CONGRESSIONAL RECORD — SENATE

August 1, 1985

S 10820

(A) provide new budget authority or spending authority described in section 401(c)(2)(C) of such Act;
(B) relate to revenues; or
(C) specify the amount of the statutory limit on the public debt.
(7) section 405 of such Act, as added by section 101 of this Act, shall apply with respect to fiscal year 1988; and
(8) section 1104(c)(2) of title 31, United States Code, as added by section 8(b) of this Act, shall apply with respect to fiscal year 1988.

By Mr. METZENBAUM:
S. 1557. A bill to provide the public with information concerning the use of products containing aspartame, to provide for the conduct of studies to determine the health effects of using products containing aspartame, and for other purposes; to the Committee on Labor and Human Resources.

ASPARTAME SAFETY ACT

Mr. METZENBAUM. Mr. President, today I am introducing a bill entitled "the Aspartame Safety Act of 1985." I consider this legislation the absolute minimum that Congress needs to do in order to protect the health and safety of American consumers who are using this chemical sweetener under its better-known brand name of Nutrasweet.

In 1984, Americans consumed over 7 million pounds of aspartame, which is equal to 1.4 billion pounds of sugar. This year we will consume over 20 billion cans of diet soft drinks, the vast majority of which are 100 percent Nutrasweet. We had better be sure that the questions which have been raised about the safety of this product are answered.

I must say at the outset, this product was approved by the FDA in 1974. However, no decision which can only be described as troubling. The FDA originally approved aspartame in 1974. However, that decision was stayed after concerns were raised about health and safety problems. In March of 1976 a special FDA task force released its report on testing practices at G.D. Searle Co., the manufacturer of aspartame. That report contained the following conclusions:

At the heart of FDA's regulatory process is its ability to rely upon the integrity of the basic safety data submitted by sponsors of regulated products. Our investigation clearly demonstrates that, in the case of Nutrasweet, we have no basis for such reliance now.

Through our efforts, we have uncovered serious errors in Searle's operations and practices which undermine the basis for reliance on the company's integrity in conducting high quality animal research to accurately determine or characterize the toxic potential of its products.

The studies we investigated reveal a pattern of conduct which compromises the scientific integrity of the studies.

Now, Mr. President, one might ask what does a 1976 report on testing practices at G.D. Searle have to do with aspartame, a chemical sweetener approved by the FDA in 1981? The answer is simple. Over 90 percent of the tests submitted by G.D. Searle to the FDA in order to get aspartame approved were submitted prior to March 1976, when the report was issued. In addition, of the 25 Searle tests examined by the FDA task force, 11 were tests not conducted with a major question hanging over the approval process is this question of how the FDA resolved the issues raised by its own task force in 1976. There are serious questions about the quality of tests that approved this chemical sweetener.

Mr. President, the questions do not stop with the 1976 task force report. For in 1977, the FDA wrote to the U.S. attorney in Chicago requesting a grand jury investigation of G.D. Searle Co. I quote from the letter sent by the chief counsel of the FDA, Richard Merrill:

We request that your office convene a grand jury investigation into apparent violations of the Food, Drug, and Cosmetic Act ... and the False Reports to the Government

In 1980, the FDA established a public board of inquiry on aspartame. What did they conclude? "The Board has not been able to present proof of a reasonable certainty that aspartame is safe for use as a food additive under its intended conditions of use."

In May 1981, 2 months before the FDA Commissioner, Arthur Hayes, approved aspartame for use in dry foods, three FDA scientists informed the Commissioner that they did not believe that aspartame had been proven safe beyond a reasonable doubt. They believed it would cause brain tumor tests which were submitted by G.D. Searle. These three FDA scientists comprised half of the so-called "Commissioner's Team" which was set up to advise the Commissioner on aspartame approval.

Despite all the questions raised by the chronology I have outlined, the FDA Commissioner decided to approve aspartame in July of 1981. He later approved aspartame for use in soft drinks in July 1983.

In May of this year I asked the GAO to undertake a full investigation of the aspartame approval process. That investigation is underway and I have high hopes that it will shed some light on the questions surrounding the Commissioner's decision to approve this product.

Pending the completion of that report, however, there are a number of steps which Congress should take with relation to aspartame. The bill I am introducing today outlines the minimum steps I feel are necessary.

The bill mandates that independent tests on aspartame be conducted under the auspices of the National Institutes of Health. These tests will focus on the general effects which aspartame has on brain chemistry as well as the specific behavioral and neurological reactions experienced by individuals—headaches, mood alterations, memory loss, and others.

The tests will also examine the health effects of aspartame on pregnant women and fetuses and whether aspartame consumption can lower the threshold for seizures. Another important area for investigation is how aspartame reacts to medicines particularly MAO inhibitors which are used in the treatment of depression, dopa used in the treatment of Parkinson's disease, and aldomet used in the treatment of hypertension.

Under the bill, there will be a moratorium imposed on new uses of aspartame in foods and drugs pending the completion of independent test or for the period of 1 year—whichever comes sooner.

These are credible questions which have been raised by eminent scientists, regarding aspartame.

Dr. Richard Wurtman of MIT has examined questions relating to aspartame's effect on brain chemistry. Dr. William Partridge of UCLA has expressed his concerns about fetal IQ. Dr. Elsas of Emory University has warned us about groups in the population at high risk from large concentrations of phenylalanine in the blood.

Dr. Matalon at the University of Illinois is particularly concerned about individuals who are genetically susceptible to phenylalanine-PKU carriers—mend who may be a sizable risk group as far as aspartame is concerned. Nearly 5 million Americans are PKU carriers.

Two researchers in Philadelphia, Prof. Gautieri and Malahill, have done additional studies to show that aspartame affected the vision of newborn mice whose mothers had been exposed to the chemical sweetener.

Mr. President, I ask unanimous consent that reports and statements concerning these scientists be placed in the Record following my statement.

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

Mr. METZENBAUM. Mr. President, one final point concerning tests. The Journal of the American Medical Association recently published an article on aspartame which, with some significant disclaimers, stated it was safe for most people. I wish that this report could ease my concerns. It does not. It merely restates the FDA position which relies solely on the tests conducted by G.D. Searle. As I have indicated, these tests are under a cloud. In addition, the concerns raised recently by the scientists I mentioned above were not even considered in the report.

Mr. President, the FDA is content to have the manufacturer of aspartame, G.D. Searle, conduct these studies. How absurd. We do not need the
CONGRESSIONAL RECORD — SENATE

August 1, 1985

people who are making millions of dollars on aspartame telling us it's safe.

Has the FDA forgotten that in 1977 it sought to have a grand jury investigation into allegations that Searle conducted fraudulent tests on aspartame? Does the agency know they are presently conducting an investigation that company for withholding information on adverse effects from another one of their drugs, Theo-24?

It is true that the current FDA is a mere shadow of what that agency used to be. Now it is more of a handmaiden to the food and chemical industry than it is a defender of the health and safety of American consumers.

In addition to mandating independ¬
et tests, my bill will require labeling which will inform consumers how much aspartame they are ingesting. This information is important not only for consumers who wish to regulate their intake of aspartame but also for physicians who may be treating indiv¬

uals who feel they have experienced side effects. Such side effects are likely to be dose related and the physician will want to know how much aspartame has been consumed. In addition, consumers have a basic right to know the makeup of the foods which they consume.

The bill will also contain the maximum allowable daily intake established by the FDA. How many consumers know that the FDA has attached such a limit to its approval of food consumption? The current ADI is 50 mg per kg. of body weight. It was originally 20 mg/kg. However, in 1983 the FDA decided to ignore its standard 100-fold safety factor by more than doubling the maximum allowable daily intake. Why did they decide to make an exception for aspartame? In 1983, they approved aspartame for soft drinks. In order to increase the limit knowing consumption was bound to increase. The justification the FDA used for violating its standard 100-fold safety factor was that the tests showed it was safe at the new levels of consumption. And guess who was responsible for all the tests—G.D. Searle Co., of course.

I intend to fully investigate the manner in which the FDA altered its safety standard for this product. In the meantime, consumers have a right to know at least that some such standard exists. Sure, if you weigh 150 pounds you would have to drink 4 to 5 liters of diet soft drink to hit the limit. But if you are a child who weighs 30 pounds, you hit that limit with 3 to 4 cans of diet soft drink. That's even without the gum, pudding, breakfast cereal—all sweetened with aspartame.

Under this bill, the Secretary will be responsible for deciding how best to express the ADI on the label so consumers can understand what it means. For example, on diet soft drinks the label might read: "Maximum Allowable Daily Intake: 3 cans per 25 lbs. of body weight." There may be better ways to express this concept. The Sec¬

retary can work on that but consumers have a right to this information particularly since the advertising for this product has left the impression that everyone in the population, including children, can consume as much as they wish of this chemical sweetener and still remain within the standard FDA recommended range of a 100-fold safety factor.

My bill designates one other labeling requirement. The label will advise that aspartame is not intended for infant feeding.

Mr. President, I would like to quote from an FDA document dated February 28, 1980:

Nevertheless, in consideration of the remote possibility that a parent might use aspartame as a non-sugar sweetener in the infant formula or food, there may be some merit in the inclusion of a statement on the label to the effect that aspartame-containing foods are not intended for use in infant feeding. Such a statement may provide adequate assurance that aspartame will not be fed to infants.

Did the FDA ever follow up on this recommendation? Of course not. Too troublesome for industry. How remote is the possibility that a parent will give nutrasweet to a child? A little diet coke in a bottle? Some pudding? A little kool-aid? Maybe some cereal?

This bill ensures that parents will know that aspartame-containing foods are not intended for infant feeding. Finally, Mr. President, my bill will establish a Rejection Committee within the FDA. Consumers who feel they have experienced side effects from aspartame should have the right to have their complaint investigated.

The FDA claims such complaints have declined to almost zero. Isn't that interesting. What the FDA doesn't tell us is that since February of 1984, G.D. Searle has not forwarded any complaints that have received to the FDA. In addition, we learn that the FDA informed its regional office to forward only "serious complaints." IEA complaint sever enough to require the attention of a physician. And did the FDA notify physicians that they were interested in collecting and analyzing reports of adverse reactions to aspartame? Absolutely not. So how are physicians to know they should even be notifying the FDA of such reports? The only notification physicians around the country have received is a medical bulletin from G.D. Searle quoting the FDA that aspartame is completely safe.

Now, however, the FDA has informed myself and Senator Hertz that they are considering establishing a Clinical Adverse Reaction Committee to collect and evaluate reports of side effects.

This bill makes it easy for the FDA. It mandates the FDA to collect and study reports of side effects and to alert physicians around the country that they are interested in knowing about such reactions.

Only then can we get an accurate picture of the problem.

Mr. President, I said at the outset that this bill represents a minimum response to the questions which surround a response to the FDA which recently sent me a letter rejecting proposals for labeling and informing me that G.D. Searle's tests are insufficient to settle the questions which are raised.

To put it mildly, that response was totally unsatisfactory. We have an agency desperately attempting to explain away its unwillingness to protect the safety of American consumers. Clearly, at today's FDA policies and ideology come before the public health.

I know there are career FDA person¬

nel who are committed to doing a good job. They are trying to be honest and professional. Their task is becoming impossible under the weight of leadership which has raised political interfer¬
ence to an art form. On the issue of aspartame, as on the issue of food dyes, the present form of the bill petitioned by the letter of us in Congress who will not rest until this agency meets its responsibilities to the American consumer. That, I can promise.

Mr. President, I ask unanimous consent that the text of the bill, the letter, and scientific studies mentioned during my remarks, and other supporting materials be printed in the Record. There being no objection, the material was ordered to be printed in the Record, as follows:

S. 1557

Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled, That this Act may be cited as the "Aspartame Safety Act of 1986".

LABELING REQUIREMENTS

Sec. 2. (a) Section 403 of the Federal Food, Drug, and Cosmetic Act is amended by adding at the end thereof the following new subparagraph:

"(q)(1) If it contains aspartame, unless its label and labeling—

(A) specify the total number of milligrams of aspartame contained in each serving;

(B) specify the allowable daily intake of aspartame (in milligrams) for each kilogram of human body weight, as established by the Secretary; and

(C) bear the following statement: 'THIS PRODUCT CONTAINS ASPARTAME, WHICH IS NOT INTENDED FOR USE IN INFANT FEEDING';

(2) The Secretary shall by regulation require that the information required by subparagraph (q)(1)(B) to be specified on the label and labeling of any food containing aspartame be included on such label and labeling in a manner which is the most useful to individuals who consume such food.

(3) The statement required by subparagraph (q)(1)(C) shall be placed in conspicuous place on the label and labeling of each food containing aspartame as proximate as possible to the name of such food and shall appear in conspicuous typeface which is in contrast by typography, layout, and color with other printed matter on such label and labeling."
CONGRESSIONAL RECORD – SENATE
August 1, 1985

S 10822

(b)(1) Section 502 of such Act is amended by adding at the end thereof the following new paragraph:

"(c) If it is a drug containing aspartame, unless—

(A) its label and labeling—

(i) specify the total number of milligrams of aspartame contained in each dosage;

(ii) state its intended daily intake of aspartame (in milligrams) for each kilogram of human body weight, as established by the Secretary and any provisions for children;

(iii) bear the following statements: 'THIS PRODUCT CONTAINS ASPARTAME, AND IS NOT INTENDED FOR USE BY INFANTS.' 

(B) the manufacturer, packer, or distributor (including all retail establishments) thereof includes in all advertisements and other printed and descriptive matter used or caused to be issued by the manufacturer, packer, or distributor with respect to such drug the information described in clauses (A)(i) and (A)(ii) and the statements specified in clause (A)(iii).

(2) The Secretary shall by regulation require that all labels required by subsection (1)(A)(ii) to be specified on the label and labeling of drugs containing aspartame be included on such label and labeling in a manner which is the most useful to individuals who consume such drugs.

(3) The statements required by subparagraph (1)(A)(ii) shall be located in a conspicuous place on the label and labeling of each drug containing aspartame as proximate as possible to the name of such drug and shall appear in conspicuous and legible type in contrast by typography, layout, and color with other printed matter on such label and labeling.

The final sentence of section 503(b)(2) of such Act is amended by striking out "and (1)," and inserting in lieu thereof "(1), and (A)(i)(B);"

MORATORIUM

Sec. 4. During the period beginning on the date of enactment of this Act and ending—

(1) on the date which is one year after the date of enactment of this Act, or

(2) the date on which all studies required under section 4 are completed, whichever is earlier.

The Secretary of Health and Human Services shall not approve or permit any use of aspartame in any food or drug if such use was not approved or permitted on the date of enactment of this Act.

RESEARCH

Sec. 4. (a) The Secretary, through the Director of the National Institutes of Health, shall request proposals for, and make grants and enter into contracts for the conduct of, clinical studies on aspartame, including studies concerning—

(1) the effect of the consumption of aspartame on brain chemistry;

(2) the health effects of the consumption of aspartame on pregnant women and fetuses;

(3) behavioral and neurological effects experienced by individuals who consume aspartame, especially children who have consumed aspartame;

(4) the interaction of aspartame with drugs, including monoamine oxidase inhibitors, alpha-methyltyrosine, and L-dihydroxyphenylalanine;

(5) the effect of the consumption of aspartame in increasing the probability of seizures.

(b) In making grants and entering into contracts under subsection (a), the Secretary shall provide for the completion of the studies required under such subsection within one year after the date of enactment of this Act.

(c) To carry out this section, there are authorized to be appropriated such sums as may be necessary.

(d) The authority of the Secretary to enter into contracts under this section shall be to such extent or in such amounts as are provided in appropriated Acts.

CLINICAL ADVERSE REACTION COMMITTEE ON ASPARTAME

Sec. 5. (a) The Secretary, through the Commissioner of the Food and Drug Administration, shall establish a Clinical Adverse Reaction Committee on Aspartame. The Committee shall collect reports of individual reactions to the consumption of foods containing aspartame, including reports of reactions from individuals taking various medications, and shall evaluate and prepare appropriate responses to such reports.

(b) The Secretary shall announce the establishment of the Committee under subsection (a) through the mailing of written notices to physicians and other health care providers and through advertisements in medical journals and in publications read by the general public. Such advertisements shall include the toll free number of the telephone service established pursuant to subsection (c).

(c) The Secretary shall establish a telephone service for the collection of individual reactions to the consumption of products containing aspartame. Calls on such telephone service shall be without charge to the caller.

SCIENTISTS SUGGEST NUTRASweet LINK TO BRAIN DAMAGE

(By Geoffrey Gordon)

WASHINGTON (UPI)—Two pediatric and geneticists who believe that pregnant women who consume aspartame, the popular sugar substitute sold as NutraSweet in soft drinks and 70 other products, may have babies with permanent brain damage.

In a contention rejected by NutraSweet's manufacturer, one of the scientists, Dr. Louis Elias of Emory University in Atlanta, also said he believes any aspartame component can cause similar damage to infants if they ingest it in the six months following birth.

"A reasonable reason why the pregnant woman or female should be taking aspartame," Elsas said, "and there's no reason why a child less than six months old should be taking aspartame, so I said the damage may not show up for years.

Meanwhile, lawyers for a 5-year-old boy who a research team said became "uncomonosely and wildly emotional" after drinking NutraSweet products have filed a $2 million damage suit against the product's manufacturer G.D. Searle Co. of Skokie, I I L.

The suit, filed three weeks ago in Washington, charges that aspartame is an "unreasonably dangerous and harmful food additive" that causes "adverse effects which in combination with glucose and given to children under six years old.

It was disclosed last month the General Accounting Office was studying the manner in which Commissioner Arthur H. Hayes of the Food and Drug Administration approved aspartame in 1981 over the objections of several prominent scientists who challenged brain tumor studies.

Officials of G.D. Searle, which last year sold more than a billion pounds of NutraSweet for diet soft drinks and other products, dismiss all the allegations and criticisms of aspartame. They assert the product has undergone the same kind of any food additive ever approved by the FDA.

"I think quite clearly, the data on aspartame does support the safety of the product," Roger Thies, Searle's associate general counsel, said in a recent interview.

Dr. Lewis Steigk, a professor of pediatrics and biochemistry at the University of Iowa, who, with funding from Searle, performed some of the pranglal studies that supported FDA approval wondered about the safety? The answer is no. Would I like to see additional studies done? Of course. That's what science is all about.

Dr. Richard Guis, vice president for nutrition and medical affairs of Searle's NutraSweet group, said aspartame has "no adverse effects on the human fetus," with the exception of a select group who are alerted to the contents in warning labels.

Elis, director of medical sences at Emory, and Dr. Reuben Matalon, professor of pediatrics and sences at the University of Illinois Medical School, have yet to publish any findings that specifically refer to aspartame. But both said they have extensively studied a key component of the sweetener—phenylalanine—and that they consider it a hazard for fetuses.

The scientists said in interviews that they approached Searle in the 1970s about their concerns, but that they believe company-sponsored studies are not adequately tested the substance for its effects on the human fetus.

"We just don't want to listen," Elsia said. "The people at Searle would like to have you think that nothing happens as long as the phenylalanine level is below the tenfold elevated level" that is the FDA's safety standard.

Elisa said that besides pregnant mothers, he is concerned about aspartame ingestion by newborns and young children who eat diet gelnats and puddings. He called Searle's studies on phenylalanine "a white paper" and said the scientists on them should be "revised" after peer review. Elia also noted that women who consume the substance while nursing could present a similar risk to their babies because the extent of phenylalanine in mother's milk has yet to be investigated.

Elisa and Matalon said consuming even moderate amounts of NutraSweet raises the concentration of phenylalanine in the blood. Matalon said he was "not too concerned" about older children consuming aspartame, because he said the damage may not show up for years.

Meanwhile, lawyers for a 5-year-old boy who a research team said became "uncomonosely and wildly emotional" after drinking NutraSweet products have filed a $2 million damage suit against the product's manufacturer G.D. Searle Co. of Skokie, I I L.

The suit, filed three weeks ago in Washington, charges that aspartame is an "unreasonably dangerous and harmful food additive" that causes "adverse effects which in combination with glucose and given to children under six years old.

It was disclosed last month the General Accounting Office was studying the manner in which Commissioner Arthur H. Hayes of the Food and Drug Administration approved aspartame in 1981 over the objections of several prominent scientists who challenged brain tumor studies.

Officials of G.D. Searle, which last year sold more than a billion pounds of NutraSweet for diet soft drinks and other products, dismiss all the allegations and criticisms of aspartame. They assert the product has undergone the same kind of any food additive ever approved by the FDA.

"I think quite clearly, the data on aspartame does support the safety of the product," Roger Thies, Searle's associate general counsel, said in a recent interview.

Dr. Lewis Steigk, a professor of pediatrics and biochemistry at the University of Iowa, who, with funding from Searle, performed some of the pranglal studies that supported FDA approval wondered about the safety? The answer is no. Would I like to see additional studies done? Of course. That's what science is all about.

Dr. Richard Guis, vice president for nutrition and medical affairs of Searle's NutraSweet group, said aspartame has "no adverse effects on the human fetus," with the exception of a select group who are alerted to the contents in warning labels.

Elis, director of medical sences at Emory, and Dr. Reuben Matalon, professor of pediatrics and sences at the University of Illinois Medical School, have yet to publish any findings that specifically refer to aspartame. But both said they have extensively studied a key component of the sweetener—phenylalanine—and that they consider it a hazard for fetuses.

The scientists said in interviews that they approached Searle in the 1970s about their concerns, but that they believe company-sponsored studies are not adequately tested the substance for its effects on the human fetus.

"We just don't want to listen," Elsia said. "The people at Searle would like to have you think that nothing happens as long as the phenylalanine level is below the tenfold elevated level" that is the FDA's safety standard.

Elisa said that besides pregnant mothers, he is concerned about aspartame ingestion by newborns and young children who eat diet gelnats and puddings. He called Searle's studies on phenylalanine "a white paper" and said the scientists on them should be "revised" after peer review. Elia also noted that women who consume the substance while nursing could present a similar risk to their babies because the extent of phenylalanine in mother's milk has yet to be investigated.

Elisa and Matalon said consuming even moderate amounts of NutraSweet raises the concentration of phenylalanine in the blood. Matalon said he was "not too concerned" about older children consuming aspartame, because he said the damage may not show up for years.

Meanwhile, lawyers for a 5-year-old boy who a research team said became "uncomonosely and wildly emotional" after drinking NutraSweet products have filed a $2 million damage suit against the product's manufacturer G.D. Searle Co. of Skokie, I I L.
August 1, 1985

CONGRESSIONAL RECORD—SENATE

S 10823

Matalon said those studies are "not based on a lot of experiments."

He said Searle did not adequately test the levels and concentrations of aspartame in the body. He said the levels of aspartame in the body are known as metabolites—of phenylalanine in the body.

Gault and Stipes, however, defended Searle's testing and said it showed that even at "safe levels"—extremely heavy consumption of aspartame—the phenylalanine levels in the blood do not rise to a dangerous level. Gault said the levels of phenylalanine quickly drop. He said that while PKU carriers "have less ability to metabolize" than those with normal levels, it is not limiting their ability to metabolize the substance.

Consumption of aspartame, he argued, results in increases in blood phenylalanine levels "no greater than the increase in concentration after a meal... consisting of a hamburger and milkshake."

Elisas, already had published one study on humans, said he believes the potential danger extends to all present women who regard aspartame, and possibly to young children who may experience behavioral and neurological disorders if they drink or eat aspartame.

Gault called Elisas's findings "incorrect," contradicting the fetus concentrates phenylalanine only at about 1.5 times the level in the mother.

Stipes called Elisas's projections of blood phenylalanine "totally impossible" but acknowledged no research has been conducted on the effect of aspartame on pregnant women.

The Washington lawsuit is based on research by Dr. Keith Connors of D.C. Children's Hospital. He said 4-year-old boy "repeatedly ran full force into the wall, knocking himself to the floor, crying, and repeating the performance unless we restrained him" after consuming aspartame.

The suit seeks $2 million in negligence and liability damages from Searle due to the immediate adverse effects and long-term damage to a child's neurological, brain, nervous and motor systems.

Gault said, "The bottom line is that aspartame has no adverse effects on children. In view of the fact that this case is in litigation, I don't want to comment on it."

Stephen's doctors agree his injuries, subject of one of numerous complaints about NutraSweet to the Center for Drug Control, is a "known neurotoxic and other neuromuscular and psychiatric disease and side effects, ranging from behavioral changes to nightmares."

The company says those charges, that the company failed to test aspartame, failed to warn of its possible dangers, and failed to report "adverse experiences" are all "false." "The safety and efficacy of aspartame," also were lodged.

Connors, a specialist in hyperactivity and neurologic disorders in children, would not comment on his research concerning aspartame. But in testimony to Congress, he said, "We are inclined to believe that the clear result of aspartame (and/or its vehicle) is causing deviant behavior of quite severe proportions in this boy."

The FDA has never required adequate neurological pediatric testing to determine this kind of reaction on children. And to allow this on children in testing is a crime."

Although Searle officials maintain the product is safe, company-sponsored tests—investigating aspartame's possible effect on hyperactivity and seizures in children, seizures in adults, and headaches—are under way.

**STUDY ON MICE SHOWS ASPARTAME PROBLEMS, RESEARCHERS SAY**

**PHILADELPHIA (AP)—**Two researchers are calling for further studies into the effects on pregnant women of the artificial sweetener aspartame in their diet. Research mice showed that offspring had trouble with their eyes.

Aspartame, labeled as a sugar substitute under the trade name NutraSweet and as an additive under the name Nutrasweet, was studied by Ronald F. Gaugeti, professor of pharmacology at Temple University School of Pharmacy.

Gaugeti and Michael P. Mahallik, assistant professor of pharmacology at the Philadelphia College of Osteopathic Medicine, reported their findings in a recent issue of Research Communications in Psychology, Psychiatry, and Behavior.

In their study, the eyes of newborn mice whose mothers were not exposed to aspartame began focusing 20 days after birth. Babies born to pregnant mice fed 1 gram of the sweetener per kilogram of their weight took 2 days longer to focus, and 4 grams extended the focusing time to 4 days.

"Something affected the neurosensor system," Gaugeti said.

"In the last year, a growing number of researchers have shown pregnant women should avoid aspartame because of unknown consequences to fetuses."

"Sometimes bad things happen over the long term," Mahallik added. "We feel that byproducts of aspartame somehow affect the processes of myelination, the sheaths that cover nerves."

"We think the study supports the previously stated opinion that aspartame could affect some brain functions."

The Food and Drug Administration and the National Centers for Disease Control, reacting to more than 500 consumer complaints of headaches and insomnias, have said tests reveal no problems with the sweetener. But the CDC also said it did not examine any possible problems relating to pregnancy.

The National Institutes of Health is conducting a 3-year study on aspartame.

The FDA's acceptable daily intake of the sweetener is 40 to 50 mg per person weighing 130 pounds. That is equivalent to six quarts of soda containing Nutrasweet or 150 pack of Equal.

**GAO INVESTIGATING NUTRASWEET APPROVAL**

**(By Gregory Gordon)**

WASHINGTON (UPI)—The General Accounting Office is investigating the manner in which the Food and Drug Administration approved the popular artificial low-calorie sweetener aspartame in 1981 over the objections of several agency scientists, it was disclosed Wednesday.

The inquiry was begun at the request of Sen. Howard Metzenbaum, D-Ohio, who said in a letter last week to Comptroller General Charles Bowsher that there were "serious deficiencies" in testing aspartame marketed as NutraSweet by G.D. Searle & Co.

Officials of G.D. Searle, a Tattoo, Ill.-based firm that last year sold more than 600 million packages of aspartame, said Wednesday they are absolutely convinced the product, widely used in diet soft drinks, is safe.

They acknowledged they have been "cautiously optimistic" about new studies of the effects of the sweetener on humans, including whether it might be linked to increased headaches. They said Searle is conducting new tests, four of which should be completed by early next year.

"If there is a real problem we'd better be the first ones to know because we're going to need some time lead to correct it, take the product off the market, or whatever," said James Turner, a Washington consumer lawyer who has challenged the FDA's approval process that began in 1970, asserting that "Searle's undertaking of these new tests is an admission that this product has not been shown to be safe for marketing."

Turner is appealing a federal court law aimed at forcing the FDA to hold public hearings on the safety of aspartame. Initial government-ordered hearings were obtained by the United Press International show that Commissioner Arthur Hull Hayes of the Food and Drug Administration overturned G.D. Searle's application to market aspartame in 1981.

Three of six scientists on the "Commissioner's Team on Aspartame" said on May 18 and 19, 1981, that tests they had reviewed did not prove the product was "serious harm," as required by FDA regulations, according to agency memos obtained by UPI intern Joshua Moyer.

Metzenbaum last week asked the FDA to require labels showing the amount of aspartame a product uses; to ensure that "focused clinical tests" take place; and to commission a qualified independent lab to repeat the animal tests questioned by the FDA researchers.

In his letter to Bowsher, he said that "very serious questions have been raised regarding this approval process, questions which must be resolved if we are to have complete confidence in the safety of aspartame."

GAO officials confirmed that Congress' investigative arm is looking into Metzenbaum's request for an inquiry into:

The validity of G.D. Searle's tests on brain tumors in rats, challenged in 1979 for being sloppy and criticisms made and criticized again by the three scientists on the panel advising Hayes.

Why Hayes overturned the FDA-appointed Public Board of Inquiry which closed the approval of aspartame in 1980 on grounds the brain tumor studies were inadequate. Walla Nauta, chairman of the board, has indicated he may have opposed the approval even more strongly than it had known that G.D. Searle planned to widely market it in soft drinks. Nauta has said that
CONGRESSIONAL RECORD — SENATE

August 1, 1983

a different set of tests should have been conducted for soft drink use.

Roger Thies, Searle's associate general counsel, asserted in an interview Wednesday that the artificial sweetener aspartame would be used in carbonated beverages was made clear to the board and that the dosages tested proved as safe as sugar as a food additive. He said, "It would be almost inconceivable to me that somebody could drink enough (diet) soft drink in a day to go beyond the consumption levels that we have shown to be safe."

Hayes' decision to overturn the board of inquiry's decision over the claims of the "Japanese study" submitted after the board's decision. The study, UP1 learned, was conducted by the Almonno Co., Inc., the Japanese licensor to the contestant in the aspartame litigation. It has alleged that Hayes had no legal basis to rely on a study that was not part of the administrative record.

The extent the FDA evaluated the concerns of Dr. Richard Wurtman of the Massachusetts Institute of Technology, who raised questions about the effects of aspartane on brain chemistry, and Dr. William Farbridge of UCLA, who suggested women who consume aspartane may give birth to infants with lower IQ levels.

Whether officials of the Carter White House, House, or Reagan transition team discussed aspartane approval with FDA officials. Thies denied that Searle Chairman Donald Rumfield, a former top aide to President Gerald Ford, had any contact with White House or FDA officials about aspartane after joining the firm in 1971.

The most controversial test questioned by FDA scientists continue to be the foundation of proof of safety relied on by the agency in approving NutraSweet.

Gauld contended that aspartane, the three components of which are aspartic acid, phenylalanine and methanol, is "the most tested product ever approved by the FDA."

The Centers for Disease Control in Atlanta recently issued a report on the side effects of aspartane on humans, asking the FDA to start "focused, clinical studies" on the product's safety on an "expedited basis."

Two-thirds of 200 complaints reviewed in the report were considered adverse neurological or behavioral reactions—such as restlessness, bizarre dreams, dizziness, loss of appetite, depression and mood swings.

Other reactions consumers have blamed on aspartane include the formation of benign skin tumors, menstrual irregularities and many other problems.

Thies said a small segment of the 100 million Americans who have tried aspartane products may have a "sensitive or allergic reaction, or idiosyncratic reaction" to aspartane.

In opposing aspartane approval, three of the six FDA scientists advising Hayes focused on G.D. Searle's brain tumor studies and concluded that aspartane "has not been shown to be safe and therefore may not be approved for marketing."

The term head wrote in 1981. One of them, Dr. S. Satya Dube, said in a letter to team leader Joseph Levitt that "statistical results obtained so far point out many problems...and some of them may be cancer-related sexual dysfunction."

Also objecting were Dr. Robert Condon and Dr. Douglas Park, the staff science advisor for the Office of Health Affairs. Gauld said that although "three internal scientists raised questions about the brain tumor studies and the statistics on that, there is nothing new about the fact that not everyone agrees within a regulatory agency on every decision."

"(From the New York Times, July 3, 1985)"

A SWEETENER'S EFFECTS: NEW QUESTIONS RAISED

(By Marian Burton)

In 1984, G.D. Searle & Company of Skokie, Ill., sold 108 million worth of the artificial sweetener aspartane, on which it holds the exclusive United States patent. Produced under the trademarks NutraSweet and Equal as a table-top sweetener, aspartane is found in a wide variety of products—from puddings, bubble gum and breakfast cereals to some of the best known diet products marketed by Coca-Cola, Pepsi and Seven-Up.

Recently, however, aspartane has been the target of criticism from several scientists conducting studies of the sweetener or its components. While their findings are not conclusive, preliminary data have indicated that aspartane may be responsible for a range of problems from temporary dizziness to mental retardation.

Their contentions are strongly denied by Searle, which has done its own studies on aspartane in the past and is conducting new ones. "When any new product is marketed and attention is paid to people, people tend to ascribe any adverse experience to that new product," said Dr. Frank M. Sturtevant, a pharmacologist who heads the office of scientific affairs at Searle. "We expected a lot more in the way of complaints than we got: only 600 out of 70 million people who have used it."

Aspartane has been controversial since Searle first sought to market it in 1974. After considerable debate about its safety, the FDA approved the sweetener with the United States Food and Drug Administration in 1981. But this spring questions about its effects began to surface again.

In May, the Senate Committee on Labor and Human Resources received testimony from two researchers favoring quantitative labeling of products containing aspartane. In accordance with Federal law, it is now listed on labels as an ingredient; no amount is specified. Dr. William Farbridge, an associate professor of nutrition at the University of California at Los Angeles, said that too much of the artificial sweetener might cause serious kidney trouble. Even Dr. Richard J. Wurtman, director of the clinical research center at the Massachusetts Institute of Technology, said that consuming aspartane for more than 200 years could double aspartane's effect on the brain.

On June 17, Dr. Louis Elias, director of the division of medical genetics at Emory University in Atlanta, said that neither pregnant women nor infants under the age of 6 months should consume aspartane because of the chance of brain damage to the fetus or infant.

Dr. Sturtevant, who calls these contentions "at best, highly speculative," says dozens of tests done by Searle prove the safety of aspartane. Dr. Sanford Miller, director of the FDA's Center for Food and Drugs, said that the claims against aspartane are unfounded.

And the American Diabetics Association has reaffirmed its faith in aspartane, saying that FDA's studies appear sufficient to demonstrate its safety.

Since the marketing of aspartane four years ago, the Centers for Disease Control in Atlanta has received over 600 complaints from people who said they suffered dizziness, headaches, blurred vision or general malaise symptoms typically associated with consuming aspartane. The centers called for studies to determine individual sensitivity to the sweetener.

On July 23, a $2 million lawsuit was filed against Searle in United States District Court in Washington on behalf of a 3-year-old boy in Olney, Md. The suit charged that consumption of NutraSweet caused brain damage, but it did not specify the amount consumed.

In granting approval of aspartane—which is 180 times as sweet as sugar with only one-tenth of the calories—Dr. Arthur Hull Hayes Jr., the P.D.A. Commissioner in 1981, overruled several of the agency's scientists. A big board of inquiry set up to evaluate the Searle studies of aspartane's effect on animals. These scientists said that Searle's research did not adequately answer the safety questions about carcinogenicity. According to Congressional testimony from Dr. Alexander M. Schine, a former F.D.A. Commissioner, some of the experiments were "poorly conceived, carelessly executed or inaccurately analyzed or reported."

The recent review of the Searle studies, Dr. M. Adrian Gross, a senior scientist advisor at the Environmental Protection Agency and a former pharmacologist to the office of Senator Howard M. Metzenbaum, a member of the Committee on Labor and Human Resources. His letter sets forth that in the experiments, "at least one of those studies has established beyond any reasonable doubt that aspartane is capable of inducing brain tumors in experimental animals."

In a telephone interview, Dr. Sturtevant asserted that some of the data presented to Congress were for review. Only if the correct tabulations, he contended, were contained in a document that he wrote for the board of inquiry impaneled by the F.D.A. Sturtevant showed how in the experiments, "at least one of those studies has established beyond any reasonable doubt that aspartane is capable of inducing brain tumors in experimental animals."

Aspartane-sweetened foods now carry a warning directed at phenylketonurics—people who are unable to metabolize phenylalanine, one of two amino acids that make up aspartane. Victims of phenylketonuria, or PKU, will become permanently retarded if the condition is not diagnosed at birth and consumption of phenylalanine strictly controlled.

According to Dr. Elias, about 2 percent of the population are carriers of the PKU gene and are unaware of the condition. He has created babies of phenylketonuria on unborn children of PKU carriers.

"A small change in the phenylalanine level in a pregnant woman's blood is magnified by the placenta into the fetal blood, and the fetal brain will concentrate that further," Dr. Elias explained. "High levels of phenylalanine in unformed or forming brains could cause irreversible damage. No one knows what degree of elevation in the mother's blood may cause brain damage in the fetus."

Dr. Elias's concern is based on two studies of the effects of phenylalanine on two groups of people—10 healthy men between the ages of 8 and 24—who have PKU but have developed normally. In these studies, the first of which was published in the Journal of Clinical Investigation, Dr. Elias observed that the patient's reaction time was affected and the production of adrenalinlike chemicals in the brain was reduced.

The second study, just confirmed, confirms the first, he said, adding, "All of the brain changes were reversed over a three-month period, but it took longer for full mental functions to return."
August 1, 1985

CONGRESSIONAL RECORD — SENATE

S 10825

Dr. Elzas said that anybody over the age of 6 months should consume "aspartame in moderate amounts or they should get their phenylalanine blood level checked."

"The test says that Dr. Elzas is scaring people unnecessarily. "It is not physically possible for an unknown PKU carrier to maintain a phenylalanine blood level in the 20-200 milligrams per deciliter range," Dr. Elzas has said. "There is no experimental evidence to suggest a risk to the fetus."

Searle has eight studies under way exploring the effects of aspartame on the brain. Dr. Wurtman of M.I.T. does not believe that moderate amounts of aspartame are a hazard to normal people. "But" he said in a recent interview, "I think there are some numbers of people who are at risk."

Dr. Wurtman, who is a consultant to Searle on products other than aspartame, said that when he and Searle "talk about aspartame we tend to go no by no."

Dr. Wurtman's own animal studies show that "you double the effect of the phenylalanine in the brain when you have aspartame in your stomach together, no one knows what a safe amount is," he said. "There are several groups of people who might be especially susceptible to high doses. Those include people who are taking drugs that act on the brain like antihypertensives, people with a history of seizures, young and pregnant women."

For adults who do not fall into the above categories, Dr. Wurtman said half a gram to one gram of aspartame a day should be safe. "But," he added, "if a 7-year-old, weighing about 45 or 50 pounds, drinks a 2-liter bottle of Diet Coke, which contains about 1,200 milligrams, he is already exceeding the allowance by far on a daily basis for aspartame suggested by F.D.A."

Dr. Wurtman said he knew of a dozen patients with "first-time seizures confirmed in university hospitals who were consuming very large amounts of aspartame." It is very important," he said, "that such people be subjected to real studies.

Dr. Wurtman also said all foods containing aspartame should state the amount on the label.

But Searle and soft-drink manufacturers disagreed. "We have no objection to F.D.A. requiring quantitative labeling for food ingredients," Dr. Wurtman said. "But we do object to F.D.A. singling out aspartame, because there is no scientific evidence suggesting that it need be labeled."

"Aspartame is safe," said Dr. Miller of the F.D.A. but he added: "We are not moving very rapidly to approve new uses. If there is another segment of the population besides phenylketonurics who are sensitive, we do whatever we have to do—from putting something on the label up to banning it if the population is large enough."

[From The Washington Post, July 3, 1985]

EXPERT STILL TROUBLED BY ASPARTAME

(By David Ziman)

Aspartame, the sugar substitute marketed as NutraSweet, is one of the most successful stories of the 1980s. In the four years since the artificial sweeter was found to be safe, the American people have consumed more than 100 million Americans have tried it. They have tasted it in more than 90 types of products ranging from diet soft drinks to soups to instant coffee to "diet" pasta. G.D. Searle & Co., reported sales soaring to $353 million. By 1986, some expect it to top $1 billion.

But there is a possible dark side to all this. Aspartame contains a potentially harmful component, an amino acid called phenylalanine. Too much of it can cause brain damage, especially in young children and newborns of phenylketonuric women, according to studies done by Dr. Louis Elzas of Emory University in Atlanta.

"The serious question," said Elzas, "is if pregnant women taking artificial sweeteners can elevate their blood level of phenylalanine to concentrations that add up to a risk?"

"It is damage from phenylalanine produced by a threshold effect? Or do little bits of this problem occur at lower levels?"

"Aspartame is being promoted as something good for you. But I don't think that it is a legitimate thing for or notion to be exposed in large quantity," said Elzas.

Searle has reported potential adverse effects of aspartame on pregnant women and infants were "misleading" and do not present a "disservice to consumers." The Chicago-based firm pointed out that in 1981, the Food and Drug Administration found the product to be safe and effective.

Searle does not dispute the contention that high levels of phenylalanine can cause damage in infants with a rare genetic disease known as "PKU," because for alarm because current consumption amounts are not even close to a point where they might pose a problem. Most importantly, says Elzas, studies on pregnant animals show that even at "abuse levels," aspartame presents no hazard to the fetus. Nonetheless, he said, "a small percentage of medical genetics at the Atlanta school, said he is concerned. Because the sweetener's sale has been so massive and there are still some unknown about the product. What worries him—and this is not based on any study but his own personal thoughts as a scientist—is that the fact that one's blood could be low and subtle. They could take a generation or more to uncover."

"It's not going to be so over an explosion," Elzas said recently on "Nightline," an ABC-TV news program. "We may not be able to see the effects for a generation. And then we'll suddenly see a lot of kids with behavioral abnormalities, with IQs that aren't reaching what...we anticipated from their educational or their genetic input.

Searle says that more than 20 years of testing in animals has shown aspartame to be safe over long periods. Elzas acknowledges there had been "well-documented negative side effects of aspartame. Nor has he personally conducted a study on the sweetener.

But he has done research with children and young adults with gene defects who ingested phenylalanine at high levels and found that their reaction time had slowed. That means phenylalanine can produce quantifiable changes in brain function. "I believe," he says, "the unlimited use of phenylalanine products, should be moderated especially in certain groups."

A pediatrician and a biochemist, Elzas is focusing on a genetic disorder called phenylketonuria or PKU. These individuals cannot metabolize foods containing phenylalanine. As a result, the chemical concentrates in their bodies. This can cause retardation in fetuses and newborns who have this genetic disorder. Many states require tests to discover PKU babies who must be put on special diets. Elzas is also concerned about parents of these children, who are normal but may be affected if the are exposed to aspartame. Elzas said Elzas. "They, too, they may be able to metabolize phenylalanine."

Since it is not always possible to detect them, people should have their PKU baby is born, the vast majority don't know who they are. About 1 percent of babies delivered each year are born to mothers who are carriers.

People in whom high levels of phenylalanine may pose problems, Elzas said, are:

Pregnant women. If blood phenylalanine rises in early enough, irreversible brain damage by slowing formation of mature brain cells and by altering the formation of myelin cells that insulate parts of the brain.

Older children and adults carrying the PKU disorder. A high blood concentration of phenylalanine will reduce the brain's ability to function as quickly and efficiently. But these changes are reversible once the level of phenylalanine returns to normal.

The flaw in Elzas' argument, says Daniel Azarnoff, a professor of development for Searle, is that he has no idea what is a dangerous level of phenylalanine concentration in the brain. Azarnoff is concerned that people may be getting toxic amounts of phenylalanine in the face of scientific data. "He is saying people eat a lot of aspartame," says Azarnoff. "The evidence is they don't."

The FDA has set 50 milligrams of aspartame per kilogram (2.2 pounds) of body weight as an acceptable daily intake. To reach that amount, Searle says, a 132-pound person would have to drink 18 cans of diet soda a day. The average 12 oz. can of diet soda contains 170 milligrams aspartame, Searle says.

But Dr. William Patridge of the University of California at Los Angeles says the FDA has underestimated consumption of aspartame. Patridge was not reached for comment. However, the magazine Chemical & Engineering News has noted that the FDA in 1983 cited figures showing how children eating aspartame-sweetened foods all day could be on the way to consuming the safety assessment.

Searle says that tests it sponsored show no harmful effects have been seen, at least 20 times the FDA's intake standard. However, the quality of Searle-sponsored studies has been criticized. Sen. Howard Metzenbaum (D-Ohio) has complained that the FDA overruled many scientific questions raised about the reliability of testing. A federal investigation is now under way.

Elzas also argues that the FDA's own publications show that the daily phenylalanine intake of some children ages 7 to 9 goes as high as 70 milligrams per kilogram of body weight—exceeding the agency's acceptable daily amount of 50 milligrams. What Searle's studies do not show, he says, is long-term effects at intermediate levels. In addition, one scientist, Richard Wurtman of the Massachusetts Institute of Technology, describes some food's "intensity of flavor" of phenylalanine. "If you drink a beverage containing aspartame at the same time one eats a carbohydrate-rich food," Wurtman says, "then aspartame's effect on brain phenylalanine is doubled."

To try to clarify the situation, Dr. Reuvan Matalon of the University of Illinois has studied the effects of high intake of phenylalanine to look at the effects of aspartame on PKU carriers as well as on normal individuals. The study will take about two years.
"In the meantime, I don’t think it is fair to express concerns about aspartame as conclusions,” he said. "There is no data to implicate it as anything difficult to understand. At the same time, we do not know what a high level of intake will do and where the danger point comes. Until we get the data, if I were the FDA, I would recommend that pregnant women use caution. Moderation should be the key."

**SWEET SUSPICIONS**

Steve Wilson. They say it’s the biggest breakthrough in diet drinks, a better taste from a new product everybody is talking about.

**Commerical.**

Steve Wilson. T’-up has got it, too. And orange soda, and Dr. Pepper. And the fact is it’s virtually impossible to find a can of diet soda without Nutrasweet.

**Commerical.**

Steve Wilson. Powered drink mixes have it, too. And Cay-ser, Wyley fruit drinks, chocolate drink mixes. It’s in Jello, too, in all kinds of sugar-free products. You can buy it in little drinks in the brand name Equal. It’s 200 times sweeter than sugar and Americans sure like the way it tastes. The company that makes it at $95 a pound made more that’s a million dollars worth last year and may sell twice as much in 1985—unless nagging safety questions slow down sales.

**MOS.** My girlfriend just told me yesterday it’s not supposed to be good for you. So, now I’m not sure if I’m drinking the right thing.

**MOS.** I’d like to know how safe it is, I imagine it’s to a degree because it’s in everything you drink now-a-days.

**MOS.** It’s cool. It’s safe.

**Steve Wilson.** Unquestionably?

**Robert Shapiro.** Unquestionably!

**Steve Wilson.** Not a doubt in your mind?

**Robert Shapiro.** Not a doubt in my mind.

**Steve Wilson.** Nobody expresses more confidence in the stuff than the man who is president of the Nutrasweet Group, the division that brings in 70 percent of the total profits of the big Searle Pharmaceutical Company.

**Steve Wilson.** Why is it that you can’t seem to convince so many others of that?

**Robert Shapiro.** That’s just not right. The fact is we have convinced all the folks whose opinion we sought.

**Steve Wilson.** He’s not talking about Joyce Moscasto. She’s one of thousands of people who have come forward about serious side effects. Who of those who believes when all the facts are known.

**Joyce Moscasto.** Everybody’s going to be convinced that there are people who do have an adverse reaction to the consumption of Nutrasweet.

**Steve Wilson.** Mary Carr is another one who is not convinced by Searle’s multi-million-dollar advertising and public relations blitz.

**Mary Carr.** My body went through hell with this stuff, I really did. I think that they should take it off the market and do more research because I would not want to put anyone through what I went through.

**Steve Wilson.** But it’s not just the letters from consumers who are reporting adverse effects. It’s what so many respected scientists are saying.

**Dr. Woodrow Monte.** Every time a truly impartial team of scientists have looked at Nutrasweet, it has been turned down. It has been denied. It has been tested correctly. The tests that have been done that I consider to be honest tests show extreme dangers over the long term.

**Wilson.** When our report continues, a closer look at some of the complaints and why some scientists are still saying that despite government approval, your diet soft drink may not be as safe as you’ve been led to believe.

**Steve Wilson.** Are you telling me I shouldn’t drink the stuff?

**Dr. Woodrow Monte.** Yes, I am saying you shouldn’t drink the stuff.

**Steve Wilson.** It’s dangerous. Yes, I am saying that I believe that with all my heart.

**Robert Shapiro.** Seizures, headaches; among women it’s the early onset of menopause, serious depression. People say they can’t understand what’s happening to them except that they keep getting more and more depressed. It’s called Nutrasweet.

**Joyce Moscasto.** You really don’t want to go to work, you don’t want to deal with friends, you don’t want to communicate with the rest of the world.

**Steve Wilson.** They believe Nutrasweet, America’s newest artificial sweetener, is responsible. And despite how good it tastes in diet drinks and gelatin and all kinds of sugar-free products, people all over the nation are reporting and feeling like headaches, feeling like they’re under no unbearably painful stomach problems; various allergic reactions, even seizures. But her complaints and thousands of anecdotes are scientific unsubstantiated stories that don’t worry Robert Shapiro.

**Robert Shapiro.** No, I don’t find it scary because I’m aware of the evidence and there is no evidence to suggest that younger females or anybody else has a problem with the product.

**Steve Wilson.** He’s president of the group that makes it, the Nutrasweet Group at the G.D. Searle Drug Company where they can’t ship it fast enough. But on Capitol Hill just last month, FDA chairman Frank Young admitted to a Senate Committee that he believes it’s safe for most of us, there is a big exception.

**Frank Young.** With the exception of a sub-group in the population, young females and that is under further study at this point.

**Steve Wilson.** But diet drinks are big, with lots of young mothers who, for whom, have had the same problem Joyce Moscasto had for many months she consumed Nutrasweet—her menstrual periods simply stopped.

**Joyce Moscasto.** December 27th I quit using Nutrasweet and on January 25th I had my first period. I felt great and I’ve been normal ever since.

**Steve Wilson.** Well, despite his claims nobody has a problem with his product. Shapiro knows better and reluctantly admitted Nutrasweet—apparently can be trouble.

**Robert Shapiro.** Now it’s not just young women reporting side effects. Some of the nation’s most respected scientists have some serious concerns about the product. Dr. Richard Wylie, who at MIT believes it may adversely affect brain chemistry; that is can cause behavioral changes. Dr. John Olney at Washington University has raised questions about brain damage to children. And here on the campus of Arizona State University in Phoenix, Dr. Woodrow Monte says the big danger is from a substance left in our bodies, Nutrasweet breaks down—methyl alcohol.

**Dr. Woodrow Monte.** If I could get a public hearing, if I could have a Congressional hearing, and have a hearing before the Food And Drug Administration which they have been stopping, trying to stop, I could say this finally, that even these so-called small amounts of methyl alcohol can cause extremely serious consequences over the long term.

**Steve Wilson.** Now these complaints we’ve been hearing from all over the country are certainly alarming but what may be even more alarming is how this product Nutrasweet got past the Food and Drug Administration and onto grocery shelves.

**Steve Wilson.** Politics.

**Robert Leonard.** I would call it politics.

**Steve Wilson.** There was a congressional, never for one minute did I suspect that a product that was on the market with the approval of the FDA would be causing such harm.

**Steve Wilson.** Joyce Moscasto and many others like her say the harm—in her case depression and menstrual problems—is linked to Nutrasweet. But the artificial sweetener the Food and Drug Administration has declared safe.

**Robert McQuate.** For FDA to cavalierly approve something on a whim is totally out of the realm of possibility.

**Steve Wilson.** But you weren’t satisfied with the work that they did?

In fact the soft drink makers were so satisfied with what they believed was the lack of evidence Nutrasweet was safe, they asked the FDA to include a cautionary note in the product’s label and reverse the sanctions against the industry, for example, in a letter they wrote the FDA. He says secret tests his members paid for later answered all their questions. But others believe those who want to see Nutrasweet discarded the scientific concerns for safety in favor of higher profits brought in from better-tasting diet products but Searle, the big drug company—makes Nutrasweet and has the legal responsibility to scientifically prove to the government that it’s safe.

**Dr. G. Gross.** They lied and they didn’t submit the real nature of their observations because had they done that it would have been more likely that a great number of these studies would have been rejected simply for adequacy.

**Steve Wilson.** Dr. Gross was the chief scientist on a nine member task force that reported Searle made a number of “deliberate decisions” seemingly calculated to minimize the chances of proving Nutrasweet is toxic to danger to our health.

**Dr. Gross.** What Searle did, they took great pains to camouflage these shortcomings in their study. And just present to the FDA what they wished the FDA to know and they did other terrible things for instance animals while they were under study. Well they would remove these tumors from the animals.

**Steve Wilson.** Other laboratory animals Searle used for tests on another product in the same lab seemed to die and come back to life—this one three times.

**Robert Shapiro.** That’s apparently a recording keeping error.

The president of the Nutrasweet Group at Searle says Dr. Gross and his task force did it all wrong. But other small experiments on laboratory animals and other independent evidence, a scientific board of inquiry has also raised serious safety questions that have other respected scientists.

But the FDA approved it. So it’s safe.

**Robert Shapiro.** It has been established by the people who had the responsibility for making those decisions and they’ve made those decisions and the fact is it’s safe.

Everybody who has looked at the cancer question has said this should not be marketed on the basis of the cancer question except for Dr. Hayes. The Reagan appointment commissioner of the FDA who now works
CONGRESSIONAL RECORD — SENATE

August 1, 1985

as senior medical advisor to the Searle public relations firm.

STEVE WILSON. Mr. Arthur Hayes who approves wider use of NutraSweet is also now dean of the New York Medical College and refuses to speak publicly about this issue.

WILSON STAND-UP. Now we don't know if NutraSweet is safe or not. We do know that a lot of good science has been done into a lot of good questions and that's the point: The law requires the FDA to establish to a reasonable certainty that the stuff is safe before we start using it. And all that's certain at this point: there's big money riding on the outcome and so too is our health. At Searle Company headquarters in Chicago…(Steve Wilson reporting).

NUTRASWEET UP-DATE

COMMERCIAL. "It's a little red swirl next to the name NutraSweet Brand Sweetener." STEVE WILSON. Thanks to a fortune spent on ads like this, even young Americans know what NutraSweet is.

COMMERCIAL. "100 percent NutraSweet. Oh, that's the good stuff." Without ever having reported more about all the questions still unanswered in regard to the safety of NutraSweet, there have been some new developments.

Sen. PETZELBAUM. There's enough reason to be suspicious.

Sen. Wilson. Senator Metzzenbaum says he's seen enough now to have real suspicions and he requested the General Accounting Office to investigate. Specifically, his letter to the Comptroller General asks for an investigation of NutraSweet test results, which are really happening during the formal FDA approval process, and to what extent was the White House involved in the approval of the product.

Sen. PETZELBAUM. Where there's smoke, there's fire. The Food and Drug Administration ought to act with dispatch to investigate these, the safety of this product. Too many people are drinking too many diet drinks to permit this to go on and they shouldn't need a Congressional prod in order to do the job that is truly their own responsibility.

Sen. WILSON. By the way, another Metzzenbaum letter suggests that Senator Heinz puts some sharp questions to the F.D.A. The Senators want to know if more stringent labeling requirements are in the works and why is the industry allowed to hold back much of the stuff is safe to drink, what's being done to validate the test data the manufacturer provided, and who's monitoring and encouraging medical reports from doctors across the nation when they see evidence of medical problems possibly related to NutraSweet?

Searle—the maker of NutraSweet—is still standing behind the product, calling it absolutely safe. But the company has acknowledged now at least eight more studies are being done on the product's safety questions, perhaps the biggest here at Duke University. Scientists on this campus and elsewhere will study whether NutraSweet causes headaches, seizures and special problems for children.

In Atlanta, scientists at Emory University are out with a report that links NutraSweet consumption with neurological symptoms and defects and problems with infants who eat or drink it. And in Maryland late last month, what may be the first lawsuit as a result of NutraSweet use, a little boy is seeking $2 million from Searle claiming the child has suffered serious and permanent neurologic and psychiatric injuries from NutraSweet.

The product, meanwhile, is still selling briskly. Sales are expected to top $1 billion this year.


Hon. SAMUEL K. SKINNER, U.S. Attorney, Northern District of Illinois, 219 South Dearborn Street, Chicago, IL.

Dear Mr. Skinner: We request that your office convene a Group B investigation of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 331(e), and the False Reports to the Government, 18 U.S.C. § 1001(a), and report to the G.O. Searle and Company and three of its responsible officers for their willful and knowing failure to make reports to the Food and Drug Administration required by 21 U.S.C. § 355(l), and for concealing material facts and making false statements in reports of animal studies conducted to establish the safety of the drug Alidacone and the food additive Aspartame. Concealing material facts relative to the Alidacone study also resulted in that drug being misbranded within the meaning of 21 U.S.C. § 352(a) and 321(n), in violation of 21 U.S.C. § 331(a).

1. THE STATUTORY/REGULATION SCHEME

A. Investigational New Drugs. The Food and Drug Administration's responsibility for assuring that drugs marketed in this country are safe for their intended uses and are accurately labeled under the Federal Food, Drug, and Cosmetic Act prohibits the marketing of any 'new drug' in interstate commerce unless a new drug application (NDA) is filed with the FDA containing substantial evidence of the safety and effectiveness of the drug has been approved by the FDA. Before an NDA is approved for use of a drug, that drug may lawfully be used only for investigative tests, first in animals and thereafter in human beings, if it is permitted only in accordance with 21 U.S.C. § 355(l) and regulations promulgated thereunder.

The original statutory basis for regulating the investigational use of new drugs was provided in 1938 by the basic Federal Food, Drug, and Cosmetic Act. The Drug Amendments of 1962 authorized the FDA to establish a list by regulation of investigational reporting requirements to assure that information about significant hazards, contraindications, side effects, and other important findings associated with the investigational use of new drugs is disseminated rapidly. These regulations specify the form, content, and timeliness of the submission of such information. Failure to comply with such requirements is prohibited under the Act, 21 U.S.C. § 331(e).

A major purpose of the investigational new drug regulations, 21 CFR Part 312, is to safeguard human subjects during the investigational phase of drug development. Accordingly, the regulations require that prior to the administration of any investigational drug to human subjects, the sponsor of the drug must file with the FDA a notice of claimed investigation for a new drug (IND), which contains adequate information about preclinical (animal) investigations of the drug and any studies and other data necessary for the safety of the drug. The IND applicant has concluded that it is reasonably safe to initiate clinical (human) testing. A careful evaluation of the animal toxicological and pharmacological studies and some assurance of the expected effects when the drug is administered to humans. If the data submitted in an IND justify a finding that the drug may likely be tested in humans, the FDA permits the sponsor to ship the drug to investigators. It is not uncommon, as is the case with any new drug, that an IND applicant may have an approved NDA for certain uses while simultaneously being tested in animals and/or humans for other uses under an IND.

Because the IND procedures provide a limited exemption for the distribution of a drug which has not as yet been shown to be safe, for effectiveness, or for safety in controlled clinical investigations, the regulations require the sponsor to closely monitor the progress of pre-market investigations and to provide that progress reports of such investigations be submitted to the FDA at reasonable intervals, not to exceed one year. 21 CFR Part 312. Further, the regulations require that a sponsor shall "promptly investigate" and report to the FDA "any findings associated with the use of a drug which suggest hazards, contraindications, side effects or precautions pertinent to the safety of the drug." If such a finding is "alarmant," it must be reported "immediately" and clinical investigation discontinued or modified until the finding is adequately evaluated and a decision is reached that it is safe to proceed. 21 CFR § 312.1(a)(6).

The results of drug testing are critical not only to establish the basic safety and effectiveness of the product but also to establish possible side effects, contraindications, and the need for special warnings, all of which must be included in the drug labeling. The sponsor of every new drug must make formal labeling for FDA approval at the time of initial marketing and thereafter to reflect new information resulting from subsequent testing.

B. Food Additive Petitions. The Act also provides for FDA approval of food additives. Approval of an additive is codified in a regulation describing conditions under which the additive may be safely used. The regulation is promulgated solely on the basis of a manufacturer's petition, filed pursuant to 21 U.S.C. § 348(b), which includes reports of studies establishing the safety of the additive. As with investigational drugs, the FDA does not perform safety testing of food additives, and it must rely upon the data developed by the petitioner. Studies supporting a petition are ordinarily performed only on animals; human testing is uncommon.

The major purpose of the food additive provisions, added to the Act in 1958, is to prevent the unrestricted marketing and consumption of substances in food, with or without reasonable assurance that these substances will not adversely affect man, either immediately, over a lifetime or in the next generation.

C. Monitoring Test Integrity. Reports of studies submitted to the FDA as part of INDS or NDAs of drug investigations must be complete, balanced and truthfully if the Agency is to fulfill its duty of assuring that these products are safe and that new drugs contain accurate labeling based on the result of preclinical and clinical testing.

The FDA has not routinely monitored the conduct of animal test results submitted in support of either new drugs or food additives. The reliability of the testing is normally checked by FDA review of the sponsor's reports of test data. If the FDA determines that a new drug may cause risk to health, the FDA may review the underlying raw data itself in the possession of the sponsor. The FDA may also select manufacturers or provide for monitoring by licensed, independent surveillance inspectors.

When there is reason to believe that there are irregularities or discrepancies in the conduct of testing, the FDA may conduct a compliance inspection in order to evaluate the testing facilities, practices, and record keeping procedures, and resolve any disparity between the raw data and the report or to determine the truthfulness of data presented in the report.

FDA experience has identified significant problems in the manner in which this
many preclinical laboratory studies are performed. Deficiencies in the quality and integrity of these data have prompted the Commission of Food and Drug to establish a bioresearch monitoring program, and to propose the promulgation of good laboratory practices, which will delineate proper procedures for conducting preclinical laboratory studies. Congress has increased FDA’s budget for the fiscal year 1977 by $10 million to provide the required funds to help achieve the goals of the new program.

II—THE SEARLE INVESTIGATION

The genesis of the investigation of studies conducted by and for G.D. Searle was the FDA’s discovery in 1972 of certain discrepancies in Searle tests submitted in support of a large-selling anti-infective drug, Flaygl. FDA review of the data was initiated because independent investigators had reported evidence that Flaygl was a carcinogen (an agent capable of producing cancer). Searle’s own long-term toxicity study, submitted in 1970, had not concluded that Flaygl was a carcinogen. In April 1974, Searle submitted more data on the issue of Flaygl’s carcinogenicity and also submitted corrected data on other deficiencies in Searle preclinical testing and reporting of test results.

On July 23, 1974, Dr. Alexander M. Schmidt, then the Commissioner of Food and Drugs, established a special internal Task Force to review the conduct of animal experiments conducted by and for G.D. Searle and report its findings. The Task Force was conducted at Searle and at three independent laboratories, Baselon Laboratories, Vienna, Virginia; the Wisconsin Regional Primate Center, Madison, Wisconsin; and Microscopy for Biological Research, Albany, New York, which had conducted or participated in the evaluation of animal studies for Searle.

The Task Force reviewed inspection reports covering 26 separate studies on seven different kinds of animals—approximately 500 pages plus 15,000 exhibits. Based on this information, data originally submitted by Searle, and scientific evaluation of animal tissue slides and data, the Task Force issued its report to the Commissioner on March 24, 1976. A copy of the Task Force report was forwarded to the Consumer Affairs Section, Antitrust Division, Department of Justice, and to your office in April.

Among other observations, the Task Force questioned Searle’s handling of data applicable to the drug Aldactone and the reporting of studies on the food additive Aspartame.

The Task Force report was provided to Searle and the firm requested an opportunity to submit a written reply and to meet with the Commissioner to respond to the conclusions and recommendations of the Task Force. The meeting was held on May 18; Searle submitted its written reply to the Task Force report on May 21. An enclosure a copy of the May 18 meeting and the written reply of Searle to the Task Force report (Exs. 1a, 1b). At the meeting, Searle requested an opportunity to make further written submission to two memoranda by FDA pathologist M. Adrian Gross, a Task Force consultant who had reviewed numerous preclinical testing data. This Searle reply was sent to the Agency on June 21, 1976.

III-INFORMAL ADMINISTRATIVE HEARING

After review in my office and in the office of the Associate Commissioner for Compliance of all the material relating to this matter, on September 3, 1976, the Agency issued, published, and provided a Notice of Hearing to G.D. Searle and Company, and ** for apparent violations of the Federal Food, Drug, and Cosmetic Act and related violations of 18 U.S.C. 1001 concerning Aldactone and Aspartame. The hearing, originally scheduled for September 21, 1976, was postponed for a period of time until October 20. An amended Notice of Hearing dated September 15, 1976, was issued to correct an inadvertent omission from the earlier notice with regard to a hearing date. A copy of the Notice of Hearing was forwarded to the Consumer Affairs Section and to Attorney Fred Branding of the Division of Hearings.

At the October hearing, Searle submitted lengthy written replies to the 305 Notice. Copies of this document, in addition, Searle reiterates a request for the Agency’s investigational file covering the apparent violations which were the subject of the hearing. Searle’s request indicates that it was an earlier Searle request for “discovery” which referenced the Jenkins Act, the Federal Rules of Evidence and Brady v. Maryland. Copies of the information concerning these requests have been provided to the Consumer Affairs Section and Mr. Branding.

As you know, preliminary reports of discrepancies in preclinical testing conducted by and for Searle were partially responsible for hearings on drug-related research held before the Senate Subcommittee on Health of the Committee on Labor and Public Welfare and the Subcommittee on Administrative Practice and Procedure of the Committee on the Judiciary both chaired by Senator Edward Kennedy on July 10, 1975. Subsequent testimony updating the investigation and the positions of the FDA and Searle were taken before the joint subcommittees on January 30 and April 8, 1976.

IV—FAILURE TO SUBMIT SAFETY DATA ON ALDACTONE

A. The Drug. Aldactone is a new drug marketed by Searle pursuant to NDA 12-151. The drug was first approved in 1960 for use as a diuretic (an agent that increases the secretion of urine) for congestive heart failure and for hyperaldosteronism, a relatively rare but severe disorder of the adrenal cortex often resulting in high blood pressure. By 1974, Aldactone and a related drug utilizing the same active ingredient, Aldactazide, constituted approximately of Searle’s total pharmaceutical sales, approximately a year. Current sales are reported to be a year.

In 1963, Searle submitted IND 714 to conduct studies to demonstrate the use of Aldactone in massive doses in the treatment of myasthenia gravis (serous muscular paralysis). In 1969, Searle amended its IND to cover testing of Aldactazide for severe congestive heart failure at dosage levels much higher than those approved in the NDA.

B. The MBR / “MUR” Report. In 1970 Searle designed two 78-week studies in the rat on Aldactone, one to support the long-term use of the drug at dosage levels approved in the NDA, and the other to support higher dose levels in the treatment of severe congestive heart failure. The first study, later extended to 104 weeks in duration, was conducted at the National Institutes of Health, Vienna, Virginia; the second was performed by Searle in its own laboratories. A study conducted at Searle in August 1970 and rates were sacrificed and necropsied (autopsied) during February and May 1972.

In November 1972, consistent with prior practices, Searle submitted the slides of sections of organ tissues of the rats from the studies to the outside consultant pathologist for examination. The slides were examined by Dr. Jacqueline Mauro, a board-certified pathologist, at Micropath, a Biological Laboratory of the University of Albany, New York (MBR). The report of her readings—the MBR report—was submitted to Searle on March 21, 1973. In a letter dated March 31, 1973, the outside consultant pathologist informed Dr. Mauro that she had not received the report which "looks just fine.”

In the summary of the MBR report, Dr. Mauro stated that her pathology review of the data suggested a group relationship, meaning a drug-related or drug-induced relationship, with the livers and testicles of the testes and liver. She also noted a significant number of thyroid tumors and non-tumor conditions involving the thyroid lesion, which she called “adenomatous goiter.” Dr. Mauro then stated that she would not sign the MBR report that these findings be measured for statistical significance. A statistical review of pathology reports, Dr. Mauro stated, since an absolute cause-and-effect relationship usually cannot be established in experimental biology. Therefore, an association between an agent and an effect of fate on organ abnormality. If the incidence of a toxic response, such as a lesion, is found among animals not exposed to the agent, the established practice is to regard the agent as responsible for that finding. But here, the toxic reaction is the development of tumors. It is likely to result in restrictive labeling imposed by FDA or even revocation of marketing approval of the drug.

C. Searle’s Reaction to the MBR Report.

In early August 1973, a statistically significant relationship between the administration of Aldactone and liver and testicular tumors, as well as thyroid tumors, was confirmed by Searle’s Mathematics-Statistics Department based on the MBR report. Thereafter, at the request of Searle, slides of the liver tissue slides were reviewed by a selected panel of Searle pathologist Dr. Rudolf Stejskal. Dr. Stejskal examined Dr. Mauro’s analyses as “incorrect” and too “unreliable” since certain slides which she had diagnosed as revealing benign tumors (adenomas) were, in his opinion, inactivations (hyperplasia) and that other slides that she had diagnosed as being benign tumors were in fact malignant tumors. On the basis of the Dr. Stejskal’s limited review of the liver slides, Searle did not submit the MBR report to the FDA.

In April or May 1974, Dr. Stejskal reviewed much of the slides which had been analyzed in the MBR report. This time, he felt that the slides revealed more thyroid tumors than had been reported by Dr. Mauro. Thus, while having concluded that her characterization of the liver slides was too restrictive, he also found that her characterization of the thyroid lesions had been too restrained. In various interviews with FDA personnel and in written submissions to the Agency, Dr. Mauro has never commented on the MBR report of Dr. Stejskal, which, according to Searle’s Mathematics-Statistics Department, were, as Dr. Mauro stated, drug-related and statistically significant.

In August 1974—sixteen months after it received the MBR report—Searle sent the slides for examination, and approximately 1,000 additional slides from the same study, to another contract pathologist. Dr. Donald A. Willigan. His report was re-
ceived by Searle in December 1974. It reveals a statistically significant drug-related increase in tumors of the thyroid and testes, as well as a decrease in the incidence of tumors in the liver. The concern at Searle over the liver pathology of the MBR report must have been particularly acute, and may account for the firm's action of including that information would have to be included in the Aldactone labeling, with a probable label change. The possible increase in tumors of the testes and thyroid of the test animals, at statistically significant levels, must also have been unwelcome news but, in the absence of any firm conclusions in these endocrine glands, Searle was prepared to argue that these tumors would be less likely to concern the FDA and the prescribing physician. We agree with Searle's discounting the tumors of endocrine glands. However, the liver findings were more alarming because there was no theoretical ground upon which they could be discounted. Thus, unlike the MBR report, the Willi- gan report was submitted to FDA promptly upon receipt at Searle.

Immediately after the first Congressional hearings and the Commissioner's establishment of a Task Force, and immediately prior to the initiation of inspections by the FDA Task Force, which Searle had every reason to know would include Aldactone, Searle finally disclosed the MBR report to the FDA in July 1975, some 27 months after it had been received.

D. Revolution 21 U.S.C. 311(e) and 18 U.S.C. 1001. The FDA regards the MBR report as containing “alarming findings,” namely, statistically significant drug-related tumors of the liver and also of the thyroid and the testes, especially given the wide use of the drug in humans. Accordingly, Searle was required to submit these findings to FDA in writing and to include in the Agency's submission the entire MBR report. However, if one were to conclude that these findings were “alarming,” they unquestionably were of the type that suggested significant hazards, contradictions, effects and precautions pertinent to the safety of the drug and therefore should have been submitted to the Agency promptly as also required by 21 CFR 312.1(a)(4). If one were to conclude that the findings were “not alarming,” they were not of the type that suggested significant hazards.

The primary purpose of the requirement that findings be submitted to the Agency promptly is to permit the agency to assess for itself whether the investigational exception should be modified or revoked. A manufacturer is not entitled to withhold damaging information in the hope that ultimately it might be proved incorrect. Moreover, the regulations do not preclude a manufacturer from providing by expert criticism or, for example, by following the reported study. In short, under any view of the facts, Searle was not entitled to disclose only some of the slides, that it did not provide a complete report. However, Dr. Steinjäckle's review of some of the slides for only one of the tissue types. Moreover, to give great weight to Dr. Steinjäckle's view of the slides, many months before the hearing. In May 1974 Searle had reason to believe, based upon his subsequent review of more of the slides, that administration of Aldactone is not associated with an increased number of thyroid tumors than reported by Dr. Mauro.

21 U.S.C. 331(e) prohibits the failure to make available, by 21 CFR 312.1(a)(5). The decision not to submit the MBR report was a conscious one and thus our Notice of Hearing charged this violation as a intentional act under the felony provisions of the Act, 21 U.S.C. 333(b). Failure to submit the MBR report also constitutes concealment of a material fact, a violation of 18 U.S.C. 1001.

S. Labeling of Aldactone: Violation of 21 U.S.C. 331(a). In March 1975 the FDA received from Searle the report of Dr. Willi- gan saying that the firm had seen significant incidences of thyroid and testes tumors reported to Searle two years earlier by Dr. Mauro, the Agency became concerned that this information was inadequate. On June 15, 1975, it convened the Cardio-Renal Advisory Committee, a group of experts to review the data then known on Aldactone. Even prior to the disclosure of the MBR report in July 1975, and based upon the result of the tissue slide examination by Dr. Willigan and the analysis at FDA's request of certain liver slides by Dr. John Boitnott, a pathologist at Johns Hopkins University, the Advisory Committee concluded that while the toxicological studies were incomplete they showed “definite and significant increases in neoplasia (tumor) formation, testes tumors, possibly breasts and liver. They certainly warrant a warning to the medical profession and a curtailment in the recommendations for use.” As a result, FDA's report of June 15, 1975, was issued. Aldactone has now been relabeled consistent with the Committee's views. In view of the fact that normally significant thyroid and testes tumors in the MBR and Willigan reports, and the findings of liver lesions by both patholo- gists, we believe Searle's failure to submit the MBR report resulted in violation of 21 U.S.C. 331(a) for causing the shipment in interstate commerce of Aldactone which was misbranded within the meaning of 21 U.S.C. 352(a) in that its labeling did not reveal the potential of the drug to cause tumors, a po- tential disclosed in the MBR report. As you can see, the Advisory Committee's conclusion also supports FDA's view that the find- ings in the MBR report were “alarming.”

1. Analysis of Searle's Explanations for Failure to Submit the MBR Report

The administrative process, including the special Task Force and the 305 Notice and hearing, has been extensive. Much of the discussion has focused on the process rather than on the issues. TheAtIndexor of this case, we believe, must discuss the MBR report in order to comprehend and accurately reflect the context of this case. Regrettably, the length of this presentation precludes this goal.

Searle's explanation for its failure to submit the MBR report, set forth in various documents, is best summarized in the firm's response to the Notice of Hearing which was submitted to the FDA on October 20, 1976. Without attempting to provide at this time a point-by-point criticism of the Searle's submission, we note that the main recurring themes provided in Searle's defense may be useful.

1. From the beginning, Searle has repeatedly taken the position that the MBR report was "proven" by its own pathologist to be "incorrect" and thus Searle was under no obligation to submit it to the Government.

Searle's contention that Dr. Mauro's pathology results were unreliable must be evaluated in light of the fact that pathology is a judgmental discipline. Proliferative les- sons of the liver cells can be subclassified according to the nature of the cell population. A diffuse increase in hepatocellular elements is usually termed "diffuse hyperplasia," or mostly, "hyperplasia." There, no diffuse type is a rather spotty distribution throughout the tissues with islands or zones of proliferating cells. The term "nodular hyperplasia" is utilized. When such nodules of hyperplasia are so large as to be mistaken for neoplasia, the term "neoplastic nodule" is applied; this is a "nodule" or group of cells which have "crossed the boundary" on the way to becoming a liver tumor. Various other terms such as "adenoma" or "adenoma" also would apply in this case.

The most extreme form of cellular proliferative stage, the malignant tumor variety, is commonly termed "hepatocellular carcino- mation along the continuum or by different phrases from another one, but basically they imply the same problem. The process of experts to use different terms in liver pathology was recently demonstrated at a workshop at the National Cancer Institute in "Cancer Research", Vol. 30, No. 1979.

Searle also argues "extreme variation and contradictions in diagnoses" between Drs. Steinjäckle and Weissman. However, Dr. Mauro, the other FDA believes that the differences in diagnoses were not extreme and reflect merely the continuum of diagnostic evaluations of tissues that are well recognized in the field of pathol- ogy. 2. Searle argues that the IND regulations presume that the data which must be submitted must be accurate and reliable. 305 Rev. pages 10, 15, 21 CFR 312.1(a)(5) refers only to "findings" which are significant or alarming. Accuracy is not used as a standard precisely because such findings at this preliminary stage may, in many cases, be unconfirmed. By requirement to submit progress reports within a year does state they be "accurate," reflecting the Agency expectation that by then any discrepancies will have been resolved.

Searle argues that the applicable statute and regulations do not require reports of all animal studies conducted during the course of IND investigation, but only of testing on humans and of those animal tests conducted before human testing is initiated. In addition, Searle contends the IND regulations are ambiguously. These arguments are without merit.

In the interest of protecting patients taking experimental drugs, regulations require the reporting of the results of animal tests before tests on humans are
CONGRESSIONAL RECORD — SENATE
August 1, 1985

allowed. However, the regulations also permit so-called Phase I and Phase II clinical (human) trials to proceed before all the preclinical (animal) work is concluded. According to the regulations,Item 10a of the form for the “Notice of Claimed Unusual Preclinical Exemption for New Drugs” notes that these first two phases “may overlap and, when necessary, be conducted concurrently.” Item 11a(2x) notes the regulations therefore contain no provision for additional animal studies when testing in humans.

Searle also seems to rely on the phrase “such investigations” in the IND statutory provision, arguing that this refers to human test results only. This is incorrect. The regulations referred to in subsection 3 are those, as the statute goes on to state, “as the Secretary (by delegation, the Commissioner) finds will enable him to evaluate the benefits and risks of such drug in the event of the filing of a new drug application.” Thus, reports must be submitted to the Commissioner to permit him to determine whether a new drug application will be approved or denied. 21 U.S.C. 355(b) provides that NDAs must contain preliminary studies of the drug which have been made to show whether or not a drug is safe for use. There is no distinction between clinical and preclinical investigations; the statutory phrase includes both. Indeed, a new drug application may not be approved unless “substantial evidence” is submitted in support of the safety and effectiveness of the drug. The Act, 21 U.S.C. 355(d), as enacted, is consistent with the need for both early and well controlled investigation of the drug in the preclinical and clinical investigations. Obviously, the Act presupposes that reports will be submitted of preclinical investigations, otherwise the specific reference to “clinical investigations” would be meaningless.

Searle argues that the use of the term “investigatory” in the regulations necessarily means investigators involved in clinical investigation. This is not true and the regulations do not give such meaning to the term. If anything, the regulations make clear that where clinical investigations are meant to be specified, that phrase is used.

Searle further argues that the MBR report cannot be considered a “finding” under the regulations identified by the charge. There is no question that the readings of a pathological or tissue slides are findings” in preclinical tests; the results of an entire study are usually stated in terms of the tissue slide pathology. If anything, the use of the word “findings” in the regulations suggests that information must be submitted to the Agency whether or not it can be considered, of itself, a completed or final “report.”

3. Searle notes that the 78-week rat study in question involved much higher dose levels than would be human levels and thus the tumor findings were neither alarming nor even significant in terms of safety. 305 Reply, page 1. Most investigational toxicity studies in drug development involve massive doses of the drug being tested. The reason for the use of large doses of a drug in test animals such as laboratory animals is to enable the scientists to design experiments to identify toxic reactions in those portions of the user population who are most susceptible to the drug. Accordingly, to accenate the probability that adverse reactions will become manifest, the relatively small number of test animals are given large doses. In fact, because the purpose of a preclinical toxicity study is to determine a toxicological profile of a drug, the humane doses are an almost meaningless comparative measure. In animal studies, the question is what reactions are manifested, not how much can the animal tolerate.

Even if the comparison were valid, the level of the animal dose as compared to the human dose is misleadingly represented by Searle. The animal study in question was designed specifically to establish human use of the drug on the treatment of slightly shorter heart failure at dose levels four to six times larger than the human dose for which the drug is marketed. Moreover, while comparing the animal test dose with the human use, Searle fails to acknowledge that at the time of this animal study, it was testing Aldactone on humans at six times the dosage of the drug then approved. In its written reply to the 305 Notice, Searle also emphasizes the lack of significant findings from the study done at Hazleton which was completed on Aldactone at approximately the same time as Searle’s own study. The effectiveness of the balance of the Searle study since, among other reasons, the amount of Aldactone received by the highest tested animals in the Hazleton study was an amount between 200 and mid-doses for the Searle test animals.

Searle contends that the MBR report was insufficient for its review and, as received by Searle and ultimately submitted to the Agency, is in precisely the same form as other pathology reports by Dr. Mauro and Dr. Searle himself that were submitted to the FDA. In fact, Searle itself was capable of “completing” the study by adding to Dr. Mauro’s “raw data” and then conducting a statistical analysis it performed in August 1973 and the gross observations from the necropsy. Searle chose not to do so and instead claims that the data of Dr. Willigan’s diagnosis were more unfavorable to the drug and thus Searle cannot be accused of hiding “damaging” information. 305, page 8.

This assertion is very misleading. Dr. Willigan’s diagnosis were unfavorable in the same respect (thyroid and testes) as Dr. Mauro’s reports were unfavorable; his diagnosis simply made bad news worse. The real significance of Dr. Willigan’s diagnosis is that he did not find a statistical significant correlation between the incidence of tumors and thyroid and testes of Searle was Searle’s greatest concern with the MBR report and was the reason why Dr. Stejskal instructed Searle to review the liver slides, not all slides. It should also be noted that until May 1974, when Dr. Stejskal reviewed not only liver slides but numbers of the thyroid and testes slides, the only basis upon which Searle could conclude that the entire MBR report was unreliable was Dr. Stejskal’s review of some of the liver slides and control groups. Dr. Mauro, on the other hand, looked at approximately 5,000 slides, including 277 liver slides. But even the refutation of Searle’s argument is quite clear the point: The IND regulations are designed to funnel data to the FDA before it is reevaluated, when the findings are published to either confirm or undermine the initial conclusions.

In a similar vein, Searle also discounts the admittedly unfavorable thyroid and testes findings in the MBR in the report. In July 1974, Searle had the IND regulations to drug-related reactions since Aldactone is not to be an endocrine-active drug. This “organ-organ” argument is untenable.

Even assuming that a drug acts where it is “expected” to act, the nature of the reaction in laboratory animals is largely toxicology studies are conducted to determine the range and severity of reactions. There were many abnormalities in the “target organs” of the rats on this study. A tumor is one of many reactions; it is one of the more serious kinds of toxic reactions as those that are seen. Moreover, animal toxicity studies are regulatory submitted to the FDA which reveal little or no significant toxic reactions, even in that organism is “expected” as being the “target organs.” Because every agent known to cause tumors in men also causes tumors in animals, tumors in animals constitute alarming implications for human toxic reaction.

FDA has required Searle and other manufacturer of oral contraceptives, which are endocrine-active compounds, to conduct long-term animal toxicity testing. When tumors of the mammary gland, one of the endocrine glands, are discovered, the FDA has forced the removal of the particular drug from the market and prevented testing in humans. With the oral contraceptives, all the adverse effects, some have caused tumors in test animals, others have not. Obviously, therefore, the “target-organ” tumors are not predictive.

6. Searle justifies its failure to submit the MBR report based in part on Dr. Mauro’s supposed decision to evaluate pathology information on the slides. As Searle notes, it is truly arguable that her choice of words speaks Dr. Mauro’s unlikelihood as a pathologist. Dr. Stejskal has also stated that her report could not be relied upon.

What Dr. Mauro classified as an “adenomatous goiter”, a non-tumorous hyperplasia of the thyroid, was classified by Dr. Willigan and Dr. Stejskal as an “adenoma”, that is, a benign tumor. Searle never notified Dr. Mauro or MBR of any questions about Dr. Mauro’s report, including its timeliness. On June 1, 1973, — wrote to MBR stating that Searle had received the MBR report and that Searle was happy that this reference applies not to the liver or other readings themselves but rather to the form of the report.

Whether form includes terminology we can only speculate. The fact is that the term “adenomatous goiter” is recognized as a very precise reference to a non-tumorous condition of the thyroid gland that is not from a metabolic imbalance. Thus, while Dr. Stejskal suggests Dr. Mauro’s analyses were invalid and that Mauro’s readings appear to have pin-pointed a significant distinction is thyroid proliferative lesions.

VI—SEARLE REPLY TO ALLEGATION OF MISREPRESENTATION

Searle’s reply to the allegations of causing Aldactone to be misbranded is essentially to accuse the FDA of not moving promptly in its role to review labeling. 305 Reply, pages 22-26. In fact, the Willigan report was submitted to FDA in March 1975; the Agency reviewed it and convened the Carden-Renal Advisory Committee in July 1974, prior to its submission to the Agency of the final report in March 1975 but rather after submision of the MBR report and, notably, after creation of FDA’s investigatory Task Force.

The burden to provide adequate labeling is placed upon the shoulders of the manufacturer-producer of a product. Moreover, in order to promptly advise physicians, FDA drug regulations provide that warnings and hazards may be
added to drug labeling without prior approval by the Agency. 21 CFR 314.8(d)(1). Searle did nothing to react to the MBR report even after May 1974, when the thyroid tumor problem was pointed out. That report was confirmed by Dr. Stejkal.

FDA, of course, did not have an opportunity to comment on the MBR labeling on the basis of the MBR report until that report was submitted in mid-July 1975. Searle questions whether the labeling would have been changed on the basis of the MBR report which would not be the case had it been submitted in mid-July 1974 (38 F.R. 27137). The Commissioner concluded that the evaluation of the data in the MBR report was not included in the preparation of the labeling in March 1974. Based on the Commissioner's conclusion in July 1975, he found that the labeling of certain animal studies conducted by Searle was questionable, and in conjunction with the establishment of the Task Force, issued an order to Searle, under the Federal Register of December 5, 1973 (40 F.R. 56907).

After the issuance of the Task Force report, March 1976, FDA began to consider methods by which certain of the studies submitted by Searle would be reevaluated by a panel of experts. This process, to be performed under a contract approved by the FDA and paid for by Searle, is soon to begin.

The 52-week toxicity study in the infant monkey

A. Initiation and Basic Description of the Study. In November 1989, Searle officials decided it was Dr. Walsman's opinion to begin the study. Walsman was a leading researcher associated with the University of Wisconsin Regional Primate Center. The first infant monkeys born in the study's conditions were delivered on January 15, 1970, and terminated on or about April 28, 1971. Searle submitted the report to the FDA on October 18, 1972. A copy of the report of the study, including appendix tables, is enclosed. Unfortunately, during the course of this study, in March 1974, seven new-born Rhinos monkeys were placed on a diet which included Aspartame. The first infant monkeys became part of the study in January 1970; the last were added, at birth, in October 1970. The daily feeding of the monkeys, and monitoring and recording of all actions, was performed by Mr. Gunther Shaffer, a laboratory technician with a bachelor's degree who was selected by Dr. Walsman. The tables contain all feeding schedules and the like which constitute the summary of raw data of the Searle report, were prepared primarily by Mr. Walsman. In order to select the new-borns for inclusion in the study, his selection was consistent with criteria which may have been set by Dr. Walsman. Although Dr. Walsman had access to and was familiar with the monkey colony at the Primate Center, in all likelihood he rarely if ever directly participated in the conduct of the study. He and Searle were responsible for the study design.

The Aspartame monkey study did not have "untreated controls as is more common for most studies". In the study conducted by the Agency, the group of new-born monkeys identified and monitored for comparative purposes which were not fed Aspartame. The study was conducted in several months after initiation of the study, the monkeys were to be kept on a diet with Aspartame for one year, then returned to a basal diet, subjected to behavioral and learning tests; and finally sacrificed and necropsied (autopsied) for the preparation of tissue slides to be reviewed microscopically for alteration (post-mortem work-up). Of the seven test monkeys, one died after 300 days; four were kept on Aspartame for approximately 360 days before the administration of Aspartame for two others was ceased on March 31, 1971. After approximately 300 days, no changes were observed in weight or health.

B. Conflicts Between the Agency and Searle's Reports. Before commenting briefly on the specific falsifications listed in the 308 Notice and to clarify why this study came to the attention of the Agency, you should note the many great Federal officials took in drafting its report. Searle has repeatedly contended that Dr. Walsman was working on his own, that Searle had little or no control over his activities, that the Searle protocol for this study was drafted after the inception of the study in order to attempt to bring a retrospective structure to the work done by Dr. Walsman and that because of Dr. Walsman's study was uncontrollable! Were "suggestions" experiment, its shortcomings are itemized, all but enthusiastically.

Yet, while containing a few carefully worded disclaimers, the report of this toxicity study was submitted to the Agency just like any other of the 150 studies; it bears no relationship to the personality of Walsman for the study, namely, Searle and Walsman. In that order; it bears a Searle Pathology-Toxicology project number; it is in standard format setting forth methodology, observations, and the like, including a study design and conclusions.

Searle wanted data comparing Aspartame with phenylalanine. Dr. Walsman was the expert in the field and his name would carry great weight. The report to FDA is drafted in manner which could reflect an inadequacy of the design, control and documentation of the study. However, when Searle is accused or representing this study, he loses all knowledge or involvement with its initiation, design or performance; Searle cannot have it both ways.

Searle's conclusion that it had "no control over conduct of the study, and Dr. Walsman did not have to, nor did he, follow any suggestions by Searle" is difficult to understand. Searle documents in the possession of the FDA establish that in November 1969, Searle sought to involve Dr. Walsman in a study. He was asked, in order to compare its toxicity, particularly seizures and learning defects due to brain damage.
with that of phenylalanine. In January 1970, such a study was initiated. It is also inaccurate. In fact, a number of papers in a September 4, 1970, conversation with Dr. Waisman, --- reports that he suggested to Dr. Waisman that two animals be placed in the colony at the necropsy levels with the few next days. This is exactly what happened. Searle asserts that the behavioral testing was only carried out on the post-mortem study but rather on a subsequent study which was being planned by an associate of Dr. Waisman, 305 Reply, page 34. However, various reports obtained by the Task Force Investigators, written both during the subsequent to the monkey study, establish and report that behavioral testing, as well as the necessary post-mortem work-up, was originally planned for this study.

C. Specific False Statements or Concealed Facts. The 305 Notice delineates four false statements and entries in Searle's report of this study. (1) The report failed to reveal that the infant monkeys were not available for the study. (2) The report states that acceptable historical and contemporary data on monkeys were nonexistent, thereby eliminating the necessity for concurrent control groups of monkeys. (3) The report falsely states that animals were not available for purchase and sacrifice (and necropsy) at the termination of the administration of the test compound, as originally planned, because of personal and professional reasons. This statement also gives the misleading impression that the animals incapable of being purchased when in fact they were available for purchase, although not immediately, after the test compound had ceased to be administered. (4) The report falsely states that the monkey was dispatched to Searle due to "similar" reasons, namely, confusion and personal reasons after Dr. Waisman's death. In fact, the data were available and were obtained at the Regional Primate Center by FDA investigators during the Task Force investigation. Moreover, the monkey died approximately five months before Dr. Waisman's death.

1. The first specific violation listed in the 305 Notice, and in part, upon January 19, 1973, memorandum written by --- reflecting the reservations of Mr. Scheffler about the reliability and documentation of monkeys for the study, which conflicted with the report's transmission with Mr. Scheffler's note: "no extensive records on individual monkeys." In addition, 305 Reply, page 59, 1973, the appraiser was aware of the fact that one of the seven monkeys on the study "never should have been included in your experiment since he had an obvious birth defect." Searle asserts that neither nutritional nor reproductive histories of the mothers of the infant monkeys were in fact made because of legal requirements. However, the report states that only "infant rhesus monkeys (Macaca mulatta) from full-term, normal pregnancies and deliveries." In fact, the era were laboratory monkeys and had been on other tests. The impact of the mother's health, nutrition, reproductive history, etc., would not be noted at this time.

2. The second specific allegation in the 305 Notice was that the report falsely states that a comparison control group of monkeys (in the study that were monitored but not exposed to Aspartame) were unnecessary because acceptable historical and contemporary data on untreated monkeys were nonexistent. Searle admits that there were no existing post-mortem data available for the monkeys in the colony but notes that there was such ante-mortem (pre-sacrifice) data for other species and that this data could be correct. And in view of the fact that the study did not include behavioral and post-mortem aspects as originally planned, the non-existence of post-mortem data for monkeys was rendered essentially irrelevant. Accordingly, this alleged falsehood now appears to have been adequately explained.

3. The third charge of falsification in the 305 Notice alleges that the reasons given by Searle for necropsy of the monkeys after the "termination of administration of the test compound", namely, shortage of personnel and drain of supervision following Dr. Waisman's death, are untrue. Searle's reply to these allegations focuses upon the statement that the monkeys were necropsied post-mortem without a post-mortem feeding allegedly without notice to Searle, and were thus "unavailable at the time of termination." The documents available to the FDA do not now establish that Searle had knowledge of the termination dates of administration of Aspartame (approximately April 25, 1971) until mid-June 1971. But the fact that the availability of these monkeys for post-mortem examination was not immediately coincided with the termination of the Aspartame feedings is not relevant; the protocol for this study originally provided for cessation of administration of Aspartame prior to sacrifice and necropsy. Thus, Searle's lack of immediate awareness of the termination of Aspartame administration does not negate the fact that Searle later had the opportunity to buy the monkeys. Searle could not truthfully assert in its report to FDA that the monkeys were "unavailable," so Searle stated that they were "unavailable at the time" when they were taken off Aspartame feeding.

Searle's failure to necropsy the animals, including examining brain tissue for those monkeys which had manifested seizures, is of particular concern. After Dr. Waisman had no post-mortem comparative data. If Searle had found adverse effects, it would have had no way to show that the consequences ascribed to Aspartame Searle did not want to take this chance. But Searle also did not want to admit the real reasons for its indifference. The same apprehensions were reflected in Searle memoranda discussing the potential consequences of Dr. Waisman's feeding of Aspartame to pregnant monkeys. Reliance upon alleged personnel shortages and lack of supervision do not explain why Searle did not closely monitor this study. The FDA investigation did not reveal that things were plucked into chaos by Dr. Waisman's death as Searle has repeatedly suggested. 305 Reply, page 58. Treatment was continued for two to three monkeys to death on monkeys M-79 and M-14, completing their one-year treatment as scheduled. During interview, in February of this year by FDA Task Force, Mr. Scheffler stated that there were plenty of personnel on hand when Dr. Waisman died and that when the last animal took over, he dismissed a number of employees because they were not needed. Searle asserts that it makes no difference what reason was given for a certain event as long as the events are true. We disagree. None of the real reasons for Searle's decision not to purchase the monkeys for post-mortem examination will be included in the submission to FDA: the monkeys were available for purchase and post-mortem work-up, but advised ---, and Saunders that the monkeys should not be purchased; they concluded. Nevertheless, it may be literally true that the monkeys were not known by Searle to be available "at the termination of administration of the test compound".

4. Finally, the report given in the FDA states that necropsy data on the one non-surviving monkey, which received high doses of Aspartame and died after 390 days, was lost to Searle due to Dr. Waisman's death. In fact, the data were available from the Regional Primate Center and were obtained by the Task Force. The monkey died approximately five months before Dr. Waisman's death. Searle does not reply to this charge directly, but rather states that its use of the term "necropsy data" meant tissue slides, not the autopsy report. October 22, 1970, which Searle claims it never received. It is undisputed that on October 21, 1970, Dr. --- was made aware of the death of the monkey and that sacrifice was planned. Apparently, Searle failed to follow up on this and determine that a report had been generated.

Searle now admits that it does not know what became of the necropsy data; nonetheless, the report gives the impression that the facts were known, namely, that the data were lost in the confusion after Dr. Waisman's death. The confusion as a result of no information, rather than the truth.

The 46-week toxicity study in the hamster

The study. On April 20, 1970, Searle initiated what was to have been a 104-week toxicity study on Aspartame in the hamster. The study was completed after 46 weeks of treatment, due to an unexpectedly high mortality in both control and treated animals as well as the animals known as "wet tail." Searle submitted its report to the Agency on December 8, 1972.

A. The Violation of Title 18. The alleged violation of Title 18, Section 1001, set forth in the FDA Notice of Hearing, is based on the following set of facts: Blood from certain animals was included in the hematology and for blood chemistry at the scheduled 26-week interval. Samples were taken and six different kinds of tests were conducted. The second week to have experienced methodology problems with one of these, the test for serum glucose level. Searle did not have a problem with the glucose testing until approximately twelve weeks later. By that time, however, approximately 20 percent of the previously tested animals had died. Accordingly, at the 38th week of the study, other hamsters were taken as substitutes from the same feeding groups and blood was collected from them. The glucose levels of these new animals were reported by Searle as being those of tests run at 26 weeks on animals from the original group, which had since died. The glucose values represented for one set of animals at a different time.

B. Searle's Inappropriate Edification. Searle asserts that its report contains this false information, but argues that this did not result from willful conduct or negligence. Searle argues that this falsehood is not material to the appraisal of the safety of Aspartame. Most Courts of Appeal have held that a violation of Title 181001 can be sustained only upon a showing of the materiality of the falsehood. However, the courts generally define a "material" statement as one which has the tendency to influence or is capable of influencing. Actual reliance upon false in-
CONGRESSIONAL RECORD — SENATE
S 10833

August 1, 1985

formation need not be shown. Nor must the
Government prove that the preparation was
that a statement was false; rather, a reck-
less disregard for the truth or evidence of a
conscious purpose to avoid learning the truth.
Here, documents in the possession of FDA
establish at least that — — knew of the need
to report the glucose test result and that
hamsters were dying and substitutes were
needed.
Searle suggests that these data were gath-
ered and reported by technicians reporting
to Mr. Martines, and that neither — — nor
was aware of the existence of the problem
on the raw data sheets until they received FDA's Notice of Hearing. However, he
discusses in his 305 reply that he was in-
volving in resolving the serum glucose prob-
lems, although he claims that he did not
review this matter when drafting the report.
The substitute animals were iden-
tified as substitutes on the raw data sheets
which, we believe, — — the authors of this
study, were obliged to review and may in
fact have reviewed in order to attest to the
accuracy of the test results. Further evidence of disregard for the truth will
have to be developed by the Grand Jury.
Searle argues that there was no motive
for any intentional misrepresentation or con-
cealing of the fact that glucose values for one
animal was inadvertently reported for the
other. While the question of glucose levels
seems to have been non-controversial in this
study, the crucial point is that the Searle report
simply notes the substitution of test results
could be attributed to the fact that at the
time of the substitution the animals were
collected and no problem was generated
and the study was ac-
cordingly threatened. Also, the reason for
the wide variation in glucose values was, at
first, not known. Until — — confirmed that it was a laboratory problem, the unexplained
variation in test results might have been thought to
indicate severe liver or pancreas reactions in
the test animals.
It is true that these entries may not have been material to a determination of the
certainty of Asparatane. However, as
Searle points out, numerous studies have been
conducted and submitted to the Agency in support of the safety of this
product, and any such study would be
provide evidence to the Agency that was not
wholly fabricated study might not qualify as
material in the sense of being a "but for"
corresponding sufficient basis for a deci-
dion.
We believe that the law permits prosecu-
tion for a falsehood that has the potentiality
for influencing the Government in its
evaluation of the immediate report in which
the falsehood is contained whether or not
the sum of the safety data is altered by the
falsehood at issue. Moreover, in this case,
the hamster study was selected by the FDA
Task Force as one of a few Asparatane stud-
ies for review upon the consultation with toxobiologists in the FDA Bureau of Drugs.
Both this study and the monkey study met
the criteria for selection of studies estab-
lished by the Task Force.
Searle argues that the original records
relating to the glucose substitutions are in
existence and only their destruction or modi-
fication would be consistent with an inten-
tional effort to avoid learning the truth.
The claim made by Searle, of course, is not a necessary prerequisite to a
finding of intent; if it were, every defend-
ant charged with a crime involving a crime
of intent would argue, perversely, that his fail-
ure to destroy evidence of his culpability estab-
lished his lack of intent.
Congressional hearings on Asparatane studies.
In considering the extent to which the re-
ports were written to convey impressions
more favorable than the underlying data
would support, reference should be made to
the memorandum of December 28, 1970,
from Mr. Helling of Searle to, among others,
Dr. Saunders, entitled "Food and Drug
Sweetener Strategy." In that memorandum,
Searle states that, had the Searle personnel
engaged in an independent review by FDA
personnel to seek to de-
volve in the "subconscious spirit of par-

cipants in the Searle studies. What FDA
needs instead, and must have to evaluate
products, are adequate and controlled stud-
es, supported by the raw data, and reported
accurately and in a timely fashion. The
admission that these reports can be relied on
is at the heart of FDA's mission; the agency
cannot possibly look over the shoulder of
each laboratory and draftsmen involved in
each of the thousands of animal and human drug studies conducted each year.
The FDA must receive the truth, not
psychological warfare. To emphasize the im-
portance of safety data on Asparatane, we
note that if ultimately approved for market-
ing, the Vice-President for research and
development expected to be part of the daily diet of every
American.
IX — INDIVIDUALS WHO APPEAR TO BE RESPONSIBLE
FOR THE MISTAKES CHARGED IN FDA'S NOTICE OF
HEARING

A principal purpose for convening an in-
vestigatory Grand Jury would be to identify
these persons and, by any violations of the
crime investigated by the Agency. The
persons named in the FDA 305 Notice were
identified on the basis of information
obtained by the Agency, but without the
benefit of compellable process. All Searle
officers, employees, and former employees,
were interviewd by Task Force investigators
in the presence of Searle counsel or
monitors.
A. Overall Corporate Organization.
The organization of the information
available to the FDA reveals the following
major outlines of responsibility within the
Searle Company.
In 1971, T.B. Carney, Sr., was the Vice-
President of Searle Laboratories for Re-
search, Development, and Control. — —
was the Vice-President for research and
Development, under Mr. Carney. The re-
search and development group consisted of
six branches: Dr. — — was the Director of
diabetes, which was in the heart of the
pathology/toxicology section. In February
1972, — — replaced Mr. Carney as the
head of the R&D and became the Director.
Dr. Francis J. Saunders replaced — — as the
head of the R&D. The Director of Chemistry,
a branch on equal level with Biology was Dr. Paul D. Klimstra.
In April 1972, became President of
Searle Laboratories, a division of G.D. Searle
and Company — — was designated as Vice-
President for Research and Development.
In July 1972, at about the time that Searle
was beginning to deal with the MBR
report, the research and development group
was reorganized. Mrs. Klimstra was made
the Director, Pre-Clinical Research and De-
velopment, operating directly under — —
was the director of Pathology/toxicology
and reported directly to Dr. Klim-
stra. Dr. Saunders was given the title of Di-
rector, Research Liaison at the same level as
e the MBR report. The results of this
were, in a position to know of the report and cer-
tainly had authority to decide not to submit it, we have no evidence of
intelligence.
2. The 305 Replies.
In the Searle 305 reply, we are told that
Dr. Willigan only had an advisory role in
the Klimstra of the findings of Dr.
Willigan. This does not necessarily mean
that Dr. Klimstra was advised of the earlier Mauer findings, but it may raise an
tive question of whether Dr. Klimstra, Dr.
Saunders and — — were similarly advised
when the MBR report was received in
March 1973, particularly in view of the fact
that Searle had no basis for discounting the
MBR report until Dr. Stejskal's August
review.
In — — 305 reply, he states that he first
learned of the existence of the MBR report
on June 17, 1975, as assertion that is cer-
tainly appropriate for one on the sub-
jects on the institutional action of G.D. Searle and Com-
ping, at page 2 of his reply, that the
MBR report was sent to him "by hand" since it "did never contain

mortem data, text or results of statistical
analyses that are necessary for a final, com-
parent and full report of the data. The

This characterization of Dr. Maer's pa-
thology findings is nonsense. A pathologist's
role in a study is to report examination of material very clearly. The analyst
pathologist never generates antemortem data or analytical data; the MBR report
did not contain these and neither did the report from Dr. Willigan which was submitted to
PDA. When a firm, such as Searle, receives a report from an outside pathologist, the firm itself provides the anatomicum data and considers the report. The FDA then states that the firm is responsible for the adequacy of the report and that the firm may well be subject to a characterization under the Act or Title 18, that will with reasonable probability establish a violation before the next inspection. The scope of the Agency's 305 Notice was far more limited than the findings of the Task Force, whose investigation was designed primarily to review laboratory practices. Our selection of apparent violations for inclusion in the 305 Notice does not, of course, limit the inquiry of your office or by the Grand Jury.

One of the recommendations of the Task Force is for the Department of Justice that Grand Jury proceedings be instituted in the Northern District of Illinois using compulsory process in order to identify more particularly the nature of the violations and to identify all those responsible for such violations. Indeed, there are areas in which the Task Force investigation has raised serious questions that we believe your office should consider for presentation before the Grand Jury. The 305 Notice was made in the 305 Notice primarily on the ground that the notice is designed to give persons an opportunity to respond to the apparent violations to which the Agency, on the basis of available evidence, intends to recommend for prosecution. The extent to which evidence was available to the Task Force reflects the fact that inspections began three months after the Task Force was created; Searle knew it was going to be inspected.

Four decisions or courses of conduct by Searle were specifically considered by our office for Grand Jury review. These are set forth in the memorandum of Mr. Arthur Levine to me dated August 6 and 30, 1976, copies of which have previously been provided to the Committee on Appropriations and to Mr. Blanding. Two of these appear to us to be reasonably fruitful areas for Grand Jury investigation.

The Willigan report submitted to the Agency in March 1976 contained a computer-printout summary table of tumor findings which did not include four malignancy mammary tumor sets which had in fact been diagnosed by Dr. Willigan and reported in his raw data. Searle explained the omission as the error of a programmer in the Mathematics-Statistics Department who listed the mammary tumors as benign, although the raw data on the sets were stated that they were malignant. These errors were not detected, or at least not corrected, by the supervisory statistician in that department or by Dr. Stehlik, the pathologist responsible for the study in Pathology/Toxicology Department. Thus the Searle report, based on the pathology examination of Dr. Willigan's raw data.

All of the individuals involved in this episode have been interviewed by the FDA, and no one has made an error. The FDA investigatory file does not now contain information which would establish a willfully false submission under Title 18. From the viewpoint of the drug industry generally and Searle particularly was concerned about evidence of malignant mammary tumors in test animals (Ex. 22). In order to accept the Searle evidence the unfavorable mammary malignancy data were innocently omitted from the summary table four separate times by three different individuals.

2. With respect to the discrepancies between the submission to FDA and the underlying data for the 72-week rat study on Plasyol, I concur in Mr. Levine's suspicions that was asked to prepare for submission to the Agency an animal study which was poorly controlled and documented. That the error may well have been in the study contained inaccuracies or at least that the data was incomplete and could not be confirmed, but did not reveal these facts from the other report of the study submitted to the FDA.

Two other actions by Searle, discussed in paragraphs 3 and 5 of the August 6 memorandum and which are the subject of the August 30 amended memorandum, do not now appear to be fruitful matters for further investigation within the context of the Adacitone 72-week report. The general inadequacy of Searle statistical and sampling methods was admitted by Dr. Dutt, former head of the Mathematics-Statistics Department. See Ex. 21. The Grand Jury may wish to investigate consequences of these practices which, unlike the case with Adacitone, were not subsequently remedied. Moreover, Searle's theoretically conceivable but in fact inapplicable arguments over the specific facts pertaining to Adacitone demonstrate that the elements required for conviction in order to avoid admitting any error, even an error which turns out to benefit their product or further their procedures. See August 30 memo., para. 2.

C.-PROCEDURE

The issues discussed in this transmittal letter as well as those raised by the Task Force report are based upon reports and documents which have been known to almost 20,000 pages. The Task Force report, Mr. Levine's memoranda of August 1976, and the Notice of Hearing focus these data into an area of potential litigation. It may not be necessary that each document be reviewed by your office in order to develop the charges that must be submitted to the Grand Jury. However, Mr. Levine of our office (8-443-4380) and Mr. Carlson Sharp, a compliance officer in the Bureau of Drugs and Chairman of the Searle Task Force (8-443-1940), both of whom are intimately familiar with the facts of this case, would be pleased to provide any assistance in identifying pertinent documents and in the support of each charge in the Task Force report, the August 30 memorandum, and the Notice of Hearing.

If you desire to review the exhibits and other significant data, such initial review might most efficiently be conducted in Rockville, Maryland. The two memoranda, documents, together with Messrs. Levine, Sharp, and the other members of the Searle Task Force, are located. We would also be pleased to bring to Rockville, or to Chicago, at your request, the lead inspector for the Task Force, Mr. Philip Brodsky, and any or all others of the investigative team. As issues are delineated and screened, Messrs. Levine and Sharp would be anxious to come to Chicago for whatever time necessary to continue discussions and preparation for the Grand Jury investigation.

In view of the breadth of the FDA investigation, the scientific matters raised, and the large volume of documents already assembled, this investigation is not yet complete. Moreover, such a procedure would eliminate any question, whether or not meritorious, that documents obtained by the Grand Jury may be kept confidential by the Department of Justice and not with the Food and Drug Administration.

As I mentioned previously, Mr. Fred Brandtling of your office has been advised of all pertinent developments in this case. Many of the attorneys in our office have had the privilege of working with him in cases recommended by our office. In his
August 1, 1985

CONGRESSIONAL RECORD — SENATE

Page 10835

August 1, 1985 conversations with Mr. Levine over the last month, he has expressed a strong interest in this case and we would welcome the opportunity to support his designation as the attorney in your office responsible for reviewing the matter and handling the presentation to the Grand Jury.

As you know, this office cooperates closely with your Office in the prosecution of cases under the Act. A copy of this transmittal letter has been sent to Mr. Robert McConachie, Acting Chief. We anticipate that we will be in sight of the review of this transmittal and we and the Consumer Affairs Section will appreciate being kept advised of any developments.

Mr. Chairman, I would like also to take this opportunity to express my appreciation to the Senate subcommittee on your staff who have been instrumental in informing the public of the dangers of this product. Your efforts in this regard have been appreciated.

I am sure you are aware of the potential health consequences of the use of aspartame and I believe the Senate should take a position to counteract this exposure in the public's best interests.

In conclusion, I would like to restate my belief that the FDA's position on this matter is not based on adequate scientific data. It is my hope that the Senate will take a stand on this issue and require the FDA to conduct further studies to ensure the safety of aspartame.

Thank you for your attention to this matter.

Sincerely yours,

RICHARD A. MERRILL
CHIEF COUNSEL

Food and Drug Administration.
CONGRESSIONAL RECORD — SENATE

August 1, 1985

...there was little continuity of technicians that performed feeding and observing the animals for tissue masses, etc., with respect to a particular study, but performed those functions for various studies in progress at one time.

The technicians weighing, withdrawing blood, feeding and observing the animals for tissue masses, etc., were not involved in the provision of the diet and new stability tests were not performed on the new diet-substance mixture.

In previous studies, mixtures of active substance with food were used and Searle used blenders that were not electrically grounded. This is of concern because of the potential for the incorporation of toxic properties of the test substance to cause it to adhere to the metal walls of the mixer and/or to distribute unevenly through the food, thereby preventing a homogeneous food-test substance mixture.

In view of the problems noted with the third formulation, preparation of the test substance mixture, the failure of both Searle and Cutler to analyze for concentration, homogeneity, and stability of the mixtures. After the addition of the feed and the practices of feed replenishment, there is no way in which it can be assured that animals received the intended dosage.

An exterminator company is employed by Searle to control the animals in the animal rooms. This company has a blanket order to spray the animal rooms twice a month and additional instructions may be given for specific animal rooms as required.

The investigators were informed that animals are not removed from the animal rooms during the time they are being fogged with insecticides. Evidence indicates that this practice has been in effect at least since 1979. A memorandum dated Septem

...while Searle did not conduct tests on the purities of the test material, he replied that Hazleton's policy is that the composition of the test material is assumed to be 100% pure and is not subject to the contrary by the client. Tests for (chemical) stability, (biologic) potency and homogeneity of the test material were performed only at the client's specific request. Cutler never made such a request of Hazleton in its protocols. Further, Dr. Reno stated that the feed be assayed for residual drugs, pesticides and other contaminants. Hazleton did not conduct such tests for Searle nor were there any restrictions placed on the use of treatment mixtures maintained for studies performed for Searle.

It was noted in the investigation of the Aspartame (DKP) 115 week rat study that the drums of the product for each dosage level were identified with color coded labels to match the test containers and that the identification card on the animal cages. When the animal rooms at Searle were inspected on October 17, 1975, it was noted that each drum contained a number of different test compounds and that the labels of these containers were of various colors. If the current label were to come off, the technician could easily be confused by the color underneath (thus) resulting in a feed mix-up.

This is the only study where we found evidence of contamination of the test substance in the diet mixture, but that evidence was negated when, during the course of the study, there was a change in the supplier of the diet and new stability tests were not performed on the new diet-substance mixture.

...the protocol called for dogs to be 150 to 160 days of age and yet three dogs were used in this study that were approximately 70 days older than the protocol specified.

...at Hazleton Laboratories rats and mice were said to be held for a week prior to being put in the study. The 104 week rat study at Hazleton Laboratories is the Aldacote 78 week study and there were deviations from this holding period when rats were put in the study and held for only five or six days respectively.

...the one element common to all animals in a toxicological study is to assure that the test animals receive the active ingredient under test. When the substance is to be tested is incorporated into the diet, its homogeneity and concentration in the diet mix should be determined by the start of the study. Randomly mixing of freshly mixed batches should be performed periodically during the course of the study to ensure that the proper mixing and formulation procedures are being used. In studies conducted by both Searle and Hazleton, little concern was evidenced for the need of proper quality control of homogeneity, concentration, or stability of the active ingredient-diet mixture.

...when Dr. Frederick Reno of Hazleton Labs was asked why Hazleton did not conduct tests on the purities of the test material, he replied that Hazleton's policy is that the composition of the test material is assumed to be 100% pure and is not subject to the contrary by the client. Tests for (chemical) stability, (biologic) potency and homogeneity of the test material were performed only at the client's specific request. Cutler never made such a request of Hazleton.

...the criteria were followed. However, exceptions were found in the 104 week rodent study of Aspartame, where the protocol called for dogs to be 150 to 160 days of age and yet three dogs were used in this study that were approximately 70 days older than the protocol specified.

...the study was not done in 104 week rat study at Hazleton Laboratories is the Aldacote 78 week study and there were deviations from this holding period when rats were put in the study and held for only five or six days respectively.

...in the study was not done in 104 week rat study at Hazleton Laboratories is the Aldacote 78 week study and there were deviations from this holding period when rats were put in the study and held for only five or six days respectively.

...in the study was not done in 104 week rat study at Hazleton Laboratories is the Aldacote 78 week study and there were deviations from this holding period when rats were put in the study and held for only five or six days respectively.

...in the study was not done in 104 week rat study at Hazleton Laboratories is the Aldacote 78 week study and there were deviations from this holding period when rats were put in the study and held for only five or six days respectively.

...in the study was not done in 104 week rat study at Hazleton Laboratories is the Aldacote 78 week study and there were deviations from this holding period when rats were put in the study and held for only five or six days respectively.

...in the study was not done in 104 week rat study at Hazleton Laboratories is the Aldacote 78 week study and there were deviations from this holding period when rats were put in the study and held for only five or six days respectively.

...in the study was not done in 104 week rat study at Hazleton Laboratories is the Aldacote 78 week study and there were deviations from this holding period when rats were put in the study and held for only five or six days respectively.

...in the study was not done in 104 week rat study at Hazleton Laboratories is the Aldacote 78 week study and there were deviations from this holding period when rats were put in the study and held for only five or six days respectively.

...in the study was not done in 104 week rat study at Hazleton Laboratories is the Aldacote 78 week study and there were deviations from this holding period when rats were put in the study and held for only five or six days respectively.

...in the study was not done in 104 week rat study at Hazleton Laboratories is the Aldacote 78 week study and there were deviations from this holding period when rats were put in the study and held for only five or six days respectively.

...in the study was not done in 104 week rat study at Hazleton Laboratories is the Aldacote 78 week study and there were deviations from this holding period when rats were put in the study and held for only five or six days respectively.

...in the study was not done in 104 week rat study at Hazleton Laboratories is the Aldacote 78 week study and there were deviations from this holding period when rats were put in the study and held for only five or six days respectively.

...in the study was not done in 104 week rat study at Hazleton Laboratories is the Aldacote 78 week study and there were deviations from this holding period when rats were put in the study and held for only five or six days respectively.

...in the study was not done in 104 week rat study at Hazleton Laboratories is the Aldacote 78 week study and there were deviations from this holding period when rats were put in the study and held for only five or six days respectively.

...in the study was not done in 104 week rat study at Hazleton Laboratories is the Aldacote 78 week study and there were deviations from this holding period when rats were put in the study and held for only five or six days respectively.

...in the study was not done in 104 week rat study at Hazleton Laboratories is the Aldacote 78 week study and there were deviations from this holding period when rats were put in the study and held for only five or six days respectively.

...in the study was not done in 104 week rat study at Hazleton Laboratories is the Aldacote 78 week study and there were deviations from this holding period when rats were put in the study and held for only five or six days respectively.

...in the study was not done in 104 week rat study at Hazleton Laboratories is the Aldacote 78 week study and there were deviations from this holding period when rats were put in the study and held for only five or six days respectively.

...in the study was not done in 104 week rat study at Hazleton Laboratories is the Aldacote 78 week study and there were deviations from this holding period when rats were put in the study and held for only five or six days respectively.

...in the study was not done in 104 week rat study at Hazleton Laboratories is the Aldacote 78 week study and there were deviations from this holding period when rats were put in the study and held for only five or six days respectively.

...in the study was not done in 104 week rat study at Hazleton Laboratories is the Aldacote 78 week study and there were deviations from this holding period when rats were put in the study and held for only five or six days respectively.

...in the study was not done in 104 week rat study at Hazleton Laboratories is the Aldacote 78 week study and there were deviations from this holding period when rats were put in the study and held for only five or six days respectively.

...in the study was not done in 104 week rat study at Hazleton Laboratories is the Aldacote 78 week study and there were deviations from this holding period when rats were put in the study and held for only five or six days respectively.
course of the study and the animals were continued on the study.

"Page 52, paragraph 1: The removal of tissue masses from rats in a chronic toxicity study is a necessary step in conducting the experiments. The following necropsies or post-mortem examinations of the carcasses and tissues of the experimental animals; the on-the-job training was performed by Mr. Searl and Mr. Spelt, and the gross pathology was later characterized by Dr. Rudolph Stejskal, who was designated as the supervising pathologist on this project. The observations of the slides will confirm these observations, and consequently, could not have verified the presence, absence or extent of the findings on the record by Mr. Spelt. When questioned by the investigators as to why he made these changes, Dr. Stejskal stated that Mr. Spelt was employed for only a few months and was encouraged to write down everything that appeared to be questionable or unusual. He also informed investigators that Mr. Spelt sometimes used wrong terms in the description of his findings. The gross pathology observations, submitted to the Food and Drug Administration (FDA), were selected by Dr. Stejskal and represented his interpretation of Spelt's observations. Dr. Stejskal indicated that he did not confirm a gross observation microscopically, he would then omit the gross observation from his report. Actually, failure to confirm a gross observation microscopically may not be due to the usage of a wrong term but simply due to a failure to collect for microscopic examination a representative portion of the lesion actually present. It is possible that what Dr. Stejskal may have very likely achieved here was to withhold the attention of the FDA from the possibility of the occurrence of animals in which Aspartame was tested for safety. It is likely that the presence of such animals may have been missed.

"Page 57, paragraph 2: Histopathology (the lesions manifested in any tissue by examination through a microscope) is an extremely important morphological indicator of the effects of an insult upon a tissue or cell. Careful preparation, cutting, slicing, mounting, staining, and interpretation of histological slides from animal tissues to determine the changes occurring in test animals during the test is of utmost importance. Unfortunately, the slides were lost during the course of the study. Dr. Stejskal, the pathologist at G.D. Searle Co., was responsible for the pathology operations on this particular study. He was asked how the slides for this mass had been read microscopically when the technician responsible for preparing the slides indicated that the mass was not contained in the specimen bottle.

"Page 62, paragraph 2: The ability of an agent on test to elicit developmental or birth anomalies in the newborn assessment of the potential to cause teratogenicity (the ability of an agent on test to elicit developmental or birth anomalies in the newborn assessment of the potential to cause teratogenicity)."
processes constitutes an extremely impor-
tant phase in safety evaluation. The rapid rate of biochemical, physiolog-
al and physiological properties of the con-
ceptus, the embryo, and the neonate pre-
sents major problems. Important consider-
ations are selectivity, appropriate dose, and absorption of test substance. The plan-
ing, performance and evaluation in this sphere requires a high degree of sophistica-
tion.

The person responsible for most of the reproductive studies reviewed was appar-
etly inexperienced in conducting similar studies in this nature and yet was given full responsibility at Searle with a title of Senior Re-
searcher in Reproductive Toxicology. His prior ex-
perience was one year’s employment at the Illinois Wildlife Service where his work involved population dynamics of the cotton tail rabbit. When asked by the investigators during an interview what qualifications or training he had for conducting reproduction and teratology studies, he replied that shortly after his employment (beginning in 1972) he went to a meeting (lasting at most for a few days) of the Teratology Soci-
ety and Searle and then was asked to make a report on the subject he wanted. This individual was also responsible for the training and super-
vision of a research assistant and two technicians.

(Page 64 paragraph 3): “Review of 5 repro-
duction and teratology studies for Aspar-
tame revealed poor animal husbandry prac-
tices and problems in the design of some of the studies. In a memorandum of October 19, 1973, from a technical assistant to Dr. Rao, with copies to his superior and to Dr. Waisman (of Searle), regarding the con-
ception rate in the rabbit teratology study exist for the 15th week after insemination. The conception rates were provided some possible reasons for the observed poor conception rate in the remaining animals following the death of animals in this study. The memorandum includes statements regarding the poor physical condition of the animals when they were received by Searle, e.g., diarrheas; the lack of an adequate acclimatiza-
tion period, e.g., 6 days instead of 3 weeks; breeding the animals before they were sexually mature, e.g., inoculation at 96-116 days instead of 118 days; and pregnancies because of injection of hor-
mone. The memorandum concludes with this paragraph:

“...In view of the information that I have received, I feel the majority of the animals used for this study were sexually immature. A sample of the 57 rabbits may have also contributed to the lower con-
ception rate. Some of these points were dis-
ussed at the beginning of this study, how-
ever we decided to go ahead as scheduled. Perhaps this information can be utilized in future teratology studies so that this type of problem will be eliminated.

A July 15, 1975, letter to Searle from one of its consultants on reproduction and tera-
lology (Dr. Geoffrey Palmer from Great Britain) was critical of the quality of the studies as follows: ‘... even following the track you did, it seems to you have only con-
cluded the issue by a series of studies most of which are deficient in an obvious lack of expertise in the management. Because of the(t)se twin fac-
tors, a more careful and detailed examina-
tion of fetuses and infants is imperative. The inter-
pretation and summarization is of little aiding since the shaky foundation.’

We conclude that Searle rarely monitors the ac-
knowledge of work done for it under contract (by our laboratories or institutions).

(Page 64 paragraph 12): Searle characterized the 52 week monkey study (with aspar-
tame) by Dr. Waisman at the University of Wisconsin as a first priority with the Searle Company. Yet, to the investigators, Searle disclaimed any direct control in the study, despite the fact that detailed specifications on how the study was to be carried out for the study was written by Dr. McConnell (of G.D. Searle & Co.) and Dr. Waisman in January 1970; that frequent high-level commu-
nications took place between Searle ex-
ecutives and the investigators prior to and during the study; that Dr. Waisman was paid $15,000 by Searle for consultation on Aspartame; and that Searle provided Dr. Waisman with thousands of Aspartame to conduct the studies.

While high-level communication between Searle and Dr. Waisman, and knowledge of his activities (Waisman gave a seminar at Searle on his work in October 1975) is evident, there was virtually no effec-
tive monitoring of this work.

From what can be inferred from an inter-
view with Dr. McConnell on October 14, 1975, he has been more concerned about the quality of the study, but his real concern was about substantiating his reservations, there was no way to set a termination point in a submission to FDA (i.e., he gave no indication whatsoever to the FDA on such reserva-
tions as Searle had).

(Page 65 at the top): “In the Aspartame 46 week hamster study, blood samples report-
ed in the submission to FDA as 26 week values (for certain specified animals) were in fact found by our investigators as being, in fact, values for different animals which were bled at the 30th week; the animals for which these values were reported to the FDA were dead at the 38th week.”

In attempting to understand the entries in Table 4 in the Section 7 Additions to Petition (submitted to the FDA by G.D. Searle & Co.) which described chemical analy-
ly values (Exhibit B-14 to the inspection report of the 46 week hamster study), the investigators interviewed Dr. K.S. Rao (of the G.D. Searle & Co.) on November 11, 1976, and asked him to clarify certain BUN (Blood Urea Nitrogen) values reported in that table. After reviewing the table from the submission (to the FDA) and the original data (G.D. Searle & Co. of observations from which allegedly what was re-
ported to the FDA originated), Dr. Rao re-
plied in writing stating:

“It is apparent from the report, that the Appendix portion contains all the individual (animal) values of clinical lab data available from the raw data, whereas a portion of these values appear to have been used in computing group means (which were reported to the FDA). It is not clear what criteria may have been used for selecting a portion of the data or for deleting the others in computing the means (reported to the FDA).

‘For the above reasons, I cannot compre-
the results of the BUN values indicated (in the report submitted by G.D. Searle & Co. to the FDA, from the data available in the Appendix portion) at all.”

“In the Aspartame 115 week rat study, the investigators point out that, in the original data reported to Searle (in its own files) and the other in the submission (by G.D. Searle & Co. to the FDA) it is im-
possible to determine how some of the values in the submission (by G.D. Searle & Co. to the FDA) it is im-
possible to determine how some of the val-
ues are determined. In Table 1 (where 2 in the instance the submitted values appear to be average of the two values shown in the raw data, and in other cases, it appears the mean of the values was selected from the two values which appear in raw data. These findings appear on pages 10 and 11 of the inspection report of this study and in Exhibits R34 and R35.”

Following these quotations from the Final Report of the Searle Task Force, it would be useful to refer to here what happened in the Fall of 1975 following that investigation at G.D. Searle & Co., particularly in reference to the aspartame studies.

Inasmuch as only a very small fraction of the fairly large number of studies on aspar-
tame carried out, or for G.D. Searle & Co. could be audited by the investiga-
tors at that time, the decision was made by the FDA to have the original records from G.D. Searle & Co. made available. The balance of those studies sealed in place at G.D. Searle & Co. so as to preserve their au-
thenticity for a future date when they might also be audited.

In fact, however, the only additional audit as far as aspartame studies are concerned that was carried out by the FDA did not take place until April to August 1977, i.e., almost two years subsequent to the original audit. Even then, only three additional studies were audited; two of them were relatively minor ones on the embryotoxic and ter-
atiogenetic potential for aspartame (one in the mouse and the other in the rat). The third study was the same as the previous study, but 115 weeks with DPK that had already been investigated during the original audit in 1975. From what I know, no additional efforts at auditing any further study on aspartame was made by the FDA despite the fact, as mentioned earlier, that a relatively large number of non-human experimental animals have been conducted by or for G.D. Searle & Co. for this particu-
lar purpose.

This apparent refusal by the FDA to do what would have been the “right” thing to do in this case is even more difficult to comprehend by the public functionally that.

In December 1975 i.e., as a consequence of the initial findings by the FDA on the reli-
ability of the aspartame studies conducted by and for G.D. Searle & Co., the FDA decided to prevent aspartame from entering the market;

The findings during the 1977 audits not only confirmed those made in 1975 with re-
spect to the lack of reliability of the studies of aspartame, but actually extended them in a substantial way.

Despite all this, the FDA refused to allow its findings on the reliability of the aspar-
tame studies to be put before the Scientific Board of Inquiry on aspartame which had been convened following a request of Dr. John W. Olney of the Washing-
ton University School of Medicine in St. Louis, Mo., and Mr. James Turner, a Wash-
ington, DC attorney. This refusal took place even though the two gentlemen insisted that such concerns on the reliability of the two studies were directly related to the evi-
dence (or lack of it) for the safety of aspar-
tame.

Although largely as a result of the find-
ings arising from the 1975 investigation at G.D. Searle & Co., the U.S. Congress appro-
proved an additional $16,000,000 or so to the FDA for the express purpose of doing a better job at monitoring the quality of the studies carried out by the regulated industry and although the FDA took this money and a large number of investigators al-
legedly to devote to this purpose, only the limited audits carried out in 1977 by the FDA with respect to aspartame, apparently nothing more in the way of audits were carried out for this particular product.

Therefore, most of the raw data that had originally been sealed by the FDA at G.D. Searle & Co. in 1973 were released and returned to the custody of G.D. Searle & Co., without any further attempts at validating the reliability of such reports.
as that firm had elected to submit to the FDA on the safety of aspartame.

The kind of track record on the part of the FDA does not inspire much confidence that the health of the people of this country is in fact adequately protected by the agency's activities.

As to what was uncovered as a result of the 1977 audit, you may recall that I had given you a copy of that particular EIR (Establishment Inspection Report); that 76-page document came to be known as the "Bressler Report" after the name of the leader of the team of investigators and scientists involved in the particular audit, Mr. Jerome Bressler, an FDA investigator located in the Chicago District. A perusal of its contents reveals that the original (1975) findings with respect to the 115-week rat study with DKP, or diketopiperazine, a breakdown product of aspartame, were confirmed with respect to:

Discrepancies between what was found in G.D. Searle's own internal records on the circumstances of the conduct of this study and on the observational findings actually made and what was actually reported by that firm to the FDA with respect to:

- The alive/dead status of each animal at any given time;
- The presence of certain microscopically evident lesions when the G.D. Searle & Co. records indicate that such findings could not possibly have been made since no such examinations were made;
- Problems with clinical laboratory determinations;
- The multifaceted evidence for this study being flawed due to:
  - Substitution of some of the animals in the study;
  - The presence of intercurrent disease and the administration of drugs to combat this, neither of which were completely reported to the FDA;
  - Incomplete examination of tissues from the experimental rats;
  - Evidence that certain masses likely to be tumors from live animals in this study;
  - Absence of batch records and records for the mass of each substance into the diet of the experimental animals;
  - Incomplete stability studies for the agent on test;
  - Absence of homogeneity studies for the agent on test;
  - Deficiencies in the methods of chemical analysis for the actual DKP which was mixed into the diet of the experimental rats;
  - Problems with the dosage of DKP given to the experimental rats;
  - Problems with the fixation in-toto and autolysis;
  - Failure to report to the FDA of all tissue masses (likely to be tumors) which were found in the test animals;
  - Failure to report to the FDA of all internal tumors present in the experimental rats, e.g., polyps in the uterus (Animal K9MF, ovaria, including follicles (Animals H10CF, H19CF, and H7HP) as well as other lesions (Animal D28CF);
  - Inconsistencies between different parts of the report on this study submitted by G.D. Searle & Co. to the FDA on the percise nature of the lesions manifested by the test rats;
  - Numerous transcription errors in that report.

Interestingly, the Bressler Report found not only that no homogeneity tests were conducted by G.D. Searle & Co. on the mixture of the test agent with the diet of the experimental rats, but they obtained direct evidence that in fact the distribution of the test agent was not homogenous due to failure to have the test agent ground in a sufficiently fine manner. A polaroid photograph of a sample of that diet obtained during the examination actually shows the test agent in the form of coarse particles within the diet. It follows that the rats were exposed to that diet without actually touching the DKP and, consequently, no one could state with any assurance just how much DKP (if any) those rats were actually exposed to in the course of that study.

In sum, problems such as this leave rather gaping holes in the reliability of such tests of safety as were conducted by G.D. Searle & Co. not only in general with respect to any of their products, but more specifically with respect to aspartame itself. And yet, it seems as if none of this had inhibited in any way or restrained the FDA from approving this product for marketing in an extremely widespread fashion.

(b) The problem with the brain tumors noted in the experimental animals:

You must have noticed the material that I had given you there was a rather extensive prepared statement by Dr. Olney before this hearing. I shall not comment here on the bulk of Dr. Olney's concerns on the safety of aspartame, rather I shall limit myself here to one, only one aspect caused by him: the matter of the tumors of the central nervous system of the exposed rats. This can be found in Part III of that prepared address of Dr. Olney's.

Table 1 of Part III in that presentation by Dr. Olney presents the pertinent data on this—no brain tumors were noted among the 120 control or unexposed rats, 5 were found with brain tumors amongst the 160 rats exposed at the low level of aspartame (1-2 grams/kg body weight) and 7 were found with brain tumors amongst the 160 animals exposed to the high rate of 4-8 grams/kg body weight. These three rates represent incidences of respectively 0.00%, 3.13% and 4.38%.

The question that arises as soon as a distribution of tumors is quite simple—did the agent on test, aspartame in this case, cause the brain tumors noted among the animals exposed to it, or rather can one view the occurrence of such tumors only in the two groups of rats exposed to aspartame as merely a "chance" event, an occurrence unrelated to their exposure status?

The usual way the FDA (and any other recognized scientific institution) answers this kind of question is to compute the probability that a distribution such as the one observed here can arise due to sheer chance; if it turns out that such probability is rather small (0.05 or 5%) the investigative scientific circles is to state that the result observed has achieved "high statistical significance". What this indicates is the probability of the incidences observed arising by chance alone (i.e., that they are unrelated to the agent on test) is so small (5% or less) that one would conclude (the so-called p-value) that the test agent was not a factor causing such incidences.

In one word, if whenever the results of an appropriate statistical test for significance yields a p (for probability) value equal or to less than 0.05 or 5%, the policy in the FDA and investigated scientific circles is to regard the agent on test as being a cause of the increase in incidence of whatever kind of lesion is being evaluated amongst those rats as compared with the control incidence. I am saying therefore, that whether the agent on test had in fact caused that particular increase in incidence is not a matter that is usually decided according the "opinion" of any scientific group of scientists, it is not a matter that is put to some kind of "vote", or on which there must be some form of "consensus" as to whether the results of the test for statistical significance—the "p" value is either larger than 0.05 and one then views the results as not having achieved statistical significance for it is 0.05 or less in which case one must conclude that the results are statistically significant i.e., that they are extremely unlikely to be due to chance alone.

The data on brain tumors amongst the rats exposed to aspartame that were presented by Dr. Olney in his Part III, Table 1, have been analyzed statistically by me and the following are the results of my computations:

- Slope of dose-response function: 0.005,897
- Standard error of this slope: 0.003,046
- Chi square for significance for this slope: 3.724
- "p" or probability of this chi square: 0.077

The entry in that chart for p = 0.027, indicates that the results on the incidence of brain tumors that were tabulated by Dr. Olney, in fact achieved rather high statistical significance and is 0.027 is barely more than half p = 0.05.

In fact, the statistical significance that applies here is considerably larger yet if one considers that brain tumors amongst rats are ordinarily very rare. In his Table 2 of Part III, Dr. Olney presents the results of the literature that had been gleaned from the world literature on this subject—the "control rate" for such tumors amongst large populations of rats indicates that no more than 48 animals afflicted with them have been found amongst nearly 60,000 rats, an incidence rate of less than one tenth of 1 per cent.

Interestingly, the FDA seems to have a policy that whenever faced with decisions of this sort, it never fails to consider this aspect of the "historical control" incidence; an example of this can be seen in their decision concerning the carcinogenicity or cancer-induction propensities of a number of other chemical substances that arose as recently as last year. One cannot help wondering why they failed to consider this particular aspect in reference to the cancer-induction of aspartame had they in fact addressed the "historical incidence" of brain tumors amongst rats as presented by Dr. Olney, they could not have failed to conclude what I have concluded—namely, that the significance that attaches to those tumors amongst the rats exposed to aspartame increases manifold over the already high significance mentioned above when what was observed merely in this particular study is considered.

In other words, all these indications that the cancer-causing potential of aspartame is a matter that had been established way beyond any reasonable doubt, one can ask—why is the reason for the apparent refusal by the FDA to invoke for this food additive the so-called Delaney Amendment to the Food, Drug, and Cosmetic Act? Is it not possible to apply any criteria that aspartame had caused brain tumors or brain cancer in animals, and is this not sufficient to support the achieved provisions of that particular section of the law?

Given that this is so (and I cannot see any kind of tenable argument opposing the view that this is so) one may indeed ask why the FDA justify its position that it views a
CONGRESSIONAL RECORD — SENATE

August 1, 1985

It is clear that risks of this magnitude for what the FDA regards as "a very low level of exposure to aspartame represent outright calamity or disaster. In fact, were the Allowable Daily Intake of aspartame be limited to half the amount that the FDA, i.e., in the neighborhood of merely 5 mg/kg/kg weight-body, the table on the next page will indicate that the upper limit on the brain tumor risk would be as large as approximately 1/10,000 population for the log-probit method and possibly 5/10,000 population for the one-hit procedure, both of which would seem to me to be clearly and totally unacceptable. Even if the FDA's ADI were one-hundredth smaller (i.e., no more than 0.5 mg/kg/kg weight-body) the upper limit on the brain tumor risk can be seen in the table on the previous page here to be approximately between 1 and 5/1,000,000, considering the widespread consumption of soft-drinks containing this food additive in this country alone, I should think that even this would represent a rather high risk.

This concludes my remarks that were briefly summarized near the bottom of the first page of this issue and I should add here that the views given above are strictly my own and that they do not represent in any way those held by the U.S. Public Health Service, where I am currently employed; that agency has no regulatory jurisdiction or interest in food-additives like aspartame.

Wishing you and Senator Metzenbaum the very best and continued success in all your legislative efforts, and particularly those that involve aspartame, I remain, Mr. Wagoner.

Sincerely yours,

M. ARTHUR CROSS, Senior scientific advisor, Benefits and Use Division, Office of Pesticide Programs.

STATEMENTS FROM COMMUNITY NUTRITION

A national organization, Aspartame Victims and Their Friends, Inc. was launched today at a Washington, D.C. press conference in which one of the organization's founders municipalities announced that their group would be filed against G. D. Searle and Company, makers of aspartame under the Nutritional Rights Law.

The organization, which is affiliated with the Aspartame Resource Center of the Community Nutrition Institute, a Washington-based consumer group, will be located in Ocala, Florida, and will operate a national telephone hotline.

A founding member of the organization, Mrs. Shannon Roth, of Ocala, who recently lost vision permanently in one eye, said the onset of her blindness began with the use of Nutrasweet and her vision deteriorated over a period of several months during which she consumed large amounts of the sweetener.

Her loss of vision is linked to aspartame by her physician and other medical authorities.

Both Roth and Searle are filling a personal injury lawsuit against Searle in Florida, where she is joining with several other members of "Victims" to file a personal injury claim against Nutrasweet as large as that desired by the FDA. James Turner, an attorney and consumer activist, said that an administrative petition is being filed with the Justice Department seeking to void the FDA's approval of Nutrasweet and award the eventual personal injury lawsuit against Searle.

CINTS' Executive Director, Rod Leonard, said the new organization is providing a link between aspartame users who have experienced adverse reactions and have suffered injury and economic loss. He described
AUGUST 1, 1985

CONGRESSIONAL RECORD — SENATE

S 10841

THE SYMPTOMS WHICH INCLUDE GRAND MAL SEIZURES, EPISODIC DEPRESSION, DEAFNESS, AND PERMANENT BLINDNESS, MENTAL PROBLEMS, AND OTHER SEVERE DISORDERS. LEONARD SAID THAT HE AND TURNER ALSO ARE F U N C T I O N S OF THE FDA, WHICH ADMINISTERS THE NATIONAL SURVEILLANCE PROGRAM ON ASPARTAME COMPLAINTS. HE SAID FDA COMMISSIONER FRANCIS YUHANIC HAD CONCLUDED WITH SENATORS JOHN HEINZ AND HOWARD METZENBAUM THAT THE AGENCY IS CONSIDERING THE ESTABLISHMENT OF A CLINICAL ADVERSE REACTION REVIEW COMMITTEE ON ASPARTAME, INCLUDING THE ORDERLY COLLECTION AND TRANSMISSION OF REPORTS FROM FDA FIELD OFFICES.

"The orderly collection and transmission of information will be a character of the program," Leonard said, "unless the FDA also sends a memorandum to physicians, health clinics, psychologists, allergists, and other specialists informing them of its plan by FDA to collect data on adverse reactions." He and Turner said a national monitoring program must include expression of physicians.

"Turning is also representing CNI and others in a legal action to require FDA to hold a public hearing to review the decision to use aspartame in food products. The lawsuit, which is currently pending in the U.S. Circuit Court of Appeals, asks the court to direct the FDA to suspend the use of aspartame as a food additive pending the outcome of the hearing.

COMMUNITY NUTRITION INSTITUTE, WASHINGTON, DC, SEPTEMBER 13, 1984.

Dr. Frank E. Young.

"Congressional Food and Drug Administration, Rockville, MD."

DEAR MR. COMMISSIONER: This letter is a request for the Food and Drug Administration to maintain a surveillance program to monitor the complaints of all consumers regarding aspartame, a sweetener product that is marketed as NutraSweet by Scarle and Company. When FDA approved in July 1983 the use of aspartame in liquids, the agency was aware of health concerns by scientists, particularly the instability of the substance in liquids and consumers and said it would monitor complaints.

However, no monitoring program was established until February, some eight months later, after we specifically requested that FDA officers be directed by FDA to fulfill its July pledge. We requested the Centers for Disease Control be asked to make an epidemiological evaluation of the complaints, and we were subsequently informed that a monitoring program had been initiated—incorporating a CDC evaluation.

We have learned enough information to question whether an aspartame monitoring program ever has been, in fact, carried out by FDA. The evidence suggests that FDA has sought to avoid the collection and analysis of complaints, and has instructed regional offices to withhold data from its Washington headquarters.

For example, FDA has informed us that it has received some 800 complaints that were forwarded to CDC, with the implied conclusion that this is the total number of complaints. However, in discussions with the Food and Drug Administration (FDA) at FDA, we learn that those complaints were all received prior to April, and that March of this year, and do not include any complaints received subsequently.

In addition, the FTO office said that regional offices had been told that only "serious" complaints should be forwarded to FDA headquarters; and, for the guidance of regional office staff, a "serious" complaint is one in which the illness is severe enough to require the attention of a physician.

Thus, not only was FDA unable to determine the actual extent of consumer reactions to NutraSweet, or to analyze and correlate these reactions in a regional office—located in Philadelphia—we understand that NutraSweet complaints filed since June have not even been examined.

We also had requested FDA early this year to notify physicians the agency was monitoring consumer adverse reactions to aspartame, or NutraSweet. We were told that FDA had no intention of inviting physicians to send in reports of complaints. This attitude, we observe, is on the part of an agency that instructs its field offices to forward only those complaints which have been filed by individuals who sought the counsel of their physician because of the severity of their reaction.

This also is a full-filling argument for the basic FDA position that complaints about aspartame, or NutraSweet, have no pattern, and that all of them can be explained by the placebo effect—i.e., whenever any new product is introduced, it will be seized upon by the public as the source of their ailment. FDA has made no efforts to alert medical professionals for information, but instead waits on consumers who seek medical advice about their complaints to make a report to FDA to the problem. Thus, FDA has consistently limited its knowledge as to whether a problem may or may not exist.

On the surface, FDA has made a gesture towards monitoring that the agency hopes will satisfy the public. In fact, the agency appears to have no information and is making no effort to acquire data on adverse reactions.

The material sent to CDC is meaningless, and no substantive conclusions can be drawn from an epidemiological assessment of data that has made its way through the indifference of public officials. The reports available to CDC are not reflective of the complaints that have been directed to FDA, nor do they represent a random selection of information.

This episode illuminates a darker problem within FDA and the procedures now employed in the regulation of food additives. Had it been established as a drug or a drug, physicians would be routinely monitoring the reaction of their patients when prescribing the substance or use in weight control or for other special purposes. The effects of aspartame, specifically the amino acid components, have been characterized by a number of scientists as the same as those of a drug. In approving the substance as a food additive, however, FDA has told physicians, in effect, that no adverse reactions should be expected; i.e., symptoms of aspartame use cannot be ascribed to the substance, according to the federal government.

The health consequences of aspartame have been a controversy of long standing within FDA. Over the 14 years prior to its approval, the Agency has repeatedly examined the data on its health implications and could not make a declarative scientific finding that the substance is safe for use in the diet. American University studies, and further analysis of the data have served only to raise additional questions that preclude a finding that the product is safe. Jeffrey Berman, a neurologist at the Bada de Scrippa Institution in La Jolla, CA, found that potentially harmful chemical changes occur when NutraSweet is heated in liquid form. Your staff recently reviewed the study "purely out of scientific interest," which is an odd reaction considering that the test performed by Dr. Bada should have been conducted by FDA before approving the substance. In the face of this pattern of scientific controversy, which is further buttressed by the nature of the complaints of those consuming the substance, the least the FDA could do is to begin monitoring the effects of aspartame on its consumers.

Thus far, FDA has spurned its responsibilities, and has no monitoring program. As the newly appointed Commissioner, you have the opportunity to take a more responsible role than did your predecessor, and I urge you to develop and implement a comprehensive and intensive surveillance program to monitor the health consequences of the consumption of aspartame, so that consumers can readily assist you in any way that we can.

Sincerely,

RODNEY E. LEONARD

JAMES S. TURNER

STATEMENT OF RICHARD J. WURTMAN, M.D., MASSACHUSETTS INSTITUTE OF TECHNOLOGY, TO SENATE COMMITTEE ON LABOR AND HUMAN RESOURCES

Thank you for inviting me to comment on the FDA's recent consumer concerns about aspartame when used as an artificial sweetener.

I am a physician, a research scientist, and a professor of neuroendocrinology and neuropharmacology at the Massachusetts Institute of Technology. For the past 15 years, much of my research has dealt with the effects of food on the composition of the brain, and on various brain functions and types of behavior. I have studied these effects in experimental animals, in normal people, and in people with brain disorders. My interest in aspartame derives from the fact that it contains two amino acids, phenylalanine and aspartic acid. Phenylalanine is an essential amino acid in all levels of these amino acids in the blood stream, and one of them—phenylalanine—thereupon produces chemical changes in the brain.

In 1980 I was invited to testify before the Board of Inquiry on aspartame, convened by the Food and Drug Administration, concerning the possibility that the aspartic acid in aspartame might do damage to the brain. I concluded then and continue now that there is no significant risk of toxicity from the aspartic acid in aspartame. Subsequently, however, I became concerned about risks that might result from the consumption of aspartame. As it seemed likely—the introduction of aspartame into soft drinks would increase the quantities that some people consumed beyond the FDA's consumption estimates (for example, on a hot day). My laboratory initiated pilot studies on this question about two years ago, and in July of 1984 we received a grant from the National Institute of Neurological and Communicative Disorders and Stroke to extend these studies.

I believe that the information now available about aspartame is far from definitive, and that following conclusions about its possible effects on the brain:

When aspartame is consumed by laboratory rats in doses consonant with those sometimes ingested by people, it changes the chemical composition of the brain: It increases the brain's levels of some amino acids, and thereby affects the production and release of some of the neurotransmitters that the brain uses to carry signals from one nerve cell to another. However, it enhances the consumption of a food that is rich in carbohydrate (as happens, for example, when something sweetly tastes good when eaten along with diet soda). The changes in neurotransmitter release are likely to affect nu-
CONGRESSIONAL RECORD — SENATE

August 1, 1985

Severe clinical investigators and organizations such as the Centers for Disease Control and the American Academy of Pediatrics are deciding on how to address these issues. There is much debate among them about whether the usual methods of monitoring are sufficient. In any case, if you are pregnant, breastfeeding, or have had symptoms directly related to ingesting phenylalanine-containing sweeteners.

**BIOCHEMICAL AND NEUROPSYCHOLOGICAL EFFECTS OF ELEVATED PLASMA PHENYLALANINE IN PATIENTS WITH TREATED PHENYLKETONURIA**

*Model for the Study of Phenylalanine and Brain Function in Man*

**ABSTRACT**

Phenylalanine provides a model for the study of the effects of increased concentrations of phenylalanine in the brain. Although irreversible mental retardation is preventable through dietary restriction, controversy exists regarding the effects of increased concentrations of phenylalanine in the brain. We have studied the effects of increased phenylalanine concentrations on the brain in 9 patients who received a diet that included a repeatable battery of neuropsychological tests, analysis of plasma amino acids, and determination of urine amino acids, phenylalanine, and phenylketonuria. In all 10 patients, plasma phenylalanine rose from 900 to 4,000 μM. In 9 of 10 patients there was an inverse relationship between plasma phenylalanine and urinary phenylalanine excretion. When blood phenylalanine was increased, these patients had prolonged performance times on neuropsychological tests of higher but not lower integrative function. Urinary serotonin fell during phenylalanine loading in all patients. The concentration of phenylalanine in the urine was proportional to the plasma phenylalanine at concentrations below 1.5 mM. In one patient, neither performance time nor serotonin excretion varied as blood phenylalanine rose or fell. We interpret these data as follows: Phenylalanine above 1.5 mM impairs performance on neuropsychological tests of higher integrative function; this effect is reversible, and one mechanism may involve impaired biogenic amine synthesis.

**INTRODUCTION**

Nearly a half-century ago Poling [1] attributed a syndrome of mental retardation and aberrant behavior to an inherited metabolic error. Since then, phenylketonuria (PKU) has been the prototype for investigations of the effect of phenylalanine on central nervous system function in man. It is clear that if plasma phenylalanine is normalized before age 3 wk through dietary restriction of phenylalanine irreversible mental retardation is prevented [2]. The mechanisms of phenylalanine-to-brain transport and permanent structural damage remain unclear, but several hypotheses have developed. Decreased or abnormal serotonin formation and/or impaired monoamine synthesis are possible explanations for the observed phenomena.

**STATEMENT OF DR. LOUIS J. ELIASI**

Thank you for your interest in the effects of increased concentrations of phenylalanine in the brain. Although irreversible mental retardation is preventable through dietary restriction, controversy exists regarding the effects of increased concentrations of phenylalanine in the brain. We have studied the effects of increased phenylalanine concentrations on the brain in 9 patients who received a diet that included a repeatable battery of neuropsychological tests, analysis of plasma amino acids, and determination of urine amino acids, phenylalanine, and phenylketonuria. In all 10 patients, plasma phenylalanine rose from 900 to 4,000 μM. In 9 of 10 patients there was an inverse relationship between plasma phenylalanine and urinary phenylalanine excretion. When blood phenylalanine was increased, these patients had prolonged performance times on neuropsychological tests of higher but not lower integrative function. Urinary serotonin fell during phenylalanine loading in all patients. The concentration of phenylalanine in the urine was proportional to the plasma phenylalanine at concentrations below 1.5 mM. In one patient, neither performance time nor serotonin excretion varied as blood phenylalanine rose or fell. We interpret these data as follows: Phenylalanine above 1.5 mM impairs performance on neuropsychological tests of higher integrative function; this effect is reversible, and one mechanism may involve impaired biogenic amine synthesis.

**REFERENCES**

known. Since ~1 in 10,000 Caucasian newborns (Georgia statistics) is affected with PKU, and effective newborn screening has prevented mental retardation among children born since 1970 in the newborn screen, an answer to the question of whether high plasma phenylalanine is neuronal dysfunction becomes more urgent for this accumulating population.

Silverman and Guthrie (unpublished observations) also discovered the phenomenon of entrainment one loading dose of phenylalanine to control subjects, heterozygotes, and homozygous patients with PKU and compared errors in response time among the three groups. Their results suggested a difference among the three groups with the homozygous phenotype subjectively to the concentrations of plasma phenylalanine achieved.

In 1980, Waalbroeck et al. reviewed the available literature on psychological assessment of children after termination of phenylalanine-restricted diets. Results were mixed, some showing a drop in IQ and other achievement test scores and others showing no change. Numbers of patients, study design, and assessment tools varied greatly among the studies. The Pioneering Congenital Phenylketonuria Study began a prospective study in 1967. Results of achievement tests (Stamford Binet, Wechsler Intelligence Scale [WISC], Wechsler Adult Intelligence Scale [WAIS], etc.) on 81 children, 38 of whom had continued the diet beyond 6 yr of age and 43 of whom had been continued beyond 6 yr of age postnatally, were reported in 1982. Results at 8 yr of age showed slightly lower achievement in reading and spelling in the discontinuers. No significant difference in IQ between the groups was observed after this 2-yr interval. Brunner et al. in a recent study (1982) reported a negative correlation between IQ and plasma phenylalanine levels. In this study, plasma phenylalanine concentration on the day of testing in a group of early treated patients age 6–13 yr. None of these studies used the patient as his/her own control. Individual variability in the interpretation of results.

In the in vitro systems, phenylalanine influence on biologic activity of neurotransmitters, dopamine and serotonin, which are critical compounds in neurotransmission. Both tyrosine hydroxylase (E.C.C.14.16.14) and tyrosine hydroxylase activity in amine synthesis have been studied and shown to be dependent on phenylalanine at millimolar concentrations. Another potential inhibitory effect of phenylalanine on biologic activity is through impaired uptake of tyrosine and dopa across the blood-brain barrier. Phenylalanine, tyrosine, and tryptophan share the same transport system and compete for a common transport function at physiological concentrations. Since transport of amino acids across the blood-brain barrier is the rate-limiting step in the movement of neurotransmitters into the brain, these findings suggest that phenylalanine concentrations may play a role in neuronal function in the brain.

The current study compares specific neuropsychological tests with changes in plasma phenylalanine and biologic amine production in young adults and other children with PKU. Although the dopamine excreted in the urine is a reflection of multiple sources of dopamine, we chose to measure urine dopamine, since it reflects 24-h production of the amine, not an acute level, and because urine collection is a noninvasive method of obtaining biologic fluids. Assessment is not made of competitive inhibition by phenylalanine as a metabolic transport study by kidney tubule. We use a triple-blinded, crossover, clinical protocol to circumvent the influence of individual variations in this disease.

METHODS

Study design. Ten patients with PKU, aged 6–24 yr, were admitted on a 21-d protocol to the Emory University Clinical Research Center. Patients were divided into two groups: adult patients or from the parents of patients <21 yr of age. Each patient served as his or her own control. Patients admitted on one of two double crossover protocols and five were studied in each protocol group. Either the patient entered on a low dietary phenylalanine which was increased the second week and decreased the third week (low-high-low) or in the reverse pattern (high-low-high). Patients equilibrated for 7 d after each change in dietary phenylalanine. Past plasma concentrations of phenylalanine on known intake and genotyping of PKU were considered.

The amount of phenylalanine added to patient formulation was restricted as follows: 23,24. Patients whose entering concentration were high or low, respectively, because of poor control or because of diet discontinuation for several years were on the lower half of the protocol. Five other patients who had been in consistently good dietary control entered the study on the low-high-low protocol.

The study diet was based on Phenylfree or Lofenalac as a phenylalanine-free amino acid acid. A specified amount of phenylalanine was added to the formula to form a 5% concentration. The study was triple-blinded: neither the patients nor their parents could taste the difference in formula. In addition, the patients were unaware of their experimental condition: the psychologist administering the neuropsychological tests was uninformered of the patients' blood phenylalanine concentration; the laboratory personnel performing amino acid, organic acid, and amine analyses did not know the condition under which samples were drawn.

Biochemical tests. Blood and urine samples were obtained on all patients at the beginning of the week as a baseline and at the end of the treatment period. Plasma phenylalanine concentrations were measured using gas chromatography on a HP 5982 gas chromatograph/mass spectroscopy and quantitated on a HP 5970 gas chromatograph. Organic acids were extracted with ethyl acetate and ether, and chromatographed with 3° methylamine and 3°(trimethylsilyl)trifluoroacetamide (TMS-TFAA). The level of sensitivity for phenylalanine in urine was increased to 1.5 g/mL. Specific lactic, pyruvic, and phenylpyruvic acids were >80 and 85%, respectively. All calculations were based on these measurements.

Renal clearances were calculated from phenylalanine, tyrosine, and tryptophan, from timed 24-h urine collections and mid-point plasma collections. Both specimens were quantitated using acidified ethanol: dichloromethane extractions. The glomerular filtration rate (GFR) was calculated from the creatinine clearance, as were the rates of a specific amino acid filtration, excretion, and net reabsorption using the following formula: P = GFR x C, where F, V, and T are the filtered amino acid, excreted amino acid, and TAMCO (reabsorbed amino acid), respectively. All measurements were expressed in mg/mL. Percent reabsorption was calculated as TANCO/filtered amino acid, respectively.

Neuropsychological tests. Measurements of general intelligence and achievement were based on the Wechsler Intelligence Scale for Children (WISC) and the Wechsler Adult Intelligence Scale for adults and the WISC for children) and the WISC. To determine the influence of phenylalanine concentrations on neuropsychological performance, a repeatable battery of tests was developed and administered as a baseline on admission to the study and at the end of each 1-wk treatment period. A confounding variable inherent in such studies is the effect of learning. Two procedures were incorporated in the study design to reduce the artifacts due to learning. For one group of test (type I), the subject was instructed to practice the task until the asymptote of the learning curve was reached. Any changes in performance after becoming maximally competent with the task then reflected experimental manipulation of the patient. This procedure would not eliminate learning artifacts from a second group of tests (type II, Table 1). It was necessary to use repeated measures of neuropsychological variables to compare results from groups. Table I lists the test names and the neuropsychological variables they measure.

Interpretation of data. Data are arrayed for all subjects in tabular form (Tables II, III, IV, and V) to emphasize intradividual differences because of the wide interindividual variability in age, sex, intellectual competence, and phenylalanine requirements. From these tables, individual differences and choice reaction time and the direction of change between the two dietary conditions are calculated and plotted against changes in plasma phenylalanine during the same intervals in Figs. 2 and 3.

The antibody bound 69% of [3H]-serotonin in the absence of free serotonin. Less than 1 ng of free serotonin was detected by standard displacement methods.

The disease was characterized by gas chromatography on a HP 5982 gas chromatograph/mass spectroscopy and quantitated on a HP 5970 gas chromatograph. Organic acids were extracted with ethyl acetate and ether, and then chromatographed with 3° methylamine and 3°(trimethylsilyl)trifluoroacetamide (TMS-TFAA). The level of sensitivity for phenylalanine in urine was increased to 1.5 g/mL. Specific lactic, pyruvic, and phenylpyruvic acids were >80 and 85%, respectively. All calculations were based on these measurements.

Renal clearances were calculated from phenylalanine, tyrosine, and tryptophan, from timed 24-h urine collections and mid-point plasma collections. Both specimens were quantitated using acidified ethanol: dichloromethane extractions. The glomerular filtration rate (GFR) was calculated from the creatinine clearance, as were the rates of a specific amino acid filtration, excretion, and net reabsorption using the following formula: P = GFR x C, where F, V, and T are the filtered amino acid, excreted amino acid, and TANCO (reabsorbed amino acid), respectively. All measurements were expressed in mg/mL. Percent reabsorption was calculated as TANCO/filtered amino acid, respectively.

Neuropsychological tests. Measurements of general intelligence and achievement were based on the Wechsler Intelligence Scale for Children (WISC) and the Wechsler Adult Intelligence Scale for adults and the WISC for children) and the WISC. To determine the influence of phenylalanine concentrations on neuropsychological performance, a repeatable battery of tests was developed and administered as a baseline on admission to the study and at the end of each 1-wk treatment period. A confounding variable inherent in such studies is the effect of learning. Two procedures were incorporated in the study design to reduce the artifacts due to learning. For one group of test (type I), the subject was instructed to practice the task until the asymptote of the learning curve was reached. Any changes in performance after becoming maximally competent with the task then reflected experimental manipulation of the patient. This procedure would not eliminate learning artifacts from a second group of tests (type II, Table 1). Because of this limitation, equivalent forms of type I, test were developed to be given at the end of each of the experimental conditions. Table I lists the test names and the neuropsychological variables they measure.
CONGRESSIONAL RECORD — SENATE

August 1, 1985

TABLE I. NEUROPSYCHOLOGICAL TESTS USED AND THE VARIABLES MEASURED BY THEM

<table>
<thead>
<tr>
<th>Test name</th>
<th>Type</th>
<th>Age</th>
<th>Variables</th>
</tr>
</thead>
<tbody>
<tr>
<td>Choice reaction time</td>
<td>1</td>
<td>56</td>
<td>Visual-perceptual disorientation and complex visual-spatial construction.</td>
</tr>
<tr>
<td>Digits</td>
<td>2</td>
<td>56</td>
<td>Auditory memory and visual-spatial memory.</td>
</tr>
<tr>
<td>Digits-repetition</td>
<td>2</td>
<td>56</td>
<td>Visual memory.</td>
</tr>
<tr>
<td>Digits-discrimination</td>
<td>2</td>
<td>56</td>
<td>Attention.</td>
</tr>
<tr>
<td>Attention</td>
<td>2</td>
<td>56</td>
<td>Short-term auditory memory.</td>
</tr>
<tr>
<td>Visual-perceptual</td>
<td>2</td>
<td>56</td>
<td>Visual-perceptual memory.</td>
</tr>
<tr>
<td>Visual-spatial</td>
<td>2</td>
<td>56</td>
<td>Visual-spatial memory.</td>
</tr>
<tr>
<td>Hand-in-hand tapping</td>
<td>2</td>
<td>56</td>
<td>Fine motor skill.</td>
</tr>
</tbody>
</table>

1. A test which could be repeated over several testing sessions. 2. A test which could not be repeated and must be presented as equivalent forms over several testing sessions. All age levels 6 years plus greater age.

- Patient profiles and study design. Age, sex, IQ, and achievement scores for all patients are listed in Fig. 1. Each patient was given a symbol which was used in subsequent graphs. IQ scores below 85 in A.S. and K.K. were explained by their late diagnoses and treatment at 5 and 18 mos of age, respectively. K.K. is the older brother of T.K. Both W.J. and T.K. were diagnosed and treated before 3 wk of age and both had IQ scores which were consistent with parental scores (D.A.'s parents' scores were 103 and 83; W.J.'s were 88 and 70).

Biochemical data. Plasma and urine amino acid and organic acid concentrations are presented for all patients in Table II during each of the three experimental conditions. The level of dietary phenylalanine was calculated from actual intake in the Clinical Research Facility, Emory University. The time interval of 7 d required for the plasma phenylalanine concentration to reach a constant diet was determined by sampling one subject daily. A new plate of blood phenylalanine concentration was made on the sixth to seventh day after each diet change. The plasma phenylalanine reflected the diet changes, and the relationship between the three conditions is presented in Table III. Plasma phenylalanine concentration ranging from 0 to 100 mg/dl was determined by high-performance liquid chromatography.

Urinary phenylalanine are not detected in the urine of normal subjects. Four of the five patients were on the low, high-low, and high-low-high protocols. The results of the high-low-high protocol and not recently been on any restriction phenylalanine intake were excreting large amounts of phenylpyruvate and phenylpyruvate at the end of high phenylalanine intake. Excretion of both phenylalanine and phenylpyruvate increased after the end of the high-low-high protocol. In the high-low-high group who had been on a continuous dietary control before entry into this study, all of the group except one patient were on a dietary control. The group was then divided into two subgroups: 1) the group who had been on a dietary control and 2) the group who had not been on a dietary control. The group who had been on a dietary control showed a decrease in the level of phenylalanine and phenylpyruvate.

- Effects of dietary manipulation of phenylalanine (PHE) on concentrations of PHE, tyrosine (TYR), and tryptophan (TRP) in plasma and urine.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Wk</th>
<th>Plasma (mg/dl)</th>
<th>Plasma Phenylalanine (mg/dl)</th>
<th>Plasma Tyr (mg/dl)</th>
<th>Plasma Trp (mg/dl)</th>
<th>Ure Phe (mg/dl)</th>
<th>Ure Tyr (mg/dl)</th>
<th>Ure Trp (mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 1</td>
<td>1</td>
<td>15.250</td>
<td>46</td>
<td>121</td>
<td>16</td>
<td>6.4</td>
<td>68</td>
<td>89</td>
</tr>
<tr>
<td>Patient 2</td>
<td>2</td>
<td>18.792</td>
<td>33</td>
<td>46</td>
<td>12</td>
<td>7.1</td>
<td>10</td>
<td>37</td>
</tr>
<tr>
<td>Patient 3</td>
<td>3</td>
<td>15.271</td>
<td>33</td>
<td>46</td>
<td>12</td>
<td>7.1</td>
<td>10</td>
<td>37</td>
</tr>
<tr>
<td>Patient 4</td>
<td>4</td>
<td>13.371</td>
<td>33</td>
<td>46</td>
<td>12</td>
<td>7.1</td>
<td>10</td>
<td>37</td>
</tr>
<tr>
<td>Patient 5</td>
<td>5</td>
<td>14.257</td>
<td>33</td>
<td>46</td>
<td>12</td>
<td>7.1</td>
<td>10</td>
<td>37</td>
</tr>
<tr>
<td>Patient 6</td>
<td>6</td>
<td>13.452</td>
<td>33</td>
<td>46</td>
<td>12</td>
<td>7.1</td>
<td>10</td>
<td>37</td>
</tr>
<tr>
<td>Patient 7</td>
<td>7</td>
<td>14.341</td>
<td>33</td>
<td>46</td>
<td>12</td>
<td>7.1</td>
<td>10</td>
<td>37</td>
</tr>
<tr>
<td>Patient 8</td>
<td>8</td>
<td>13.300</td>
<td>33</td>
<td>46</td>
<td>12</td>
<td>7.1</td>
<td>10</td>
<td>37</td>
</tr>
</tbody>
</table>

- Studies of membrane transport. To explore the possibility that increased concentration of phenylalanine might competitively inhibit tyrosine or tryptophan uptake by the renal tubular system, a number of patients were studied using a renal tubular transport system. Renal tubular reabsorption data were obtained from 8 patients under these conditions of phenylalanine loading and are presented in Table IV. Phenylalanine did not inhibit tyrosine reabsorption by renal tubular epithelium at the levels of filtered phenylalanine reached in these patients. At the highest filtered phenylalanine (45 mg/min/2M2 in patient A.S.), the filtered load of tyrosine was reduced by only 15% of the filtered load of phenylalanine. These findings are consistent with the data reported by Limes and Waisman, who reported a decrease in aminoaciduria in PKU patients and suggested the possibility of competitive inhibition of reabsorption by high filtered load of phenylalanine. However, their data were not adjusted for renal mass area. Our data for renal tubular transport provide negative evidence for a significant effect of phenylalanine on tyrosine uptake in the proximal renal tubule at the same time that dopamine excretion is reduced. Whether or not the lack of effect of increased phenylalanine reabsorption of...
CONGRESSIONAL RECORD — S 10645

Amino acids in the proximal renal tubule is an appropriate reflection of transport across the blood-brain barrier is not known. Evaluation of blood-brain barrier transport using invasive techniques is not ethical in healthy children. Nuclear imaging techniques may be useful in the future.

**TABLE III.—EFFECTS OF DIETARY MANIPULATION OF PHENYLALANINE (PHE) ON THE EXCRETION OF DOPAMINE AND SEROTONIN**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Week</th>
<th>Dietary Phe (mg/kg)</th>
<th>Plasma Phe (μM)</th>
<th>Urine dopamine (μg/24 h)</th>
<th>Urine serotonin (μg/24 h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>B. R.</td>
<td>7</td>
<td>1.175</td>
<td>1.706</td>
<td>6.2</td>
<td>1.784</td>
</tr>
<tr>
<td>J. W.</td>
<td>2</td>
<td>2.54</td>
<td>5.46</td>
<td>166</td>
<td>204</td>
</tr>
<tr>
<td>L. J.</td>
<td>3</td>
<td>1.175</td>
<td>1.706</td>
<td>6.2</td>
<td>1.784</td>
</tr>
<tr>
<td>K. K.</td>
<td>1</td>
<td>2.54</td>
<td>5.46</td>
<td>166</td>
<td>204</td>
</tr>
<tr>
<td>A. S.</td>
<td>1</td>
<td>2.54</td>
<td>5.46</td>
<td>166</td>
<td>204</td>
</tr>
<tr>
<td>D. A.</td>
<td>1</td>
<td>2.54</td>
<td>5.46</td>
<td>166</td>
<td>204</td>
</tr>
<tr>
<td>M. B.</td>
<td>2</td>
<td>1.175</td>
<td>1.706</td>
<td>6.2</td>
<td>1.784</td>
</tr>
<tr>
<td>J. F.</td>
<td>3</td>
<td>1.175</td>
<td>1.706</td>
<td>6.2</td>
<td>1.784</td>
</tr>
<tr>
<td>T. W.</td>
<td>2</td>
<td>1.175</td>
<td>1.706</td>
<td>6.2</td>
<td>1.784</td>
</tr>
</tbody>
</table>

**Neuropsychological tests.** Part of the purpose of this study was to determine the kinds of tests most suitable for determining possible changes in performance in treated PKU children challenged with phenylalanine. We found that many of the standard tests were too difficult to be applicable across the age group we were assessing and data could not be obtained on all 10 subjects. More complete analysis of these issues will be presented in a separate paper. Results are presented here for those tests on which data were obtained for all subjects. Data were obtained from 10 subjects on the Choice Reaction Time when figures were used for matching. They were also completed on the Pegboard Test, the Tapping Test, and on Trails "A". Table V summarizes the results of the Choice Reaction Time and the Grooved Pegboard Test. The latter is a test of visual-spatial-kinesthetic coordination and motor speed, whereas the Computerized Choice Reaction Time is a test of visual-perceptual discrimination, and by comparison is a test of higher level intellectual function. The Grooved Pegboard Test results are typical of results of tests of lower integrative function, i.e., no significant relationships were observed for all conditions. In three other tests of lower integrative function of which the Grooved Pegboard is representative, 3 of 10 showed changes consistent with changes in plasma phenylalanine. Those results are not reported here. In the Choice Reaction Time Test, 7 out of 10 subjects showed changes consistent with changes in plasma phenylalanine, i.e., reaction time was prolonged with increased plasma phenylalanine. M.P., who did not demonstrate typical changes in his Choice Reaction Time, also did not have a decrease in urinary dopamine when plasma phenylalanine concentrations were elevated (compare Table V with Table III, week 1 to week 2). Differences in Choice Reaction Time were not as consistent in K.K. and A.S., as in the other subjects. It is pertinent to note that K.K. and A.S. were not treated effectively early in life, and were less competent by achievement testing than many of the other patients (see Fig. 1). A graphic display of changes in plasma phenylalanine and changes in Choice Reaction Time among those 10 patients is shown in Fig. 3. A direct relationship was seen between changes in plasma phenylalanine concentration and reaction time. When plasma phenylalanine increased, the choice reaction time increased, that is, performance worsened. Conversely, when phenylalanine concentrations fell, choice reaction times were shorter, which indicated improved performance. Solid symbols again represent episodes on high-low-high dietary protocols and open symbols those on low-low-high dietary protocols. Symbols in quadrant II represent changes of increased choice reaction time with changes reflecting increased plasma phenylalanine concentrations. Symbols in quadrant IV indicate decreased choice reaction time with decreased plasma phenylalanine (Fig. 3). (Figures 1, 2, and 3 not reproduced for the Record.)

**TABLE IV.—ABSENCE OF AN EFFECT OF INCREASED FILTERED PHENYLALANINE ON RENAL TUBULAR REABSORPTION OF TYROSINE (TYR) AND TRYPTOPHAN (TRP)**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Week</th>
<th>Urine tyrosine (mg/24 h)</th>
<th>Urine tryptophan (mg/24 h)</th>
<th>Tissue tyrosine (μg/min)</th>
<th>Tissue tryptophan (μg/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>E. R.</td>
<td>1</td>
<td>1.700</td>
<td>2.54</td>
<td>1.2</td>
<td>1.3</td>
</tr>
<tr>
<td>J. W.</td>
<td>2</td>
<td>1.700</td>
<td>2.54</td>
<td>1.2</td>
<td>1.3</td>
</tr>
<tr>
<td>L. J.</td>
<td>3</td>
<td>1.700</td>
<td>2.54</td>
<td>1.2</td>
<td>1.3</td>
</tr>
<tr>
<td>K. K.</td>
<td>1</td>
<td>1.700</td>
<td>2.54</td>
<td>1.2</td>
<td>1.3</td>
</tr>
<tr>
<td>A. S.</td>
<td>1</td>
<td>1.700</td>
<td>2.54</td>
<td>1.2</td>
<td>1.3</td>
</tr>
<tr>
<td>D. A.</td>
<td>1</td>
<td>1.700</td>
<td>2.54</td>
<td>1.2</td>
<td>1.3</td>
</tr>
<tr>
<td>M. B.</td>
<td>2</td>
<td>1.700</td>
<td>2.54</td>
<td>1.2</td>
<td>1.3</td>
</tr>
<tr>
<td>J. F.</td>
<td>3</td>
<td>1.700</td>
<td>2.54</td>
<td>1.2</td>
<td>1.3</td>
</tr>
<tr>
<td>T. W.</td>
<td>2</td>
<td>1.700</td>
<td>2.54</td>
<td>1.2</td>
<td>1.3</td>
</tr>
</tbody>
</table>

**DISCUSSION**

Although mechanisms are unclear, the negative effect of increased blood phenylalanine on the developing human brain during infancy and early childhood is clear. Early dietary restriction of phenylalanine prevents irreversible brain damage in children detected and treated for phenylalanine hydroxylase deficiency. The studies carried out here investigate whether elevated blood phenylalanine in the older child and young adults is associated with altered mental function, and if so, by what mechanism. Early studies by Wellenburger, Nadler and Hsia, and McKean demonstrated decreased levels of catecholamines in blood, urine, and autopsied brains of untreated patients with phenylketonuria. McKean also demonstrated improvements in visual evoked response in three severely retarded adult untreated patients with phenylketonuria. Phenylalanine was restricted when catecholamine precursors were administered without restricting phenylalanine in the diet. He postulated that although concentrations of tyrosine (1.2 x 10^-4 M) of brain in brains of untreated phenylalanine patients were well above the Kᵣ reported for tyrosine hydroxylase in mammalian brain tissue (5 x 10^-6 M), phenylalanine itself might inhibit tyrosine hydroxylase activity directly. This hypothesis was supported by in vitro observations of Undeutsch who found that phenylalanine was a competitive inhibitor of rat brain L-tyrosine hydroxylase with a Kᵣ 1.7 x 10^-3 M. Since the concentrations of phenylalanine found by McKean in his autopsy material were...
CONGRESSIONAL RECORD—SENATE
August 1, 1983

A averaged 8.4 x 10⁻⁴ M, such a mechanism of competitive inhibition was possible.

Phenylalanine may impair production of two psychoactiveamines, namely dopamine and serotonin. Curtius et al. described decreased serotonin and dopamine synthesis in patients with high plasma phenylalanine concentrations associated both with plasma phenylalanine hydroxylase deficiency and disorders in the tetrahydrobiopterin pathway. He also postulated a competitive inhibition of both tyrosine and tryptophan hydroxylase by high plasma phenylalanine at 1,500 and 600 μM concentrations, respectively. Katz et al. demonstrated the dissociation constant of 20 μM phenylalanine to tyrosine hydroxylase inhibition but the release of free tyrosine in rat brain striatal spontaneous preparations. Phenylalanine was only 2% as good a substrate for this enzyme as tyrosine. However, he suggested that phenylalanine could be a substrate for tyrosine hydroxylase in the presence of saturating concentrations of tetrahydrobiopterin, and could be a competitive inhibitor as well.

TABLE 1—EFFECTS OF DIETARY MANIPULATION OF PHENYLALANINE (PHE) ON CHOICE REACTION TIME AND GROoved pegboard ASSEMBLY

<table>
<thead>
<tr>
<th>Patient</th>
<th>Week</th>
<th>Plasma PHE (μM)</th>
<th>Choice reaction time (msec)</th>
<th>Grooved pegboard score (x10 per peg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>1</td>
<td>1.250</td>
<td>875</td>
<td>71</td>
</tr>
<tr>
<td>B</td>
<td>2</td>
<td>753</td>
<td>654</td>
<td>51</td>
</tr>
<tr>
<td>C</td>
<td>3</td>
<td>1231</td>
<td>855</td>
<td>74</td>
</tr>
<tr>
<td>D</td>
<td>4</td>
<td>1127</td>
<td>704</td>
<td>69</td>
</tr>
<tr>
<td>E</td>
<td>5</td>
<td>1127</td>
<td>704</td>
<td>69</td>
</tr>
<tr>
<td>F</td>
<td>6</td>
<td>753</td>
<td>654</td>
<td>51</td>
</tr>
<tr>
<td>G</td>
<td>7</td>
<td>1127</td>
<td>855</td>
<td>74</td>
</tr>
<tr>
<td>H</td>
<td>8</td>
<td>1127</td>
<td>855</td>
<td>74</td>
</tr>
<tr>
<td>I</td>
<td>9</td>
<td>1127</td>
<td>855</td>
<td>74</td>
</tr>
<tr>
<td>J</td>
<td>10</td>
<td>753</td>
<td>654</td>
<td>51</td>
</tr>
<tr>
<td>K</td>
<td>11</td>
<td>1127</td>
<td>855</td>
<td>74</td>
</tr>
<tr>
<td>L</td>
<td>12</td>
<td>1127</td>
<td>855</td>
<td>74</td>
</tr>
<tr>
<td>M</td>
<td>13</td>
<td>753</td>
<td>654</td>
<td>51</td>
</tr>
<tr>
<td>N</td>
<td>14</td>
<td>1127</td>
<td>855</td>
<td>74</td>
</tr>
<tr>
<td>O</td>
<td>15</td>
<td>753</td>
<td>654</td>
<td>51</td>
</tr>
<tr>
<td>P</td>
<td>16</td>
<td>1127</td>
<td>855</td>
<td>74</td>
</tr>
<tr>
<td>Q</td>
<td>17</td>
<td>753</td>
<td>654</td>
<td>51</td>
</tr>
<tr>
<td>R</td>
<td>18</td>
<td>1127</td>
<td>855</td>
<td>74</td>
</tr>
<tr>
<td>S</td>
<td>19</td>
<td>753</td>
<td>654</td>
<td>51</td>
</tr>
<tr>
<td>T</td>
<td>20</td>
<td>1127</td>
<td>855</td>
<td>74</td>
</tr>
<tr>
<td>U</td>
<td>21</td>
<td>753</td>
<td>654</td>
<td>51</td>
</tr>
<tr>
<td>V</td>
<td>22</td>
<td>1127</td>
<td>855</td>
<td>74</td>
</tr>
<tr>
<td>W</td>
<td>23</td>
<td>753</td>
<td>654</td>
<td>51</td>
</tr>
<tr>
<td>X</td>
<td>24</td>
<td>1127</td>
<td>855</td>
<td>74</td>
</tr>
<tr>
<td>Y</td>
<td>25</td>
<td>753</td>
<td>654</td>
<td>51</td>
</tr>
<tr>
<td>Z</td>
<td>26</td>
<td>1127</td>
<td>855</td>
<td>74</td>
</tr>
</tbody>
</table>

Note: The space between patients A and S and D and R indicates the patients on the high- and low-phenylalanine periods. The choice reaction time represents a mean of 20 trials. The pegboard results represent a mean of 10 trials.

As discussed, our results in vivo in treated PKU patients conform to the hypothesis that high plasma phenylalanine inhibits dopamine synthesis, since 24-hr urine dopamine excretion fell when plasma phenylalanine concentrations were maintained at an elevated concentration for days by dietary manipulation. A consistent relationship was not found between plasma phenylalanine and serotonin excretion in our study. Serotonin was inhibited to some extent, and this inconsistency may be related to the high “background noise” of excretion of stored serotonin during a 24-hr period.

The results from our experiments do support the hypothesis that brain function is altered by phenylalanine at the equilibrium concentrations achieved in the study. The battery of neuropsychological tests showed no differences in a motor test which required higher integrative function rather than fine motor coordination. This was consistent over the whole group, regardless of the age or condition of the patients. Although many test batteries have been used in other surveys, the computerized reaction time has not been reported. We are currently attempting to determine whether patient competency, age, attention, or other factors influence the neuropsychological response to increased plasma phenylalanine, and determine tests to maximize changes in accordance with patient competency.

We support a mechanism for prolonged phenylalanine inhibition by phenylalanine of biogenic amine synthesis. In our study when dopamine excretion fell, blood pressure and performance times were prolonged. Data from two patients deserve special attention: the patient with the lowest IQ (K.K.) who was not diagnosed until he was 21 years old. We demonstrated an expected biochemical change in urinary dopamine excretion when plasma phenylalanine concentrations were increased, but test scores on the Computerized Choice Reaction Time were unchanged. It is not surprising, in view of his overall low performance and achievement, that reaction times improved over the 3-wk period independent of the plasma phenylalanine, which suggested significant interest in evaluating the relationship to biochemical status. It is also likely that intellectual competency of a patient will control the amount of change produced by altered levels of both the drugs for which the individual’s competency, the less change might be expected. The one major outlier (M.D.) did not exhibit any significant changes in neuropsychological tests or in catecholamine excretion, despite attaining a concentration of 1,402 μM plasma phenylalanine, since he excreted barely measurable amounts of the derived organic acids. We can speculate that he has other “protective” functions. Possibly the mechanism involved transport of phenylalanine, across the blood brain barrier or an increased rate of phenylalanine incorporation into new protein synthesis. He could also have some “protective” variation in tyrosine hydroxylase which prevents inhibition by phenylalanine. He emphasizes the individuality of patients with phenylketonuria and the “sensitivity” of brain function to phenylalanine loading.

The impairment in choice reaction time and decrease in choice reaction time seen with increased plasma phenylalanine were reversible within the week periods studied.

We are currently examining a variety of repeatable neuropsychological and electrophysiological tests with which to assess performance in patients with varying competence, age, and condition.

These data support the hypothesis that high concentrations of phenylalanine reversibly affect neuropsychological performance, probably through some “protective” L-dihydroxyphenylalanine and dopamine production. The mechanisms may be through increased intracellular phenylalanine and competitive inhibition of brain tyrosine-3 hydroxylase. Whether intracellular concentrations of brain tyrosine are diminished is unknown. Although concentrations of blood phenylalanine attained in our studies did not inhibit renal tubular reabsorption of L-tyrosine, it should be noted that the transport Kₚ for phenylalanine, tyrosine, and tryptophan in brain and kidney differ. Additionally, the blood-brain barrier is saturated at normal plasma phenylalanine concentrations, whereas the renal tubular epithelium is not (16-18).

Since nearly 80% of all brain dopamine is found in the corpus striatum, decreases in dopamine synthesis or reuptake, may affect neurotransmitter functions that involve both nigrostriatal and corticostriatal pathways. This could explain the deterioration in response of our patients. We have computed the Computerized Choice Reaction Time Test, which required integration of stimuli and a motor response. We have recently observed a change in the mean power frequency of electrical impulses detected by EEG in a different group of patients with phenylketonuria who were studied under similar research protocols. This type of electrophysiological approach could assist in anatomical localization of changes in brain function.

(Report From Anti-Parkinsonism, Internal Medicine, February 1983)

ASPARTAME-INDUCED GRANULOMATOUS PANCREATITIS
(Nelson Lee Novick, M.D.)

The low-calorie artificial sweetener, aspartame, was developed by G.D. Searle & Co. (Skokie, Illinois), a synthetic racemic mixture of aspartic acid and the methyl ester of phenylalanine. It is currently used in many diet soda, 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 phenylketonuria), its potential for toxicity remains controversial. This report describes the first confirmed case of aspartame-induced granulomatous pancreatitis.

A 24-year-old otherwise healthy woman had numerous, bilateral, nonender, nodular lesions with her legs for which she was seen. The patient denied having used any oral, systemic or topical medications during the preceding 6 months and had also denied any history of recent infections or trauma, or any accompanying constitutional symptoms. For the previous 6 years, the patient had habitually used 1,000 to 1,300 mL (36 to 44 fl oz) daily of a popular sugar-containing diet soft drink. Approximately 10 weeks before her presentation for evaluation, she had switched to the aspartame-sweetened new aspartame-sweetened diet soda. She made no other changes in her diet. Two weeks before she presented, the patient first noted the onset of several nodular, deep seated lesions 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 in size 0.5 to 2 cm in diameter were palpable over the thighs and calves. The overlying skin appeared normal. The nodules were firm and in some instances formed large deep plaques that were freely mobile over the underlying fascial tissues. No adenopathy or other cutaneous or mucous membrane lesions were present. Physical examination of the general physical findings were normal.

Complete blood and differential count, erythrocyte sedimentation rate, serum electrolyte and amylase levels, and urinalysis were normal; liver function tests, serum protein electrophoresis, direct and indirect immunofluorescence studies, tuberculin skin test, and tests for antinuclear antibody and anti-streptolysin-O were negative. The patient refused a chest roentgenogram.

Histologically, a septate pseudocyst with lymphocytes and histiocytes infiltrated within the thickened fibrotic stroma. Many multinucleated histiocytic giant cells and a lymphomatoid histiocytic 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 residual. She was then advised to resume daily consumption of the suspected aspartame-sweetened diet drink; 10 days later, she again developed large, deep seated lesions on both legs, this time in greater number than before. With 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 capsules provided by G. D. Searle & Co. Ten days later, nodules reappeared on her legs. Withdrawal of aspartame resulted in spontaneous clearing of all lesions.

Wright observed 180 timesgath greater than sucrose and is metabolized primarily to aspartic acid, phenylalanine, and methanoic acid. Several previous reports of "dermal eruptions" and positive patch tests have been recorded in the literature. A species linking aspartame to any cutaneous eruptions. Several unconfirmed reports of "dermal eruptions" and positive patch tests have been received from the manufacturer according to Robert L. Albert, M.D., Director of Medical Communications, G. D. Searle & Co. In addition, the Study Drug Reaction Report System of the American Academy of Dermatology has received one unconfirmed report of a macular, erythematosus, contact pruritic eruption in a man who had consumed large amounts of an aspartame-sweetened diet cola. (Arne, et al., 1179221284, reported in March 1984 and transferred to the FDA 10 April 1984).

The precise classification and pathogenetic mechanism of the eruptions is not certain. Affected patients are clear. Absence of tenderness in the involved lesions, overlying skin changes, constitutional symptoms, and residual pigmentary changes are inconsistent with erythema nodosum, whereas the histopathologic finding of septic panniculitis favors that diagnosis.

The formation of toxic metabolites of aspartame, either during the drug's shelf-life or as metabolic byproducts, offers one possible explanation for the reaction seen in this patient. Boehm and Bada have recently reported that the heating of aspartame results in conversion of some of its amino acids to intermediates. Although they note that the possibility of consuming large amounts of these intermediates 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 present rather than nonexistent. Fortunately, in the present patient, mere discontinuation of the aspartame-containing beverage resulted in complete resolution of the condition without residua.

Mr. LAXALT (for himself and Mr. HECHT)
S. 1558. A bill to settle certain claims affecting the Pyramid Lake Paiute Indian Tribe of Nevada, and for other purposes; by unanimous consent jointly referred to the Committees on Indian Affairs, and Energy and Natural Resources, and Judiciary. Provided that Indian Affairs Committee report the measure, the Energy and Natural Resources Committee and Judiciary Committee have 13 days in which to report the measure or be automatically discharged.

PYRAMID LAKE PAIUTE AND TRUCKEE RIVER Setlement Act

Mr. LAXALT. Mr. President, I introduce with my distinguished colleague [Senator HECHT] a bill which settles a very longstanding water allocation dispute involving the waters of the Truckee and Carson Rivers. It settles the water rights for the Pyramid Lake Paiute Tribe, the cities of Reno and Sparks, NV, and the Newlands reclamation project. It is a compromise, an understanding, extremely pleased to be able to bring this bill to the Senate after many years of litigation and negotiation.

Specifically, the bill allocates among the water users certain waters of Lake Tahoe, Stamped Dam, and the Truckee River. The measure also incorporates, as a separate title, a water compact agreed to by the States of Nevada and California, assigning water rights to both the Truckee and Carson River. It establishes a fund from which the Pyramid Lake Tribe will provide for the propagation of the fishery at Pyramid Lake and other tribal enterprises. It directs the Secretary of the Interior to maintain and improve the fish habitat of the Truckee River for the cutthroat trout, a particularly impressive game fish, and for the other native fish, found nowhere else in the world. Finally, the bill provides for the dismissal of some six pending lawsuits.

Mr. President, I commend the parties who negotiated this agreement for putting aside longstanding disputes, for working in a statesmanlike atmosphere, and for their willingness to compromise in behalf of a final agreement. Special thanks must go to Mr. Bob Broadbent, Assistant Secretary for Water and Science at the Department of the Interior, for all the time and effort he put into this effort.

Mr. President, at Governor of Nevada, in 1972, I called an emergency session of the Nevada Legislature in an effort to resolve the disputes surrounding this resource. Unfortunately, those early efforts were unsuccessful but they made the introduction of this bill today even more gratifying.

I believe the bill fully addresses all the issues involved and allocates to all the parties fair and just water rights to the limited water resource. To the extent that minor disagreements may remain in portions of the bill, I call upon the negotiating parties to continue in their good faith, open-handed way to reach agreement on those matters and let us proceed as a united Nevada family behind this settlement.

Mr. President, the Senate will be called on to approve this settlement and to provide part of the wherewithal to make it work. I assure my colleagues that this bill is far and away preferable to the course of the last 60 years of litigation and conflict. If the measure can be improved, I stand ready to work diligently to that end, but hope that the same willingness of the Nevada negotiators will prevail in this body not to press narrow special interest but look rather to the total package to benefits to all. Mr. HECHT. Mr. President, today I am very pleased to be able to join my colleague, Senator LAXALT, in introducing a bill that will, at long last, settle some extremely nettlesome Indian water rights issues in northern Nevada. For more than half a century the waters that flow in the Truckee and Carson River Basins have been the source of litigation and conflict, as well as a source of life and economic progress.

The longstanding disputes surrounding the Newlands reclamation project, Pyramid Lake Paiute Indians, local farmers, and the growing cities of Reno and Sparks all rely on water provided by the project. After many years of legal battles, involved are now prepared to turn their backs on water for a better future. They urge to the Congress requests that will set in motion the process they have agreed upon to be water in a fair and noncontroversial manner.

It is important that Congress should and appropriate to move forward, to support and urge their support on the Lake Paiute and Truckee River Act, for the positive process of.

By Mr. DURENBERGER, for himself and Mr. HECHT, S. 1558. A bill to establish the Social Security Act method of payment of capital related costs under care program; to the Committee.

MEDICAL CAPITAL PAYMENT Act

Mr. DURENBERGER. Mr. President, today I am introducing an amend title 18 of the Social Security Act, to restructure payment to hospitals for capital costs under Medicare and Medicaid to more closely resemble this bill by my colleague from Indiana, Mr. QUAYLE, who is a leader in health system reform. I will also be joining him today in introducing a bill to redefine the Federal commitment to health planning is a bill consistent with the intent of S. 1558.

Mr. President, 2 years ago Congress set in place a new payment system for Medicare hospital services. This system, based on a payment for episode of illness for 458 diagnosis related groups, was designed to change the incentives for hospitals—encourage them to manage resources more efficiently. This new payment has had a tremendously positive effect on the health care system. But not all of Medicare's expenses for hospital services were included in the new methodology.

Excluded from the fixed-price was a service sufficient for hospital capital costs. We were reticent to commit Medicare to a capital policy because the data we had on hospital capital costs was clearly not as adequate as what we had on the operating expenses. But, an agenda for restructuring capital pay-