Amino Acids: How Much Excitement Is Too Much?

Some common substances can cause brain damage by exciting neurons to death. Should they be regulated by the FDA?

THE SOCIAL ISSUES COMMITTEE of the Society for Neuroscience has a message for the Food and Drug Administration: University neuroscientists are a valuable resource whose research can help the agency evaluate food safety. That message, in the form of a letter being drafted by the committee, is one result of a round-table discussion on the toxic effects of excitatory amino acids on the brain that was held at the society's annual meeting last October. Notably absent from the session, despite the organizers' efforts to include them, were any representatives of the FDA.

The absence of the FDA left unanswered the question of how carefully the agency is willing to listen to the scientific community on the question of excitatory amino acids and the brain. The picture is further confused by a second unanswered question: Are excitatory amino acids really worth worrying about? Some neuroscientists think they are. The round table revived a 20-year debate over the safety of the amino acid glutamate, which is commonly added to processed foods as the flavor-enhancer monosodium glutamate (MSG). An amino acid abundant in protein, glutamate functions in the brain as an excitatory neurotransmitter—released by some neurons, it stimulates others to higher levels of activity. But glutamate also acts as an excitotoxin: when present in excess it can actually stimulate nerve cells until they die.

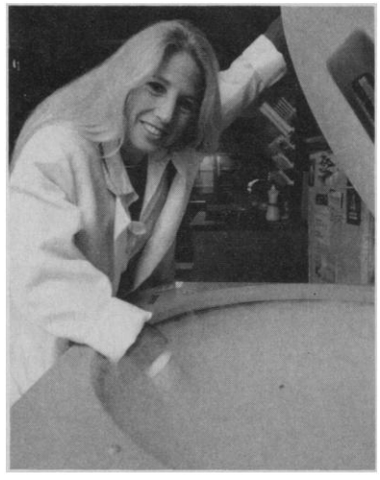
The origins of the current controversy extend back two decades, to the time when a Washington University neurophysiologist tried to get the FDA to ban glutamates from children's food (see box). John Olney lost his battle with the agency, but he did win a partial victory when baby food manufacturers voluntarily stopped putting MSG into their products.

Olney still thinks young children are at risk, however. Extrapolating from experiments on rodents and monkeys, he argues that a 20-pound child can receive a dose of glutamate dangerously close to toxic levels from the 1000 to 1300 milligrams of MSG found in one 6-ounce serving of any of a number of brands of instant soups. Olney cites rodent studies that show MSG can cause hypothalamic damage that leads to obesity or stunted growth.

After reviewing all the data, including Olney's, the FDA has elected to keep MSG on the list of additives generally regarded as safe. As the discussion at the round table suggested, the neuroscience community is divided on the issue. Some of those who were present at the round table suspect Olney has made extrapolations that aren't fully supported by the data; others strongly echo his concerns.

If that debate isn't basis enough for opening a dialogue between neuroscientists and the FDA, whole new areas of concern about excitotoxins are now emerging in the scientific community. Research on these substances today ranges far beyond the issue of glutamate as a food additive. One reason is that excitotoxic compounds mimicking glutamate's actions have been found to occur naturally in some foods at levels high enough to cause brain damage when eaten. Excitotoxins have been linked to a diet-related spastic disease in parts of Africa and Asia, to a neurodegenerative disease on Guam, and to a shellfish poisoning incident in Canada that caused a form of memory loss resembling Alzheimer's disease.

Excitotoxins from the environment are not the only cause of concern. Research has also established that glutamate made within the brain can, under certain circumstances, become excitotoxic. A buildup of glutamate in parts of the brain is apparently the specific cause of the brain damage due to stroke, hypoglycemia, trauma, and seizure. And some researchers propose that the nerve degeneration in Huntington's, Parkinson's and Alzheimer's diseases may be due to glutamate metabolism gone awry.



Stirring the pot. *Nancy Wexler chairs the committee discussing excitotoxins.*

These emerging concerns made the time seem right not only for a round table, but also for involving the FDA. As Nancy Wexler, who chairs the society's Social Issues Committee, told *Science*: "Neuroscience is zipping ahead, and the translation of that into improved social policy and public health has to be through the regulatory agencies." But this argument wasn't enough to get the FDA to show up, despite an invitation many months in advance.

David Hattan, deputy director of the FDA's Division of Toxicological Review and Evaluation, says he wanted to send someone who had both scientific and regulatory experience with excitotoxins and that both he and Tom Sobotka, of the FDA's neurobehavioral laboratory (who is the only other person he felt would be appropriate to attend the panel), had previous commitments.

What the FDA representatives missed was a lively presentation of a series of case studies beginning with the shellfish poisoning episode. In December 1987, about 150 Canadians got sick after eating mussels that were later found to have been high in domoic acid, a potent glutamate analog. Four people died, and 12 who survived suffered permanent memory loss reminiscent of Alzheimer's disease. Autopsies on those who died revealed that they had suffered damage to neurons in the hippocampus, a brain structure implicated in memory.

Many questions remain unanswered in the mussel story. One of the most significant, according to FDA seafood toxicologist Sherwood Hall, is the puzzle of why, among the thousands of people who probably ate the contaminated mussels, only a handful experienced irreversible damage. Answers to such questions may ultimately help to show whether certain subgroups in the population are at increased risk from excitotoxins. That information in turn may ultimately have important regulatory consequences, consequences that extend to excitotoxins beyond domoic acid. For the time being, both the Canadian government and the U.S. Food and Drug Administration are periodically screening mussels for domoic acid contamination.

Another intriguing case discussed at the round table was that of the chickling pea, a plant eaten by some people in Asia and

Africa during times of famine. As a means of warding off starvation, the pea has its price: it contains a naturally occurring excitotoxin called beta-oxaloamino-alanine. That compound kills neurons in certain parts of the brain, causing a disease characterized by spastic movements.

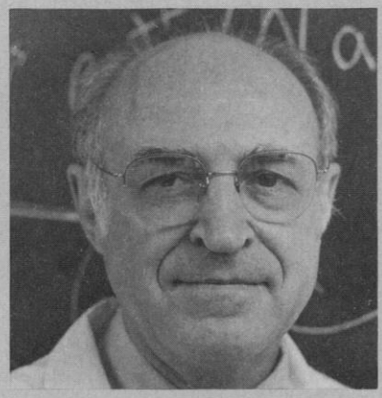
Perhaps the most interesting case, however, according to Stanford University neurologist Dennis Choi, is that of a neurodegenerative disease prevalent on Guam. Monkey studies by Peter Spencer, a toxicologist at Oregon Health Sciences University, suggest that the disease—called Guam ALS Parkinson's dementia for its resemblance to amyotrophic lateral sclerosis (ALS) and to Parkinson's disease—may be caused by beta-methylamino-alanine (BMAA), a substance present in a type of seed eaten by people on Guam during the famine that followed World War II.

The hypothesis that BMAA caused Guam ALS Parkinson's dementia is still controversial. But if it is true, its implications are disturbing, Choi says, because some people who ate the seeds didn't come down with the disease until many years later. A simple explanation is that the excitotoxin may kill some nerve cells when it is ingested, but that the disease does not develop until much later, when age-related cell loss causes the number of neurons in the damaged part of the brain to drop below a crucial threshold. Such a model raises the possibility that nerve cell damage resulting from exposure to environmental excitotoxins could pave the way for other neurodegenerative diseases, such as Alzheimer's, Parkinson's, or ALS, whose symptoms would become apparent only decades later.

This unsettling possibility is by no means the only hypothesis. Indeed, there is a second—and more widely favored—model, also involving excitotoxins, that Choi calls "the enemy within." It proposes that some neuro-

MSG: A 20-Year Debate Continues

In 1969 Washington University neurophysiologist John Olney showed that a single dose of monosodium glutamate (MSG) given orally to rats or monkeys raises blood-glutamate levels and causes damage to the hypothalamus, a region of the brain that is not well protected by the blood-brain barrier. With that important observation the concept of excitotoxicity—the ability of amino acids such as glutamate to literally excite nerve cells to death—was born.



Consistent crusader. *John Olney has campaigned for MSG regulation.*

Today excitotoxicity is an accepted concept, and the study of how glutamate receptors mediate that toxicity is a hot area of neuroscience. It's possible that if some tantalizing leads pan out, the study of excitotoxicity could lead to an understanding of common neurodegenerative diseases such as Parkinson's and Alzheimer's (see accompanying story).

Olney's finding did more than launch a new area of research; it also convinced him that food additives such as MSG were harming children. In his studies Olney found that infant animals were more susceptible to excitotoxic damage than adults were. He concluded that the same is likely to be true in humans, perhaps placing children and especially infants at risk from MSG added to foods. This conviction fueled his 20-year crusade for FDA regulation of MSG.

Although his early efforts succeeded in convincing makers of baby food to remove the flavor enhancer from their products, Olney feels that isn't enough: MSG is still added to packaged soups and other foods fed to small children. He also argues that children are at risk from the artificial sweetener aspartame, because it contains aspartate, an amino acid that also activates the brain's glutamate receptors.

While Olney's discovery of excitotoxicity has been universally accepted by scientists, his concerns about excitatory amino acids in food have not. MSG remains unregulated because reviews of the scientific literature by a committee of the National Academy of Sciences in 1970, and by the Federation of American Societies for Experimental Biology in 1978 and again in 1980, concluded that the additive was safe. FDA-ordered reviews found aspartame to be safe as well.

Olney charges that many of the studies contradicting his findings were hastily and inexpertly done—and tainted by food industry support. At least one should be invalidated, he says, because the monkeys in it were treated with phencyclidine (PCP), an animal tranquilizer widely used in the 1970s that is now known to protect neurons from glutamate damage.

Recent data show that the neurons Olney found to be susceptible to glutamate damage are particularly sensitive in young animals, and Olney interprets that data as supporting his view that children are at heightened risk from exposure to MSG.

But the debate isn't over. Olney's critics cite studies showing that glutamate taken in during a meal does not raise blood levels as much as the doses Olney administered on an empty stomach. Stanley Gershoff, dean of the Tufts University School of Nutrition and coauthor of some of the papers contradicting Olney's findings, argues that MSG is unlikely to be seriously harmful even to children, since in some countries—such as Thailand—huge amounts are eaten without obvious pathology appearing.

Citing whole cultures misses the point, says Joseph Coyle, who studies excitatory amino acids at Johns Hopkins University: "The problem is heterogeneity in the population. The evidence is overwhelming that activation of glutamate receptors by glutamate and/or aspartate will kill neurons in the brain. But since we are only now beginning to understand the glutamate system, we don't know if there is heterogeneity in the population with respect to the ability to deal with a glutamate or aspartate challenge."

If sensitive subgroups are the problem, there is a regulatory dilemma, says consumer advocate and attorney James Turner. The absence of an FDA ban suggests MSG is safe for everyone—and it may not be. Yet it may not be appropriate to ban MSG merely because a small subgroup is vulnerable to it. One answer, according to Turner, is informational labeling spelling out possible health effects of additives such as MSG. David Hattan, of the FDA's Division of Toxicological Review and Evaluation, said the FDA is considering informational labeling on some foods. But, he adds, the agency would need a solid case that there are people at risk from the additive to justify such regulation. ■ **M.B.**

degenerative diseases, including those with a clear hereditary cause, such as Huntington's disease, could result from a genetic or acquired abnormality in glutamate metabolism or in the glutamate sensitivity of certain neurons. Either situation could lead to the overstimulation and subsequent death of neurons. This model also raises the possibility that there are vulnerable subgroups within the population at large: a person with such a disease or the predisposition to it might be particularly susceptible to dietary excitotoxins.

Social Issues chair Wexler, whose own research is on Huntington's disease, says the major message from the round table is that more research is needed on the possible role of excitotoxins in neurological diseases. Since that role is as yet only speculative, Choi and others agree it does not presently provide a basis for regulatory action. But Wexler notes that since research might identify excitotoxin-containing foods that pose a threat to all or part of the population, regulatory agencies do need to be drawn into the process.

Hence the letter to the FDA, which is being drafted by Olney and consumer advocate attorney James Turner and must be approved by the board of councillors of the Society for Neuroscience before being sent. The letter will not take a position on glutamate or any other specific issue, Turner says, since no consensus exists as yet among members of the society. "We are looking on this as a friendly communication in which we're trying to bring [excitotoxin research] to the attention of the FDA and to point out that the Society [for Neuroscience] provides a resource to help work their way through this issue."

The FDA's Hattan told *Science* he agrees that the agency could benefit from better communication with those who are doing research on neurotoxins: "The FDA doesn't have the basic science resources immediately available to us to follow up on some of these [areas]. It would be useful to have principal investigators, when they have a critical mass of data, come to the FDA and talk to us about it."

Wexler hopes for more than merely opening an avenue of communication. She wants to get across a subtle message: that the FDA should listen more carefully to researchers whose funding comes from government grants. To Wexler, those supported by the food industry are caught in a potential conflict of interest that has clouded at least one debate—the one about glutamate. "The Society for Neuroscience has all these neuroscientists who are using tax dollars to do research," she says. "If the [regulatory] arm of the government doesn't pay any attention to their research findings, that makes no sense." ■ MARCIA BARINAGA

Academy Panel Raises Radiation Risk Estimate

What was once an extreme view becomes mainstream as statisticians recalculate the effects of the Japanese atomic blasts

THE MILLS OF the National Academy of Sciences may be slow, but they sometimes grind exceedingly fine. In December they produced a 421-page report* that pulverizes an argument made by a group of experts 10 years ago that the dangers of low-level radiation were being exaggerated.

The new study concludes that the risks have been underestimated until now. Not only that, but it says that the likelihood of getting cancer after being exposed to a low dose of radiation is three to four times higher than that given in the earlier Academy report, which itself was denounced by some old hands at the time as alarmist. Thus, an evolving scientific understanding of health effects has made the alarmist viewpoint of the 1970s appear moderate today and it has given some former alarmists a chance to say "I told you so" about their predictions.

The person responsible for bringing this risk assessment to a soft landing—unlike the last one in 1979 which shattered on impact—is Arthur C. Upton, the unflappable chairman of the Academy's fifth committee on the Biological Effects of Ionizing Radiation (or BEIR V). Upton, who heads the Institute of Environmental Medicine at New York University, is scrupulously balanced in his presentation of these issues. This helps to explain why his group was able to reach a consensus while the last one, BEIR III of 1979–1980, broke into factions.

BEIR V deals with low levels of penetrating radiation that impinge on humans from outside the body, essentially x-rays, neutrons, and gamma rays, which make up the bulk of the public threat that has concerned health officials in the past. A special study issued last year, BEIR IV, deals with a different problem that gets increasing attention these days—internal short-range "alpha" radiation primarily from radon gas. Thus, while BEIR IV has implications for clearing the air in homes and uranium mines, BEIR V has implications for policing man-made sources such as medical diagnostic machines and the nuclear industry.

Although BEIR V was not officially asked to comment on public safety, Upton said at a press conference that he expected there would be "some response" from regulatory authorities in the form of tighter standards. At least one activist group, the Nuclear Information and Resource Service of Washington, D.C., is already citing the new BEIR V data as it seeks to prevent federal deregulation of very low-level radioactive waste streams (emitting less than 10 millirem per year). Warren Sinclair, president of the National Council on Radiation Protection and Measurements, an industry advisory body, says that given the "pressure" of BEIR V, his council "might very well feel that now is the time" to reduce the maximum occupational exposure limit from 5 rem per year to something less.

Even so, perhaps in the interests of preserving calm, Upton takes a low-key approach to the implications of his report. "There has been no revolution in the assessment of risk, no frightening increase [in the perceived health effects]," Upton told an audience at the Academy on 19 December. But he said it is possible to be much more specific about the degree of risk now because there has been a tremendous improvement in three areas of analysis. The most

Unflappable chairman. *Arthur Upton's steady direction helped achieve a consensus.*

*"Health Effects of Exposure to Low Levels of Ionizing Radiation" (National Academy Press, Washington, D.C., 1990).