stimulating allogeneic lymphocytes are identical to those which express the Ia product in mice—namely macrophages (*13*), lymphocytes (*13*), epidermal cells (*4*), and sperm cells.

Evidence suggests that sperm exhibit haploid expression of HL-A antigens (*9*) and possibly other products of the MHC. Such haploid expression on human sperm offers a number of theoretical and potentially practical applications in diverse fields such as transplantation and reproductive biology.

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References

1. F. H. Bach, Ed., *Immunobiology of Transplantation* (Grune & Stratton, London, 1973).
2. R. K. Main, K. D. Cochrum, M. D. Jones, S. L. Kountz, *Proc. Natl. Acad. Sci. U.S.A.* **68**, 1165 (1971).
3. R. W. Gillette, S. Cooper, E. M. Lance, *Immunology* **23**, 769 (1972).
4. W. R. Levis and A. E. Miller, *Lancet* **1972-II**, 357 (1972).
5. W. R. Levis, J. J. Whalen, R. J. Sherins, *ibid.* **1974-II**, 954 (1974).
6. W. R. Levis and J. H. Robbins, *Blood* **40**, 77 (1972).
7. J. A. Powell, J. J. Whalen, W. R. Levis, *J. Invest. Dermatol.* **64**, 357 (1975).
8. D. M. Mumford, P. B. Barsales, K. D. Ball, H. L. Gordon, *J. Urol.* **105**, 858 (1971); R. P. Erickson and D. P. Stites, *Lancet* **1975-I**, 112 (1975).
9. M. Fellous and J. Dausset, *Nature* **225**, 191 (1970).
10. E. J. Yunis and D. B. Amos, *Proc. Natl. Acad. Sci. U.S.A.* **68**, 3031 (1971).
11. G. J. Hämmerling, G. Manup, E. Goldberg, H. O. McDevitt, *Immunogenetics*, **1**, 428 (1975).
12. C. G. Fathman, B. S. Handwerger, D. H. Sachs, *J. Exp. Med.* **140**, 853 (1974).
13. W. R. Levis and J. H. Robbins, *Transplantation* **9**, 515 (1970).

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Rapid Oral Mixing of Glucose and Saccharin by Rats

Abstract. *Within 5 minutes after initial contact rats show excessive consumption of a mixture of saccharin and glucose solutions. With a glucose solution in one bottle and the saccharin solution in another, a combination of which matches the above mixture, the rats also show large intakes. The pattern of drinking from the glucose and the saccharin bottles indicates that the rat mixes the solutions in rapid order, producing the preferred concentration of saccharin and glucose.*

It is widely recognized that many vertebrates have a "sweet tooth," and the evidence is clear that sweet-tasting substances reinforce behavior by virtue of their direct sensory effect (*1*). No example of this sweet preference is so profound as that described by Valenstein *et al.* (*2*). The normal fluid intake of rats was increased by nearly a logarithmic unit when the animals were offered a mixture of glucose and saccharin. Each liter of fluid in this standard mixture contained 1.25 g of sodium saccharin and 30 g of glucose (S + G solution). The consumption of this S + G solution in a 24-hour period occasionally exceeded the rat's body weight, which would be equivalent to an adult human male drinking more than 80 liters of fluid per day.

One concludes from the report of Valenstein *et al.* that the S + G solution is consumed in large quantities because it tastes good. They described the fluid as highly palatable, possessing a minimum of postingestional inhibiting factors. Many investigators (*3*) have subsequently used the standard S + G solution for its polydipsic effects in various experimental designs, but, as far as we know, no study has yet been reported that would clearly explain the basis of this highly unusual drinking behavior.

In an effort to delineate the basis of the synergistic action, Valenstein *et al.* conducted several experiments. Using male rats, we have replicated in this laboratory all of the experiments described in the study of Valenstein *et al.* (*2*) with essentially the same results. In support of their contention that the maximum contribution is from taste inputs and a minimum contribution is from postingestional factors, Valenstein *et al.* demonstrated that rats show no time delay in developing a high rate of consumption of S + G solution. The rats that Valenstein *et al.* used consumed an average of 10.3 ml of the solution in the first 30 minutes of contact. Our first experiment makes this point even more emphatically. Using the electronic lick circuits described below, we plotted cumulative licking for 10 minutes with 20 rats on their initial exposure to saccharin or the standard S + G solution. The characteristic neophobia or hesitation in drinking saccharin (*4*) demonstrated by rats on their first contact with the solution is eliminated when the glucose is added. The difference in cumulative licking between saccharin and the standard S + G solution is clear within the first 1 or 2 minutes of exposure. Although local lick rates did not vary between the two solutions, the steady licking (that is, the elimination of pausing) of the standard S + G solution led to increased consumption within the 10-minute session. Our conclusion was similar to that of Valenstein *et al.*; that is, the standard S + G solution is very palatable to the rat.

The results of a second experiment by Valenstein *et al.* (*2*), however, were more difficult to understand. They stated that rats drink far more of the standard S + G solution than "equivalent solutions of glucose and of saccharin presented in separate bottles." They presented 13 male rats with 0.125 percent (by weight) saccharin and 3 percent (by weight) glucose in separate bottles and observed no excessive intake; that is, the total fluid consumption never exceeded 65 ml over 24 hours. There are two possible explanations of why the rats did not consume saccharin and glucose separately as they did the standard S + G solution. (i) Rats tend to have discrete drinking bouts in which they drink either the glucose or the saccharin solution, and these were probably separated by minutes, perhaps even hours. Therefore, they would not normally mix these two solutions. (ii) If the rats did mix the 3 percent glucose and the 0.125 percent saccharin solutions, these concentrations used by Valenstein *et al.* would result in a weak S + G solution, in fact, one that would be half as concentrated as the standard S + G solution.

In our second experiment we attempted to determine if a 6 percent glucose solution and a 0.25 percent saccharin solution presented in separate bottles (a 1 : 1 mixture of these two solutions results in the standard S + G solution) would result in the polydipsia described by Valenstein *et al.* If the excessive drinking of the standard S + G solution were based on taste factors, it seems possible that in this two-bottle test the taste of the saccharin may linger long enough to interact with glucose drinking or vice versa, so that the synergy would be formed.

For our experiments 20 male Charles River albino rats were housed in individual cages and given Purina Chow freely. For 11 days the rats were given a choice between 0.125 percent saccharin and 3 percent glucose. The bottles were removed from the cages, washed, and refilled with fresh solutions each day. After this test and 4 days of unlimited water, the rats were tested for 9 days on 6 percent glucose and 0.25 percent saccharin solution simultaneously presented in two bottles. Another 4 days of unlimited water followed, and finally the rats were given a choice between the standard S + G solution and water. In all the tests the positions of the bottles were reversed daily to allow for any position preferences. The total fluid consumption for each day was determined for each rat and averaged over the 11-, 9-, and 10-day test periods. The median total intake of the 0.125 percent saccharin and 3 percent glucose solutions was 136 ml. The median intake of the 0.25 percent saccharin and 6 percent glucose was 236 ml, and the

median intake of the standard S + G solution was 251 ml. An analysis (Friedmann) (*5*) over these three groups yielded a significant F (< .01), and a subsequent test revealed that the test with the standard S + G solution and the test with 0.25 percent saccharin and 6 percent glucose were not different ($P > .05$). These results indicate that, if the rat is given 6 percent glucose in one bottle and 0.25 percent saccharin in a second bottle, the characteristic S + G synergy is apparent.

To be sure that the sequence of presentation of the solutions did not affect the outcome, eight more rats were tested. Half received the 6 percent glucose and 0.25 percent saccharin solutions first; the other half received the 3 percent glucose and 0.125 percent saccharin first. The results indicated that order of presentation had no effect on the results, and the statistical analysis of the results for these eight rats was identical to that of the original 20 subjects. Since the rats drank approximately equal quantities of the 6 percent glucose and the 0.25 percent saccharin solutions, it appears that they were mixing the two solutions and essentially receiving the standard S + G solution.

In our final experiment we attempted to observe the rat's pattern of drinking the 6 percent glucose and the 0.25 percent saccharin to see if there was any tendency for the rat to show an alternation between the glucose and saccharin during a drinking bout. Special individual home cages were constructed so that each rat had access to either one of two sipper tubes. These tubes were inserted partially in slots 3.5 cm long by 0.95 cm wide. In either slot the rat's tongue interrupted an infrared beam with each lick. The infrared receptors, in turn, through electronic circuits, operated high-speed relays which controlled the pens of two event recorders. The paper drive of one recorder operated at a speed of 7.6 cm/min and the other at 10.2 cm/sec.

More than 20 rats have been tested, and half of them demonstrate a pattern of drinking never before reported in the literature. During a drinking bout these rats alternate between the two sipper tubes, essentially mixing the standard S + G solution in the mouth. Figure 1 shows a typical drinking bout recorded at 7.6 cm/min which lasted 3 minutes 48 seconds. During this bout the rat switched from one bottle to the other 35 times. Data from the higher-speed recorder made it possible to count individual licks during these bouts. Seldom did a rat lick one tube more than 20 times (or about 4 seconds) before changing to the other tube. There is no consistent difference in lick rate on the glucose or the saccharin tubes. The rat shown in Fig. 1 consumed a slightly larger volume of glucose than saccharin (although the amounts of each solution consumed varied with each rat tested).

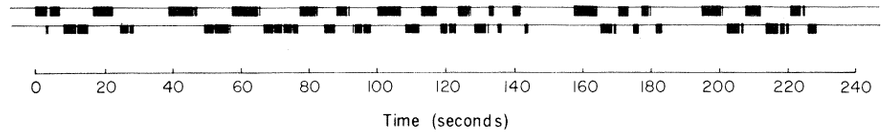

Fig. 1. Reproduction of an event recording of a drinking bout showing a pattern of rapid alternation by the rat between 0.25 percent saccharin solution (top) and 6 percent glucose solution (bottom).

Alternation appears to be a robust phenomenon. Rats which had demonstrated the alternating behavior with glucose and saccharin solutions and were then given a choice of standard S + G solution versus water in two tubes failed to exhibit the alternating pattern with the new two-bottle system. However, when the saccharin and glucose solutions were reintroduced, the alternating behavior reappeared. Since rats which develop the alternating pattern consistently drink more glucose and saccharin than nonalternators, it seems that these animals are in essence "mixing a cocktail" on their tongues.

Valenstein *et al.* have emphasized the value of the standard S + G solution for experimental purposes requiring consumption of large volumes of fluid. Our own studies have shown its additional utility in view of the fact that the animals show a marked reduction of neophobia. The alternating behavior manifests a potential for even broader application in taste research and raises many questions relative to the observation of consumption of other taste substances.

In the design of two-bottle preference tests the results presented here point to the necessity of examining not only the consumption but also the patterns of drinking to ascertain that the mixing of solutions has not contributed to the amount consumed. Whereas it has been found that some animals develop a clear pattern of alternation as early in their exposure to saccharin and glucose as day 1, some take several days to acquire the pattern and some (less than 50 percent) fail to exhibit this behavior after 10 days of exposure. We hypothesize that a forced-learning type of design might facilitate acquisition of this unusual behavior. Clearly, the alternation phenomenon presents a model of an expressly unique pattern of drinking behavior.

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References

1. C. Pfaffmann, *Am. Sci.* **52**, 187 (1964).
2. E. S. Valenstein, V. C. Cox, J. W. Kakolewski, *Science* **157**, 552 (1967).
3. P. J. Capretta, *Psychon. Sci.* **21**, 133 (1970); J. W. Cullen, *J. Comp. Physiol. Psychol.* **72**, 72 (1970); S. Hsiao and C. Rasmussen, *Psychon. Sci.* **10**, 97 (1968); J. W. Kakolewski, V. C. Cox, E. S. Valenstein, *ibid.* **11**, 317 (19 → *Science* **162**, 458 (1968); J. W. Kakolewski and E. S. Valenstein, *J. Comp. Physiol. Psychol.* **68**, 31 (1969).
4. M. E. Carroll, H. I. Dinc, C. J. Levy, J. C. Smith, *J. Comp. Physiol. Psychol.* **89**, 457 (1975).
5. M. Friedmann, *J. Am. Stat. Assoc.* **32**, 675 (1937).

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Selective Brain Dopamine Depletion in Developing Rats: An Experimental Model of Minimal Brain Dysfunction

Abstract. *Administration of 6-hydroxydopamine to neonatal rats produces a rapid and profound depletion of brain dopamine. Total activity of treated animals is significantly greater than that of controls between 12 and 22 days of age, but then declines, an activity pattern similar to that seen in affected children. This suggests a functional deficiency of brain dopamine in the pathogenesis of minimal brain dysfunction.*

Minimal brain dysfunction (MBD) in children is one of the most common and difficult problems in present-day pediatrics. Conservative estimates indicate that it affects 5 to 10 percent of the elementary school population and is a major cause of school learning and behavior problems. Clincially the disorder is characterized by a constant involuntary hyperactivity that completely surpasses normal, short attention span, impulsivity, and a variety of cognitive and perceptual problems (*1*). We have produced an experimental model in developing rats that is strikingly similar to the clinical syndrome of MBD. The model is effected by the intracisternal administration of 6-hydroxydopamine (6-OHDA) to neonatal rat pups, resulting in a rapid and profound depletion of brain dopamine.

We demonstrate that rat pups treated with 6-OHDA as neonates are significantly more active than their littermate controls during the period of behavioral arousal that occurs between 2 and 3 weeks of