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Mr. DOMENICI. I see no reason whatsoever. The President has twice sent the compact to the Congress and I would strongly resist any implication that he has not sincere in doing so. In the discussions with the administration leading to this resolution, the original assumption contained in the President's budget that funding would occur in function 150 in the Department of State was dropped by the administration. The assumption of this resolution is the same as has twice been agreed upon by the Budget Committee, and that is that funding for the freely associated states will continue in function 800 in the Department of the Interior. I can not conceive of the Department of the Interior, with the full support of the Office of Management and Budget, not transmitting the necessary supplemental in sufficient time for enactment prior to fiscal year 1986. I would like to commend the Senator for his strong support for the compact, and it is a tribute to him and also to the distinguished Senator from Louisiana, Senator JOHNSTON, that the compact has twice been reported unanimously to the Senate. I look forward to its early passage as reported by the committee and can assure the Senator of my full support in enactment of the necessary supplemental which the President will request.

SACCHARIN STUDY AND LABELING ACT AMENDMENTS OF 1985

The PRESIDING OFFICER. Under the previous order, the hour of 4 p.m. having arrived, the Senate will turn to the consideration of S. 484, which the clerk will state by title.

The assistant legislative clerk will read as follows:

A bill (S. 484) to amend the Saccharin Study and Labeling Act.

The Senate proceeded to consider the bill which had been reported from the Committee on Labor and Human Resources, with an amendment:

On page 2, line 3, strike "1985", and insert "1987".

So as to make the bill read:

S. 484

Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled. That section 3 of the Saccharin Study and Labeling Act (21 U.S.C. 348 nt.) is amended by striking out "During the period beginning on the date of enactment of this Act and ending twenty-four months after the date of enactment of the Saccharin Study and Labeling Act Amendment of 1983" and inserting in lieu thereof "During the period ending May 1, 1987".

Mr. HATCH. Mr. President, I bring to the floor for final consideration S. 484, which extends the Saccharin Study and Labeling Act for 2 years. It is subject to a time agreement worked out between myself and the committee majority.

The Labor and Human Resources Committee ordered the bill reported on April 17, 1985 without opposition.

The Saccharin Study and Labeling Act was passed in 1978 in response to a proposal by the Food and Drug Administration to remove saccharin from the market. This proposal followed a study report implicating saccharin in increased bladder tumor incidence in rats. At that time saccharin had been in use as an artificial sweetner for over 80 years and had never been causally linked to any illness or death in humans. It was an important factor in the physical and emotional health of diabetics and others who need to control their weight or caloric intake.

The FDA proposal prompted considerable congressional interest. After pursuing its own inquiry, Congress felt that the evidence at that time was insufficient to conclude that saccharin was a significant health risk in humans, and found that it conferred real benefits on a significant portion of the population. Congress response was the Saccharin Study and Labeling Act, which forbade FDA from moving against saccharin solely on the basis of data available when it was enacted. This step clearly conveyed to FDA Congress' intent that the agency have more solid and substantial evidence of a human health risk before it restricted or eliminated the use of the sweetener.

Despite the passage of 7 years, the essential conditions have not changed, thus S. 484's extension of the act is completely appropriate. Specifically, though several important studies have been completed since that time, no scientists at the hearing on the bill felt that saccharin has been demonstrated to be a significant human health risk or that the current evidence warrants its removal from the market. Additional studies are currently underway to try to determine saccharin's mechanism of action in humans. But 7 years after passage of the original act, there is still no evidence that saccharin is a carcinogen in humans, despite an unusually long marketing history. And the Commissioner of the Food and Drug Administration testified:

(A)s in the past, we still do not adequately know the answer to all of the questions and uncertainties giving rise to the original 1977 saccharin moratorium. The actual risk, if any, of saccharin to humans still appears to be slight, however.

Further, saccharin's importance to the health of diabetics and others, while somewhat diminished in several applications by the availability of aspartame, remains significant. Thus, the American Diabetes Association and the Juvenile Diabetes Foundation, among others, support the extension.

I note in conclusion that the so-called moratorium in the Saccharin Study and Labeling Act is not absolute, but simply imposes certain limitations on regulatory action against the sweetener. Should information come available during the next 2 years demonstrating a public health risk from continued use of saccharin, under S. 484 the FDA retains the authority to take regulatory action.

Thus I have no hesitation in asking my colleagues to support this bill. It is a bipartisan bill, and it is passed out of committee without an opposing vote.

We have agreed to a time agreement on this bill with one amendment.

Mr. President, I reserve the remainder of my time.

Mr. KENNEDY addressed the Chair.

The PRESIDING OFFICER. Who yields time?

Mr. METZENBAUM. Mr. President, I yield the Senator time.

Mr. KENNEDY. Mr. President, I support this bill to extend the Saccharin Study and Labeling Act.

Saccharin is an important part of the diets of many Americans who need to avoid sugar intake. It is particularly important for diabetics.

While some things have changed in the artificial sweetener field since the last extension of this legislation—including the development of aspartame and new studies suggesting cyclamates may not be carcinogenic—there does not appear to be a fully satisfactory substitute for saccharin currently available.

The committee hearings we held reinforced my belief that an extension of the saccharin ban moratorium is appropriate at this time.

Senator METZENBAUM will be offering an amendment to require quantity labelling of aspartame in soft drinks. While the FDA has found aspartame to be generally safe, the center for disease control has recommended that further tests of aspartame be conducted to determine whether some groups may suffer harmful effects from aspartame consumption—particularly at high dose levels.

Our committee report mandates that these tests occur. It seems to me appropriate that consumers should be able to monitor their own consumption of aspartame.

Mr. President, I hope that the Members of this body will support Senator METZENBAUM's amendment to insure that the consumers of this country would be able to make that determination in terms of their own consumption.

Mr. President, on the bill itself, was there not time yielded to the Senator from Massachusetts?

The PRESIDING OFFICER. I did not catch the request of the Senator from Ohio.

Mr. KENNEDY. On the bill itself, is not the time divided between the Senator from Utah and the Senator from Massachusetts?

The PRESIDING OFFICER. It is divided between the Senator from Utah and the Senator from Ohio or their designee. I did not catch how much time the Senator from Ohio yielded.

Mr. KENNEDY. I thank the Chair.

Mr. METZENBAUM. Mr. President, I appreciate the support of the distinguished Senator from Massachusetts, whose record in the field of health legislation is second to none in this Congress. We have before us the bill to extend the period of exemption from the Delaney Act for the continued use of saccharin. I supported that extension because the distinguished chairman of the committee was kind enough to set a hearing not alone on the issue of saccharin but on the issue of saccharin and other sweeteners, including cyclamate and aspartame.

Out of that hearing, the Committee concluded that there should be an extension of the saccharin exemption, not for 3 years but for 2 years. In addition, the Committee provided that the Food and Drug Administration must report to the Congress on how the label laws for saccharin are being observed. It is a fact that some companies are complying with the law while others are not. For others it is a question of degree—some labels are in typeface so tiny that it is almost impossible to read.

The real issue that we have before us here today, Mr. President, relates to the aspartame labeling amendment which I shall shortly send to the desk. What this amendment would do is amend the Saccharin Study and Labeling Act to provide that any soft drink which contains aspartame shall state the total number of milligrams of aspartame contained in such serving of such soft drink.

I want Members of this body to understand where we stand on this issue. I shall not raise my voice during this debate. I shall not implore Senators to vote for my amendment. I shall ask them only to consider the merits of the issue. If they consider the merits of the issue, then they have to vote for the amendment because, on the merits, people have a right to know how much aspartame is in the product that they are drinking. That is all.

Nobody is saying that consumer cannot use aspartame. I point out to my colleagues that, as a matter of fact, the National Soft Drink Association, the organization that represents all of the soft drink people, at one point was prepared to take a position totally opposed to the use of aspartame in soft drinks. They never took quite that position as I shall discuss later.

Mr. President, if this amendment passes, the industry will have 18 months to implement its provisions. We are willing to give the industry adequate time to make the changes on the cans so that people may learn what is in the product that they are ingesting.

Mr. President, let me at the beginning deal with a prevalent misconception about this amendment. Lobbyists have been on the telephone, scurrying around all over the Hill, calling Members of this body, telling everyone that this amendment will, in some way, injure the bill. They have indicated that there is an urgent need for the saccharin extension and that my amendment will slow the bill down and even kill it.

I want Members of this body to understand that that claim is totally absurd. The FDA Commissioner, Dr. Young, testified at our hearing as follows:

I must emphasize that even if the ban were not extended, it would take a period of time for FDA to evaluate its action and then proceed through preliminary and final rulemaking which would be in itself, a couple of years' process . . . with the most rapid action it is 180 days to a year.

It appears my colleague, with whom I worked very well, the chairman of the committee, wrote a letter on this subject. He indicated in that letter that the attachment of my amendment to this bill would jeopardize the bill's fate in the House. I thought that was an important statement for him to be making, so I called the distinguished chairman of the House committee having jurisdiction over this matter.

I am pleased to report to my colleagues that he does not confirm that it would cause delay. Actually, he said that until he knows what the amendment specifically provides, he is hardly in a position to make any such indication. However, there is certainly no indication that it would kill the bill.

Mr. SIMON. Would my colleague yield for 1 minute?

Mr. METZENBAUM. I do indeed yield.

Mr. SIMON. I thank him for yielding.

Mr. President, I think the point he made a moment ago needs underscoring. He mentioned lobbyists contacting Members of the Senate on his amendment. They were contacting on the basis that he had a 6-month time limitation. In fact, with that 18 months, there should be no difficulty for any bottler to accommodate to this reality. It just seems to me that the Senator's amendment can do no harm and very well may do some good in safeguarding the people of this country, particularly some who may have some very real problems with this particular ingredient.

Mr. METZENBAUM. Mr. President, I very much appreciate the comments and the support of my friend and colleague from Illinois. I have no reservation in saying that, indeed, at one point, we were contemplating 6 months.

The Senator from Illinois had indicated his concern about that being too short a period of time. I agreed with the Senator's contention, and therefore I put in the 18-months figure. However, the issue is not so much how long the industry will have to implement the amendment. The issue is can we prevail upon the industry to disclose how much aspartame is in the can or the bottle?

Mr. SIMON. I thank the Senator from Ohio.

In his leadership on this matter as in many others, I have referred to him, half in jest and half not in jest, as the tiger of the Senate. He is that. He gets hold of an issue and fights for the cause. He has been fighting for the health of the people of this country. I commend him, and I am pleased to support his amendment.

Mr. METZENBAUM. I appreciate the support of the Senator from Illinois, who has served well and with distinction in the Congress of the United States, and we are happy to have him in this body.

Mr. President, I should like now to get to address the substance of this issue.

During the committee hearing, we had an aspartame scientific panel as well expert FDA testimony on aspartame. Aspartame issues were examined in extensive detail. This amendment evolved from that hearing and I would now like to offer three basic reasons for its passage.

Reason No. 1 is the consumer's right to know. People have a right to know about the makeup of the products they consume. It is no secret that the distinguished Senator from Florida [Mrs. HAWKINS] and I have a bill pending which has to do with the labeling of products generally.

Reason No. 2, the FDA as well as doctors around the country have received hundreds of complaints from people who believe that they have had adverse physical reactions to NutraSweet.

Professor Wurtman of MIT made a very strong case at the hearing for quantity labeling, on the basis that physicians treating these complaints would at least know how much has been consumed. They will be able to take into consideration, in making their diagnosis, whether the taking or the use of aspartame was a factor.

Professor Wurtman also argued that those with symptoms who consumed large amounts of NutraSweet will be able to gauge their consumption, and those who think they have symptoms but in reality have consumed only small amounts of NutraSweet would be able to stop worrying.

Third, significant medical and safety questions have been raised about NutraSweet, and I will get into some of those questions as we proceed in the debate this afternoon.

Clearly, we need to provide people with more information about this product than they already have. With respect to the criteria of aspartame or NutraSweet safety, the food and safety law is clear. The Government does not have to prove that a particular food additive or artificial sweetner is harmful. The Government does not have that burden of proof. The manufacturer must prove that it is safe and that there is reasonable certainty that no harm will result from its use.

I should like to share with my colleagues the history of NutraSweet. In

1977, the Food and Drug Administration recommended that Searle—it is their product—be brought before a grand jury, on the basis that its testing procedures were irregular and that false statements were made. It was the FDA that made that recommendation. These tests included many of the key NutraSweet tests.

In 1980, a public board of inquiry recommended that NutraSweet not be approved until further tests on brain tumors could be dealt with. The FDA Commissioner rejected that finding and approved NutraSweet. I will return to that issue at a later point in the debate.

At the hearing, we referred to in-house FDA memos which showed that three of the six FDA scientists advising the Commissioner, the so-called Commissioner's team, recommended that NutraSweet not be approved because certain tests were still dubious. We have, in addition, the concern expressed by Dr. Wurtman about the effects on brain chemistry of aspartame, concerns which the Soft Drink Association itself cited in its draft objection to NutraSweet in 1983. I will return to that draft objection of the Soft Drink Association subsequently, as well.

Clearly, questions surround this product.

In addition to those questions having to do with the testing and approval of NutraSweet, there is also the issue of the ADI for NutraSweet, or the acceptable maximum daily intake.

I should like to quote from an FDA memorandum dated January 8, 1983:

> The Bureau of Foods had previously evaluated the results of data from an extremely comprehensive animal testing program and established the acceptable maximum daily intake, the ADI, for aspartame to be 20 milligrams per kilogram of body weight per day. This figure is based on application of a hundredfold safety factor to the no-effect dose, 2,000 milligrams per kiligram, in a chronic rat study.

What does that mean? It means that the FDA normally applies a hundred fold safety factor to regulated food additives. In the case of aspartame, they made an exception. They increased the ADI to 50 milligrams per kilogram, and they said they had the tests to prove that this could be done safely.

What does an ADI really mean.

What an ADI means is this: If you weigh 150 pounds, you would have to drink 17 cans of diet soda with 100 percent NutraSweet to hit the acceptable maximum daily intake.

I do not really believe that many people drink 17 cans of diet soda with 100 percent NutraSweet and hit the ADI. However, if you are a child weighing 25 to 30 pounds, you would hit that limit with three or four cans of soda. That is not something that is going to happen to all kids. But certainly large numbers of children are likely to consume NutraSweet at these levels.

Nobody is saying that someone is going to keel over if they exceed the ADI on a given day. But with all the concerns raised about the safety of NutraSweet, does it not make sense, is it not logical, for individuals and their physicians to know how much NutraSweet is in the diet soda?

What could be so terrible about stating the amount? How else will the user or the physician know if the person is exceeding reasonable consumption limits, particularly during the summer months?

Some would say, "Well, even if we told them the amount, they wouldn't understand." Some would. Some would not. But what in the world is so horrific? What in the world is so terrible? Why is it such a problem for the industry, within 18 months, to change their cans to indicate the amount of aspartame—that is NutraSweet—in the product?

Some would say, "Why label only soft drinks?" The answer to that is soft drinks are the major source of NutraSweet consumption.

Those who argue against the amendment on the basis that it singles out soft drinks are very quick to point out that they do not support labeling of any products containing NutraSweet.

Besides, if we mandate labeling of soft drinks, do you not think the other manufacturers will get the message and seriously consider implementing their own labeling?

Some would argue—and it has been stated—"Why don't you indicate how much sugar there is on the label?" As a matter of fact, if somebody cares to offer an amendment or to suggest such labeling, I would have no problem with that. I am one who firmly believes that the more the individual is able to know about the food he or she consumes, the better chance that individual has in seeing to it that the food ingested by him or her will be healthful and not dangerous to his or her life.

Dr. Roberts, of the National Soft Drink Association, testified at the hearing and said if a consumer wants to know how much NutraSweet is in a can of diet soda, they can write the National Soft Drink Association in Washington to find out. He said:

> We like people to have this information so we have no objection whatsoever, and, in addition, we try to provide additional information by putting our associated kinds of brochures.

So they are saying, "You can get the information, we are willing to give it to you, we might even make up a brochure, but we don't want to put it on the can."

Why? Is it that there is no room on the can? Is it that the people are just too nosy, to find that out?

I went to a can of Diet Coke to see what was on the can. Mr. President, they have enough reading material on the can to fill the CONGRESSIONAL RECORD.

On the front label they say, "100 percent NutraSweet brand sweetener." They say, "Saccharin-free, low-calorie cola: "phenylketonurics," contains "phenylalanine."

Let us take a look at the back of the Diet Coke label.

Nutrition information per serving

Serving size (ounces)	6 oz.
Servings per container	2
Calories per serving	0
Protein	0
Carbohydrate	(*)
Fat	0
Sodium (milligrams)	35

* Less than 1 gram.

And it continues on. They have a lot of material on the back of that label.

Perentage of U.S. recommended daily allowances (U.S. RDA): contains less than 2 percent of the U.S. RDA of protein, vitamin A, vitamin C, thiamine, riboflavin, niacin, calcium, and iron. Contains carbonated water, caramel color, aspartame, (NutraSweet brand), phosphoric acid, potassium benzoate preservative, natural flavors, citric acid, caffeine.

That is not all. It has more on the back label. "NutraSweet and the NutraSweet symbol," says the back label, "are the trademarks of G.D. Searle & Co. Consumer information: call 1-800-GET-COKE," and then the number "438-2653."

Well, I guess it would not be too much of an imposition for the soft drink industry to indicate that there are 180 to 200 milligrams of NutraSweet in that can of Diet Coke. It would not ruin the can or its appearance.

Now, the Soft Drink Association has also said that if consumers want to know how much aspartame is in a can of Diet Coke, they can call the number on the can; 1-800-GET-COKE.

Now, my staff did just that. At 9:09 a.m. on May 1, my staff called the Coke consumer information line, 1-800-GET-COKE, and after listening to a jingle, the operator came on the line. She was a very nice woman. Her name was Pat. My staff asked her the following question: "Can you tell me how much NutraSweet is in the can?" Her reply, "No. I'm sorry, I don't have that information." My staff then asked, "Is there any limit to the amount you should consume?"

Reply: "No. You can drink 40 cans a day." My staff asked her about kids. Could they drink that amount? Her reply, "No problem."

Now, FDA's acceptable maximum daily intake for a 150-pound person is 17 cans, and for a 25- to 30-pound person, 3 to 4 cans.

So I say that dialing 1-800 GET-COKE does not get you very far in obtaining information on how much NutraSweet is in a can of Diet Coke. Would the Chair be good enough to advise how much time the Senator from Ohio has remaining?

The PRESIDING OFFICER. The Senator has 32 minutes remaining.

Mr. METZENBAUM. I thank the Chair.

I ask my colleagues to keep in mind that the soft drink association, which is strongly opposed to letting consum-

ers know how much NutraSweet they are consuming, is the same association which in 1983 prepared a draft legal document objecting to NutraSweet ever being allowed on the market, citing serious and unresolved questions about the public health.

Let me explain the significance of that statement. The National Soft Drink Association, along with the law firm of Patton, Boggs & Blow, prepared a document that was to be submitted before the U.S. Department of Health and Human Services, Food and Drug Administration. The document was entitled "Objections of the National Soft Drink Association to a Final Rule Permitting the Use of Aspartame in Carbonated Beverages and Carbonated Beverage Syrup Bases and a Request for a Hearing on the Objections." The issue before the Food and Drug Administration at that time, according to this draft objection was aspartame; food additives for direct addition to human food. 48 Federal Register 31376, July 8, 1983.

I want to explain to my colleagues that the draft legal document was not filed, but it was prepared and I ask unanimous consent that at the conclusion of my remarks the entire contents of that draft objection be included in the RECORD.

The PRESIDING OFFICER. Without objection, it is so ordered.

(See exhibit 1.)

Mr. METZENBAUM. Although it was not filed, that does not mean that it was not the position of the organization at that time. It does not mean that the findings and the conclusions reached in that document were not valid. It only indicates that for reasons best known to them, unquestionably business reasons, they decided not to file it.

But they were not objecting to labeling, which is all that my amendment would do. My amendment would only indicate the amount of aspartame that is in the product.

Their objection took the position that aspartame should not be included in soft drinks. That draft objection indicates that the organization had significant health concerns with the product before it was approved for soft drinks.

Let me direct your attention to some of the things that they said in that draft document:

G.D. Searle and Company has not demonstrated to a reasonable certainty that the use of aspartame in soft drinks, without quantitative limitation, will not adversely affect human health as a result of the changes such use is likely to cause in brain chemistry and under certain reasonable anticipated conditions of use.

For these reasons, Searle has not met its burden of demonstrating to a reasonable certainty that the unlimited use of aspartame, especially in combination with carbohydrates, will not adversely affect human health.

It went on to say that:

The questions posed by Dr. Wurtman are significant because of the seriousness of the potential effects E.G., changes in blood pressure and because of aspartame's anticipated widespread use—one that includes consumption by potentially vulnerable subgroups, such as children, pregnant women, and hyperactives.

They went on to say in that document:

Specifically, Searle has not met its burden under section 408 . . . to demonstrate that aspartame is safe and functional for use in soft drinks.

And they further stated:

Collectively, the extensive deficiencies in the stability studies conducted by Searle to demonstrate that aspartame and its degradation products are safe in soft drinks intended to be sold in the United States, render those studies inadequate and unreliable.

Now, the National Soft Drink Association in August 1983, thought that aspartame should not be used in soft drinks. But so many of my colleagues have been called recently and told that they should not vote for this amendment. Yet this amendment does not provide that the product should not be sold, only that the people who use the product have a right to know how much of it they are consuming.

Now, I think that it is important to know what occurred at the Department of Health and Human Services when aspartame was approved. I would like to share with my colleagues a memo dated May 19, 1981, from the Acting Associate Commissioner for Health Affairs on the subject of aspartame to the Commissioner of the Food and Drug Administration.

In this memo, they state the following:

The first and primary agenda item relates to the brain tumor issue. This was the point on which the Public Board of Inquiry concluded that safety had not been shown. A first draft "final decision" on this issue is attached.

They went on to say:

The major issue discussed at the hearing was the background rate for spontaneous brain tumors in the specific strain of rat used by Searle.

They talked about the conduct of the study.

The conduct of all three rat studies has been criticized by Dr. Olney. Some of the staff scientists believe the studies were adequately conducted, while others tend to agree with Dr. Olney that one or more of the studies was severely flawed. Again, the different positions are documented.

Mr. President, I ask unanimous consent that the FDA memo be printed in the RECORD at the conclusion of my remarks.

The PRESIDING OFFICER (Mr. GORTON). Without objection, it is so ordered.

(See exhibit 2.)

Mr. METZENBAUM. Now, Mr. President, my colleagues may go ahead and defeat this amendment. But I hope they will remember this debate in the months ahead. I do not claim children will develop brain tumors. I do not know that. I do know that the FDA was worried about it. I do know that three of the six FDA scientists advising the FDA Commissioner on final approval were sufficiently worried about it that they were not willing to approve the product. The FDA's own scientists were split on the issue.

So what we are talking about is, do we agree that there will be labeling indicating how much aspartame is in the product or do we close our minds to all the questions surrounding this product and turn our backs on the consumer's right to know.

I am frank to tell you I stand on the floor and I do not have all the answers. But I believe that this body has some responsibility to the children, grandchildren, and adults who are consuming these soft drinks. And all I am asking for here today is that which I consider to be the very minimum. To tell the people who are drinking these diet sodas how much aspartame is in the product.

Now I might note that some have said that the Diabetes Association opposes this amendment. My staff spoke with their Washington representative today. They do not oppose this amendment. Their official position is to advise caution for pregnant women and children for both aspartame and saccharine consumption.

In conclusion, Mr. President—and I will confess that I have spoken at some length, but I speak at some length because I am concerned about what aspartame may do to people if ingested in too great quantities. I am concerned about the possibility of brain tumors and other forms of brain damage. Those who studied the issue at the FDA were concerned as well.

This amendment is basic. It is simple. It does not really ask for much, and for the life of me, I cannot understand why the Soft Drink Association has spent so much time and has done so much lobbying. What have they got to hide? All we are asking is how much aspartame is in the soft drink. And we are saying take 18 months, if you need that amount of time, in order to change your cans in order that we will not place an economic burden on your business.

My amendment is no big deal. It is not going to save the world. It is not going to solve problems in Nicaragua and it is not going to balance the budget. But it is one little step in the right direction. We will be providing people with the minimum amount of information they deserve about a substance which poses many unanswered questions about basic consumer health and safety.

Mr. President, I do not wish to delay the Senate with lengthy debate. I would like to submit for the record a number of scientific and other submissions relating to aspartame. I ask unanimous consent that they be printed in the RECORD.

There being no objection, the material was ordered to be printed in the RECORD, as follows:

[From the Washington Post, April 24, 1985]

SWEETENERS FACE SCRUTINY OVER SAFETY

(By Sally Squires)

Just in time for spring dieting, three artificial sweeteners—aspartame, saccharin and cyclamates—are in the news.

Last week, a Senate panel rejected an amendment requiring labeling on soft drinks containing aspartame. This week, Congress considers whether to keep saccharin on the market. Meanwhile a National Academy of Sciences committee is reviewing the health effects of cyclamates, which were banned in 1970 because of a possible link with cancer.

Despite growing scientific evidence that aspartame causes alterations in brain chemicals and may change behavior, the Labor and Human Resources Committee defeated an amendment requiring soft drinks containing aspartame to list the amount of the chemical on the package.

Aspartame, marketed under the trade name NutraSweet by G.D. Searle and Co., is used in a variety of foods and beverages, ranging from diet soft drinks to the table sugar substitute known as Equal. Products containing NutraSweet carry a label warning people with the genetic disease phenylketonuria (PKU) to avoid these food and beverages. PKU sufferers are born lacking an important enzyme that allows them to digest the amino acid phenylalanine—a building block of protein and an important constituent of NutraSweet. PKU infants who consume phenylalanine become severely brain-damaged, and thus must be placed on a restricted diet for the rest of their lives.

Studies in humans and in animals suggest that aspartame can cause changes in neurotransmitters—the chemical substances that send messages throughout the brain. These changes are particularly pronounced when aspartame is consumed with carbohydrates. Among the health effects associated with aspartame consumption are headaches and behavioral changes.

The FDA has established guidelines that suggest limiting aspartame consumption to 50 milligrams per kilogram of body weight. A kilogram is equal to 2.2 pounds. This means that a 25-pound child (about 11 kilograms) should consume no more than 550 milligrams of aspartame a day—about the amount in four cans of diet soda.

Without labels describing how much aspartame is included in a product, "it is difficult if not impossible for the patient or his physician to know how much aspartame he has eaten or drunk," Dr. Richard Wurtman, a professor at the Massachusetts Institute of Technology, reported at a recent hearing before the Labor and Human Resources Committee. "I doubt that one consumer (or physician) in a thousand now realizes, for example, that a can of Tab provides less than one fourth as much aspartame as a can of Diet Pepsi or Diet Coke."

"Although we've made some progress with further NutraSweet and saccharin tests, we still have not fully protected the health and rights of consumers," said the amendment's sponsor, Sen. Howard M. Metzenbaum (D—Ohio).

"I believe that it is essential that companies which include aspartame in their products be required to indicate on the labels how much of the sweetener is present in each can or serving," adds Wurtman, who says he uses aspartame himself. "I think that it would be very good to have labeling of all artificial sweeteners."

A spokesman for Searle said that the company is not "against labeling if it appears on all food products. We thought it would be unfair to single out just NutraSweet."

"It is a very safe product. NutraSweet is the most tested product on the market today."

Other recent scientific evidence suggests a link between the development of nonmalignant skin lesions and the consumption of aspartame. Research also suggests headaches and perhaps even high blood pressure can result from combing aspartame with certain medications.

One study, published in the Annals of Internal Medicine described how a 22-year-old woman who drank daily 36 to 44 ounces of an aspartame-sweetened diet drink developed skin lesions on her thighs. Controlled tests over a period of weeks documented that the woman's lesions disappeared and reappeared with the use of aspartame. Two other reports published earlier this year in the American Journal of Psychiatry and the British journal Lancet document behavioral changes among aspartame users.

Cyclamates could again become a choice for dieters and diabetics. A National Academy of Sciences committee is currently reviewing the scientific literature regarding the banned artificial sweetner—at the request of the Food and Drug Administration (FDA)—to help determine whether it causes cancer. The committee is expected to report its findings in June. If the scientific evidence is inconclusive, then the committee will design research that could answer the safety question of cyclamates once and for all.

Saccharin could soon be banned if Congress refuses to extend the most recent moratorium on prohibiting saccharin sales, which expired Monday. In 1977, despite evidence that saccharin caused bladder cancer in rats, Congress passed a law that allowed it to remain on the market. But FDA Commissioner Frank Young told a congressional committee recently that even if the moratorium is not renewed this week, it would take between six months and a year for saccharin to be removed from the market.

[From the Science Times, Feb. 5, 1985]

SWEETENER WORRIES SOME SCIENTISTS

(By Jane E. Brody)

As sales of aspartame, the nation's newest artificial sweetener, expand rapidly among millions of users, scientific concern is also growing among some researchers about its safety.

The researchers are alarmed by recent reports that a small percentage of users, including at least two young children, may have suffered severe adverse reactions to aspartame. Especially worrisome are reactions involving the brain, including seizures, incapacitating headaches, dizziness, behavioral changes and depression.

Although there is at present no evidence, there is concern, too, over the possibility that in some consumers, aspartame may cause subtle disruptions in the balance of brain chemicals that influence mood, alertness and hunger for certain nutrients. Animal studies have raised the issue but its investigation is only just beginning.

Two scientists, Dr. C. Keith Conners of Children's Hospital in Washington and Dr. Richard Wurtman of the Massachusetts Institute of Technology, believe that the Food and Drug Administration misled the public on aspartame's safety by understating the concern voiced in a recent official scientific analysis of consumer complaints.

"If you read the C.D.C. report," Dr. Wurtman said in an interview, referring to the national Centers for Disease Control, "it doesn't sound nearly so complacent as the F.D.A. Talk Paper that interpreted the findings for the public."

According to the C.D.C., its detailed investigation of 200 consumer complaints, out of more than 600 received, suggests the need for a systematic study of adverse effects, especially neurological and behavioral effects, which accounted for 67 percent of the complaints received.

"The number of instances of persons challenging themselves several times with aspartame-containing products and reporting symptoms with each rechallenge suggests that some individuals may be sensitive," the report states. "The only way to clearly determine this is through focused clinical studies." Citing the "subtlety and potential seriousness of some of the manifestations" reported by consumers, the disease control centers said the studies should concentrate on such symptoms as "headaches, mood alterations and behavior changes."

The manufacturer of aspartame, G.D. Searle & Company, said a proposal for a clinical study has been submitted to the F.D.A., but there are as yet no plans to actively monitor the effects of aspartame in the general population.

Searle says the C.D.C. findings are not surprising, given the fact that more than 100 million people now use aspartame. Dr. Gerald E. Gaull, vice president for nutrition and medical affairs for aspartame at Searle, said it is possible that "a few people may be allergic or sensitive to it." He added that "for those few people, the issue is not one of safety but rather of food selection."

Both the drug agency and Searle say aspartame is the most extensively studied food additive in history and that the studies clearly establish its safety. Dr. Gaull noted, "It's not just the F.D.A. that has viewed the tests as adequate, but also the World Health Organization and comparable regulatory agencies in Canada, the United Kingdom, Japan and about 37 other countries."

Dr. Sanford Miller, head of the F.D.A.'s Bureau of Foods, said: "I don't know of any substance in recent years that's been looked at with the intensity of aspartame. No one had yet come up with the slightest evidence to show we were wrong in approving it."

However, some researchers and consumer organizations assert that the studies have not been careful or far-reaching enough to establish the safety of aspartame, which is now entering the food supply at an unprecedented rate following its approval in 1983 for use in soft drinks.

For example, Dr. Walle Nauta, a Massachusetts Institute of Technology psychologist who heads a public board of inquiry that was asked by the F.D.A. in 1980 to review safety concerns about aspartame, has said that had the panel known how widely aspartame would be used, it would have issued stronger recommendations. He told Common Cause, a public affairs organization that completed a nine-month investigation of aspartame last year, that use of aspartame in soft drinks "never figured in our decision making."

Dr. Nauta's panel was also limited in its assessment to interpreting the results of safety tests. Whether the tests were properly conducted in the first place was not considered, he said.

FOUND IN WIDE VARIETY OF FOODS

Aspartame, marketed as Nutra-Sweet (when used as a food additive) and Equal (the table-top version), is now found in such foods as soft drinks, gum, breakfast cereals, mixes for hot chocolate and cold drinks and pudding mixes. Although in most products it is combined with either sugar or saccha-

n, a trend is already evident toward the se of aspartame as the sole sweetener in rocessed foods. Coca-Cola and Pepsi-cola, or—example, announced they would be sing it alone in diet soft drinks, and Ralston-Purina has just introduced a new ereal, Sunflakes, sweetened only with spartame. Several food processors have iled proposals to use the sweetener in ogurt, ice cream and flavored drinks.

Since it was approved for use in this country in 1981, worldwide sales of aspartame have grown from $74 million in 1982 to $800 million last year. It has been an enormous financial boost for a company that a decade ago was embroiled in costly controversy over the quality of its safety tests on several major drugs and aspartame.

Aspartame was originally approved for marketing in 1974, but the approval was quickly stayed when a scientist, Dr. John Olney of Washington University, and an attorney, James S. Turner, objected on the basis of Dr. Olney's findings in animals that aspartame might cause cancerous brain tumors. Dr. Olney remains a strong critic of aspartame approval. Mr. Turner, a consumer advocate with the Community Nutrition Institute in Washington, said the studies needed to clarify this risk had not yet been properly done. The institute recently petitioned the United States Court of Appeals for the District of Columbia to halt further marketing of aspartame products pending the outcome of a requested public hearing on aspartame's safety.

Nor were a number of key studies that had been called into question as scientifically lacking in design and execution ever redone, according to Common Cause and Mr. Turner. Nonetheless, in 1981, Arthur Hull Hayes, then Commissioner of Food and Drugs, approved aspartame for use in dry foods and as a table-top sweetener. Two years later Mark Novich, as acting commissioner, approved aspartame for use in soft drinks. Soon after Dr. Hayes left the agency and took a job as senior medical consultant for Burson-Marsteller, a public relations agency that represents Searle. The company says Dr. Hayes, who is also dean of New York Medical College, has never consulted on anything having to do with aspartame or any other product he ruled on at the drug agency.

MANY FACTORS IN POPULARITY

Among the reasons aspartame is so popular are that it provides the sweetening power of sugar at one-tenth the caloric cost; unlike products made with saccharin, it does not carry a warning about cancer risk and it tastes very much like sugar but, unlike saccharin, has no unpleasant aftertaste.

The drug agency has set an allowable daily intake of 50 milligrams of aspartame per kilogram of body weight, and the agency predicted that actual average use would run around eight to ten milligrams. According to Dr. Gault of Searle, levels of use found in a national survey last spring showed that the average was then already twice that—19 milligrams—and the maximum level consumed by "aspartame abusers" was 28 milligrams. A United States attorney representing the F.D.A. said in court last month that average consumption is now 30 milligrams and that many consumers are above the 50 milligrams maximum suggested.

According to Dr. Wurtman, some consumers can easily reach consumption levels that have been linked in animal studies to adverse effects on brain chemicals. Ironically, he added, those using the sweetener to control calories may be defeating their purpose, since his studies show high levels of aspartame may trigger a craving for carbohydrates by depleting the brain of a chemical that registers carbohydrate satiety.

Dr. Conners is worried about aspartame's effects on certain highly sensitive individuals. He has studied two young children who suffer extreme agitation following doses of aspartame equivalent to the amount found in a six-ounce serving of Kool-Aid sweetened with NutraSweet. One of the children becomes so agitated he has to be restrained, Dr. Conners said. The other, who is sensitive to sugar, becomes even more aggressive when given aspartame, he said.

Aspartame is the product of two amino acids (the chemical building blocks of protein), aspartic acid and phenylalanine, which are found in rather large amounts in ordinary protein-rich foods. When digested and metabolized, aspartame breaks down into its component amino acids and methyl alcohol.

Scientific concern has focused on phenylalanine, since some people are unable to process it properly, causing a buildup in the body that can damage the developing brain. A phenylalanine buildup, should it occur in response to aspartame, could endanger an unborn child whose mother has high levels of phenylalanine in her blood in pregnancy, some scientists say. Dr. William Pardridge of the University of California at Los Angeles, for one, is worried about possible detrimental effects on I.Q. in the children of phenylalanine-intolerant women who consume large amounts of aspartame in pregnancy.

Phenylalanine is also the precursor to tyrosine, a neurotransmitter in the brain. A recent study in rats by researchers in Dr. Wurtman's laboratory showed that aspartame can cause large buildups of phenylalanine and tyrosine in the brain. However, Dr. Wurtman has noted that rats process phenylalanine differently from people. He added that a federally financed study of the behavioral effects of aspartame in animals and people was now under way in his laboratory.

[Western Union Telegram, Apr. 22, 1985]

Senator HOWARD METZENBAUM,
Capitol One DC.

With your permission I would like to amplify some of my responses to the questions that you asked me during the recent committee hearings on artificial sweeteners:

1. Many foods besides aspartame apparently cause chemical changes in the brain. Examples include virtually all carbohydrates (sugars and starches), proteins, lecithins, and caffeine. However, the particular changes that follow aspartame consumption have not been associated with other foods, and thus must be fully evaluated to determine their effects on health and behavior. This evaluation should be pursued vigorously. Hereafter it must be assumed that all new food additives will require a similar careful evaluation.

2. For the reasons that I indicated, I believe it is important that food labels should now include the quantities of aspartame that the products contain. I also believe, though, that similar information should be provided about their contents of other food additives, because this is good nutritional policy; because health questions have also been raised about other sweeteners; and because the biologic effects of combining two chemicals (like sweeteners) can sometimes be quite different from the effects of giving the individual compounds by themselves.

3. I am not proposing that the ADI for aspartame be changed at this time; I'd have difficulty justifying any specific number rigorously. Rather, I believe that the ADI should be subject to continuing review, as new information about aspartame's effects (or lack of effects) accumulates. Ultimately I would like to see labels also include information about the upper limits of daily consumption for children and adults, but for the present, I believe that indicating the quantities of aspartame in each product would constitute an important and necessary first step.

4. I believe that well designed, placebo-controlled clinical studies should be initiated, particularly on aspartame's possible involvement in headaches and in lowering seizure thresholds. These studies should also determine whether aspartame metabolism is abnormal in subjects who develop such side effects (for example, whether the plasma amino acid pattern changes abnormally after aspartame consumption). The proposed studies should use ADI doses of aspartame, given acutely and chronically for many days, in circumstances similar to those in which people may actually use the sweetener (for example, taken along with some dietary carbohydrates and by people on weight reduction diets). I hope soon to initiate such studies at MIT's clinical research center, and understand that other institutions are also doing so.

Thank you for considering these comments.

Sincerely yours,

RICHARD WURTMAN, M.D.,
Professor, M.I.T.

UNIVERSITY OF CALIFORNIA,
LOS ANGELES,
April 22, 1985.

Statement to Senator HOWARD METZENBAUM:

Thank you for giving me the opportunity to express my views on the potential safety issues related to the effects on the brain of high dose usage of a new dipeptide sweetener, aspartame.

1. If high dose aspartame usage does have harmful effects, the sequelae are likely mediated via the phenylalanine component of aspartame, and not via the two other components of the compound, e.g., aspartate or methanol, or via the dipeptide itself. Among the tissues of the body, the brain is selectively vulnerable to large increases in blood phenylalanine. Thus, if aspartame is to have any harmful effects, it is most likely that the brain will be the target organ of aspartame-induced sequelae. Indeed, the Center for Disease Control recently concluded, "the highest priority for any in-future investigation might be in the neurologic/behavioral area".

2. A central question is, "what is a substantial increase in blood phenylalanine caused by aspartame ingestion?" The 1980 Public Board of Inquiry concluded that a minimum toxic threshold of blood phenylalanine of 0.5–0.6 mM may be used in man, and blood concentrations below this critical threshold may be considered harmless. If the threshold concept is true, then I do not believe that aspartame will cause harmful effects since even high dose aspartame usage will rarely cause an increase of blood phenylalanine up to 0.5–0.6 mM. However, a review of the medical literature indicates that there is insufficient evidence to conclude that the relationship between high blood phenylalanine and brain disorders follows a threshold relationship. Recent evidence indicates that the relationship between blood phenylalanine increases and brain effects is a linear one (1,2), and that changes in brain function occur when blood phenylalanine rises in increments of 0.25 mM (1,2). For example, there is a 10.5 point drop in I.Q. in infants born of mothers with blood phenylalanine increases in the range

of 0.25 mM over normal levels (1,3). Another study shows that neuropsychologic performance in children, e.g., choice reaction time, is altered when plasma phenylalanine is increased in the 0.25 mM range (2). These two studies are illustrative in that they describe effects in the two groups who are most at risk to develop high blood phenylalanine: (a) developing fetuses, owing to the ability of the placental membrane to concentrate phenylalanine inside the fetus, and (b) 7-12 year old children who, owing to their reduced body weight, consume high doses of aspartame in terms of mg/kg/day.

3. The studies showing effects on the brain in man of blood phenylalanine in the 0.25 mM range are of importance since the available data indicates that plasma phenylalanine will increase to this level in humans consuming aspartame on the order of 25 mg/kg, three times a day, particularly in heterozygotes (4) (and there is an estimated 4-20 million heterozygotes in this country) (1). Although 25 mg/kg three times per day, or 75 mg/kg/day, is nearly ten-fold greater than the expected FDA or industry projections of aspartame intake, the evidence in the literature indicates this is a likely daily intake for many consumers. For example, 7-12 year old children are found to consume up to 77 mg/kg/day (5). Normal weight adults are found to consume up to 32 mg/kg/day (6).

On the basis of the likelihood of a linear relationship between blood phenylalanine increases and brain function, I think it is essential that a case be made for labeling products with the mg of aspartame per product on the label. Thus, the physician who attempts to relate any possible neurologic/behavioral effects to aspartame intake may be able, through dietary survey, to compute the patient's average daily intake of aspartame in mg/kg. For example, if the physician determines that the daily intake is 10-20 mg/kg, then it is very unlikely that the patient's neuologic/behavioral problems are related to aspartame. On the other hand, if the daily intake is on the order of 50-75 mg/kg/day, then the physician may undertake a retrospective and prospective analysis of the possible relationship between aspartame-induced high blood phenylalanine and the patient's neurologic/behavioral problems.

Yours very truly,

WILLIAM M. PARDRIDGE, M.D.,
Associate Professor of Medicine.

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SEVERE BEHAVIORAL REACTIONS TO ASPARTAME IN A FOUR YEAR OLD BOY

(C. Keith Conners, Karen Wells, Sandra Kronsberg and Ellen Schwab)

BACKGROUND

The subject of this study is Stephen, a 4 year old boy who was referred for evaluation by his mother. During August of 1983 mother had begun providing Stephen with Sugar Free Kool-Aid with NutraSweet (Cherry artificial flavor) over a period of 3 weeks. He was thought to drink approximately 20 ounces/day in a more diluted form than called for on package instructions.

His behavior became increasingly erratic over this period (as reconstructed by the mother later). He became tearful, easily frustrated, had unprovoked angry outbursts and was extremely irritable. This culminated in a dramatic episode in which he became inconsolably and wildly emotional. He had to be isolated to his room where he repeatedly ran full force into the wall, knocking himself to the floor, crying, and repeating the performance until he was restrained.

Mother called her pediatrician who suspected that the new Kool-Aid might be responsible, and advised her to remove it. She did so and his behavior then returned to normal within 24 hours. About 2 weeks later the mother re-introduced the Kool-Aid, whereupon another violent reaction occurred within about 30 minutes. This episode subsided the same day. Suspecting the Aspartame in the drink, mother called us upon the advice of the pediatrician who had heard of our interest in sugar products and behavior. After some hesitation, she agreed to examine the problem in an experimental, double-blind fashion. An informed consent was obtained.

HISTORY

Stephen weighed 10.5 pounds at birth. Mother gained 55 pounds during pregnancy (twice the recommended amount), and delivery was 2.5 weeks late. He was described as "a great baby, a good sleeper and good eater." He had some feeding problems as an infant, exhibiting rhinitis and diarrhea following feedings of formula. He eventually tolerated formula feedings of Similac with iron (a cow's milk formula). Upon examination he was found to be a well-developed, well-nourished four year old at the 30th percentile of weight (16 kg) for his stature (105.4 cm).

Stephen is reported to be a very active boy, "going all the time". He still naps every afternoon. He is described as quite oppositional, saying 'no' to everything. Mother appears to try to manage mostly by 'yelling and screaming', though she was observed to be quite tender and solicitous of Stephen in the waiting room. He is quite a happy boy on the whole, seems very bright and precocious, but he can be quite aggressive and "beats his brother (7 years old) to a pulp". Sugar appears to make him more energetic.

There is some question of a possible milk allergy and allergy to molds. Mother says she cannot eat apples, pears, peaches or plums because of allergy to pectin. She is also allergic to jellied candies, pollen, penicillin and macrodantin.

Stephen's mother filled out a 93-item parent questionnaire (Conners Parent Questionnaire). The Restless-Impulsive factor showed an elevation of about 2 standard deviations, but was otherwise within normal range.

METHOD

Ratings. Mother was asked to fill out the 10-item Hyperactivity Scale on a daily basis. These items measure restless, impulsive, emotional behaviors. She was asked to obtain data over a 2-week period to establish Stephen's baseline.

Observations. On four occasions, about one week apart, Stephen and his mother returned to the hospital where they were observed through a one-way mirror for an hour or more. For the first half of the session mother was instructed to simply sit in the room and let Stephen do whatever he wanted. A variety of toys were available and he was asked to play by himself while mother sat and busied herself with some work. For the second half of the hour mother was instructed to issue various commands, such as "pick up the toys", "clean up the room", "sit in the chair", etc.

The behavior was videotaped from the other side of the room and later scored blind (without knowledge of the conditions) by an experienced behavioral observer. Behavior was coded in 15-sec blocks using an interval-sampling procedure developed by Hanf and Forehand. The main category of interest is child noncompliance to commands. Other categories include "whine/cry", and "destructive".

Challenge. Just prior to each observation period Stephen was given a 6 ounce cup of Cherry Kool-Aid to drink. On two occasions this was the sugar-sweetened version and on two occasions it was the NutriSweet version. The dietician (E.S.) made the determination of order of challenge, and neither parent, child, nor other observers had knowledge of the sequence. As it turned out, the sequence chosen was ABAB, with A=Aspartame, B=Sugar.

RESULTS

The results of the Hyperactivity Ratings is shown in Figure 1. After a stable baseline there is a clear increase in deviant behavior on the Aspartame days compared with the sugar days.

Figure 2 shows the percent of scoring intervals during which noncompliance occurred. Again there is a substantial increase in this behavior during the Aspartame challenge days.

Followup. Mother has continued to restrict Stephen from Aspartame, but on several occasions he has accidentally had drinks provided at school or at friends' parties. On each and every occasion mother claims that he has become quite disturbed. On one of these occasions he became very tearful and repeatedly said something was wrong, crying "Mommy, Mommy, please help me, I can't stand it."

Conclusion. We cannot be sure at this point that the observed reactions were truly due to the Aspartame. The artificial color in the drink is another possibility. It is also possible in a child that has a high rate of deviant behavior, that occasional challenges could, by chance coincide with an episode. One cannot, of course, generalize beyond this single case.

However, we are inclined to believe that the clear results from both direct observation and home observations, obtained under strict double-blind conditions, are sufficiently compelling to conclude that Aspartame (and/or its vehicle) are causing deviant behavior of quite severe proportions in this boy. We believe that further study of this problem in children is clearly indicated.

[From the Am J Psychiatry 142:2, February 1985]

INTERACTION OF ASPARTAME AND CARBOHYDRATES IN AN EATING-DISORDERED PATIENT

SIR: Wurtman (1) has pointed out that the acute ingestion of aspartame, particularly when combined with carbohydrates, can have a marked effect on the level of tyrosine in the brain. He speculated that the re-

sulting acute elevation of brain tyrosine level might induce behavioral or functional changes in the predisposed individual. In the following clinical case this appears to have happened.

Ms. A, a 22-year-old white woman, began to binge eat and purge soon after she developed secondary sexual characteristics at age 13. This habit evolved into a binge-purge cycle that took place an average of 15 times a day; she had a marked fear of obesity and a craving for carbohydrates. At age 21 she was placed on a regimen of fenfluramine and metoclopramide for her bulimia. Within a few weeks she stopped binge eating and vomiting. She then began to restrict her food intake excessively; her weight began to decrease and she became increasingly depressed. When her weight reached 79 lb, she was hospitalized. In addition to behavioral and psychotherapeutic treatments, she was given full therapeutic trials of imipramine, desipramine, and nortriptyline for her depression, which persisted despite her regaining a normal body weight. As an outpatient, she developed the habit of chewing her food and spitting it out to enjoy the sweet taste of carbohydrates and to avoid the excess calories. Each day she used about 10 packets of an artificial sweetener that contains aspartame. She was given a trial of a monoamine oxidase inhibitor (MAOI) to treat her "tricyclic-resistant" depression.

After being on a regimen of 10 mg/day of tranylcypromine for approximately 2 weeks, the patient noticed severe headaches that coincided with times when she was eating and spitting out high-carbohydrate foods and consuming the aspartame. She described the headaches as throbbing and said she felt flushed and sweaty. On each of five occasions when she experienced these symptoms, the headaches stopped within a few hours of stopping ingestion of the sweetener.

Ms. A refused to take the artificial sweetener and have her blood pressure checked. The headache was sufficiently unpleasant and the correlation between the ingestion of the sweetener and the headache was so strong that she preferred to use saccharine, which did not produce further headaches.

In this clinical case it appears that aspartame combined with carbohydrates led to the symptoms one might expect from an elevated CNS level of tyrosine in a patient who was taking an MAOI. It is important to keep this possible interaction in mind, particularly with the increased use of MAOIs to treat patients with eating disorders and atypical depressive states.

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JAMES M. FERGUSON, M.D.
La Mesa, Calif.

(From the Annals of Internal Medicine, Vol. 102, No. 2, February 1985)

ASPARTAME-INDUCED GRANULOMATOUS PANNICULITIS

(By Nelson Lee Norick, M.D.)

The low-calorie artificial sweetener, aspartame (NutraSweet; G.D. Searle & Co., Skokie, Illinois), a synthetic combination of aspartic acid and the methyl ester of phenylalanine, is currently used in many diet sodas, cereals, and chewing gums and as a substitute for granulated sugar. Although the Food and Drug Administration has approved aspartame for routine use (except in patients with phenylkentonuria), its potential for toxicity remains controversial (1-4). This report describes the first confirmed case of aspartame-induced granulomatous panniculitis.

A 22-year-old, otherwise healthy woman had numerous, bilateral, nontender, nodular lesions on both legs for 2 months. The patient denied having used any oral, systemic, or topical medications during the preceding 6 months. She also denied any history of recent infections or trauma, and she had no accompanying constitutional symptoms. For the previous 6 years, the patient had habitually consumed between 1080 and 1320 mL (36 to 44 fl. oz) daily of a popular saccharin-containing diet soft drink. Approximately 10 weeks before presenting for evaluation, she had switched to the same manufacturer's new aspartame-sweetened diet soda. She made no other changes in her diet. Two weeks later, the patient first noted the onset of several nontender, deep nodules on her left thigh. New lesions subsequently appeared elsewhere on her legs while the previous lesions slowly enlarged; none disappeared.

On examination, numerous deep nodules ranging from approximately 0.5 to 5 cm in diameter were palpated bilaterally on the thighs and calves. The overlying skin appeared normal. The nodules were firm and in some areas coalesced to form large deep plaques that were freely movable over the underlying facial tissues. No adenopathy or other cutaneous or mucous membrane lesions were present; the rest of the general physical findings were normal.

Complete blood and differential count, erythrocyte sedimentation rate, serum electrolyte and amylase levels, and urinalysis findings were normal; liver function tests, serum protein electrophoresis, direct and indirect immunofluorescence studies, tuberculin tine test, and tests for antinuclear antibody and anti-steptolysin-O were negative. The patient refused a chest roentgenogram. Histologically, a septal panniculitis with lymphocytes and histiocytes predominated within the thickened fibrotic septae. Many multinucleated histiocytic giant cells and a lymphohistiocytic infiltrate extended into the adjacent fatty lobules, consistent with erythema nodosum.

The patient was advised to stop using the recently introduced aspartame-sweetened beverage. During the next 4 weeks, no new lesions appeared and all previous lesions spontaneously resolved without residua. She was then advised to resume daily consumption of the suspected aspartame-sweetened diet drink; 10 days later, she again developed the nodular lesions on both legs, this time in greater number that before. Withdrawal of the beverage once again resulted in gradual and complete resolution of all lesions.

The patient was next challenged with pure aspartame, 50 mg four times daily, in capsule form (supplied by G.D. Searle & Co.). Ten days later, nodules reappeared on her legs. Withdrawal of aspartame resulted in spontaneous clearing of all lesions.

Widely used, aspartame is 180 times sweeter than sucrose and is metabolized primarily to aspartic acid, phenylalanine, and methanol (5). No previous reports could be found in the literature conclusively linking aspartame to any cutaneous eruptions. (6). Several unconfirmed reports of "dermal eruptions" and urticaria have been received by the manufacturer according to Robert L. Alberti, M.D., Director of Medical Communications, G.D. Searle & Co. In addition, the Adverse Drug Reaction Report System of the American Academy of Dermatology has received on unconfirmed report of a macular, erythematous, confluent pruritic eruption in a man who had consumed large amounts of an aspartame-sweetened diet cola (Report no. 1170031284, reported 12 March 1984 and transferred to the FDA 10 April 1984).

The precise classification and pathogenetic mechanism of the panniculitis in my patient are unclear. Absence of tenderness in lesions, overlying skin changes, constitutional symptoms, and residual pigmentary changes upon resolution is inconsistent with erythema nodosum (7), whereas the histopathologic finding of septal panniculitis strongly favors that diagnosis (8).

The formation of toxic metabolites of aspartame, either during the drugs shelflife or as metabolic byproducts, offers one possible explanation for the reaction seen in this patient. Boehm and Bada (9) have recently reported that the heating of aspartame results in conversion of some of its amino acids to their racemates. Although they note that the possible toxicity of consuming large amounts of these racemates remains to be determined, they speculate that some food or beverage components may catalyze the racemization of aspartic acid and phenylalanine in aspartame at room temperature. Furthermore, despite extensive prior testing, no such reaction has yet been reported, suggesting that this phenomenon may be idiosyncratic rather than dose-related. Fortunately, in the present patient, mere discontinuation of the aspartame-containing beverage resulted in complete and relatively rapid resolution of the condition without residua.

(From the Food Chemical News, Apr. 15, 1985)

INTERNAL FDA UNCERTAINTIES ABOUT ASPARTAME SAFETY REFLECTED IN 1981 MEMO

A 1981 briefing memorandum on aspartame reflects internal Food and Drug Administration uncertainties about the safety of the artificial sweetener in the months immediately preceding the decision of then FDA Commissioner Arthur Hull Hayes to permit its use as a food additive.

The May 19, 1981 briefing memorandum which was referred to during recent hearings on the extension of the saccharin moratorium (See FOOD CHEMICAL NEWS, April 8, Page 26), reveals that statisticians in FDA were uneasy about concluding that the brain tumors observed were not statistically significant and that questions were also raided about the conduct of the studies.

"I do not concur that aspartame has been shown to be safe with respect to the induction of brain tumors," Robert J. Condon, of FDA's Center for Veterinary Medicine, wrote in a "dissenting opinion on the brain tumor issue," explaining that his opinion was "based on. . . three reasons: (1) positive results seen. . . for female rats (in one of the studies); (2) problems in the conduct (of two of the studies); and (3) power of the studies."

Similarly, a memo from Satya D. Dubey of FDA's Center for Drugs and Biologics, pointed out "certain statistical difficulties" associated with the key studies "within the framework of statistical principle, theory, method and practice."

The two statisticians were members of the Commissioner's Team on Aspartame, as was Douglas L. Park, now with the Center for Food Safety and Applied Nutrition, who noted in a memo that "the available evidence is limited and provides clear proof neither of the safety nor of lack of safety."

Appendices to the memorandum made available following the hearing reveal that FDA scientists also questioned the data on risk of aspartame ingestion in terms of amino acid imbalance, a question raised also by outside researchers, specifically MIT's Dr. Richard Wurtman.

One of these appendices cautioned that "a four-fold increase in phenylalanine might cause some adverse effects if the diet is deficient in protein."

Another, prepared by FDA's Barry N. Rosloff, of the Center for Drugs and Biologics, pointed out that conclusions on aspartame were dependent "on how well the studies performed reflect the conditions of anticipated usage, particularly regarding (1) dose levels, (2) concentration of aspartame in solution, and (3) concomitant consumption of food, particularly carbohydrates."

"The latter factor is particularly important since the presence of carbohydrates has been shown to reduce the increase in plasma glu (glutamic acid) seen with MSG feeding," Rosloff noted.

Noting the studies with aspartame were performed with orange juice or a flavored beverage base and there there was no information on how much carbohydrate was present in the vehicles or when food had last been consumed by the subjects, Rosloff commented, "Hopefully these variables do not deviate in a significant way from the anticipated conditions of aspartame consumption."

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HOW SAFE IS YOUR DIET SOFT DRINK?

(By Florence Graves)

(NutraSweet has been touted as the most tested food additive in history, but our investigation reveals such serious flaws in the government's approval of NutraSweet that Congress should begin its own investigation immediately.)

NutraSweet, America's newest sugar substitute, has been an overnight sensation. Low in calories, with a taste almost like sugar, NutraSweet is not only converting former saccharin users but drawing consumers away from sugar as well. Robert Shapiro, president of the NutraSweet Group at G.D. Searle & Co., which owns the patent on NutraSweet, declared at a gathering of soft drink companies last December that NutraSweet is "one of the most important developments in the history of food and beverages." In a recent interview with Common Cause Magazine, Shapiro said he realizes that NutraSweet "sounds too good to be true."

Ironically, Shapiro may be right. A Common Cause Magazine investigation based on dozens of interviews and a review of thousands of pages of documents, many obtained under the Freedom of Information Act, raises serious concerns about whether the Food and Drug Administration (FDA) established that aspartame—the scientific name for NutraSweet—is safe. The investigation shows that some scientists say tests have not resolved major health issues—including whether aspartame can cause cancerous brain tumors, and whether it can affect brain chemistry and therefore behavior. The magazine has also learned that some scientists have serious concerns about the sweetener's potential effects on children and pregnant women.

Meanwhile, the FDA acknowledges receiving at least 600 consumer complaints relating to aspartame. In these complaints—which Common Cause Magazine obtained under the Freedom of Information Act—people allege that they have suffered headaches, rashes, dizziness, menstrual problems and seizures after consuming aspartame. The complaints, most of which were received this year, are being investigated by the Centers for Disease Control in Atlanta.

Our investigation reveals such serious flaws in the FDA's approval process that Congress should begin its own investigation immediately. The investigation shows that then FDA commissioner Arthur Hull Hayes approved aspartame three months after taking office in April 1981, despite the fact that some of the FDA's own scientists had serious reservations about the validity and quality of pivotal tests used in his decision. (Hayes, through an assistant, refused to be interviewed.)

Hayes' decisions to approve aspartame for use in dry foods such as cereals in 1981 and soft drinks in 1983 does not square with the role the FDA is supposed to play. The FDA is the government agency that reviews and approves all tests submitted by companies before allowing food additives on the market. The law requires a manufacturer—in this case, Searle—to prove to the satisfaction of the FDA that there is a "reasonable certainty" that a food additive is safe. The government does not have to prove that it is harmful—an important distinction. If tests are inconclusive, an additive is not supposed to be approved by the FDA.

In deciding to allow aspartame in dry foods in 1981, Hayes ignored not only the recommendations of some FDA scientists, but also a recommendation by a 1980 scientific Public Board of Inquiry appointed by the FDA. The board said aspartame should not be approved because it had not been conclusively shown that the sweetener did not cause cancerous brain tumors. The board called for further testing to resolve the issue. In 1983, just two months before leaving office, Hayes approved aspartame for use in soft drinks, dramatically expanding its use.

Hayes defended his 1981 approval, saying, "Few compounds have withstood such detailed testing and repeated close scrutiny, and the process through which aspartame has gone should provide the public with additional confidence of its safety."

But in fact, a 1975 special FDA task force had raised serious concerns about a number of the tests that Hayes eventually relied on in his decision to approve aspartame. Despite the fact that one former FDA commissioner said what was discovered about a number of Searle's tests—including pivotal brain tumor tests—was "reprehensible," our investigation shows serious questions about the tests were never resolved and the tests eventually relied on were never repeated.

Consumer attorney James Turner, who has gone to court to try to force a public hearing on aspartame, charges that Hayes picked "his way through a mass of scientific mismanagement, improper procedures, wrong conclusions and general scientific inexactness." Turner represents the Community Nutrition Institute, a Washington, D.C.-based public interest group.

Two FDA officials have told Common Cause Magazine that Hayes was determined to push aspartame forward, in part as a signal that the Reagan administration was ushering in a new regulatory era. One official privy to some of the deliberations made at Hayes' level says the "people at the top" were not receptive to important concerns raised about the quality and validity of some of the key tests submitted in support of aspartame.

"There were real questions" about the reliability and interpretation of the data "that were glossed over" at the commissioner's level, this official says, adding that Hayes and his close associates wanted FDA scientists to concentrate on providing rationales for overturning the 1980 Public Board of Inquiry instead of focusing on the fact that there were unresolved issues about a number of key tests.

The financial consequences of Hayes' decisions are enormous for G.D. Searle & Co. A Kidder Peabody financial analyst says Searle's U.S. sales of NutraSweet and Equal (the powdered sugar substitute) reached $74 million in 1982. By the end of 1983, following soft drink approval in the summer, sales had jumped to $336 million. Most of that increase was accounted for by soft drink use, the analyst says.

Meanwhile, a number of scientists continue to raise questions about aspartame's safety, especially with the widely expanded soft drink market.

Dr. Walle Nauta, head of the 1980 Public Board of Inquiry and an institute porofessor in the Department of Psychology and Brain Science at the Massachusetts Institute of Technology (MIT), says "extensive testing" is needed regarding a theory raised by MIT's Dr. Richard Wurtman that consuming large amounts of aspartame—especially with carbohydrates—may affect brain chemistry. In light of the consumer complaints, Nauta said in a recent interview, "I would think [the FDA] should be following [the issue] with great concern. Dr. Wurtman may be right." Aspartame "may be harmful in the long run."

In extending aspartame approval to soft drinks, Hayes dismissed Wurtman's concerns, saying his hypothesis is not supported by his data. The FDA says it is not requiring tests concerning Wurtman's theory.

Searle's Robert Shapiro agrees with the FDA, and Searle has said that "the various hypotheses suggesting a potential health risk from aspartame consumption are not supported by the scientific evidence submitted by Searle and exhaustively reviewed by FDA prior to aspartame's approval."

In an interview, Sanford Miller, chief of FDA's food safety division, defended the FDA's approval and said, "The same dead horses keep getting dragged up again and again and again."

Miller said aspartame is the most tested food additive in history, and he points to the more than 100 tests Searle submitted to the FDA.

But as one FDA scientist said in an interview, it doesn't matter how many tests are done on a food additive, the proper question is, how many of them are valid? And do they prove the additive is safe?

The key element of the controversy is that the vast majority of the tests—90 of 113 entries—were submitted by Searle in the early to mid-1970s. All aspartame tests submitted during that period by Searle and its major contractor, Hazleton Laboratories Corp., were called into question by a 1975 FDA special task force investigation. The special task force's findings were so serious that they led the FDA general counsel to request a grand jury investigation of Searle.

All aspartame tests that have been described by the FDA as "pivotal" were conducted during this period. Eighty-eight percent were done by Searle or Hazleton. Dr. Alexander Schmidt, FDA commissioner from 1972 to 1976, said in a recent interview that Searle's testing then was "incredibly sloppy science." He added, "What was discovered was reprehensible."

Schmidt says a pivotal test is one that is so important that it must be repeated if found invalid. The important question, he says, is, "Were there new pivotal experiments?" Our investigation shows that only one pivotal test was repeated. The FDA later said it was not used in the agency's safety assessment.

Despite the fundamental questions concerning the tests submitted before the end of 1975, Hayes and the Bureau of Foods relied on some or all of these tests when they made their decisions that aspartame is safe. Our investigation found no evidence in the public record that Hayes or the bureau