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.

FRANK R. BLOOD
*Department of Biochemistry, Vanderbilt University, Nashville, Tennessee 37203*
BERNARD L. OSER
*Food and Drug Research Laboratories, Inc., Maspeth, New York*
PHILIP L. WHITE
*Council on Foods and Nutrition, American Medical Association, Chicago, Illinois*

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26 May 1969

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.

J. W. OLNEY
*Department of Psychiatry, Washington University, St. Louis, Missouri 63110*

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9 June 1969

## 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-

omy and Electrophysiology of the Dorsal Column-Medial Lemniscus System." It has been prepared by one of us (A.C.N.) whose training and research experience have been in sensory physiology. The review will be distributed both by the Government Printing Office and the UCLA Brain Information Service (BIS). It will be kept up-to-date by the author, the new material being distributed by BIS. Specific inquiries in this field, both factual and bibliographic, are also being handled by the BIS. The preface to this review will include a more detailed account of the proposed method for updating.

The author of each review will accept comments from qualified individuals, particularly those whose work is cited in it. When appropriate, the text could be amended to take account of the comments. Thus the text is intended to reflect the views of all those concerned with the topic, not merely those of the author.

The Brain Information Service plans to offer to the scientific public additional reviews in the basic neurological sciences.

PETER AMACHER
VICTOR E. HALL, ALLEN C. NORTON
*Brain Information Service,*
*University of California, Los Angeles,*
*School of Medicine, Los Angeles 90024*

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9 June 1969

## Thermoregulation and Norepinephrine

Simmonds and Iversen (*1*) have shown that the radioactivity of tritiated norepinephrine (NE) which was injected intracisternally in rats declined significantly in the whole hypothalamus after the animals were warmed to 32°C. In so doing they suggest that hypothalamic NE may regulate heat loss under normal physiological conditions in the rat and indicate that this finding is consistent with the amine theory of thermoregulation proposed by Feldberg and myself (*2*). Unfortunately, the interpretation of their results constitutes an oversimplification and may even be incorrect.

If one assumes that an action of a given transmitter substance can be mimicked by the intraventricular application of this substance, then a 5-hydroxytryptamine (5-HT) mechanism in the hypothalamus of the rat, rather than a noradrenergic one, mediates heat loss systems (*3*). We have found that 5-HT, injected into the cerebral ventricles of unrestrained rats, produces a dose-dependent, long-lasting fall in temperature. The precursor of this indole amine, 5-hydroxytryptophan (5-HTP), also evokes the same degree of hypothermia. On the other hand, NE given in low doses by the same route causes a dose-dependent rise in temperature. Also, the precursors of NE, dopamine and L-dopa (dihydroxyphenylalanine), produce the same type of elevation in temperature although their action is somewhat more sluggish. Feeding often accompanies the NE hyperthermia, but the pharmacological specificity of adrenergic thermogenesis is further substantiated by the fact that isoproteronol, a $\beta$-adrenergic agonist, causes only the rise in temperature when it is injected intraventricularly (*3*). In view of these findings, it is essential that a shift in the amount of radioactivity of labeled 5-HT be demonstrated in relation to changes in environmental temperature. This would serve as a logical control to the specific nature of NE, even though the tissue content of $^3$H-NE in the hypothalamus may not reflect the actual presynaptic release of this "candidate transmitter" to activate postsynaptically the heat production pathways.

The experiment of Simmonds and Iversen was based on a result of Feldberg and Lotti (*4*) who reported that intraventricular NE causes a transient hypothermia. We could confirm this finding, only if the catecholamine was given in high doses. The discrepancy between our two studies may be due to the fact that Feldberg and Lotti restrained their rats, and this condition may have interacted with an action of NE, particularly since "emotional hypothermia" can develop in association with restraint (*5*). What then do the results of Simmonds and Iversen mean?

The only experiments done thus far on the hypothalamic "mapping" of temperature responses to NE and 5-HT were in monkeys, and these amines were found to act mainly within the anterior, preoptic region (*6*). Moreover, "push-pull" perfusions of the monkey's hypothalamus revealed that an increase in 5-HT release occurs only in the anterior, preoptic region during exposure to cold stress (*7*). Because the anterior region constitutes only one-eighth of the entire hypothalamus (*8*), and because so many other systems traverse the area comprising the other seven-eighths of this diencephalic structure, it is difficult to imagine that the decline of $^3$H-NE from the whole hypothalamus could be attributed solely to an alteration in environmental temperature. Aminergic systems in different regions of the hypothalamus are already thought to be involved in many other functions, including feeding (*9*), drinking (*10*), hormonal release (*11*), emotional or affective states (*12*), levels of arousal and activity (*13*), and rewarded behavior (*14*). Among other effects, heating a rat to 32°C may simply (i) elevate its thirst drive, (ii) decrease its food drive, (iii) make it placid, (iv) lower its level of arousal, or (v) interefere with its motivational state. Any one of these processes could override and thus mask the actual effect of elevated temperature on the afferent impulses to the anterior, preoptic area (*15*). In conclusion, a biochemical assay of the whole hypothalamus may have little value for establishing a relation between a single function and a specific chemical change in this entire structure.

R. D. MYERS
*Laboratory of Neuropsychology,*
*Purdue University,*
*Lafayette, Indiana 47907*

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