small compared with what is observed on continuous choice of glucose solutions, but it is obvious that our formal conditioning paradigm could have been suboptimal in a variety of ways. The result was definite evidence for conditioning of a sort that would explain the phenomenon under examination. There was no evidence for a contribution of adaptation to the preference shift per se.

Experiments 16–18

At about this time we located a source of supply for maltodextrins. These are mixtures of glucose, maltose, gluco-oligosaccharides, and water-soluble dextrins (polysaccharides of D-glucose, related to starch). We chose the maltodextrin (MD05) lowest in glucose and maltose content (5% of each), and thus the least sweet. By mixing MD05 and sodium saccharin in various proportions, we were able to prepare solutions which were fairly similar in initial relative acceptability during brief choice tests, but differed widely in carbohydrate concentra-

tion. We chose to use 3% MD05 as a basal carbohydrate level, to mask any bitterness or aversive aftertaste of concentrated saccharin when it was used (Valenstein, Cox, & Kakolewski, 1967b). We compared this with 10% MD05 in one group of rats and with 50% MD05 in another. In this way we hoped to determine whether the preference switch originally observed between 10% and 35% or 50% glucose solutions was attributable to acquired preference reinforced by dilute carbohydrate or acquired aversion reinforced by concentrated carbohydrate. The result with 50% MD05 was unexpected and so finally we compared 3% glucose and 50% glucose.

Method

In pilot brief-access tests of relative preferences among pairs of solutions of MD05 and saccharin, there appeared to be even greater lack of additivity between MD05 acceptance and saccharin acceptance in mixtures of the two than between sucrose or glucose and saccharin in their mixtures (Valenstein et al., 1967b; Young & Madsen, 1963). We needed to avoid extremes of preference within any pair of solutions so that there was adequate opportunity for each solution pair to show a preference shift in either direction. In Experiment 16, comparing 3% with 10% MD05, we compromised on solution pairs containing .1% and .25% sodium saccharin. One group of rats had a choice between a mixture of higher MD05 and higher saccharin concentrations and a mixture of the lower concentrations. Another group had a choice of the reverse associations of carbohydrate and saccharin concentrations. A third group had 6.5% MD05 in both solutions. The first access to the solution pair was a 30-min. two-stimulus pretest. After a 2-day interval, 5 days of continuous choice were given, recording intake after the first 2 hr. and at 24-hr. intervals. Finally, a 30-min. posttest was given 24 hr. after ending continuous choice. Three replications were run with three rats per solution pair in each group.

Experiment 17 tested the effect of 50% MD05 relative to 3%. Each solution pair was a mixture of .25% sodium saccharin and MD05 alongside simply MD05, the saccharin paired with 50% MD05 in one group and with 3% MD05 in another. A third group had 26.5% MD05 in both solutions. Continuous choice was given for 10 days, recording the initial 2-hr. intakes and the daily intakes. Two replications of four rats per group were run.

Experiment 18 compared 50% glucose with 3% glucose, with .25% sodium saccharin in one concentration of glucose in one group and in the other in a second group. A third group had 26.5% glucose in both solutions and .25% sodium saccharin in one. Two 30-min. choice tests were made on successive days and then, after a 2-day interval, continuous choice was presented for 4 days. A final 30-min. choice was given 24 hr. after the end of continuous choice. Two replications were performed, one with three rats per group and one with four.

Results

The replications within each of the three experiments gave similar results in each experiment and so the data were combined.

Experiment 16. Figure 12 shows that the proportion of the total solution volume drunk as the more dilute saccharin solution changed toward greater intake of the mixture containing 10% MD05, with whichever saccharin concentration it was mixed. No change in preference occurred in the control group having 6.5% MD05 in both solutions. Fractional intake of the dilute saccharin was reliably greater than the control group on Days 3, 4, and 5 when saccharin was mixed with 10% MD05 and was reliably less than control on Day 5 with 10% MD05 mixed with the more concentrated saccharin ($ps < .02$). The two experimental groups also reliably differed in the brief-access posttests ($p < .05$).

Experiment 17. The intake pattern was confused when 50% MD05 was given, with or without saccharin, alongside 3% MD05, without or with saccharin (Figure 13). There was no definite tendency for 50% MD05 to make the saccharin-containing solution become less preferred. A prolonged choice of plain 50% MD05 and .25% saccharin mixed with 3% MD05, far from increasing the initial marked preference for the saccharin, actually decreased it rapidly, although only to the indifference point. The preference in the control group changed, initially toward a complete preference for the saccharin-containing solution, although later perhaps returning toward indifference.

Experiment 18. When the carbohydrate in 50% solution was glucose, however, a simpler systematic pattern emerged (Figure 14). The concentrated glucose induced an increasing aversion to the solution containing it, whether that was adulterated with saccharin or presented alongside the saccharin-containing solution. No reliable changes in preference occurred in the solution pair with 26.5% glucose in both solu-

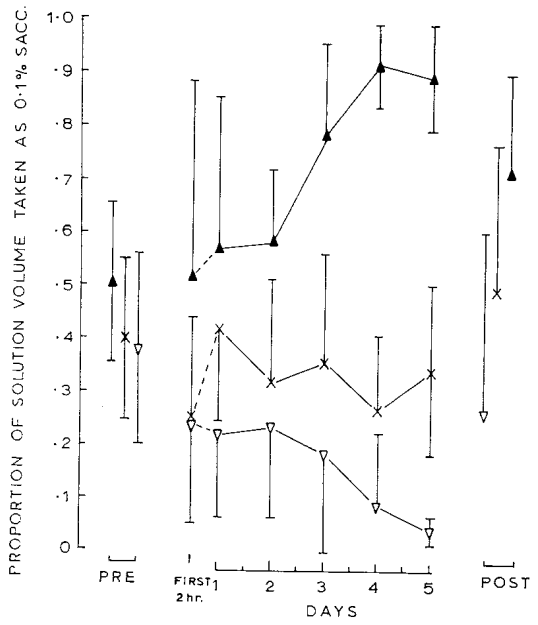

FIG. 12. Preference ratios on continuous choice between solutions containing 10% polysaccharide and 3%. (Pretests and posttests: 30-min. choice. Solid triangles: .1% saccharin + 10% MD05 vs. .25% saccharin + 3% MD05 [preference ratio rises if 10% positively reinforcing]; open inverted triangles: .1% saccharin + 3% MD05 vs. .25% saccharin + 10% MD05 [preference ratio falls if 10% positively reinforcing]; crosses: .1% saccharin + 6.5% MD05 vs. .25% saccharin + 6.5% MD05 [control]. Vertical bars represents standard deviations [group $ns = 9$].)

tions. The preference ratio for this control group was never different from .5, except with marginal reliability in the second pretest ($p = .05$). On Day 3 of continuous choice, the preference ratio was reliably greater than on the first day or in the second pretest, for the group with saccharin and concentrated glucose mixed. The preference ratio was lower than in the pretests on Days 2, 3, and 4 of continuous choice when the saccharin solution was the alternative to plain 50% glucose ($ps < .02$). The difference between these two experimental groups in pretest preference ratio was in the opposite direction to the difference in the posttest ($p < .05$).

Discussion

It appears that inclusion of 10% MD05 in a solution causes the development of an acquired preference for that solution, whether or not it was initially the preferred solution. Valenstein (1967) found that rats switched from taking .25% saccharin to taking glucose, with increasing rapidity from 3% through 6% to 10% glucose. We have also found that preference switches to 10% glucose, and also 5% and perhaps 15% and 20% glucose (Figure 3), when a choice is given between them and more concentrated glucose. Thus glucose in free or combined form, when taken at concentration of 10% ± 5%, seems to be able to reinforce the acquisition of increased preference for the oral cues which it provides itself or with which it is paired.

On the other hand, 50% glucose and possibly concentrations down to 30% or 25% (Figure 3) provide reinforcement of acquisition of a decrease in preference relative to the same 3% carbohydrate against which 10% can provide positive reinforcement. Thus oral cues provided by concentrated glucose, or material with which it is mixed or contiguously presented, acquire aversiveness. However, unlike the acquired attractiveness, this aversiveness is not introduced

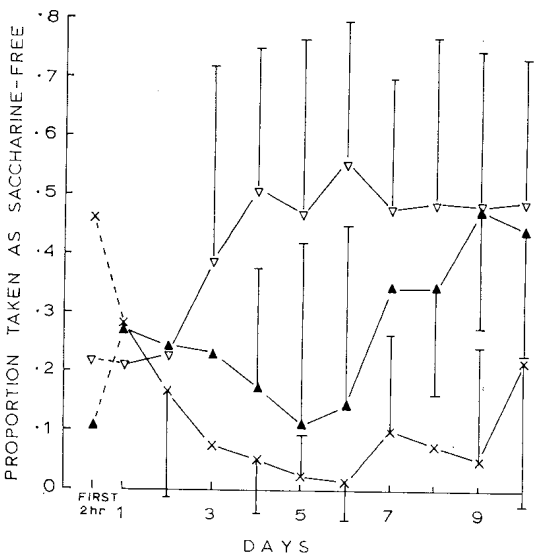

FIG. 13. Preference ratios on choice between 50% and 3% MD05. (Solid triangles: 3% MD05 vs. .25% saccharin + 50% MD05 [rise expected if 50% negatively reinforcing]; open inverted triangles: 50% MD05 vs. saccharin + 3% MD05 [fall expected if 50% negatively reinforcing]; crosses: 26.5% MD05 vs. .25% saccharin + 26.5% MD05 [control]. Vertical bars represent standard deviations [group $ns = 8$].)

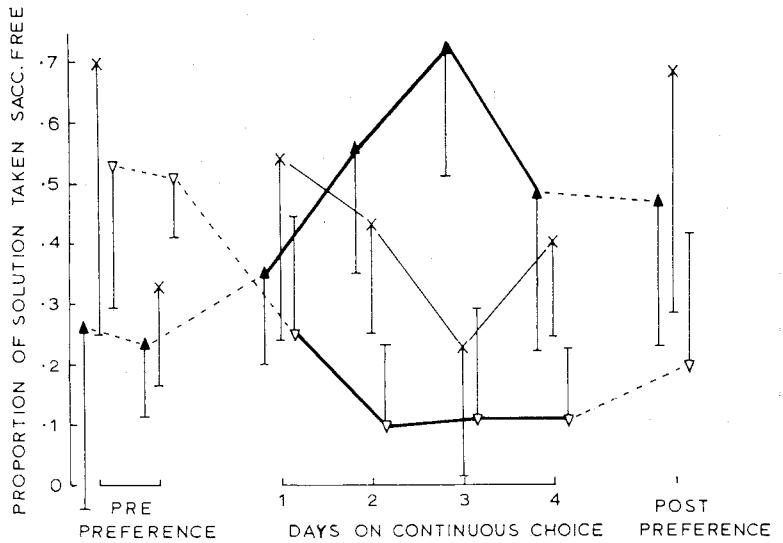

FIG. 14. Preference ratios on choice between 50% and 3% glucose. (Solid triangles: 3% glucose vs. .25% saccharin + 50% glucose [rise expected if 50% negatively reinforcing]; open inverted triangles: 50% glucose vs. .25% saccharin + 3% glucose [fall expected if 50% negatively reinforcing]; crosses: 26.5% glucose vs. .25% saccharin + 26.5% glucose [control]. Vertical bars represent standard deviations [group *ns* = 7].)

by glucose in polysaccharide form. Indeed, in Experiment 17 a mixture of dextropolysaccharide, maltose, and glucose seemed to provide some positive reinforcement at a 50% carbohydrate concentration; however, this might have arisen from the fact that 50% MD05 is actually 2.5% glucose which could be the source of positive reinforcement.

These results exclude all explanations of the preference reversal solely in terms of sensory receptor or central adaptation. The direction of preference change is determined by the carbohydrate content of the solution, independently of the contribution of that carbohydrate to oral stimulation or sensation. The behavior changes under the control of whatever level of sweetness the experimenter chooses, and it changes in a direction determined by the experimenter-imposed postingestive contingencies—that is, the reversal of sweetness preference gradient is truly a form of conditioning or learning.

General Discussion

From our impression of the literature on sweet fluid intakes in the rat, a rejection of concentrated glucose in favor of dilute glucose on continuous choice between two concentrations seemed completely anomalous. Previous results with glucose, sucrose, and saccharin intakes were interpretable in terms of addition between (*a*) an oral factor (closely related to sweetness in man) which facilitates initial acceptance (choice) and its maintenance (initial rate of drinking) and increases monotonically with concentration, in the case of sucrose at least, and (*b*) a postingestive factor or set of factors which inhibits acceptance (satiates) and becomes more intense with increasing hypertonicity (McCleary, 1953; Shuford, 1959). Thus, intakes on prolonged access (1 hr. or more) to a single solution of glucose (with water also available) are well known to show a maximum in volume terms or to approach an asymptote in solute weight terms at around 10% (Jacobs, 1962; Richter & Campbell, 1940; Young & Chaplin, 1949) which is thought to be a compromise between these two factors. The consistent tendency for the proportion of glucose taken as 10% rather than 35% to remain below .5 in the single-stimulus tests of Experiment 2 is presumably the reflection of a

marginal failure by postingestive regulation to overpower the effect of increasing sweetness. Very brief access to a single solution reveals a general increase of initial acceptance with rising concentration, uncontaminated by interference from postingestive effects (Young & Greene, 1953a, 1953b; Young & Madsen, 1963). Greater intake of the more concentrated solution in two-solution tests has been widely demonstrated for both brief (down to a few seconds) and prolonged (up to several days) access to sucrose or saccharin solutions (Collier & Bolles, 1968; Collier & Novell, 1968; Young & Greene, 1953a, 1953b). As Young and Greene (1953a) argue, one should expect prolonged choice to be as good as very brief choice tests as an indicator of relative acceptability uncontaminated by postingestive effects. This is because, if the rat samples both solutions adequately, it should generally spend most of a drinking bout taking the solution preferred by initial choice. So, even if a high concentration is rapidly satiating, the lower concentration should be consistently almost entirely rejected at successive bouts and thus its cumulative intake should be much lower than the preferred concentration.

The reversal in relative intakes in long-term two-stimulus tests should, according to this account, be interpreted as a switch in relative initial acceptability, i.e., a preference reversal. However, the account does not provide for nonadditive interactions such as a direct postingestive effect on preference gradient, or learning induced by repeated correlations of taste with postingestive effect. It appeared that less work had been done with long-term two-stimulus tests on glucose than on sucrose or saccharin and so the inadequacy of the above general account in the face of the present data could have reflected a preference-reversal phenomenon that was peculiar to glucose. In fact, the present results indicate that this is the case for the contribution to the preference reversal from the concentrated glucose solution. However, it is not the case for another factor in the reversal, which arises equally for glucose and for polysaccharide. However, a closer look at some of the reports on sucrose preference indicates that the picture might not be so simple as at first sight even for this disaccharide. Young and Greene (1953a) mention that a group of 10 naive rats given 1-hr. choice between 9% and 35% sucrose on 4 successive days showed "several unexplained reversals of preference on the last test [p. 292]." Young and Madsen (1963, Footnote 3) say that "attitudes of acceptance or rejection vary with repetition of a choice so that we are actually dealing with a stochastic process [p. 904]." Furthermore, when rats are given a prolonged choice between sucrose and saccharin solutions, even 2% sucrose is preferred to, and is a greater facilitator of preference than, any concentration of saccharin (Collier & Novell, 1968; Young & Madsen, 1963), despite the much greater sweetness of most of the saccharin solutions to human taste. Valenstein (1967) found in the rat that .25% saccharin is initially preferred to dilute glucose, but within a day or so of continuous access glucose becomes preferred. The present results show that ingestion of glucose (and other carbohydrates, including perhaps sucrose) can under certain conditions induce a preference for the less sweet of a pair of solutions. This effect may be the basis for all the above preferences for dilute carbohydrates.

We systematically varied many factors which might be expected to affect the sweetness preference and to illuminate the mechanism by which the usual preference gradient was flattened and even reversed. We found that the preference shift was not critically dependent on sex differences, food-deprivation schedule, the glucose concentrations used over a wide range, nor on there being an initial difference in preference or in osmotic pressure in the mouth or stomach. It was strongly affected by recent days of high carbohydrate intake, but was not induced simply by the presence of glucose in the gut. Thus we failed to obtain evidence for one of the two main types of mechanisms, for the preference shift which we considered—namely, an innately or experientially programmed sweet-specific preference shift triggered by high carbohydrate intake. On the other hand we obtained indi-

rect and direct evidence in support of a role for acquired changes in preference by association of the available oral cues with differences in postingestional effects between carbohydrate solutions. This case is therefore in contrast to phenomena such as sensory adaptation, or the changes in sodium preference induced by sodium dificiency, which are apparently innately determined (Handal, 1965), although learning is necessary to their expression in the absence of sodium salts (Krieckhaus, 1970). If the present results bear on the concept of "glucose appetite," they indicate that this is unlikely to be simply an innate increase or decrease in sweetness preference according to carbohydrate need.

Experiments 16–18 demonstrated that two types of association were being acquired in the preference shift from concentrated to dilute glucose solution. Some postingestive effect of dilute carbohydrate solution (monosaccharide or polysaccharide) was providing positive reinforcement of acceptance of the associated taste. Some postingestive effect of the concentrated glucose (but not polysaccharide) was negatively reinforcing preference for the associated taste. In neither case have we distinguished between acquisition of conditioned reactions (i.e., acquired attractiveness or unpleasantness of the taste) and learned acts (i.e., selection or avoidance of a fluid having a given taste, to meet the desire for, or fear of, some particular postingestive consequence).

Glucose-Induced Toxiphobia

Acquired rejection of materials discriminable by the chemical senses which has been induced by internally generated reinforcement events, of which there are now many examples, has been called *toxiphobia* (Garcia & Ervin, 1968). We regard this as a suitable term to apply to all cases of rejection acquired by pairing with presumably deleterious effects, without necessarily implying that the reinforcer is poisonous or even distressing in any way to the organism, although there is behavioral disruption in the cases of X-rays, organophosphorus poisons, and vitamin deficiency at least. Thus we do not suppose that the concentrated glucose establishes aversion necessarily by generating intestinal distress (Snowdon, 1970): In the normal rat, increasing glucose concentrations inhibit gastric clearance (Reynell & Spray, 1956). Rather, something like extreme hyperglycemia, which produces no obvious subjective symptoms in man, may generate events in tissues such as the brain or the liver which trigger a selective reduction of the acceptability of recently experienced oral cues (negative reinforcement).

Toxiphobia reinforced by effects of orally administered concentrated glucose has been observed before. Le Magnen (1959, 1969) has found that intubation of 30% glucose immediately after an odorized meal, if repeated sufficiently often, can establish a diminished preference for food of that odor. One of the criteria we have taken to establish that our results involve conditioning rather than innately determined reaction change is that preferences can be shifted against or with the original sweetness preference. These results of Le Magnen show that such conditionability is not confined to the sweetness dimension or taste modality, but extends to arbitrary odor cues.

Some indication that a glucose-generated toxiphobic reinforcement even can be postabsorptive is provided by a result of Adair, Miller, and Booth (1968). They found that continuous intravenous infusion of 30% glucose solution for 3 days at a steady rate of 27 ml/day reversed rats' preference for drinking 30% glucose rather than a solution of all the noncarbohydrate components of a complete diet. This reversal was extinguished over 3 days of subsequent saline infusion. The toxiphobic reinforcement provided by orally administered concentrated glucose is apparently also provided by intraperitoneal or subcutaneous injection in rats and dogs (Le Magnen, 1959; Russek, Rodriguez-Zendejas, & Pina, 1968), further supporting the notion of a postabsorptive action.

High concentrations of free glucose are not found in nature. High polysaccharide concentrations do not generate toxiphobic reinforcement, according to our present re-

sults. It is, therefore, difficult to believe that this conditioned reduction in food preferences plays a general role in caloric regulation of food intake. However, the mono- and disaccharides fructose and sucrose, which are sweeter than glucose to man (Moncrieff, 1967) and are preferred to glucose in the rat (Richter & Campbell, 1940), can reach high concentrations in parts of certain plants. The present findings on conditioned aversion to sugars and saccharin are more likely to contribute to an increased scientific understanding of the behavioral phenomena covered by the traditional concept of sweetness.

"Sweet" is used to refer to a sensory quality that sucrose, fructose, and glucose and moderate concentrations of saccharin and cyclamate have in common for man and that is discriminable from quinine, hydrochloric acid, and well-above-threshold sodium chloride, for example. However, sweet has also connoted the usual attractiveness of the sweet taste. Now this, and metaphorically other pleasant experiences, may fade away with repetition under certain conditions, even though the discriminable element remains. In words written by an eminent seventeenth century psychologist:

> Enough! no more:
> 'Tis not so sweet now as it was before.
>
> —SHAKESPEARE, *Twelfth Night*

Furthermore, it has long been recognized that the sweet taste can be not just neutral but strongly aversive:

> They surfeited with honey and began
> To loathe the taste of sweetness, whereof a little
> More than a little is by much too much.
>
> —SHAKESPEARE, *Henry IV*

The conditions for loathesome sweetness have not been fully established experimentally. We have here characterized a conditioning mechanism in the rat by which sugar and saccharin solutions can become aversive, according to two-stimulus preference tests. Basically the same reaction to sweetness may be reported as unpleasantness in the sweet taste in man (Cabanac et al., 1968). Cabanac and Duclaux (1970a, 1970b) apparently take it for granted that the movement from pleasant to neutral or slightly unpleasant induced by glucose intubation is identical with normal satiety. It is not possible to tell from investigations in adult man whether sugar-induced aversion to sweetness is acquired or appears independently of associative experience. In any case, satiety also is a conditioned reaction sometimes (Booth, 1972b), even though there are unconditioned satiety reactions too. However, aside from the role of conditioning, an issue which must not be ignored is whether the movement of sweetness acceptance (among other acceptances) to zero in the establishment of normal satiety is indeed continuous with, rather than orthogonal to, its movement to aversiveness after excessive intake of sugary food. The identity of satiety, in a general sense, with incipent sickliness of sweet tastes remains to be demonstrated, in man or rat. In the rat there is merely evidence that both satiety and reduced preference can be conditioned with concentrated carbohydrate as reinforcement (Booth, 1972b; Le Magnen, 1955, 1959). However, the two phenomena appear to be dissociable: Aversion is reinforced by concentrated free glucose and not by polymerized glucose (suggesting an osmotic mechanism), whereas oral satiety is reinforced by polysaccharide.

Carbohydrate-Induced Trophophilia

Dilute carbohydrate solution, whether monosaccharide or largely polysaccharide, induces an increased preference for the particular taste of that solution. We propose that acquired behavior of this type be called trophophilia (Gk. τροφη, nourishment). As far as we are aware, only three other examples of trophophilia have thus far been formally demonstrated: (*a*) increased preference for a diet which is associated with the amelioration of thiamine deficiency (Garcia et al., 1967; Zahorik & Maier, 1969); (*b*) increased preference for a flavor when it has been associated with intragastric injection of complete diet (Holman, 1969); and (*c*) increased preference

for the odor of a diet which has been associated with administration of a balanced mixture of amino acids to a protein-deprived rat (Booth & Simson, 1971). In the case of the reinforcement of trophophilia by dilute carbohydrate solution it is not obvious what the benefit to the organism might be. Furthermore, neither in this nor the other cases has the site of reinforcement (directly in the brain or via liver or gut afferents, for example) nor its nature (membrane-sensitive chemoreception or intracellular metabolic modulation of neural activity) been identified. Intravenous infusion of 10% glucose reinforces motor acts (Chambers, 1956; Coppock & Chambers, 1954) and perhaps flavor preferences (Revusky, Smith, & Chalmers, 1971). It is conceivable that moderate amounts of readily utilized energy-yielding nutrients generate a postabsorptive reinforcement event which subserves, at least in part, the great increases in food-intake weight which develop after caloric dilution of the diet (Booth, 1972a). Possibly all hunger is trophophilia—that is, association with adequate amounts of carbohydrate (or energy) generates virtually all the attractiveness of any food (Booth, 1972a) or method of nutrient intake (Holman, 1969).

The trophophilic reinforcement demonstrated in the present work to be generated by 10% carbohydrate solution probably explains the observations of Valenstein (1967), Valenstein et al. (1967a), Valenstein, Kakolewski, and Cox (1967). They found that rats given a choice of .25% saccharin and 3%–10% glucose on ad-lib food and water switched from taking primarily saccharin solution to taking the glucose solution. The preference reversal was quicker the more concentrated the glucose, taking 3 days for 3% and less than 24 hr. for 10%. Trophophilic augmentation of the acceptability of dilute glucose solution may take time to reach asymptote even with continuous access, according to the present results. So it would be expected to override the basal preference for the sweeter solution with a delay inversely proportional to the potency of trophophilic reinforcement. This may be why the switch to 10% glucose is faster than to 6% or 3%. Valenstein et al. (1967a) and Valenstein, Kakolewski, and Cox (1967) also found that the change from saccharin to glucose occurs only in male rats. We have evidence of considerably attenuated reinforcement in females. This might arise from hormonally induced differences in routes of glucose utilization.

Since completing the present work, we have found that intake bouts on a dilute polysaccharide solution greatly increase in size when they are interspersed with bouts on concentrated polysaccharide, and that the effect is largely mediated by extinction of the oral inhibition of intake which develops during a bout (Booth, 1972b). It is possible that the development of large drinking bouts on the dilute glucose contributes to the marked change to taking glucose from the dilute solution which was seen in the present experiments. However, this does not seem likely to be the whole explanation. The rats had continuous choice between the dilute solution and an initially preferred concentrated solution. So they would be expected still to take substantial amounts of the concentrated solution, if all that was happening was the development of much longer bouts on those occasions on which the dilute solution was selected.

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