At the conclusion of that experiment they were returned to individual metabolism cages (28 by 34 by 25 inches) within the quarters of the primate colony. Except for routine cleaning and handling for tuberculin testing, and so forth, these animals have not been disturbed for the past 15 months. One of the isolates, C-2, has required tranquilization on four occasions because he repeatedly bites and tears at his arms and thighs. Oral administration of 20 mg of chlorpromazine twice a day for several consecutive days effectively terminates such bouts of self-destructive behavior.

The monkeys were fed daily at 3:30 p.m. and received a vitamin sandwich, either an apple or an orange, and approximately 150 g of a commercial monkey pellet (Purina). A graduated 1-liter bottle was fixed to the back of the cage with a bracket. A stainless-steel tube 0.64 cm in diameter extended from the water bottle into the cage approximately 5 cm. This drinking system was designed to prevent spillage or leakage, and the monkey was required to suck on the tube to receive water. The water in the bottles was measured (Fig. 1A), refilled to 1000 ml, and replaced on the cage at 9:30 a.m. and at 3:45 p.m. daily. Urine samples were collected with the metabolism trays and plastic containers; the volumes were measured each day at 9:30 a.m. (Fig. 1B), and the samples were filtered and frozen for future analysis. Occasionally a sample was lost when a monkey managed to pull the drinking spout out of the reservoir bottle or shook its cage out of line with the urine container. If either measure was lost, that day's data were not included in the analysis for that animal.

The isolated monkeys drank more fluid and excreted more urine within 24 hours than the controls. These data, in fact, do not reveal the actual amount of fluid which would have been ingested in a day since, on almost every morning, the isolated monkeys had consumed the entire 1000 ml of water received at 3:45 p.m. on the previous day, whereas the controls always had several hundred milliliters left at the morning collection (*5*). Ingestion of water and output of urine by the normal controls were well within normal limits (*5*). The isolates exceed by far any of the reported normative data on water balance.

Three tests were given to determine the ability of isolated monkeys to concentrate urine during 24 hours of water deprivation (Fig. 1D). These determinations were separated by no less than 10 days of the usual regime in which 2000 ml of water were made available to permit repletion and restabilization of water metabolism after deprivation. These data suggest that the isolates conserve fluids during the deprivation period. On the one occasion on which monkeys were deprived for 48 hours, all of the monkeys excreted similar amounts of urine; C-2 and C-3 diminished their urine production during the second 24 hours to 135 and 145 ml, respectively.

After water and urine had been collected for 135 days, food consumption was measured. The regular ration of one piece of fruit and a vitamin sandwich at 3:30 p.m. was continued. In addition, beginning at 8:30 a.m. daily, the number of food pellets in the food hopper and on the floor of the cage was counted. Then 25 fresh pellets were placed in the hopper. The hoppers were checked every hour and, if the food supply was low or exhausted, additional pellets were counted and placed in the container. At 5 p.m. the remaining supply in the hopper was brought up to 25 pellets so the animals would have an adequate supply of food overnight. Figure 1C shows the mean consumption for each of the animals over 20 days. It does not include the fruit and vitamin supplement which was the same for isolates and controls. The isolates clearly overate in comparison with their normal controls; in fact, their food consumption fell within the range reported by Hamilton and Brobeck (*6*) for hyperphagia produced in monkeys with lesions of the ventromedial nucleus.

As a further test of the polydipsic phenomenon, determinations of quinine aversion were made. Quinine sulfate was dissolved in tap water in dilutions of 0.025, 0.05, and 0.1 percent (weight/volume). The solutions were administered through the drinking tubes in sequence starting with the lowest concentration. The reservoir bottle was filled with quinine solution at 9:30 a.m. and 3:45 p.m., and the amount drunk was measured. Since there was a single tube available to the animal, the only alternative to drinking the bitter solution was to reduce fluid intake. Each concentration was administered twice, with 1 day between determinations during which plain tap water was available to permit repletion of fluids. The normal monkeys reduced their intake of fluids at lower concentrations of quinine than the isolates, but, as the concentration of quinine increased, the isolates tended to approach the same relative amount of inhibition as the controls. The absolute amounts of fluid ingested by the isolates were much greater at all concentrations of quinine than the amount accepted by the controls.

Our experiments show that one of the sequelae of total social isolation during the first year of life in the infant rhesus monkey is a marked polydipsia and hyperphagia manifest at least 6 years later. Data are not yet available concerning the age of onset and development of these abnormal ingestive patterns, but it is clear that, at the time of their arrival in this laboratory, regulatory problems were present and have continued for the ensuing 3 years.

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## Monosodium Glutamate

Olney's study (*1*) was based on the subcutaneous injection into infant mice of massive doses of monosodium glutamate (MSG), ranging from 0.5 to 4 mg/g (comparable to about 1.5 to 12 g in a newborn human infant) and doses of 5 to 7 mg/g in adult mice (corresponding to 350 to 490 g in an adult man). No mention was made of the concentration of the injected solution or of the response of control mice to the solvent alone; nor were any tests reported of the response to injected doses of equivalent amounts of sodium

chloride, sodium citrate, or the salts of any other amino acid.

These observations do not have any relevance to the question of the safety of MSG as a food seasoning agent. Critical tests for the safety evaluation of food additives are based on the effects of oral, not parenteral, administration. High dietary amounts are fed to determine the extent of absorption and the subsequent metabolic fate and systemic responses. The author chose as his test subject newborn mice, not yet equipped with the complement of metabolic enzymes of the mature animal, and he asserted that these findings raise "the more specific question whether there is any risk to the human nervous system by the maternal use of MSG during pregnancy" (*1*).

Monosodium glutamate is used in a great variety of soups, meat products, sauces, and seasonings, at concentrations rarely exceeding 0.5 percent. The total estimated daily intake from all reasonably possible uses is in the order of 0.7 g per day, or 0.01 g per kilogram in an average adult. It has been the subject of extensive studies at oral doses far in excess of normal usage. This is not to say that excessive amounts might not produce disturbing responses worthy perhaps of further study, but in this respect, MSG is no different from common salt, sugar, or vinegar.

The Chinese restaurant syndrome, to which the author alluded, is quite another story and appears to have resulted from the addition of as much as 5 g per portion of soup. Even so, it is rarely observed, it may be an allergic type of reaction, and it has not been studied by an adequately controlled double-blind procedure employing other sodium salts as placebos.

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The concentration of monosodium glutamate (MSG) given to newborn mice was 0.1 g/ml with sterile distilled water as solvent. Treatment of control mice subcutaneously with equiosmolar concentrations of NaCl produces no neuronal pathology (*1*). Aspartate is known to produce retinal pathology similar to but much less extensive than that associated with glutamate treatment (*2*). The histopathological effects of aspartate on brain have not, to my knowledge, been studied although I concur in the view that such studies would be worthwhile.

My own interests and my reported findings are primarily concerned with the effects of agents such as MSG on the developing central nervous system. Blood *et al.* have misquoted me in their letter by omitting the word "developing" from my statement concerning "risk to the developing human nervous system" (*3*). In addition to my findings with baby mice we have more recently observed that the infant rhesus monkey (*Macaca mulata*) is also susceptible to brain damage after subcutaneous administration of MSG (*4*). In view of the practice on the part of the food industry of adding MSG in unspecified amounts to baby food and the well-known fact that the immature organism is not "equipped with the complement of metabolic enzymes of the mature animal," I submit that the burden of proof, concerning the relevance for humans of my research with MSG and immature animals, resides with anyone who advocates the use of MSG as a food additive either in pregnancy or in the diet of the developing human infant.

Blood *et al.* refer to extensive studies of oral doses in excess of normal usage without giving references. Can they cite published studies in which glutamate tolerance tests were performed to establish whether marked individual variations exist in ability to metabolize glutamate loads or in which brains of either adult or infant animals were carefully studied for histopathology following oral glutamate loads? The most critical approach for safety evaluation of MSG as a food additive would be to establish what blood concentrations (regardless of route of administration) are required to induce even slight brain damage at any age. These concentrations should be compared with peak plasma concentrations produced by dietary intake of MSG and a substantial margin of safety should be sought. Due regard should be given to the fact that the daily human diet may contain 15 g or more of glutamic acid in addition to the MSG added for seasoning. The possibility of wide individual as well as age variation among users of MSG in their ability to metabolize and regulate blood concentrations of glutamic acid or in their susceptibility to brain pathology at any blood concentration must also be considered. For evaluation of risk to the developing fetus, crucial periods of development of the central nervous system and glutamic acid transport characteristics of the primate placenta after maternal intake of a glutamate load must be studied.

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## Preventing Obsolescence of Scientific Reviews: An Updated-Review Project

Reviews, monographs, and textbooks are out of date before they are published. To remedy this state, we have designed a form of review, in part an adaptation of existing procedures, that can be kept continually up-to-date by a procedure assisted by automation. Further, we announce the publication of the first such review.

Briefly our procedure is this: a review is prepared by a qualified scientist in a manner basically similar to that in general use; the text is maintained on magnetic tapes from which it can be printed out either (i) as a whole for rapid printing, or (ii) in part to provide answers to specific requests for information. Then, as new experimental findings are reported, the author of the original text prepares amendments to the taped text that will take account of and incorporate the impact of these new findings.

For the first use, rapid printing, we propose publication in a loose-leaf binding and subsequent distribution of updating sheets to supplement and replace the original pages. The frequency of distribution of the updating sheets would depend on activity in the field. For the second use, a stable scientific-information organization is required with appropriate computer support so that requests for information can be received and the information required retrieved. Such a facility, or capability, is now being developed by the UCLA Brain Information Service.

The first such review has just been completed (*1*). It deals with the "Anat-

## Monosodium Glutamate

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