ASPARTAME: POSSIBLE EFFECT ON SEIZURE SUSCEPTIBILITY

SIR,—Aspartame, a sweetener in many diet beverages, contains phenylalanine but, unlike dietary proteins, lacks other neutral aminoacids that compete with phenylalanine for uptake into the brain.[1-3] Hence its consumption causes unique modifications in the plasma aminoacid pattern[3] which, in man, might be expected to increase brain phenylalanine levels (especially when carbohydrates are eaten concurrently)[2,3] and thereby affect catecholamine or serotonin synthesis.[4,5] Since diminished brain monoamine levels have been related to depressed seizure thresholds in animal preparations,[6] very high aspartame doses might also affect the likelihood of seizures in symptomless but susceptible people. Brief descriptions follow of three previously healthy adults who had grand mal seizures during periods when they were consuming such doses.

A 42-year-old secretary who drank four quarts (3¾ litres), of 'Diet Coke' and almost the same amount of 'Lite-Line' lemonade daily became "moody" with weekly episodes of headache and nausea, visual hallucinations, feelings of déja-vu, and, ultimately, a grand mal seizure. There was "no evidence for an underlying structural abnormality to account for her temporal lobe epilepsy". During her 9 days in hospital she took no diet drinks and, for the first time in months, had no headaches; they recurred when she resumed the diet drinks at home and disappeared when she again discontinued the diet drinks.

A 27-year-old programmer with no neurological history had nocturnal episodes of twitching movements and abnormal breathing, and, ultimately, a severe headache followed by a grand mal seizure. Phenytoin suppressed further seizures, but the other symptoms persisted until he discontinued his daily intake of four or five glasses of 'Crystal Light'; its subsequent resumption was followed by the return of nocturnal "twitching, trembling, jerking, and hyperventilating". All laboratory tests were normal except the electroencephalogram, which showed a grade one arrhythmia.

A 36-year-old professor who drank 900 ml or more of aspartame-sweetened iced tea daily had a grand mal seizure in bed. Angiography demonstrated a left posterior frontal venous angioma, adjudged an "incidental finding".

Such case-reports can only suggest an association between aspartame and seizures, since the size and the seizure incidence (without aspartame) of the population at risk (young adults who sometimes consume large amounts of aspartame) are unknown. However, the reports are compatible with evidence[3,5] that high aspartame doses may produce neurochemical changes that, in laboratory animals, are associated with depressed seizure thresholds.[6] It thus seems prudent for physicians to inquire about aspartame consumption and other aspects of dietary history in evaluating patients with unexplained seizures. Interpreting their responses will require that the labels on food products indicate not only the presence of the sweetener but also the actual amounts that the foods or beverages contain.

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1. Pardridge WM. Regulation of amino acid availability to the brain. In: Wurtman RJ, Wurtman JJ, eds. Nutrition and the brain: vol I. New York: Raven Press, 1977: 141–204.
2. Wurtman RJ. Neurochemical changes following high-dose aspartame with dietary carbohydrates. *N Engl J Med* 1983; 309: 429–30.
3. Yokogoshi H, Roberts C, Caballero B, Wurtman RJ. Effects of aspartame and glucose administration on brain and plasma levels of large neutral amino acids and brain 5-hydroxyindoles. *Am J Clin Nutr* 1984; 40: 1–7.
4. Fernstrom JD, Faller DT. Neutral amino acids in the brain: changes in response to food ingestion. *Am J Neurochem* 1978; 30: 1531–38.
5. Pardridge WM. Potential effects of the dipeptide sweetener aspartame on the brain. In: Wurtman RJ, Wurtman JJ, eds. Nutrition and the brain: vol VII. New York: Raven Press (in press).
6. Jobe PC, Ko KH, Dailey JW. Abnormalities in norepinephrine turnover rate in the central nervous system of the genetically epilepsy-prone rat. *Brain Res* 1984; 290: 357–60.

POSSIBLE RELATIONSHIP BETWEEN ASPARTAME (NUTRASWEET) CONSUMPTION, SEIZURES, AND OTHER CNS ABNORMALITIES

(Introductory comments presented to the Food and Drug Administration, April 21, 1986.)

Thank you for inviting Dr. Schomer, Ms. Hazerjian, and myself to meet with you today to discuss available data, and plan future studies, relevant to the possible association between aspartame (Nutrasweet) consumption, the occurrence of grand mal seizures, and other, possibly-related CNS abnormalities like migraine and other types of severe headache. We have several goals for this meeting:

1. To initiate what we hope will be a fruitful collaboration with our colleagues in the FDA. We believe that we and the FDA share a commitment to discovering the scientific and medical truth about the aspartame-seizure relationship, and to seeing to it that that truth is applied fairly and expeditiously in protecting the Public's health. We do not see the FDA's role - as was suggested, perhaps in jest, by an FDA scientist - as that of an umpire, mediating between university scientists and the companies that manufacture and use aspartame; rather, the FDA must, just like university scientists, be intellectually aggressive in continuing to search for adverse reactions to compounds like aspartame that it admits to the Nation's food supply. It seems clear to us that, although the FDA has developed effective mechanisms for evaluating in advance the risks that certain types of adverse reactions will occur (e.g., those involving carcinogenesis and mutagenesis), it was not as well equipped as it might have been to deal with the risks posed by compounds like aspartame, that may act in adults not by killing cells nor by transforming their genetic material but by changing such functional properties as their synthesis of neurotransmitters. Indeed, as you well know, the whole concept of the "ADI" and the method by which it is calculated fail to deal at all with these properties, nor with the topics that we are discussing today: seizures and headaches. Perhaps out of the aspartame story will come new strategies by which the FDA evaluates the risks posed by brain-active food constituents.

2. To present and discuss some of the "case history" data that we have been collecting on previously-healthy young adults who suffered seizures possibly related to aspartame consumption. At present we are evaluating about 80 such people, and adding one or two new cases each week. (It's surprising that we have accumulated this large a number of possible cases in the few months since my original letter, describing 3 cases, appeared in The Lancet: Certainly Nutrasweet's manufacturer, the Monsanto Chemical Co., is not advising consumers with seizures to get in touch with us, nor, we imagine, is the FDA.) As you will note, our typical subject is a woman in her thirties, whose seizure was preceded by a prodrome of weeks or months, usually including severe headaches. This apparent relationship between headaches and, ultimately, seizures - plus the evidence, discussed below, that aspartame exacerbates migraine, and the well-known relationship between migraine and seizures - raises the possibility that individuals at special risk to develop aspartame-related seizures may be largely identifiable in advance.

Our data, when complete, will be the subject of a publication, perhaps modeled after one on pyridoxine toxicity published in the New England Journal of Medicine several years ago. That study described six women who developed a peripheral neuropathy concurrent with consuming supplemental pyridoxine; the neuropathy disappeared when the pyridoxine was stopped. Based on that temporal correlation, the authors proposed that the pyridoxine had, indeed, been the etiologic agent producing the disease, and recommended that people without a special need for pyridoxine megadose stop taking them. (I understand that the FDA concurred in that conclusion and recommendation.) We believe that the available evidence relating Nutrasweet to seizures parallels the evidence used by those authors to relate excess pyridoxine to the peripheral neuropathy: They made no attempt to compare the incidence of the neuropathy in the perhaps-millions of pyridoxine-users with that in the general population, nor, of course, did they attempt to re-induce the neuropathy by giving their cured patients pyridoxine megadoses. We hope that you will agree, and will now issue a warning to physicians that aspartame consumption may be associated with a syndrome including severe headaches and, in some cases, grand mal seizures. We believe that people who do develop

severe headaches following aspartame consumption - whether they be migraineurs or those normally lacking a headache problem - should now be advised to stop consuming the aspartame, lest their symptoms evolve into something far more serious and potentially life-threatening: seizures.

3. To discuss with you the protocol of a study, directed by us, that is about to begin in MIT's NIH-funded Clinical Research Center. It should be pointed out that though that facility has adequate NIH support, our particular project is without any grant support, industry having chosen - perhaps not surprisingly - after about a year of deliberations not to support it. Perhaps that is for the best: The present system, in which the companies that sell our synthetic foods - like Nutrasweet - fund virtually <u>all</u> of the studies, FDA-mandated or not, of their safety is too vulnerable to misuse: As we can discuss, if you like, when outside investigators propose studies that might yield the "wrong" answer, a large bag of "dirty tricks" is available for derailing those studies. We hope that the evolving aspartame story will provide impetus for a new mechanism, in which companies that manufacture new, synthetic food constituents (like Nutrasweet's manufacturer, Monsanto), or those that insert it into their foods (like Coca-Cola, or Pepsi-Cola, or the makers of Kool-Aid or Crystal Lite) will be obligated to support the research that affirms their product's safety, <u>but will not be allowed to choose exactly what studies are done, nor who conducts them.</u>

Our study - which has, of course, been approved by the Institutional Review Boards at MIT and Harvard, as well as by the Clinical Research Center's Advisory Committee - may yield false negatives, in which event further studies will have to be done. For example, we may be giving the subjects the aspartame for too short a period: Analysis of the case records reveals that most of our subjects consumed aspartame for weeks or months prior to having their seizure, and many had a definite prodrome, characterized by headaches or personality changes, or even deja vu, for days or weeks prior to the seizure. Aspartame-related seizures may thus be a <u>tardive</u> phenomenon, akin to the slow effect of antidepressant drugs on clinical depression, or the slow appearancwe of tardive dyskinesia in patients taking neuroleptics; an 18-day test period may not be adequate. Another source of false negatives may be the

aspartame-breakdown products present in soft drinks, like the diketopiperazines and beta-aspartame: Perhaps these compounds, and not the "pure" aspartame that we are administering, cause the seizures. (As you all well know, the existence of beta-aspartame in soft drinks was discovered only a year ago, after perhaps 100,000,000 Americans had consumed generous amounts of it, and virtually no information is available in the Literature concerning its metabolism, absorption,uptake into the brain, and neurochemical effects. I have tried to obtain some of this compound from the Nutrasweet Division of the Monsanto Chemical Co., without success, in order to carry out such studies. I would be grateful for your assistance in this regard.)

4. To urge the FDA to require quantity labeling for aspartame. There seems no good reason why in the United States, alone of the countries that allow aspartame to be included in foods, neither the consumer nor the physician has any way of determining his aspartame intake, nor of limiting that intake to a set daily dose. While I personally concur with the view of Dr. Daniel Elsas that no pregnant woman should ever consume aspartame in any amount, I would feel a little better about the risk that its consumption imposes on her baby's brain if there were some way that she and her obstetrician could agree on a "personal ADI" of, say 250 milligrams per day, - and she could then implement that decision. Similar arguments would hold for people in other at-risk categories, i.e., small children; patients taking drugs that interact with the phenylalanine in aspartame (like L-dopa, or MAO inhibitors, or alpha-methyldopa); people with a migraine history who have not yet noted an association between headache frequency and aspartame intake.

One question that arises in any discussion of aspartame's side-effects is that of dosage: How much of the artificial sweetener need one take to increase the likelihood of seizures or migraine, and how much do Americans actually consume, - for example, in beverages on hot summer days? As you will note in reviewing our case reports, most of our subjects have taken a lot of it - perhaps 2-3 grams per day - but some have consumed surprisingly small amounts. In our forthcoming study, we intend to give the subjects the quantities that they believe they were taking during the period of their grand

5.1 = 1.79
6.1 = 1.56

mal seizure. But how much aspartame do "average" Americans now consume? Our data indicate that many people consume very large amounts, - far in excess of the ADI (even though, as mentioned above, even the ADI figure is of no obvious value in assessing a "safe" dose from the standpoint of brain function). One example: We were telephoned by a woman whose two-year-old child was having seizures. Right after birth, the woman's dentist told her that "sugar causes cavities", so she thereupon weaned her infant onto Diet Kool Aid (!). It would be interesting - and distressing - to estimate the concentrations of phenylalanine in that infant's brain. We have numerous case reports of adults consuming five and even six liters of diet soft drinks per day. Why do people consume so much aspartame? One probable reason is that no one's telling them not to do so: Nutrasweet is advertised on television as a "natural" compound (which it most assuredly is not), somehow related to cows and bucolic scenes; actors are shown opening a packet of "Equal" and swallowing its contents, undiluted. I hope very much that the FDA and, perhaps, the FTC will take steps to curtail this misleading and even dangerous advertising. I have seen last year's estimates, provided to you by what was then the Searle Company, of average aspartame intake by the various percentiles of the population. I believe that those numbers are spurious: They show, among other things, that people consume <u>less</u> aspartame in the summer than in other months, - a finding which violates good sense and reason. (This probably reflects the fact - affirmed in our laboratories at MIT - that people have much more difficulty accurately remembering snack than meal intakes.....and most of the aspartame in the American diet comes via cold beverages and other snack foods.)

Lastly, I would point out that, - although animal data are of limited value in anticipating aspartame's effects on the human brain (because the human's liver is so much less able than livers of test animals to metabolize the phenylalanine in aspartame) - there <u>is</u> evidence from animal studies suggesting an aspartame-seizure relationship. One such study, well known to the FDA, was the "first monkey study", carried out at the University of Wisconsin, in which five of the six monkeys receiving high aspartame doses for

a long period went on to develop seizures. (The other animal died.) A subsequent study, using lower doses and a shorter treatment period, carried out at the University of Illinois, failed to produce seizures, and, somehow, it was concluded that the negative study cancelled out the positive one. (In most laboratories, when an experiment done in two different ways yields opposirte answers, additional experiments are done.) Another study, conducted by Dr. Timothy Maher at the Mass. College of Pharmacy, has shown that the fraction of rodents developing seizures after receiving the drug pentylenetetrazole is markedly enhanced if the animals are also given sufficient aspartame to raise brain phenylalanine (but not tyrosine, which protects the brain from the effects of the phenylalanine) levels, - as would occur in people eating the synthetic sweetener. Of course, humans differ from the highly-inbred rodents, maintained in controlled environments, in that each person has a unique brain, with its own genetic material, its own history of trauma and diseases, and - consequently - its own seizure susceptibility. Thus, perhaps unfortunately, the only "experimental animal" in which the question of aspartame's relationship to seizures can be realistically addressed is an individual person who believes he has suffered such an event. There apparently is no shortage of such people, nor of good hypotheses that might explain why aspartame could facilitate seizures or headaches, perhaps starting with the one that led us first to focus on seizures, i.e., that the phenylalanine in aspartame suppresses the synthesis of monoaminergic neurotransmitters which are known both to raise seizure threshholds in experimental animals, and to be involved in the pathogenesis of migraine. Other good candidates include the diketopiperazines, beta-aspartame, and, sadly, additional aspartame breakdown products yet to be discovered.

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CASE REPORT

Seizure and mania after high intake of aspartame

The fairly widespread use of the artificial sweetener aspartame (*N*-L-α-aspartyl-L-phenylalanine 1-methyl ester), marketed under brand names such as Canderel, Equal, NutraSweet, and Tri-Sweet, has engendered considerable controversy, including suggestions of significant neurochemical changes.[1] Data presented by Wurtman[1] indicate that aspartame alone can almost double rat brain phenylalanine levels, while aspartame-carbohydrate combinations can raise brain tyrosine levels and suppress the physiologic increase in tryptophan that follows a carbohydrate-rich meal.[2-4] Such neurochemical changes could certainly be postulated to have potential behavioral impact, particularly in predisposed individuals. The following case is presented as a possible instance of such impact.

Case report

A 54-year-old married woman with no known medical difficulties other than a 20-year history of a unipolar affective disorder, initially treated for several years with psychoanalytic psychotherapy, continued to experience recurrent major depressive episodes until she was started 11 years ago on imipramine, 150 mg at bedtime. A dramatic response to this tricyclic had occurred. However, whenever the medication had been discontinued or tapered below 150 mg/d, she experienced a breakthrough of depressive symptomatology within several weeks. A decision was thus ultimately made for maintenance on imipramine at the 150 mg/d dosage at bedtime.

The patient had been taking this agent at this level for five years, with semiannual psychiatric visits for renewal of her prescription and brief assessment of mental status, when she suddenly experienced a grand mal seizure, followed by a profound behavioral change. Immediately after the seizure she was hospitalized for a neurologic evaluation, including CT scan. The evaluation did not elucidate the etiology of her seizure. During the hospitalization a psychiatric consultation was obtained because of euphoria, thought by the patient's internist to be quite out of character. At the time of the consultation she displayed psychomotor acceleration, flight of ideas, and grandiosity. The imipramine was discontinued and the possibility of using lithium carbonate raised, but the patient insisted on going home and was discharged on no medication.

At home she continued to display manic symptomatology, including insomnia, flight of ideas, irritability, and psychomotor acceleration. After three weeks the family insisted on psychiatric hospitalization. On admission, a diagnosis of mania was made and the patient was started on lithium carbonate, 300 mg qid. Two days after admission it was learned that it had been her custom to consume large amounts of iced tea (both she and her family reported that during the summer months her daily intake of it approached one gallon). In years past she had sweetened the tea with sugar. However, during the several weeks prior to the seizure and onset of mania, because of concern about her weight, she had used an iced tea preparation sweetened with aspartame.

As it was thought that the behavioral disturbance could be secondary to massive ingestion of aspartame, the lithium carbonate was discontinued, and within four days all evidence of manic activity had subsided. The patient was discharged six days after admission and appeared to be at her baseline level of functioning. Two months after discharge

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(on no medications) she reported recurrence of insomnia, depressive affect, and irritability, and requested that her imipramine be reinstated. This was done, again at a dose of 150 mg at bedtime. Over the ensuing 13 months she has functioned well, with no evidence of either depression or manic episodes. She continues to ingest large amounts of iced tea, sweetened with sugar rather than aspartame.

Discussion

This patient's clinical course suggests that high intake of aspartame may have triggered a seizure and subsequent manic episode. Although sustained treatment with imipramine could of course provoke mania in a bipolar patient, this does not appear likely in this case. There was no history of manic episodes, no known family history of bipolar illness, and no difficulty provoked by the same dose of imipramine five years prior to and one year subsequent to the use of aspartame. The high level of caffeine absorbed could also conceivably have played a role, but again there was at least a six-year history of consumption at essentially the same level without difficulty. Clinicians should bear in mind the possible impact of aspartame on catecholamine and indolamine metabolism, and inquire about use of this artificial sweetener when assessing patients with affective disorder. □

REFERENCES

1. Wurtman RJ: Neurochemical changes following high-dose aspartame with dietary carbohydrates. *N Engl J Med* 309:429-430, 1983.
2. Stegink LD, Filer LJ Jr, Baker GL, et al: Effect of aspartame loading upon plasma and erythrocyte amino acid levels in phenylketonuric heterozygotes and normal adult subjects. *J Nutr* 109:708-717, 1979.
3. Fernstrom JD, Wurtman RJ: Brain serotonin content: Increase following ingestion of carbohydrate diet. *Science* 174:1023-1025, 1971.
4. Fernstrom JD, Wurtman RJ, Hammerstrom-Wiklund B, et al: Diurnal variations in plasma concentrations of tryptophan, tyrosine, and other neutral amino acids: Effect of dietary protein intake. *Am J Clin Nutr* 32:1912-1922, 1979.