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(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 4(q) 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 5(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 the 100 million American consumers who are using this chemical sweetner under its better-known brand name of "Nutrasweet."

In 1984, Americans consumed over 7 million pounds of aspartame, which is equivalent 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 circumstances 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 GD 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 G.D. Searle Company, we have no basis for such reliance now.

Through our efforts, we have uncovered serious deficiencies in Searle's operations and practices which undermine the basis for reliance on Searle'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 sweetner 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 done on aspartame. One of the major questions 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 used to approve this chemical sweetner.

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 Act, by G.D. 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 the Act, and for concealing material facts and making false statements in reports of animal studies conducted to establish the safety of the drug Aldactone and the food additive Aspartame.

In 1980, the FDA established a public board of inquiry on aspartame. What did they conclude? "The Board has not been presented with 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 questioned the reliability of key 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 now under way 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 et cetera.

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 Pardridge 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—and who may be a sizable risk group as far as aspartame is concerned. Nearly 5 million Americans are PKU carriers.

Two researchers in Philadelphia, Profs. Gautieri and Mahalik, have done studies on mice which show that aspartame affected the vision of newborn mice whose mothers had been exposed to the chemical sweetner.

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 a report 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

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? Doesn't anyone in the agency know they are presently considering prosecuting that company for withholding information on adverse effects from another one of their drugs, Theo-24?

It is a sad fact 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 independent 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 individuals 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 label will also contain the maximum allowable daily intake established by the FDA. How many consumers even know that the FDA has attached such a limit to aspartame 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, so they decided 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 130 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 Secretary 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 want 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 labeling may provide added 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 Clinical Adverse Reaction 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 they 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 HEINZ 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 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 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 politics and ideology come before the public health.

I know there are career FDA personnel 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 interference to an art form. On the issue of aspartame, as on the issue of food dyes and infant formula, there are those 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 1985".

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 paragraph:

"(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 (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 (1)(C) shall be located in a 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 and legible type in contrast by typography, layout, and color with other printed matter on such label and labeling.".

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

"(u)(1) 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) specify the allowable daily intake of aspartame (in milligrams) for each kilogram of human body weight, as established by the Secretary; and

"(iii) bear the following statements: 'THIS PRODUCT CONTAINS ASPARTAME, AND IS NOT INTENDED FOR USE BY INFANTS 'PHENYLKETONURICS: CONTAINS PHENYLALANINE'; and

"(B) the manufacturer, packer, or distributor (including all retail establishments) thereof includes in all advertisements and other printed and descriptive matter issued 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 the information required by subparagraph (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)(iii) 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.".

(2) The first sentence of section 503(b)(2) of such Act is amended by striking out "and (1)," and inserting in lieu thereof "(1), and (u)(1)(B),".

MORATORIUM

SEC. 3. 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 (hereinafter referred to as the "Secretary") 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 have consumed aspartame, especially children who have consumed aspartame;

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

(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 telephone number of the telephone service established pursuant to subsection (c).

(c) The Secretary shall establish a telephone service for the reporting by individuals of 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 Geogory Gordon)

WASHINGTON (UPI).—Two pediatric and genetic researchers say many 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 manfacturer, one of the scientists, Dr. Louis Elsas of Emory University in Atlanta, also said he believes a key aspartame component can cause similar damage to infants if they ingest it in the six months following birth.

"There's no reason why the pregnant female should be taking aspartame," Elsas said, "and there's no reason why a child less than six months old should be taking aspartame. Period." He said the damage may not show up for years.

Meanwhile, lawyers for a 5-year-old boy who a research team said became "unconsolably 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, IL.

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

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

Officials of G.D. Searle, which last year sold more than $600 million in NutraSweet for diet soft drinks and other products, dismiss all the allegations and criticisms of aspartame. They assert the product has undergone the most extensive testing 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 Stegink, a professor of pediatrics and biochemistry at the University of Iowa who, with funding from Searle, performed some of the pivotal studies that supported FDA approval, said, "Am I concerned 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 Guall, vice president for nutrition and medical affairs of Searle's NutraSweet group, said aspartame "has no adverse effects on the behavior of children" with the exception of a select group who are alerted to the contents in warning labels.

Elsas, director of medical senetics at Emory, and Dr. Reuben Matalon, professor of pediatrics and senetics 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—phenylalinine—and that they consider it a hazard for fetuses and infants.

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

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

Elsas said that besides pregnant mothers, he is concerned about aspartame ingestion by newborn babies and young children who eat diet gelatins and puddings. He called Searle's studies on phenylalinine "a whitewash anecdote" that has received no scientific peer review. Elsas also noted that women who consume the substance while nursing could present a similar risk to their babies because the extent of phenylalinine in mother's milk has yet to be investigated.

Elsas and Matalon said consuming even moderate amounts of NutraSweet raises the concentration of phenylalinine in the blood. Matalon said he was "not too concerned" about older children consuming aspartame because the effects on them should be "reversible" through dietary changes.

Matalon, who began a study April 1 with a grant from the National Institutes of Health, said that one in 50 women are particularly sensitive to high phenylalinine consumption and if they ingest aspartame during pregnancy "it may cause birth defects" such as mild retardation. He said the defects would be a matter of concern because 8 to 10 million American women are believed to be sensitive to phenylalinine.

The affected women, Matalon said, are known as "carriers" of PKU—phenylketonuria—a disease resulting in reduced IQ's in babies. If not put on a special diet, PKU infants will suffer severe mental retardation as they grow, he said.

Although the FDA requires all aspartame products to carry a warning for PKU victims, no warnings is required for carriers, those who do not have the disease but have one PKU gene and are susceptible to phenylalinine.

The problem is complicated because carriers generally are not identified unless they have PKU offspring. "We don't know them and they don't know themselves," Matalon said.

Matalon, head of the PKU clinic at the University of Illinois, said he was concerned about studies showing that any rises in phenylalinine levels from aspartame consumption would still be within safe limits.

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

He said Searle did not adquately test the levels and effects of breakdown products—known as metabolites—of phenylalinine in the body.

Gaull and Stesink, however, defended Searle's testing and said it shows that even at "abuse levels"—extremely heavy consumption of aspartame—the phenylalinine levels in the blood do not rise significantly.

Gaull also said the levels of phenylalinine quickly drop. He said that while PKU carriers "have less ability to metabolize" than those with the disease, "it is not limiting in their abililty to fully metabolize" the substance.

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

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

Elsas said a woman who drinks one can of a soft drink sweetened with aspartame may experience a four-fold increase in her blood phenylalinine level. As a result, he said, the concentration found in the fetus can reach a level four times as high as the prospective mother's, because the chemical concentrates on the fetal side.

"Now the fetus's brain is growing, and that phenylalinine interferes at critical movements of brain cells, and that child could come out with severe mental retardation that's unrelated to anything you could measure after birth," Elsas said.

"I'm concerned that this could be a major health hazard that has been totally unexplored."

Gaull called Elsas's findings "incorrect," contending the fetus concentrates phenylalinine only at about 1.5 times the level in the mother.

Stegink called Elsas's projections of blood phenylalinine "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 Conners of D.C. Children's Hospital, who said "Stephen," a 5-year-old boy "repeatedly ran full force into the wall, knocking himself to the floor, crying, and repeating the performance until we was restrained," after consuming aspartame.

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

Asked about the suit, Gaull 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 allege his injuries, subject of one of numerous complaints about NutraSweet to the Centers for Disease Control, include psychotic neurosis and other neurologic and psychiatric disease and side effects, ranging from behavioral changes to nightmares.

Negligence charges, that the company failed to test aspartame, failed to warn of its possible dangers, and failed to report "adverse studies regarding the safety and efficacy of aspartame," also were lodged.

Conners, a specialist in hyperactivity and neurologic disorders in children, would not comment on his research concerning aspartame. But in testomony to Congress, he said, "we are inclined to believe that the clear results . . . conclude that aspartame (and-or its vehicle) are 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 the market without testing it on kids is a crime," Aaron Levine, a lawyer representing Stephen, said.

Although Searle officials maintain the product is safe, four 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, saying that their study using mice showed that offspring had trouble with their eyes.

Aspartame is sold as a sugar substitute under the trade name Equal and as an additive under the name Nutrasweet.

"We don't advocate stopping the use of aspartame, but we do think there is a need for more studies on its use by pregnant women," said Ronald F. Gautieri, professor of pharmacology at the Temple University School of Pharmacy.

Gautieri and Michael P. Mahalik, 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 neurosensory system," Gautieri said.

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

"Something could happen over the long term," Mahalik said. "We feel that byproducts of aspartame somehow affect the process of myelimization, the sheath that covers 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, dizziness, and insomnia, 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 3 grams for a person weighing 130 pounds. That is equivalent to six quarts of soda containing Nutrasweet or 150 packets 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 tests more than a decade ago on the product—marketed as NutraSweet by the G.D. Searle & Co.

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

They acknowledged they have commissioned eight new studies on the effects of the sweetener on humans, including whether it may be linked to intense headaches, seizures in children and adults and hyperactivity in children—all subjects of hundreds of consumer complaints filed with the Centers for Disease Control.

Dr. Gerald Gaull, vice president for nutrition and medical affairs of Searle's NutraSweet group, said the FDA had concluded the company's earlier studies were sound. He 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 lead time to correct it, take the product off the market, or whatever," Gaull said.

James Turner, a Washington consumer lawyer who has challenged the FDA's approval process that began in the early 1970s, asserted 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 lawsuit aimed at forcing the FDA to hold public hearings on the safety of aspartame.

Internal government memoranda obtained by the United Press International show that Commissioner Arthur Hull Hayes of the Food and Drug Administration overruled several agency scientists in approving 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's safety with "reasonable certainty of no harm," as required by FDA regulations, according to agency memos obtained by UPI intern Joshua Meyer.

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 consumers are to have complete confidence in the safety of aspartame."

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

The validity of G.D. Searle's tests on brain tumors in rats, challenged in 1975 for being sloppy and unscientific by an FDA task force and criticized again by the three scientists on the panel advising Hayes.

Why Hayes overruled the FDA-appointed Public Board of Inquiry, which opposed the approval of aspartame in 1980 on grounds the brain tumor studies were inadequate. Walle Nauta, chairman of the board of inquiry, has indicated the panel may have opposed the approval even more strongly had it known that G.D. Searle planned to widely market it in soft drinks. Nauta has said that

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 likelihood aspartame would be used in carbonated beverages was made clear to the board and that the dosages tested proved safety of aspartame as a food or beverage 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 based on a summary of a "Japanese study" submitted after the board's decision. The study, UPI learned, was conducted by the Ajinomoto Co., Inc., the Japanese licensee of Searle's aspartame patent. Turner 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 with the FDA regarding the effects of aspartame on brain chemistry, and Dr. William Pardridge of UCLA, who suggested women who consume aspartame may give birth to infants with lower I.Q. levels.

Whether officials of the Carter White House, Reagan White House or Reagan transition team discussed aspartame approval with FDA officials. Thies denied that Searle Chairman Donald Rumsfeld, a former top aide to President Gerald Ford, had any contact with White House or FDA officials about aspartame after joining the firm in 1977.

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

Gaull contended that aspartame, 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 aspartame 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—anxiety, seizures, extreme headaches, dizziness, severe depression and mood swings.

Other reactions consumers have blamed on the sweetener 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 aspartame products may have a "sensitive or allergic reaction, or idiosyncratic reaction" to aspartame.

In opposing aspartame approval, three of the six FDA scientists advising Hayes focused on G.D. Searle's brain tumor studies and concluded that aspartame "has not been shown to be safe and therefore may not be approved for marketing," the term head wrote in 1981.

One of the three, Dr. Satya Dubey, 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 considered serious."

Also objecting were Dr. Robert Condon and Dr. Douglas Park, the staff science adviser for the FDA Office of Health Affairs.

Gaull 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 Burros)

In 1984, G.D. Searle & Company of Skokie, Ill. sold $600 million worth of the artificial sweetener aspartame, on which it holds the exclusive United States patent. Produced under the trademark NutraSweet as a food additive and Equal as a table-top sweetener, aspartame is found in a wide variety of products—from puddings, bubble gum and breakfast cereals to some of the best known diet soft drinks marketed by Coca-Cola, Pepsi and Seven-Up.

Recently, however, aspartame 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 aspartame 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 aspartame in the past and is conducting new ones. "When any new product is marketed and attention is called to it, people tend to ascribe any adverse experience to that new product," said Dr. Frank M. Sturtevant, a pharmacologist who is director of 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."

Aspartame has been controversial since Searle first sought to market it in 1974. After considerable debate about its safety, the sweetener was approved by 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 aspartame. In accordance with Federal law, it is now listed on labels as an ingredient; no amount is specified. Dr. William Pardridge, an associate professor of medicine at the University of California at Los Angeles, said that too much of the artificial sweetener might cause subtle brain changes in young children. Dr. Richard J. Wurtman, director of the clinical research center at the Massachusetts Institute of Technology, said that consuming aspartame with carbohydrates might double aspartame's effect on the brain.

On June 17, Dr. Louis Elsas, 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 aspartame 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 aspartame. Dr. Sanford Miller, director of the F.D.A.'s Center for Food Safety and Applied Nutrition, says that the claims against aspartame are unfounded. And the American Diabetics Association has reaffirmed its faith in aspartame, saying that F.D.A.'s studies "appear sufficient to demonstrate its safety."

Since the marketing of aspartame 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 grand mal seizures (a type of epilepsy) after consuming aspartame. The centers called for studies to determine individual sensitivity to the sweetener.

On May 23, a $2 million lawsuit was filed against Searle in United States District Court in Washington on behalf of a 5-year-old boy in Olney, Md. The suit charged that consumption of NutraSweet caused irreversible brain damage, but it did not specify the amount consumed.

In granting approval of aspartame—which is 180 to 200 times sweeter than sugar with only one-tenth of the calories—Dr. Arthur Hull Hayes Jr., the F.D.A. Commissioner in 1981, overruled several of the agency's scientists and an independent public board of inquiry set up to evaluate the Searle studies of aspartame's effect on animals. These scientists said that the company's research did not adequately answer the safety questions about carcinogenicity. According to Congressional testimony from Dr. Alexander M. Schmidt, a former F.D.A. Commissioner, some of the experiments were "poorly conceived, carelessly executed or inaccurately analyzed or reported."

After a recent review of the Searle studies, Dr. M. Adrian Gross, a senior science adviser at the Environmental Protection Agency and a former pathologist at the F.D.A., wrote to the office of Senator Howard M. Metzenbaum, a member of the Committee on Labor and Human Resources. His letter said that despite the shortcomings of the experiments, "at least one of those studies has established beyond any reasonable doubt that aspartame is capable of inducing brain tumors in experimental animals."

In a telephone interview, Dr. Sturtevant asserted that some of the data presented to Dr. Gross for review were incorrect. The correct tabulations, he contended, were contained in a document that he wrote for the board of inquiry impaneled by the F.D.A. The document showed, he said, "that there is no statistically significant increase in brain tumors in experimental animals."

Aspartame-sweetened foods now carry a warning directed at phenylketonurics—people who are unable to metabolize phenylalanine, one of two amino acids that make up aspartame. 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. Elsas, about 2 percent of the population are carriers of the PKU gene and are unaware of the condition. He has expressed concern about the effects of phenylalanine 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. Elsas 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. Elsas's concern is based on two studies of the effects of phenylalanine on two groups of people—10 in each group ranging in age from 8 to 24—who have PKU but have developed normally. In these studies, the first of which was published in the Journal of Clinical Investigation in January, Dr. Elsas observed that the patient's reaction time was affected and the production of adrenalinlike chemicals in the brain was reduced.

The second study, just completed, confirms the first, he said, adding, "All of the brain changes were reversible within a three-week period, but it took longer for full mental functions to return."

Dr. Elsas said that anybody over the age of 6 months should consume "aspartame in moderation, and if they have symptoms, they should get their phenylalanine blood level checked."

Dr. Sturtevant says that Dr. Elsas "is scaring people unnecessarily." "It is not physically possible for an unknown PKU carrier to maintain a phenylalanine blood level in the unsafe range by means of consuming products containing NutraSweet," he said. "There is no experimental evidence to suggest a risk to the fetus." Searle has eight studies of its own 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 not to agree."

Dr. Wurtman's own animal studies show that "you double the effect of the phenylalanine in the brain when you have aspartame and carbohydrates together, and no one knows what a safe amount is," he said. "There are several groups of people who might be especially susceptible to high doses. These include people who are taking drugs that act on the brain like antihypertensives, people with a history of seizures, young people 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 allowable daily limit 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 subjects in controlled 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 in general," Dr. Sturtevant said, "but we do object to F.D.A. singling out aspartame, because there is no scientific evidence suggesting that it need be."

"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 will 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 Zinman)

Aspartame, the low-calorie sugar substitute marketed as NutraSweet, is one of the amazing success stories of the 1980s. In the four years since the artificial sweetener found its way onto grocery store shelves, 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 sugarfree gum. Last year, its manufacturer, G.D. Searle & Co., reported sales soaring to $535 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 fetuses and newborn of genetically susceptible women, according to studies done by Dr. Louis Elsas of Emory University in Atlanta.

"The big unanswered question," said Elsas, "is if pregnant women taking artificial sweeteners can elevate their blood level of phenylalanine to concentrations that adversely affect their fetuses. Is the damage from phenylalanine produced by a threshold effect? Or do little bits of the 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 our nation to be exposed to in large quantity."

Searle said reports about potential adverse effects of aspartame on pregnant women and infants were "misleading and do 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 fetuses. But it says there is no cause for alarm because current consumption amounts are not even close to a point where they might pose a problem. Most important, it says that studies on pregnant animals show that even at "abuse levels," aspartame presents no hazard to the fetus.

Nonetheless, Elsas, director of medical genetics at the Atlanta school, said he is concerned, in part, because the sweetener's sale has been so massive and there are still some unknowns about the product. What worries him—and this is not based on any study but his own personal thoughts as a scientist—is the notion that aspartame's effects could be slow and subtle. They could take a generation or more to uncover.

"It's not going to be so overt an explosion," Elsas 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 behaviorial 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. Elsas acknowledges there has been no 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, Elsas is focusing on patients with a rare genetic disorder called phenylketonuria or PKU. These individuals cannot metabolize foods containing phenylalanine. As a result, the chemical concentrates in their brains. This can cause retardation in fetuses and newborns who have this genetic disorder. Many states require tests to discover PKU babies who must then be kept on special diets.

Elsas is also concerned about parents of these children, who are normal but may carry one of the two genes needed to have PKU. "There is a genetically susceptible subpopulation of well over a million women whose fetuses may be at risk if they take indiscriminate amounts of phenylalanine," says Elsas. They, too, he says, may also have an impaired ability to metabolize phenylalanine.

Since it is not always possible to detect these single gene carriers before a 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 PKU carriers.

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

Pregnant women. If blood phenylalanine rises to a level high enough to cause problems, the child's brain development could be affected.

Children under 6 months. A high level of blood phenylalanine can produce 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 Elsas' argument, says Daniel Azarnoff, president of research and development for Searle, is that he has no idea what is a dangerous level of phenylalanine concentration. Moreover, he said, Elsas' concern that people may be getting toxic amounts of phenylalanine flies 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 in a day. The average 12 oz. can of diet soda contains 170 milligrms aspartame, Searle says.

But Dr. William Patridge of the University of California at Los Angeles says the FDA has underestimated consumption of aspartame. Patridge could not be reached for comment. However, the magazine Common Cause said Patridge wrote to the FDA in 1983 citing figures showing how children eating aspartame-sweetened foods all day could be on their way to consuming the maximum amounts the FDA uses for its safety assessment.

Searle says that tests it sponsored show no harmful effects have been seen even at levels of 200 milligrams—four 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.

Elsas 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, says some foods intensify the effects of phenylalanine. "If one drinks 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. Reuven Matalon of the University of Illinois has started a study funded by the National Institutes of Health 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 in any difficulty. 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.

Commercial.

STEVE WILSON. 7-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.

Commercial.

STEVE WILSON. Powered drink mixes have it too: like Kool-Aid, Wylers fruit drinks, chocolate drink mixes. It's in Jello, it's in all kinds of sugar-free products. You can buy it in little packets under 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 $80 a pound made more than half-a-billion 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 too sure if I'm drinking the right thing.

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

ROBERT SHAPIRO. 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 matters.

STEVE WILSON. He's not talking about Joyce Moscado. She's one of thousands of people who have complained about serious side effects, one of those who believes when all the facts are known.

JOYCE MOSCADO. 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's 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 this.

STEVE WILSON. But it's not just all 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's not 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.

DR. WOODROW MONTE. Yes, I'm saying that I believe that with all my heart.

ROD LEONARD. Seizures, headaches; among women its the early onset of menapause, serious depression. People say they can't understand what's happening to them except that they keep getting more and more depressed until they want to kill themselves.

JOYCE MOSCATO. 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 side effects. Like headaches—some mild, some unbearably painful; stomach problems; various allergic reactions, even seizures. But her complaints and thousands of others like them are "anecdotal", scientifically unsubstantiated stories that don't worry Robert Shapiro.

ROBERT SHAPIRO. No, I don't find it scary because I'm aware of what the evidence is 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 to meet demand. But on Capitol Hill just last month, FDA chairman Frank Young admitted to a Senate Committee that while 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 women, a number of whom have reported the same problem Joyce Moscato had for the many months she consumed NutraSweet—her menstrual periods simply stopped.

JOYCE MOSCATO. 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—aspartame—can be trouble.

ROBERT WILSON. 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 Wurtman 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 near Phoenix, Dr. Woodrow Monte says the big danger is from a substance left in our bodies when NutraSweet breaks down—methyl alcohol.

DR. WOODROW MONTE. If I could get a public hearing, if I could have a Congressional hearing, if I could have a hearing before the Food and Drug Administration which they have been stopping, trying to stop, I could prove easily, show easily, 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 our grocery shelves.

STEVE WILSON. Politics?

ROB LEONARD. I would call it politics.

STEVE WILSON. Steve Wilson (reporting).

JOYCE MOSCATO. 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 Moscato and many others like her say the harm—in her case depression and menstrual problems—is linked to NutraSweet: The only artificial sweetner 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'd done?

In fact the soft drink makers were so dissatisfied with what they believed was the lack of evidence NutraSweet was safe, they prepared a formal, 31-page protest—scientific chapter and verse raising serious questions. McQuate says now it was just designed to "spark discussion in the industry"—and it never WAS submitted to the FDA. He says secret tests his members paid for later answered all their questions. But others believe those who want to use 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. ADRIAN GROSS. They lied and they didn't submit the real nature of their observations because had they done that it is more than 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 discovering NutraSweet is toxic—a danger to our health.

Dr. GROSS. What Searle did, they took great pains to camouflage these shortcomings of the study. As I say filter and just present to the FDA what they wished the FDA to know and they did other terrible things for instance animals would develop tumors 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. It's apparently a recording keeping error.

The president of the NutraSweet Group at Searle says Dr. Gross and his task force are just wrong. But looking at other experiments on laboratory animals and other independent evidence, a scientific board of inquiry has also raised serious safety questions. So have other respected scientists. But the FDA approved it. So it's safe?

ROBERT SHAPIRO. It has been established by the people who are charged by law with 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 appointed commissioner of the FDA who now works

as senior medical advisor to the Searle public relations firm.

STEVE WILSON. Dr. 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 scientists still have 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 consuming it. About 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.

WILSON. But since we reported more about all the questions still unanswered in regard to the safety of NutraSweet, there have been some new developments.

Sen. HOWARD METZENBAUM. There's enough reason to be suspicious.

WILSON. Senator Metzenbaum says he's seen enough now to have real suspicions and he has directed the General Accounting Office to investigate. Specifically, his letter to the Comptroller General asks for an investigation of NutraSweet test results, what really happened during the formal FDA approval process, and to what extent was the White House involved in the approval of the product.

Sen. METZENBAUM. 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.

WILSON. By the way, another Metzenbaum letter, this one also signed by 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. So we'll know how 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 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 by pregnant women to birth 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 the safety concerns. The mother of a little boy is seeking $2 million from Searle claiming the child has suffered serious and permanent neurologic and psychiatric injury as a result of NutraSweet.

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

DEPARTMENT OF HEALTH,
EDUCATION, AND WELFARE,
Rockville, MD, January 10, 1977.

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 Grand Jury investigation into apparent violations of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. 331(e), and the False Reports to the Government Act, 18 U.S.C. 1001, by G.D. 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 the Act, 21 U.S.C. 355(i), and for concealing material facts and making false statements in reports of animal studies conducted to establish the safety of the drug Aldactone and the food additive Aspartame. Concealing material facts relative to the Aldactone 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).

I—THE STATUTORY/REGULATION SCHEME

A. *Investigational New Drugs.* The Food and Drug Administration has responsibility for assuring that drugs marketed in this country are safe for their intended uses and are accurately labeled. The Federal Food, Drug, and Cosmetic Act prohibits the marketing of any "new drug" in interstate commerce unless a new drug application (NDA) filed pursuant to 21 U.S.C. 355 containing substantial evidence of the safety and effectiveness of the drug has been approved by the FDA. Before an NDA is approved for any particular use of a drug, that drug may lawfully be used only for investigational tests, first in animals and thereafter in humans. This testing is permitted only in accordance with 21 U.S.C. 355(i) 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 by regulation new reporting requirements to assure that information about significant hazards, contraindications, side effects and adverse or unusual reactions associated with the investigational use of new drugs is disseminated rapidly. These regulations specify the form, content, and timeliness for the submission of such reports. Failure to comply with such requirements is prohibited under the Act, 21 U.S.C. 331(e).

A major purpose of the investigational 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 investigational exemption for a new drug (IND), which contains adequate information about preclinical (animal) investigations of the drug and any studies and other experience from which the sponsor has concluded that it is reasonably safe to initiate clinical (human) testing. A careful evaluation of the animal toxicity and pharmacological studies provides some assurance of the expected effects when the drug is administered to humans. If the data submitted in an IND justify the conclusion that the drug may safely be tested in humans, the FDA permits the sponsor to ship the drug to investigators. It is not uncommon, as is the case with Aldactone, that a drug 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 and/or effective by adequate and well-controlled clinical investigations, the regulations require the sponsor to closely monitor the progress of pre-marketing investigations. The regulations provide that progress reports of such investigations be submitted to the FDA at reasonable intervals, not to exceed one year. 21 CFR 312.1(a)(5). In addition, the regulations require that a sponsor shall "promptly investigate" and report to the FDA "any findings associated with use of a drug that may suggest significant hazards, contraindications, side effects or precautions pertinent to the safety of the drug". If such a finding is "alarming", 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 identify 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 submits proposed labeling for FDA approval at the time of initial marketing and thereafter to reflect new information resulting from its use.

B. *Food Additive Petitions.* The Act also provides for FDA approval of food additives. Approval of an additive is codified in a regulation prescribing 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 contains reports of studies establishing the safety of the additive. As with investigational drugs, the FDA does not perform safety tests on food additives; 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 in human food of chemicals without reasonable proof that these chemicals will not adversely affect man, either immediately, over a life-time or in the next generation.

C. *Monitoring Test Integrity.* Reports of studies submitted to the FDA as part of INDs or NDAs and food additive petitions must be complete, balanced and truthful 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 additive petitions. The reliability of the testing is normally checked by FDA review of the sponsor's reports of the underlying raw data. If necessary, the FDA may review the underlying raw data itself in the possession of the sponsor. The FDA may also select manufacturers or preclinical testing laboratories for routine surveillance inspections. When there is reason to believe that there are irregularities or discrepancies in the conduct of tests or the reporting of test data, the FDA may conduct a compliance inspection in order to evaluate the testing facilities, practices, and record keeping procedures to resolve any apparent discrepancy between the raw data and the report or to determine the truthfulness of data presented in the report.

Recent FDA experiences have identified significant problems in the manner in which

many preclinical laboratory studies are performed. Deficiencies in the quality and integrity of reported data have prompted the Commissioner of Food and Drugs to establish a bioresearch monitoring program, and to propose the promulgation of good laboratory practices regulations which will delineate proper procedures for conducting preclinical laboratory studies. Congress has increased FDA's budget for the fiscal year 1977 by $16.6 million specifically 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 data submitted in support of a large-selling anti-infective drug Flagyl. FDA review of the data was initiated because independent investigators had reported evidence that Flagyl was a carcinogen (an agent capable of producing cancer). Searle's own long-term toxicity study, submitted in 1970, had not concluded that Flagyl was a carcinogen. In April 1974, Searle submitted more studies on the issue of Flagyl's carcinogenicity and also submitted corrections to the data from its original long-term study. These corrected data raised further questions, resulting in FDA inspections initiated at Searle beginning in May 1974 and proceeding intermittently until the first of July 1975. These initial inspections failed to satisfactorily resolve questions of discrepancies and inadequacies in Searle preclinical testing and reporting of test results.

On July 23, 1975, 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 to him. Inspections were conducted at Searle and at three independent laboratories, Hazelton 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 25 separate studies on seven different products, totaling approximately 500 pages plus 15,000 exhibits. Based on this information, data originally submitted by Searle, the scientific evaluation of animal tissue slides and other raw 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. I am enclosing a copy of the transcript 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 reply to two memoranda by FDA pathologist M. Adrain Gross, a Task Force consultant who had reviewed much of the Searle 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, pursuant to 21 U.S.C. 335, 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 at the request of Searle until October 20. An amended Notice of Hearing, dated September 15, 1976, was issued to correct an inadvertent omission from the earlier notice and to verify October 20 as the hearing date. A copy of the Notice of Hearing was forwarded to the Consumer Affairs Section and to Assistant United States Attorney Fred Branding of your office.

At the October hearing, Searle submitted lengthy written replies to the 305 Notice. Copies of these are enclosed. In addition, Searle reiterated a request for the Agency's investigational file covering the apparent violations which were the subject of the hearing. This request was denied, as was an earlier Searle request for "discovery" which referenced the Jencks Act, the Federal Rules of Criminal Procedure and *Brady* v. *Maryland*. Copies of correspondence 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 Practices and Procedures 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 20 and April 8, 1976.

IV—FAILURE TO SUBMIT SAFETY DATA ON ALDACTONE

A. *The Drug.* Aldactone is a new drug marketed by Searle pursunat 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 a marked increase 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 develop data for the use of Aldactone in massive doses in the treatment of myasthenia gravis (serious muscular paralysis). In 1969, Searle amended its IND to cover testing of Aldactone for severe congestive heart failure at dosage levels much higher than those approved in the NDA.

B. *The MBR ("Mauro") Report.* In 1970 Searle designed two 78-week toxicity 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 by Hazelton Laboratories Vienna, Virginia; the second was performed by Searle in its own laboratories. The study conducted at Searle began in August 1970 and rates were sacrificed and necropsied (autopsied) during February and March 1972.

In November 1972, consistent with prior practices, Searle submitted the slides of sections of organ tissues of the rats from the study it had performed to an outside consultant pathologist for examination. The slides were examined by Dr. Jacqueline Mauro, a board certified pathologist, at Microscopy for Biological Research, Ltd. Alabany, New York (MBR). The report of her "readings"—the MBR report—was submitted to Searle on March 21, 1973. In a letter to MBR dated June 1, 1973, Dr. ——— acknowledged receipt of 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 tumors (adenomas) of the testes and liver. She also noted a significant number of thyroid tumors and non-tumorous thyroid lesions which she called "adenomatous goiter". Dr. Mauro recommended that these findings be measured for statistical significance. A statistical review of pathology findings is important since an absolute cause-and-effect relationship usually cannot be established in experimental biology. Therefore, an association between an agent and an effect is determined as a probability. If the incidence of a toxic response, such as a lesion, is found among animals treated with the agent under study to a significant degree greater than in animals not exposed to the agent, the established practice is to regard the agent as responsible for that toxic reaction. Where, as 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.

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 ———, some of the liver tissue slides were reviewed by a then recently hired Searle pathologist Dr. Rudolf Stejskal. He concluded that Dr. Mauro's analyses were "incorrect" and thus "unreliable" since certain slides which she had diagnosed as revealing benign tumors (adenomas) were, in his opinion, lesser lesions (hyperplasia) and that other slides that she had diagnosed as being benign tumors were in fact malignant tumors. On the basis of Dr. Stejskal's limited review of the liver slides, Searle did not submit the MPR report to the FDA.

In April or May 1974, Dr. Stejskal reviewed more 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 extreme, he also found that her characterization of the thyroid lesions was too restrained. In various interviews with FDA personnel and in written submissions to the Agency, Dr. Stejskal has never commented on the MBR diagnosis of testicular tumors which, according to Searle's Mathematics-Statistics Department, were, as Dr. Mauro suggested, drug-related and statistically significant.

In August 1974—sixteen months after it received the MBR report—Searle sent the same slides examined by Dr. Mauro, 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 tests, as did the MBR report, but most important to Searle, not tumors of the liver. The concern at Searle over the liver pathology of the MBR report must have been particularly acute; undoubtedly the firm recognized that this information would have to be included in the Aldactone labeling, with a probable decrease in sales. The production of tumors in the testes and thyroid of the test animals, at statistically significant levels, must also have been unwelcome news but, insofar as Aldactone is felt to be active 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 disagree with Searle's discountfng the tumors of endocrine glands. However, the liver findings were more alarming because there was no theory upon which they could be discounted. Thus, unlike the MBR report, the Williган report was submitted to FDA promptly upon receipt at Searle.

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

D. *Violation of 21 U.S.C. 331(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 report these findings to the Agency "immediately" pursuant to 21 CFR 312.1(a)(6). If one were to conclude that these findings were not "alarming", they unquestionably were of the type that suggested significant hazards, contraindications, 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)(6). Even if one took the view most favorable to Searle that these findings were neither alarming nor suggestive of significant precautions, they were significant and thus were required to be submitted to the Agency at least within one year of receipt by Searle. 21 CFR 312.1(a)(5).

The primary purpose of the requirement that test findings be submitted to the FDA promptly is to permit the agency to assess for itself whether the investigational exemption 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 filing expert criticism along with or following the reported study. In short, under any view of the facts, Searle was not entitled to discount the entire MBR report on the basis of Dr. Stejskal's review of some of the slides for only one of the tissue types. Moreover, to give great weight to Dr. Stejskal's analyses is to conclude that in May 1974 Searle had reason to believe, based upon his subsequent review of more of the slides, that administration of Aldactone in the study had caused even a greater number of thyroid tumors than reported by Dr. Mauro.

21 U.S.C. 331(e) prohibits the failure to make any report required by regulations under the IND provisions of the Act. 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.

E. *Labeling of Aldacone: Violation of 21 U.S.C. 331(a).* When in March 1975 the FDA received from Searle the report of Dr. Williган which confirmed the statistically significant incidences of thyroid and testes tumors reported to Searle two years earlier by Dr. Mauro, the Agency became concerned that the labeling for Aldactone was inadequate. On June 10, 1975, it convened the Cardio-Renal Advisory Committee, a group of non-FDA 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. Williган 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 (tumors) of the thyroid gland, testes and possibly breasts and liver. They certainly warrant a warning to the medical profession and a curtailment in the recommendations for use." A copy of the Committee's report is enclosed. Aldactone has now been relabled consistent with the Committee's views.

In view of the similar statistically significant thyroid and testes tumor findings in the MBR and Williган reports, and the findings of liver lesions by both pathologists, 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 interestate 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 potential disclosed by the MBR report. As you can see, the Advisory Committee's conclusion also supports FDA's view that the findings in the MBR report were "alarming".

V—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 dialogue between Searle and the FDA invovles complex issues. The following portion of this letter, as well as parallel dicussions of apparent violations involving Aspartame, must necessarily be specific in order to comprehensively and accurately reflect the context of this case. Regrettably, the length of this letter bespeaks our 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 critique of the Searle submission, comment upon the main recurrent 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 lesions of the liver cells can be subclassified according to the particular nature of the proliferation. A diffuse increase in hepatocellular elements is usually termed "diffuse hyperplasia", or mostly, "hyperplasia". When such proliferation is not diffuse but rather a spotty distribution throughout the tissues with islands or zones of proliferating cells, the term "nodular hyperplasia" is utilized. When such nodules of hyperplasia contain cells which the pathologist deems as having been permanently altered or "transformed" into neoplastic or tumor cells, the term "neoplastic nodule" is applied; this is taken to represent a group of proliferating cells which have "crossed the boundary" on the way to becoming a liver tumor. Various pathologists utilize other recognized terms such as "adenoma" to signify a benign liver tumor. A tissue slide characterized by one pathologist as an "adenoma" would also meet the criteria for "neoplastic nodule". The most extreme form of cellular proliferative stage, the malignant tumor variety, is commonly termed "hepatocellular carcinoma".

What is important, however, is that all these various terms represent a series of characterizations of stages of the proliferative process which can be viewed as a continuum. It is entirely possible that two pathologists may examine a given lesion and characterize it somewhat differently. This does not necessarily mean that one is "right" and the other is "wrong". Therefore, one must examine characterizations of liver alterations in a set of animals and ask whether a pathogenic process, such as a poliferative change, is evident.

Accordingly, it is proper to focus on the similarities among pathologists rather than emphasize the differences among them. When Dr. Mauro refers to "adenomas" and Drs. Stejskal and Williган reference "nodular hyperplasia" and Dr. Robert Squire, a cancer expert at the National Institutes of Health who reviewed some of the liver slides at the request of the FDA Task Force, talks about "neoplastic nodule", each one is calling attention to a proliferative change in the liver. One may grade such a proliferation along the continuum or by different phrases from another one, but basically they imply the same problem. The proclivity of experts to use different terms in liver pathology was recently demonstrated at a workshop at the National Cancer Institute published in "Cancer Research", Vol. 35, Nov. 1975.

Searle also alleges "extreme variation and contraindications in diagnosis" between Drs. Stejskal and Williган on the one hand and Dr. Mauro on the other. FDA believes that the differences in diagnoses were not extreme and reflect merely the continuum of diagnostic evaluations of the same class that are well recognized in the field of pathology.

2. Searle argues that the IND regulations presuppose that the data which must be submitted must be accurate and reliable. 305 Reply, pages 10, 15. 21 CFR 312.1(a)(6) 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 undermined. By contrast, the requirement to submit progress reports within a year does state they be "acurate", 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 clinical investigations but only reports of testing on humans and of those animal tests conducted before human testing is initiated. In addition, Searle contends that the IND regulations are unreasonably ambiguous. These arguments are without merit.

In the interest of protecting patients taking experimental drugs, the statute authorizes regulations requiring the reporting of animal tests before tests on humans are

allowed. However, the regulations also permit so-called Phase I and Phase II clinical (human) trials to proceed before all the preclincial (animal) work is concluded. Accordingly, it is not uncommon that long-term animal studies, such as the 78-week Aldactone study, are undertaken concurrently with initial human testing. Item 10a of the form for the "Notice of Claimed Investigational Exemption for New Drugs" notes that these first two phases "may overlap and, when indicated, may require additional animal data before these phases may be completed or Phase III may be undertaken". 21 CFR 312.1(a)(2). The regulations therefore contemplate additional animal studies uring testing in humans.

Searle also seems to rely on the phrase "such investigational use" in subsection 3 of the IND statutory provision, arguing that this refers to human test results only. This is incorrect. The results 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 safety and effectiveness 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 the subsequent new drug application will be approved or denied. 21 U.S.C. 355(b) provides that NDAs must contain full reports of "investigations" 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 include 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 substantial evidence is defined in the Act, 21 U.S.C. 355(d), as evidence consisting of "adequate and well controlled investigations, including 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 "investigators" in the regulations necessarily means investigators involved in clinical investigation. This is not true and the regulations do not use that phraseology. 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 can be no question that the readings of a pathologist of 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 used much higher dose levels than would be the usual human daily dose and thus the tumor findings were neither alarming nor even significant in terms of safety. 305 Reply, page 1. Most investigational toxicity studies in animals involve massive doses of the drug being tested.

The reason for the use of large doses of a drug in test animals is that such tests are designed to identify toxic reactions in those portions of the user population who are most susceptible to the drug. Accordingly, to accentuate the effects and maximize 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 human dose is an almost meaningless comparative measure. In animal studies, the question is what reactions will be 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 referenced by Searle. The animal study in question was designed specifically to establish human use for the treatment of severe congestive heart failure at dosage levels four to six times larger than the human dose for which the drug is marketed. Moreover, while comparing the animal test dose to the dosage for human use, Searle fails to acknowledge that at the time of this animal study, it was testing Aldactone in 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 Hazelton which was completed on Aldactone at approximately the same time as Searle's own study. The Hazelton study, however, does not balance the Searle study since, among other reasons, the amount of Aldactone received by the highest dosed animals in the Hazelton study was an amount between the low and mid-doses for the Searle test animals.

4. Searle contends that the MBR report was incomplete. However, the report, as received by Searle and ultimately submitted to the Agency, is in precisely the same form as other pathology reports by Dr. Mauro that Searle unhesitatingly submitted to the FDA. In fact, Searle itself was capable of "completing" the study by adding to Dr. Mauro's pathology examination the statistical analysis it had performed in August 1973 and the gross observations from the necropsy. Searle chose not to do so.

5. Searle also insists that Dr. Willigan's diagnosis were more unfavorable to the drug and thus Searle cannot be accused of hiding "damaging" information 305 Reply, 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 incidence of liver tumors, which was Searle's greatest concern with the MBR report and was the reason why Dr. Stejskal was asked in August 1973 to initially 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 from the high dose 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 tends to obscure the point: The IND regulations are designed to funnel data to the FDA before it is reevaluated, whether the result be to confirm or undermine the initial conclusions.

In a similar vein, Searle also discounts the admittedly unfavorable thyroid and testes diagnosis on the ground that these are endocrine glands and were the "expected" site of drug-related reactions since Aldactone is felt to be an endocrine-active drug. This "target-organ" argument is unsupportable.

Even assuming that a drug acts where it is "expected" to act, the nature of the reaction is not predictable. That is why animal toxicity 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; but it is one of the most serious kinds of toxic reactions that are seen. Moreover, animal toxicity studies are regulatory submitted to the FDA which reveal little or no significant toxic reactions, even in those organs theorized or "expected" as being the "target organs". Because every agent known to cause tumors in men also cause tumors in animals, tumors in animals constitute alarming implications for human toxic reactions.

FDA has required Searle and other manufacturers of oral contraceptives, which are endocrine-active compounds, to conduct long-term animal toxicity tests. 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 of which have basically the same therapeutic action, some have caused tumors in test animals, others have not. Obviously, therefore, "target-organ" tumors are not predictive.

6. Searle justifies its failure to submit the MBR report based in part on Dr. Mauro's use of terminology in evaluating the thyroid slides, arguing that her choice of words bespeaks Dr. Mauro's unreliability as a pathologist. Dr. Stejskal has also stated that her terminology indicated 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 tomor. Searle never notified Dr. Mauro or MBR of any questions about Dr. Mauro's report, including its terminology. On June 1, 1973, —— wrote to MBR stating that Searle had received the MBR report and that it "looks just fine". Searle now argues 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 probably resulting from a metabolic imbalance. Thus, while Dr. Stejskal suggests Dr. Mauro's analyses were overly general and thus unreliable, her slide readings appear to have pin-pointed a significant distinction is thyroid proliferative lesions.

VI—SEARLE REPLY TO ALLEGATION OF MISBRANDING

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 22-28. In fact, the Willigan report was submitted to FDA in March 1975; the Agency reviewed it and convened the Cardio-Renal Advisory Committee in June, which issued its conclusion in September. Also in September, Searle submitted proposed new labeling and thereafter a proposed "Dear Doctor" letter, both of which were inadequate. By comparison, Searle's first proposed amended labeling for Aldactone came not immediately upon their receipt of the Willigan preliminary report in December 1974, nor upon the submission to the Agency of the final report in March 1975 but rather after submission in July 1975 of the MBR report and, notably, after creation of FDA's investigatory Task Force.

The burden to provide adequate labeling is placed by the law squarely on the shoulders of the manufacturer-proponent 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 documented in that report was confirmed by Dr. Stejskal.

FDA, of course, did not have an opportunity to take action on Aldactone 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 diagnosis alone, suggesting that it would not. To the contrary, with respect to thyroid and testes, the findings of the MBR and Willigan reports were consistent; the Willigan report identifying even more tumors than the suppressed report. If Searle had used the MBR report as received in March 1973, the labeling for Aldactone would have contained a statement—as it does today—about possible dose-related thyroid, testicular and liver consequences. Contrary to the assertion in the 305 Reply, page 26, the FDA does not acknowledge that the MBR report is not the basis of the labeling change. The MBR report supports the labeling reference to liver lesions and, together with the Willigan report, substantiate the label warnings with respect to testicular and thyroid tumors.

VII—SUMMARY

In sum, Searle received in March 1973 a pathology report which contained damaging information about its largest selling drug; information that was confirmed two months later by its own Mathematics-Statistics Department. A few of the slides which concerned Searle most, those concerning the liver, were received by an in-house pathologist who took exception with some of the consultant pathologist's diagnoses. On that basis, the entire report, later confirmed by another pathologist to be substantially correct in its results, if not in its slide-by-slide analyses, was withheld from the FDA by Searle for over two years.

The legal as well as the practical answer to Searle's after-the-fact justifications for not submitting the MBR report is contained in Searle's own 305 reply. "The quality of the decision made must be judged by information available at the time, not by subsequent development". Nowhere in its submissions to the FDA does Searle explain why it initially reviewed only the MBR liver diagnoses. Unquestionably, it was the report by its Mathematics-Statistics Department that, just as Dr. Mauro had suggested, there *was* a drug-related increase in liver tumors. This was the motivation for the withholding of the MBR report, the use of a second outside pathologist and the prompt submission of his findings even though they confirmed drug-related tumors in two other organs.

VIII—CONCEALING MATERIAL FACTS AND MAKING FALSE STATEMENTS IN STUDIES SUBMITTED IN SUPPORT OF SEARLE'S FOOD ADDITIVE PETITION FOR ASPARTAME

A. *The Product.* Aspartame is the trade name of a sweetening ingredient for food manufactured by Searle. Because Aspartame is a food additive, it may be marketed only upon FDA approval of a petition establishing its safety, which approval is codified as a regulation published in the Federal Register.

Aspartame is a synthetic product based upon two amino acides, l-aspartic acid and l-phenylalanine. It is intensely sweet, about 180 times as sweet as sugar, but is metabolized in the human body as a protein unlike sugar which is metabolized as a carbohydrate. Because of its great sweetness, Aspartame used in place of sugar would provide only approximately 1/180th of the calories of a quantity of sugar yielding equivalent sweetness. The potential commercial value of Aspartame is enormous. Searle has built a manufacturing plant solely for the purpose of producing Aspartame.

B. *Status of Aspartame.* In the Federal Register of March 5, 1973 (38 F.R. 5921), FDA gave notice that a petition had been filed by Searle proposing the issuance of a regulation to provide for the safe use of Aspartame in foods as a nutritive substance with sweetness and flavor enhancing properties. In the Federal Register of July 16, 1974 (39 F.R. 27137) the Commissioner concluded that the evaluation of the data in the petition, which included approximately 150 studies and other relevant material, justified amending the food additive regulations to provide for the same use of Aspartame under specified conditions.

In response to this publication, FDA received objections to the regulation from members of the public and two requests for a hearing, provided under § 409 of the act, 21 U.S.C. .348. Issues concerning the safety of Aspartame were identified by the objectors in the first part of 1975, and it was agreed that there would be an administrative hearing, called a Board of Inquiry. Based upon the Commissioner's conclusion in July 1975 that the integrity of certain animal studies conducted by Searle was questionable, and in conjunction with the establishment of the investigatory Task Force, including auditing of certain animal studies relating to Aspartame, the FDA stayed the effectiveness of the food additive regulation in a notice published in the federal Register of December 5, 1973 (40 F.R. 56907).

After the issuance of the Task Force report in March 1976, FDA began to consider methods by which certain of the studies submitted by Searle would be authenticated at Searle's expense, by a non-government 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 1969, Searle officials decided it was "essential" to obtain the opinion of Dr. Harry A. Waisman about the differences and similarities in the side effects of Aspartame as compared with those of phenylalanine. Dr. Waisman was a leading researcher associated with the University of Wisconsin Regional Primate Center and had published extensively on the toxicity of phenylalanine. Dr. Waisman's published works establish that phenylalanine is capable of producing brain damage in Rhesus monkeys. The Aspartame study was initiated on January 15, 1970 and terminated on or about April 25, 1971. Searle submitted its report to the FDA on October 10, 1972. A copy of the report of the study, excluding appendix tables, is enclosed. Unfortunately, during the course of this study, in March 1971, Dr. Waisman died.

In this study, seven new-born Rhesus 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 their actions, was the responsibility of Mr. Gunther Sheffler, a laboratory technician with a bachelors' degree who was selected by Dr. Waisman. The tables of the laboratory test results, feeding schedules and the like which constitute the summary of raw data of the Searle report were prepared primarily by Mr. Sheffler. Presumably, Mr. Sheffler selected the new-borns for inclusion in the study; his selection was consistent with criteria which may have been set by Dr. Waisman. Although Dr. Waisman had access to and was undoubtedly familiar with the monkey colony at the Primate Center, in all likelihood he rarely if ever directly participated in the conduct of the study. However, he and Searle were responsible for the study design.

The Aspartame monkey study did not have "untreated concurrent controls", that there was no parallel group of new-born monkeys identified and monitored for comparative purposes which were not fed Aspartame. According to a Searle protest drafted 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 365 days as planned; and administration of Aspartame for two others was ceased on March 31, 1971, after approximately 200 days. No behavioral or learning tests were performed. Only the one monkey who had died during the test was necropsied and subject to post-mortem work-up.

B. *Conflict Between the Study and Searle's Report of the Study.* Before commenting briefly on the specific falsifications listed in the 305 Notice and to clarify why this study came to the attention of the Agency, you should note the very great literary license Searle officials took in drafting its report. Searle has repeatedly contended that Dr. Waisman 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 some retrospective structure to the work done by Dr. Waisman and that because of Dr. Waisman's death, the documents reflecting the daily conduct of the study were in chaos.

In essence, Searle now insists that the Waisman study was uncontrolled, and refers to it conspicuously as a "pilot" experiment; its shortcomings are itemized, all but enthusiastically.

Yet, while containing a few carefully couched disclaimers, the report of this toxicity study was submitted to the Agency just like any other of the 150 studies; it bears the authorship of the persons responsible for the study, namely ——— and Waisman, 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. Waisman was the expert in the field and his name would carry great weight. The report to FDA is drafted in a manner which covers up the admitted inadequacy of the design, control and documentation of the study. However, when Searle is accused or representing this study for far more than it was, it denies almost all knowledge of 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. Waisman did not have to, nor did he, follow any suggestions by Searle or its employees" is difficult to understand. Searle documents in the possession of the FDA establish that in November 1969, Searle sought to involve Dr. Waisman in a study of Aspartame 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 noteworthy that in a memorandum of a September 4, 1970, conversation with Dr. Waisman, ——— reports that he suggested to Dr. Waisman that two animals be placed on the study at lower dosage levels within the next few days. This is exactly what happened. Searle asserts that the behavioral testing was never anticipated on this "pilot" study but rather on a subsequent study which was being planned by an associate of Dr. Waisman. 305 Reply, page 36. However, various Searle documents obtained by the Task Force investigators, written both during the subsequent to the monkey study, establish beyond any question 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 suitable for the study. (2) The report states that acceptable historical and contemporary data on untreated control monkeys were available, thus diminishing the necessity for concurrent control groups of monkeys. (3) The report falsely states that animals were not available for purchase and sacrifice (necropsy) at the termination of the administration of the test compound, as originally planned, because of personnel shortages. This statement also gives the misleading impression that the animals were 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 necropsy data on one non-surviving monkey was lost to Searle due to "similar" reasons, namely, confusion and personnel shortages 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 is based, in part, upon a January 19, 1972, memorandum written by ——— reflecting the reservations of Mr. Scheffler about the suitability and documentation of monkeys for the study. ——— notes of a conversation with Mr. Scheffler state: "no extensive records on individual monkeys." In addition, on June 23, 1971 ——— was made 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 test monkeys were in any way significant to the study. Nevertheless, the report states that only "infant Rhesus monkeys (Macaca mulatta) from full term, normal pregnancies" were used. In fact, the mothers were laboratory monkeys and had been on other tests. The impact of the mother's health, nutrition, reproductive history, etc., would be significant were the mother to pass to her off-spring some deficiency, some altered type or rate of metabolism due to another chemical she had been exposed to previously, any or all of which might affect the infant monkey and its reaction to Aspartame. Further, these effects may be completely unnoticed by laboratory technicians.

2. The second specific allegation in the 305 Notice was that the report falsely states that a concurrent comparison control group (monkeys in the study that were monitored but not exposed to Aspartame) was unnecessary because acceptable historical and contemporary data on untreated monkeys were available. Searle admits that there were no existing post-mortem data from other monkeys in the colony but notes that there was such ante-mortem (pre-sacrifice) data for other monkeys. This seems to 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 untreated 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 the failure to sacrifice and necropsy the monkeys "at the termination of administration of the test compound", namely, shortage of personnel and lack of supervision following Dr. Waisman's death, are untrue.

Searle's reply to these allegations focuses upon the fact that the monkeys were taken off Aspartame feeding allegedly without notice to Searle, and were thus "unavailable" for sacrifice "at the point of termination". The documents available to the FDA do not now establish that Searle had knowledge of the termination dates of administration of Aspartame (March 31, April 4 and April 25, 1971) until mid-June 1971. But the fact that the availability of these monkeys for purchase and sacrifice did not immediately coincide 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 administration of Aspartame 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 more likely based on the fact that 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 were not attributable to Aspartame. Searle did not want to take this chance. But Searle also did not want to admit the real reason for its indifference. The same apprehension of a "can of worms" is 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. FDA investigation did not reveal that things were plunged into chaos by Dr. Waisman's death as Searle has repeatedly suggested. 305 Reply, page 55. Treatment was continued for two to five weeks after Waisman's death on monkeys M-79 and M-14, completing their one year treatment as scheduled. During interviews in February of this year by FDA Task Force members, Mr. Schaffler stated that there were plenty of personnel on hand when Dr. Waisman dies and that when the new laboratory director took over, he dismissed a number of employees because they were not needed.

Searle asserts that it makes no difference what reason is given for certain events 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 work-up was 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 concurred. 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 submitted to FDA states that necropsy data on the one non-surviving monkey, which received high doses of Aspartame and died after 300 days, were lost to Searle due to Dr. Waisman's death.

In fact, the data were available from the Primate Center and were obtained by the FDA Task Force investigators. 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 dated 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 information to determine that a report had been generated.

Searle now admits that it does not know what happened to the "necropsy data"; nevertheless, the report gives an answer as if the facts were known, namely, that the data were lost in the confusion after Dr. Waisman's death. This is an excuse based on no information, rather than the truth.

The 46-week toxicity study in the hamster

A. *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 terminated prematurely, after 46 weeks of treatment, due to an unexpectedly high mortality in both control and treated animals ascribed to a disease known as "wet tail" (severe diarrhea). Searle submitted its report to the Agency on December 8, 1972.

B. *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 in the study was collected for hematology testing and for blood chemistry at the scheduled 26-week interval. Samples were drawn and six different kinds of tests were conducted. Searle technicians appear to have experienced methodology problems with one of these, the test for serum glucose (blood sugar). Searle did not correct the problem with the glucose testing until approximately twelve weeks later. By that time, however, approximately 30 percent of the previously tested hamsters 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 values of these new animals were reported by Searle as being those of tests run at 26 weeks on blood samples from the original animals, which had since died. Thus, the glucose values represented for one set of animals at a different time.

C. *Searle's Inadequate Explanation.* Searle admits the fact that its report contains this false information, but argues that this did not result from willful conduct or any intentional act. Moreover, 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 under §1001 can be sustained only upon a showing of the materiality of a 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-

formation need not be shown. Nor must the Government prove that the person. knew that a statement was false; rather, a reckless disregard for the truth or evidence of a conscious purpose to avoid learning the truth will establish the requisite culpability. Here, documents in the possession of FDA establish at least that ——— knew of the need for a second glucose test and knew that hamsters were dying and substitutes were needed.

Searle suggests that these data were gathered and prepared by technicians reporting to Mr. Martinez, and that neither ——— nor ——— was aware of the existence of the problem concerning these data until they received FDA's Notice of Hearing. However, ——— admits in his 305 reply that he was involved in resolving the serum glucose problems, although he claims that he did not review this matter when drafting the report. ——— The substitute animals were identified as substitutes on the raw data sheets which, we believe, ——— as the authors of this study, were obliged to review and may in fact have reviewed in order to attest to the integrity and accuracy of the report. 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 concealing of the fact that glucose values for one animal were substituted for those of another. While the question of glucose levels seems to have been non-controversial in this study, the failure of the Searle report to simply note the substitution of test results could be attributed to the fact that at the time of the substitution the animals were contracting a disease and the study was accordingly 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 unexpected 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 ultimate safety of Aspartame. However, as Searle points out, numerous studies have been conducted and submitted to the Agency in support of the safety of this sweetening agent and thus, arguably, even a wholly fabricated study might not qualify as material in the sense of being a "but for" or independently sufficient basis for a decision.

We believe that the law permits prosecution 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 Aspartame studies for review upon the consultation with toxicologists in the FDA Bureau of Foods. Both this study and the monkey study met the criteria for selection of studies established by the Task Force.

Searle argues that the original records relating to the glucose substitutions are in existence and only their destruction or modification would be consistent with an intentional falsification in the final report. This, of course, is not a necessary prerequisite to a finding of intent; if it were, every defendant in every prosecution involving a crime of intent would argue, perversely, that his failure to destroy evidence of his culpability established his lack of intent.

One final note on both Aspartame studies. In considering the extent to which the reports 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, Drs. ———, entitled "Food and Drug Sweetener Strategy." In that memorandum, Searle commits itself to obtaining favorable review by FDA personnel by seeking to develop in them a "subconscious spirit of participation" in the Searle studies. What FDA needs instead, and must have to evaluate products, are adequate and controlled studies, supported by the raw data, and reported accurately and in a timely fashion. The assumption 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 technician or draftsman 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 importance of safety data on Aspartame, we note that if ultimately approved for marketing, this sweetening agent can reasonably be expected to be part of the daily diet of every American.

IX—INDIVIDUALS WHO APPEAR TO BE RESPONSIBLE FOR THE VIOLATIONS CHARGED IN FDA'S NOTICE OF HEARING

A principal purpose for convening an investigatory Grand Jury would be to identify those persons responsible for any violations of the law investigated by the Agency. The persons named in the FDA 305 Notice were identified on the basis of information known to or obtained by the Agency, but without the benefit of compaulsory process. All Searle officers, employees, and former employees, were interviewed by Task Force investigators in the presence of Searle counsel or monitors.

A. *Overall Corporate Organization.* The organization charts and similar information available to the FDA reveal the following major outlines of responsibility within the Searle Company.

In 1971, T.B. Carney, Sr., was the Vice-President of Searle Laboratories for Research, Development and Control. ——— was then the Vice-President for research and Development, under Mr. Carney. The research and development group consisted of six branches; Dr. ——— was the Director of Biology and was superior to ——— head of the pathology/toxicology section. In February 1972, ——— replaced Mr. Carney as the head of the RD&C and ——— became the Director for R&D. Dr. Francis J. Saunders replaced ——— as the head of Biology. The Director of Chemistry, a branch on equal level with Biology was Dr. Paul D. Klimstra. In April 1972, ——— became President of Searle Laboratores, a division of G.D. Searle and Company ——— was designated as Vice-President for Research and Development.

In July 1973, at about the time that Searle was beginning to deal with the MBR report, the research and development group was reorganized and Dr. Klimstra was made the Director, Pre-Clinical Research and Development, operating directly under ——— was made the Director of Pathology/Toxicology and reported directly to Dr. Klimstra. Dr. Saunders was given the title of Director, Research Liaison at the same level as Dr. Klimstra, but outside the reporting chain of ——— Klimstra ——— In May 1974, ——— was given the title of Vice-President for Scientific Affairs although he continued to report ——— and remained the immediate superior of Dr. Klimstra who in thru remained the immediate superior of ———. No other structural changs were made, and these designations remained the same through 1975.

B. *Responsibility for Failure to Submit the MBR Report.* When the MBR report was received at Searle in March 1973 it would have been within the immediate domain of ——— Director of the Pathology/Toxicology Department and his superior Dr. Saunders. From about the time that Searle began its Mathematics/Statistical evaluation of the report (August 1973) until its submission, it would have remained within the jurisdiction of ———, who was then reporting to Dr. Klimstra. Dr. Stejskal, who originally reviewed the MBR tissue slide evaluations, was ultimately responsible to ——— through his immediate superior in the Pathology Laboratory. ——— functioned as head of the Toxicology Laboratory also reporting to ———.

1. *Evidence of Responsibility Developed by the Task Force.* The Agency has evidence that it was ——— who originally requested Dr. Stejskal to review the MBR liver slide analyses in July or early August 1973, and it was either ——— who requested further review of liver, thyroid, and testes slides in February 1974, which Dr. Stejskal performed in April or May of that year. ——— were fully aware of Dr. Mauro's slide readings by September 1974. According to Dr. Dutt, the then head of Searle's Mathematics-Statistics Department, it was ——— who requested him to perform a statistical analysis on the MBR report in August 1973.

The FDA has no direct knowledge of the extent, if any, of personal knowledge or participation of Drs. Saunders, Klimstra, ——— in the decision to withhold the MBR report from the FDA. In view of the damaging effect of the liver findings, as well as the testes and thyroid tumors, and given the commercial importance of Aldactone in Searle's marketing line, it is difficult to believe that ——— did not advise his superiors Drs. Saunders (and thereafter Klimstra) ——— of the MBR report. Restrictive labeling for Aldactone, as in fact eventually resulted, would certainly have rendered these individuals accountable to their corporate superiors for any decline in sales of the drug. The evidence in our investigatory files leads us to the conclusion that ——— were in a position to know of the report and certainly had authority to decide not to submit it; we have however no direct evidence of their actual knowledge or participation in that decision.

2. *The 305 Replies.* In the Searle 305 reply, we are told that ——— ——— promptly advised Dr. Klimstra of the findings of Dr. Willigan. This does not necessarily mean that Dr. Klimstra was advised of the earlier Mauro findings, but it does raise the provocative 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 certainly appropriate for Grand Jury inquiry. ——— however, insists upon defending the institutional action of G.D. Searle and Company by arguing, at page 2 of his reply, that the MBR document was "preliminary and incomplete" since it "did not contain antemortem data, text or results of statistical analyses that are necessary for a final, complete and full report of the study".

This characterization of Dr. Mauro's pathology findings is nonsense. A pathologist's role in a study is to report examination of post-mortem lesions only; the contract pathologist never generates antemortem data or statistical analyses; the MBR report did not contain these and neither did the report from Dr. Willigan which waw submitted to

FDA. When a firm, such as Searle, receives a report from an outside pathologist, the firm itself provides the antemortem data and conducts statistical analysis. ——— further asserts that the MBR report lacks materiality. This is not true. The document was capable of and has influenced the Agency in its decision with respect to the labeling of Aldactone and in limiting human investigational studies.

——— also claims ignorance of the MBR report until June 1975. He admits that he was aware that Dr. Willigan had diagnosed the slides from the 78-week study, but insists that he was unaware of any prior involvement in the study by Dr. Mauro ——— asserts that ——— would not be expected to advise him of the results of pathology analysis on a rountine basis. With certain minor exceptions, the response of ——— parallels that of ———. Apparently, neither ——— was required to authorize the re-evaluation of the slides for this study by Dr. Willigan.

——— strongly asserts the corporate theory that the findings of Dr. Mauro were "so in error and so unreliable that the entire report was deemed untrustworthy"; that it was not a relevant part of the Searle Aldactone study, and in substance that it never was required to be submitted to the FDA. ——— assumes full responsibility for concluding that the MBR report was "fundamentally incapable of serving as a valid, defensible representation of the tumor data from the rat study involved". ——— claims he did not discuss the document with his superiors. Nevertheless, at page 11 of his reply, ——— states in the third person that "internal Searle records show that ——— regularly and candidly informed his superiors at G.D. Searle and Company of the toxicologic status of company products, including recommendations relating to procedures and testing programs". While he claims he discounted in toto the MBR findings, ——— also states, at page 6 of his reply, that after Dr. Willigan's findings were reported he became concerned about human test subjects.

Accordingly, he discussed with Dr. Bernard M. Wagner, Professor of Pathology at Columbia University in New York the "question of tumors in thyroid, testes and liver."

C. *Responsibility for False Statements in Reports of Studies on Aspartame.* The 305 Notice with respect to Aspartame named. They were the authors of the reports that the FDA believes contain false information and/or omitted material facts. In our view, they are responsible for failing to report the substituted glucose values in the hamster study and are responsible for any false statements or concealed facts resulting from having drafted Dr. Waisman's "pilot" monkey study so that it would appear to be a valid, thorough scientific study.

X—GRAND JURY INVESTIGATION INTO OTHER POSSIBLE OFFENSES

The FDA Task Force investigated 25 studies involving seven products. Its report lists numerous incidences of poor laboratory practices, resulting in discrepancies and inadequacies in data in one or more of the investigational studies in support of each product. Some of these poor laboratory practices were characterized by the Task Force as "deliberate decisions" seemingly calculated by Searle to minimize discovery of toxicity and/or to allay FDA concern. The Task Force report also discusses examples of poor laboratory practices in animal studies submitted in support of the drug Flagyl, which were the subject of special attention at the Congressional hearings.

The Task Force report and each report of investigation for the 25 target studies have been reviewed by my office. Because the law does not make poor animal laboratory practices a punishable offense, much of the questionable conduct by Searle may not fairly be subject to a characterization, under the Act or Title 18, that will with reasonable probability establish a violation before a Judge or jury. For this reason, 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 was that the FDA recommend to 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, but which were now included in the 305 Notice primarily on the ground that the notice is designed to give persons an opportunity to respond to apparent violations of law 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 audited.

Four decisions or courses of conduct by Searle were specifically considered by our office for Grand Jury review. These are set forth in the memoranda from Arthur Levine to me dated August 6 and 30, 1976, copies of which have previously been provided to the Consumer Affairs Section and to Mr. Branding. Two of these appeal to us to be reasonably fruitful areas for Grand Jury investigation.

1. The Willigan report submitted to the Agency in March 1975 contained a computer print-out summary table of tumor findings which did not include four malignant mammary tumors in treated females which had in fact been diagnosed by Dr. Willigan and reported in his raw data. Searle explained the omission as the inadvertent error of a programmer in the Mathematics-Statistics Department who listed the mammary tumors as benign, although the raw data sheets she was using as a reference 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. Stejskal, the pathologist responsible for the study in Pathology/Toxicology Department. Thus the Searle report, based on the pathology examination of Dr. Willigan contains, in part, false data.

All of the individuals involved in this episode have been interviewed by the FDA, and state, in essence, that they simply made an error. The FDA investigatory file does not now contain information which would establish a willfully false submission under Title 18. However, 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 explanation is to believe that 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 raw data for the 80-week rat study on Flagyl, 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, and that he may well have known that the study contained inaccuracies or at least that the data was incomplete and could not be confirmed, but did not reveal these facts in the 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 Aldactone 78-week rat study. However, 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 Aldactone, were not subsequently remedied. Moreover, Searle's theoretically conceivable but in fact inapplicable arguments over the specific facts pertaining to Aldactone demonstrate a willingness to rationalize in order to avoid admitting any error, even an error which turns out to benefit their product or further corroborates their procedures. See August 30 memo., para. 2.

XI—PROCEDURE

The issues discussed in this transmittal letter as well as those raised by the Task Force report are based upon reports and supportive documents which amount 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 areas of potential criminal liability. It may not be necessary that each document be reviewed by your office in order to develop these matters for further investigation by the Grand Jury. However, Mr. Levine of our office (8-443-4360) and Mr. Carlton 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 particular documents in support of each charge in the Task Force report, the August memoranda, 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, where the pertinent 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 investigatory 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, his assistance would be extremely valuable. Moreover, such a procedure would eliminate any question, whether or not meritorious, that documents obtained by the Grand Jury may be shared only within the Department of Justice and not with the Food and Drug Administration.

As I mentioned previously, Mr. Fred Branding of your office has been kept fully 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

conversations with Mr. Levine over the last months, he has expressed a strong interest in this case and we would warmly 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 the Consumer Affairs Section 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 apprised of your review of this transmittal and we and the Consumer Affairs Section will appreciate being kept advised of any developments. Mr. Sharp has already identified many potential witnesses to support the pathology and toxicology principles that underlie the charges in the 305 Notice and the Task Force report.

We look forward to hearing from you following your initial review of these materials, and discussing with you a schedule for future action on this important and precedent-setting case.

Very truly yours,

RICHARD A. MERRILL,
CHIEF COUNSEL,
Food and Drug Administration.

STATEMENT FROM ADRIAN GROSS, FORMER FDA INVESTIGATOR AND SCIENTIST

In the pages to follow here I am presenting a number of comments which you may find informative in any future efforts to curtail exposure to aspartame; those comments are centered around three main topics:

(a) The studies carried out by G.D. Searle & Co. to establish the safety of aspartame are to a large extent unreliable; this is a conclusion that would follow the FDA's own extensive investigations into the acceptability of experimental studies conducted by and for Searle; see top of page 2 here.

(b) Their serious shortcomings notwithstanding, at least one of those studies has established beyond any reasonable doubt that aspartame is capable of inducing brain tumors in experimental animals and that this predisposition of it is of extremely high significance; see bottom of page 16 here.

(c) I would view the Acceptable Daily Intake (ADI) set by the FDA for aspartame (50 mgm/kgm body weight/day) as totally unwarranted and extremely high in that it can be associated with completely unacceptable risks as far as the induction of such tumors is concerned; see top of page 19 here.

(a) The reliability of studies with experimental animals carried out by and for G.D. Searle & Co.

Beginning at the top of the next page there are given a number of quotes from the Final Report of the FDA's Task Force dated March the 24th, 1976, which had investigated the G.D. Searle & Co.:

It is important to realize that this particular document, although signed by the members of a special Task Force appointed by FDA Commissioner Alexander M. Schmidt, in fact represents an FDA *institutional* view. At the Joint Hearings held by the 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 of the United States Senate (both Subcommittees then chaired by Sen. Edward M. Kennedy of Massachusetts) on April 8 and 9 and July 10, 1976, Commissioner Schmidt said (page 3 of the record of that hearing): "today I would like to report to you the *final results of the Food and Drug Administration's (FDA) detailed investigation* of animal studies performed by Searle. . . ." (emphasis added).

(Page 4 of the record of that hearing):

"Senator KENNEDY. Let me ask you this. These are the conclusions of the (Task Force appointed to that) study. Do you agree with those conclusions?"

"Dr. SCHMIDT. Yes, I do."

"Senator KENNEDY. Yes, you do. Is this the first time, to your knowledge, that such a problem has been uncovered of this magnitude by the Food and Drug Administration?"

"Dr. SCHMIDT. It is certainly the first time that such an extensive and detailed examination of this kind has taken place. We have never before conducted such an examination as we did at Searle."

"From time to time, we have been aware of isolated problems, but we were not aware of the extent of the problem in one pharmaceutical house . . ."

I have reproduced here that particular exchange verbatim since in recent years and apparently at the urging of G.D. Searle & Co., Dr. Schmidt has found it expedient to distance himself from the conclusions in that particular report which he had accepted and represented as his own and as those of the agency he headed at the time (see the copy of the affidavit that he swore to on February the 4th, 1983, and the one sworn to by me subsequent to that date, both of which I had given to you).

To quote then from that particular report of the Task Force identified at the top of this page, much of which was also quoted by Commissioner Schmidt himself at the Senate subcommittee hearings mentioned above here:

(Pages 1 and 2 there):

"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 the) GD Searle Company, we have no basis for such reliance now."

"Reliance on a sponsor is justified when FDA has reasonable assurance that the sponsor will: (1) inform the agency of *all* material results, observations, and conclusions of an experiment, (2) report fully and completely *all* of the conditions and circumstances under which an experiment was conducted, and (3) submit its reports to the FDA in a timely fashion so that measures to protect the public health and safety can be taken promptly when warranted. Through our efforts, we have uncovered serious deficiencies in Searle's operations and practices which undermine the basis for reliance on Searle's integrity in conducting high quality animal research to accurately determine or characterize the toxic potential of its products."

"Searle has not met the above criteria on a number of occasions and in a number of ways. We have noted that Searle has not submitted *all* the facts of experiments to FDA, retaining unto itself the unpermitted option of filtering, interpreting, and not submitting information which we would consider material to the safety evaluation of the product. Some of our findings suggest an attitude of disregard for FDA's mission of protection of the public health by selectively reporting the results of studies in a manner which allays the concerns of questions of an FDA reviewer. Finally, we have found instances of irrelevant or unproductive animal research where experiments have been poorly conceived, carelessly executed, or inaccurately analyzed or reported."

"While a single discrepancy, error, or inconsistency in any given study may not be significant in and of itself, the cumulative findings of problems within and across the studies we investigated reveal a pattern of conduct which compromises the scientific integrity of the studies. We have attempted to analyze and characterize the problems and to determine why they are so pervasive in the studies we investigated."

"Unreliability in Searle's animal research does not imply, however, that its animal studies have provided no useful information on the safety of its products. Poorly controlled experiments containing random errors blur the differences between treated and control animals and increase the difficulty of discriminating between the two populations to detect a product induced effect. A positive finding of toxicity in the test animals in a poorly controlled study provides a reasonable lower bound on the true toxicity of the substance. The agency must be free to conclude that the results from such a study, while admittedly imprecise as to incidence or severity of the untoward effect, cannot be overlooked in arriving at a decision concerning the toxic potential of the product."

In addition to these general comments which are meant to apply to any study with experimental animals conducted by G.D. Searle & Co., that same Task Force Report contains additional references to problems encountered for individual studies carried out by G.D. Searle & Co. *specifically* for aspartame:

(Page 25, paragraph 3): "In the Aspartame (DKP) 115 week rat study, the submission (to the FDA) states that twelve lots of the test compound, di ketopiperazine, a metabolite of Aspartame, were manufactured by a Searle chemist and used in the study. However, the investigators found that some of the batch numbers were merely different drum numbers and actually only seven batches were made. Searle personnel informed the investigators that records of manufacture and assay of two batches could not be located."

(Page 26, last paragraph): "Significant deviations from the protocols of several studies were noted which may have compromised the value of these studies, including the excision of tissue masses (which are likely to represent mammary tumors) from live animals during the course of a study. There is no indication that these deviations were reviewed or approved by the Protocol Design Committee; hence they may represent serious unauthorized changes in the experiments. . . . In at least one study, the Aspartame 52 weeks monkey study, the protocol was written *after* the study had been initiated."

(Page 31, paragraph 2): "In addition, we found evidence that, as far back as 1969, top management (at G.D. Searle & Co.) concerned itself with the animal studies to determine the safety of its artificial sweetener, Aspartame. An internal strategy memorandum from the Regulatory Affairs Department to top management advises management of tactics designed to produce favorable action by FDA officials and concludes that Searle must get Aspartame into commercial channels as soon as possible to minimize the incentives of other firms to develop other sweeteners." (actually, the contents of that "strategy" memorandum originating at G.D. Searle & Co. are a veritable eye-opener; I would strongly urge you to actually read it in its entirety if you wish to obtain a whiff of exactly how G.D. Searle & Co. understand to approach their responsibility in the area of assuring the safety of their own products. I was given to understand that the memorandum to which reference is made here was included in the material sent to your Office by the Food and Drug Administration.)

(Page 32, last paragraph): ". . . there was little continuity of technicians that performed antemortem observations on animals from one observation period to another. In addition to a lack of continuity, there was a lack of adequate supervision and training of the technicians in all phases of the studies, which is documented in the . . . Aspartame (DKP) 115 week rat, and Aspartame 42 week hamster investigation reports. . . ."

(Page 33, paragraph 2): "In each study investigated, poor practices, inaccuracies, and discrepancies were noted in the antemortem phases which could compromise the study."

(Page 33, paragraph 3): "Protocols normally specified age and sex requirements of animals. In general, these criteria were followed. However, exceptions were found in the 106 week dog 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.

(Page 34, paragraph 2): "At Hazleton Laboratories rats and mice were said to be held for a two week period before they are entered into a study. In the 104 week rat studies of Aldactone and Aspartame there were deviations from this holding period when rats were introduced into the studies after only five or six days respectively."

(Page 36, paragraph 3): "One of the most elementary considerations in a toxicological study is to assure that the test animals receive the active ingredient under test. When the substance to be tested is incorporated into the feed, its homogeneity and concentration in the diet mix should be determined prior to the start of the study. Random samples from freshly mixed batches should be analyzed periodically during the course of the study to ensure that the proper mixing and formulating 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 purity of the test substance, he replied that Hazleton's policy is that the purity of the test material is assumed to be 100% unless notified to the contrary by the client. Tests for (chemical) stability, (biologic) potency and homogeneity of the treatment feed mixture are performed only at the client's specific request; Searle never made such a request of Hazleton in its protocols. Further, Dr. Reno stated that Seale never requested that the basal feed be assayed for residual drugs, pesticides and other contaminants. Hazleton did not conduct such tests for Searle nor were any reserve samples of the treatment mixtures maintained for studies performed for Searle."

"It was noted in the investigation of the Aspartame (DKP) 115 week rat study that drums of the product for each dosage level were identified with color coded labels to match the color of 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 several labels pasted over one another and that the labels underneath the current labels were of various colors. If the current label were to come off, the technician could easily be misled by the label underneath (thus) resulting in a feed mix-up. This is the only study where we found evidence of a test of stability of the test substance in the diet mixture, but the value of this test 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-test substance mixture."

"In preparing mixtures of active substance with food both Hazleton and Searle used blenders that were not electrically grounded. This is of concern because of the potential for the electrostatic 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 all stages from the receipt of the test substance, preparation of the feed-test substance mixture, the failure of both Searle and Hazleton to analyze for concentration, homogeneity, and stability of the test substance in the diets, and the practices of feed replenishment, there is *no* way in which it can be assured that animals received the intended dosage."

(Page 39, paragraph 1): ". . . investigators toured the animal facilities on October 17, 1975, and noted the following poor current practices at that time:—"

"An exterminator company is employed by Searle for general pest control 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 that they are being fogged with insecticides. Evidence indicates that this practice has been in effect at least since 1970. A memorandum dated September 25, 1970, from Dr. McConnell to Dr. Victor Drill, which appears as a General Exhibit to the Aspartame inspection report, indicates that Dr. McConnell was concerned about this practice; at the time, however, there was no evidence that this practice was ever discontinued."

"The investigators inquired whether basal diets or treatment mixtures were subjected to analysis for pesticides. No records were found to indicate that any treatment mixtures used in the studies were ever tested or assayed for pesticide content."

"Currently a mixer with a capacity of 10 to 12 kg. is used for blending treatment mixtures. The investigators were informed that the mixture is cleaned with water, alcohol, ether, or is dry cleaned, depending on the material blended. When the mixer was examined on October 17, 1975, however, it was encrusted with material from previous use."

"Records are not maintained of weighing and blending of treatment mixtures. After mixing, the mixtures are placed in plastic, teflon lined containers and are identified with color coded stickers. . . . When the investigators examined the containers on October 17, 1975, they noted that the identification stickers of different colors were present underneath the current stickers and that the edges of some of the top stickers were raised."

"Running inventory records for either treatment mixtures or the test compounds used in treatment mixtures are not maintained. Dr. K.S. Rao, Senior Research Investigator (Toxicology), indicated that it is not necessary to maintain such records as fresh treatment mixtures are prepared weeky, biweekly, or every four weeks. Clearly, the lack of inventory records, the lack of batch records, and the lack of homogeneity and stability assays, results in poor control over the treatment mixtures."

"The practices enumerated above are such that any or all of them could compromise the integrity of a study."

(Page 42, paragraph 1): "Technicians participated in many studies simultaneously. The technicians weighing, withdrawing blood, feeding and observing the animals for tissue masses, etc., were not assigned to a particular study, but performed those functions for various studies in progress (at one time). . . ."

"Technician Bartolome Tangonen stated that the appearance of his initials at the top of a page (on the sheets entitled 'Observation for Drug Effects' where the heading provides a space for the name of the technician, but which was not invariably filled in) did not necessarily mean that he actually made the observations described in the sheets or that he filled out the sheets which bear his initials. His initials could indicate that he was supervising the work of other technicians or that he was making the observations."

"Numerous errors and inconsistencies were noted in all the antemortem phases of these experiments. . . . Because many of the observations required are of a subjective nature, continuity of the persons assigned to make these observations is critical, yet the names of the observers entered on the same animal groups are often different for subsequent observations."

"Inconsistencies were noted in observations of findings during the course of the Aldactone 78 week study with animals being reported as alive when they were actually dead, and in the reporting of the presence and location of certian tissue masses. These include approximtely 20 instances of animals reported as dead and then reported as having vital signs normal again at subsequent observation periods. (See Attachment 10)."

"Similar inconsistencies are contained in the Flagyl 80 week rat study, the Cu-7 rat study, the Aspartame (DKP) 155 week rat study, and in the Aspartame 46 week hamster study."

(Page 47 penultimate paragraph); "In the supplementary Statement of Mr. Daniel C. Searle dated February 13, 1976, which was appended to the record of the Joint Hearing before Senator Kennedy held on January 20, 1976, Mr. Searle, referring to the errors on Observations for Drug Effects sheets, stated 'In the truest sense, the errors identified by the FDA (in these records) were completely irrelevant to the scientific conclusions of the study. . .'".

His comment on the irrelevancy of the mistakes on these records relates to his testimony that other records with information as to the date of death and tissue masses were kept by Searle and these other records contained the 'correct' information."

"We do not agree with Mr. Searle that the information on the Observations for Drug Effects sheets is irrelevant."

"The title printed on these 'Observations for Drug Effects' forms is 'Statistical Work Sheet'; it is therefore reasonable to expect that these 'careless' entries must have formed the basis for input for statistical operations which are crucial to the 'scientific conclusions of the study.' . . . If the alive/dead status of each animal was 'carelessly' entered on these 'statistical Work Sheets', as conceded by Mr. Searle, and if its status as a tumor-bearer at any time was largely in doubt, as demonstrated here, the statistical computations based on this kind of raw input data are of qustionable value, if any, and would clearly affect what Mr. Searle denominates as the 'scientific conclusions of the study'."

(Page 51, paragraph 1): "In the Aldactone 78 week rat study, the 115 week rat study of Aspartame, and in the Ovulen 7 year dog study, tissue masses (likely to be tumors) were excised from live animals during the

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 an unacceptable practice, since it may seriously prejudice the findings of the experiment. For example, if the removed mass, when excised, is found to be *benign*, . . . its excision may have prevented it from becoming malignant, a change which is not unusual, and which is normally a function of time. The purpose of a safety study in animals is to find out as completely as possible *all* the likely risks associated with the test products. Interference with the natural development of tumors will prejudice the findings of the experiment. . .."

(Page 52, last paragraph): "Animals found dead during the course of a study should be necropsied (examined post-mortem) promptly; when prompt necropsy is not possible, the animal remains should be refrigerated until the next working day, when the post-mortem examination must be performed. Delay or improper handling of dead animals results in the loss of valuable information through autolysis (post-mortem degeneration or spoilage) of tissues. Proper practice following necropsy is to fix (embalm) the tissue in freshly prepared neutral buffered formalin (solution) after slicing the organs and opening the respiratory and digestive tracts to permit penetration of the fixative to prevent autolysis."

"In a number of studies which we investigated at both Searle and Hazleton, loss of information through autolysis of tissues was substantial. While Searle's (written) submissions to FDA stated that animals were necropsied promptly after death, FDA investigators found that this was not always true; frequently animals were fixed in-toto (i.e., without opening up the various organ systems tracts and dissecting and slicing of organs) after opening only the thoracic and abdominal cavities and holding them for periods sometimes longer than a year before they were necropsied. Fixation in-toto is an unacceptable practice and its use by Searle had to contribute to tissue loss. At Hazleton, there was no evidence of fixation in-toto. However the unacceptably high incidence of autolysis, 14 percent in one study, indicates improper handling of the tissues."

"In the Aspartame (DKP) 115 week rat study at Searle 98 of the 196 (50 percent) animals that died during the study were fixed in-toto for periods ranging from 1 day to 1 year before they were necropsied. Of these, 20 animals had to be excluded from postmortem examinations because of excessive autolysis. Dr. K.S. Rao (of G.D. Searle & Co.) realized that Searle's procedures with regards to delays in necropsies were not proper. In a memorandum to Dr. McConnell dated July 13, 1973, Rao stated: "I realize animals which die during the study are the most critical ones to evaluate the (test) compound effects. Hence, our people are now ready to perform a complete autopsy of the dead animals. If there are any special instructions in handling the brain and spinal cord, please advise." (Exhibit R-64 to the Aspartame 115 week rat study). However, Dr. Rao did not write this memorandum until 78 weeks into this study (i.e., not until more than half of the time devoted to it has elapsed). Of the 20 animals in this study which had to be discarded because of excessive autolysis, 13 died prior to Dr. Rao's memorandum; the remaining 7 died subsequent to that memorandum, indicating that his recommendation for prompt necropsy was not followed. In fact, Searle's records show that only 3 of the 20 animals were necropsied on the day they were found dead. Similarly, in the . . . Aspartame 46 week hamster studies, a number of animals that died were fixed in-toto and necropsied at a later date."

(Page 55 at the top): "Searle had no formal training program for its prosectors (the technicians actually carrying out necropsies or gross post-mortem examinations of the carcasses and tissues of the experimental animals); its on-the-job training was minimal. An example of this is shown in the Aspartame (DKP) 115 week rat study where the necropsy of the animals was performed by Mr. Spaet. His written observations of gross pathology were later changed by Dr. Rudolph Stejskal, who was (designated as) the supervising pathologist on this study but who was *not* physically present during these autopsies (and, consequently, could not have verified the presence, absence or extent of the lesions observed and recorded by Mr. Spaet). When questioned by the investigators as to why he made these changes, Dr. Stejskal stated that Mr. Spaet was employed for only a few months and was encouraged to write down everything that appeared to be questionable or unusual. He also informed the investigators that Mr. Spaet sometimes used wrong terms in the description of his findings. The gross pathology observations submitted in the Food Additive Petition (to the FDA) were selected by Dr. Stejskal and represented his interpretation of Spaet's observations. Dr. Stejskal indicated if he could 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 part of a lesion actually present; therefore, what Dr. Stejskal may have very likely achieved here was to withhold from the attention of the FDA possibly real lesions in those experimental animals in which Aspartame was tested for safety.) . . . Had a professional (pathologist) been available to confirm Spaet's findings directly or to provide him with a practical on-the-job training during necropsies, then it would not have been necessary for Dr. Stejskal to have to change (perhaps improperly) or 'second-guess' Spaet's observations. Moreover, Mr. David Kie, a more experienced prosector, was also available during these necropsies and did some of the prosecting himself. Review of the gross pathology records disclosed that, in at least one instance, Dr. Stejskal omitted a statement made on the gross observation sheet by Mr. Kie."

(Page 57, paragraph 2): "Histopathology (the lesions manifest in any tissue by examination under the 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 histologic slides from animal tissues to determine the changes occuring in test animals during the course of, and to some extent, as a result of the administration of a test substance to the animals, is crucial if the investigator is to glean valuable information from the experiment. Much valuable histopathologic information was lost in some of the studies which we investigated at Searle and Hazleton through preparation of poor quality slides which could not be interpreted by pathologists; inadequate numbers of acceptable quality slides of certain tissues upon which conclusions were based; and violations of protocol specifications which called for slides to be made of certain tissues for histopathological evaluation which was not done."

"In the Aspartame (DKP) 115 week rat study at Hazleton 3 tissues were noted on single animal sheets as having usual or unusual lesions and, yet, contrary to the protocol, slides were not prepared of this tissue for microscopic examinations. . . ."

(Page 60, paragraph 3): "Included in the report (by G.D. Searle & Co.) to FDA of the Aspartame hamster study is the report (of findings following examination of the) slides of several organs of one animal for which our investigators determined that slides were never prepared. . . . In the Aspartame 104 week rat study conducted at Hazleton, 5 animals were described as having tumors in the histopathological incidence table. A check of the slides and blocks (of tissue from which such slides must have been prepared) reveals that neither were present for the tissues in which the observations were made. Also at Hazleton, positive findings were reported by pathologists on 15 slides of this study but no record could be found that slides were ever made of these tissues. Since the investigation, Hazleton has attempted to determine the source of these errors relating to the tumor slides. The Task Force has received no report of Hazleton's findings."

"Part of the difficulty in attempting to identify precisely what tissues have been examined and what tissues have been reported to the FDA and to make a reasonable assessment of what happened in the conduct of the study, results from the lack of "original" postmortem work sheets or documents. Such instances include the Aspartame 115 week and 104 week rate studies; . . ."

"An example of one occurence which demonstrates the inadequacy of control between gross pathology and histopathology at Searle is available in a description of animal K23CF (an unexposed female animal) in the 115 Aspartame (DKP) rat study. This animal, a control female, was reported on gross necropsy as having a tissue mass of approximately 10x8x3 cm in the left inguinal region. A notation, in a different handwriting, made at the bottom of this gross observation records states, 'no (tissue) mass found in bottle (of fixative into which specimens of such tissue masses are to be placed) so as to enable one to collect a sample of such masses for microscopic examination and characterization as to the nature of the mass)'. In the microscopic findings of this study the mammary gland is reported as having a 'necrotizing cystadenocarcinoma (a *malignant* tumor of the mammary gland); well differentiated.' Dr. Stejskal (the pathologist at G.D. Searle responsible for the pathology operations on this particular study) was asked how it would be possible for this mass to have been read microscopically when the technician responsible for preparing the slides indicated that the mass was not contained in the specimen bottle. (Note that by pretending that a control or unexposed animal manifested a malignant mammary tumor when in fact that animal did not have such tumor or even if it did, that tumor could not be found and therefore could not be confirmed to be a mammary gland cystadenocarcinoma, the significance of the incidence of such tumors amongst animals exposed to Aspartame has been improperly reduced). The pathologists's (Dr. Stejskal's) response, as reported by the investigators, was that, at the time the animals were sacrificed (i.e., killed so that their tissues could be dissected and examined) 'you should have seen things when this study was run—there were five studies being run at one time—things were a mess'."

(Page 62, paragraph 2): "Because of the serious consequences of teratogenicity (the ability of an agent on test to elicit developmental or birth anomalies in the newborn), assessment of the potential of a test substance on reproductive and developmental

processes constitutes an extremely important phase in safety evaluation. The rapid rate of change in morphological, biochemical and physiological properties of the conceptus, the embryo, and the neonate presents special problems. Important considerations are selection of appropriate species, and absorption of test substance. The planning, performance and evaluation in this sphere requires a high degree of sophistication."

"The person responsible for most of the reproduction studies reviewed was apparently inexperienced in conducting studies of this nature and yet was given full responsibility at Searle with a title of Senior Research Assistant in teratology. His prior experience was one year's employment with the Illinios 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 (began at Searle) he went to a meeting (lasting at most for a few days) of the Teratology Society and Searle provided him with any books on the subject he wanted. This individual was also responsible for the training and supervision of a research assistant and two technicians."

(Page 64 paragraph 3): "Review of 5 reproduction and teratology studies for Aspartame revealed poor animal husbandry practices and problems in the design of some of the studies. In a memorandum of October 19, 1972, from a Searle technician to Dr. Rao, with copies to his superior and to Dr. McConnell (of Searle), regarding the conception rate in the rabbit teratology study PT 1044S72, the author provided some possible reasons for the observed poor conception rate in the remaining animals following the death of 13 animals in this study. The memorandum includes statements regarding the poor physical condition of the animals when they were received by Searle, e.g., diarrhea; the lack of an adequate acclimatization period, e.g., 6 days instead of 3 weeks; breeding the animals before they were sexually mature, e.g., insemination at 96-116 days instead of 160-240 days and pseudopregnancies because of injection of hormone. 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. Pseudopregnancy of some of the 27 rabbits may have also contributed to the lower conception rate. Some of these points were discussed at the beginning of this study, however 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 teratology (Dr. Geoffrey Palmer from Great Britain) commented on the quality of the studies as follows: '. . . even following the track you did, it seems to me you have only confounded the issue by a series of studies most of which have severe design deficiencies or obvious lack of expertise in animal management. Because of the(se) twin factors, all the careful and detailed examination of fetuses, all the writing, summarization and resummarization is of little avail because of the shaky foundation.'"

(Page 66, paragraph 1): ". . . We conclude that Searle rarely monitored the performance of work done for it under contract (by other laboratories or institutions)."

(Page 66, paragraph 3): "Searle characterized the 52 week monkey study (with aspartame) 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 facts that the protocol (detailed specifications on precisely how the study is to be carried out) for the study was written by Dr. McConnell (of G.D. Searle & Co.) *after* Dr. Waisman initiated the study in January 1970; that frequent high-level communication took place between Searle executives and Dr. Waisman 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 200 grams of Aspartame to conduct the studies."

"While high-level communication between Searle management and Dr. Waisman, and knowledge of his activities (Waisman gave a seminar at Searle on his work in October 1970), is evident, there was virtually no effective monitoring of this work."

"From what can be inferred from an interview with Dr. McConnell on October 14, 1975, he had serious reservations about the quality of the study, but he then went on to indicate that, in the absence of hard data to substantiate his reservations, there was no way to set them down in written form in a submission to FDA (i.e., he gave no indication whatsoever to the FDA on such reservations as he said he had)."

(Page 80 at the top): "In the Aspartame 46 weeks hamster study, blood samples reported in the submission to FDA as 26 week values (for certain specified animals) were found by our investigators as being, in fact, values for different animals which were bled at the 38th week. Many of 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 8 of the Aspartame Food Additive Petition (submitted to the FDA by G.D. Searle & Co.) which described clinical chemistry values (Exhibit H-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, 1975, and asked him to clarify certain BUN (Blood Urea Nitrogen) values found in that table. After reviewing the table from the submission (to the FDA) and the original data (in G.D. Searle's own records of observations from which allegedly what was reported to the FDA originated), Dr. Rao replied 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 file. A selected portion of these values appears 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 compute the means for the BUN values indicated (in the report submitted by G.D. Searle & Co. to the FDA) from the data available in the Appendix portion of the report.'"

"In the Aspartame 115 week rat study, the investigators point out data appearing on two tables, one in the raw data (in Searle's own files) and the other in the submission (by G.D. Searle & Co.) to the FDA. It is impossible to determine how some of the values in the submission were arrived at, although in two instances the submitted values appear to be an average of the two values shown in the raw data, and in other cases, it appears that a single value 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 may be useful to relate 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 aspartame carried out either by or for G.D. Searle & Co. could be audited by the investigators at that time, the decision was made by the FDA to have the original records maintained by G.D. Searle & Co. for the balance of those studies sealed in place at G.D. Searle & Co. so as to preserve their authenticity 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 these were relatively minor ones on the embryotoxic and teratogenic potential for aspartame (one in the rat and one in the mouse) while the third one was the same long-term study in rats of 115 weeks with DKP that had already been investigated during the original audit in 1975. Aside from this, as far as I know, no additional efforts at auditing any other study on aspartame was made by the FDA despite the fact, as mentioned earlier, that a relatively very large number of studies with experimental animals have been conducted by or for G.D. Searle & Co. for this particular food additive.

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 if one considers additionally that.

In December 1975 i.e., as a consequence of the initial findings by the FDA on the reliability of the aspartame studies conducted by and/or 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 respect to the lack of reliability of the studies of aspartame, but actually extended them in a substantial fashion;

Despite all this, the FDA refused to allow its findings on the reliability of the aspartame studies to be put before the Scientific Board of Inquiry concerning aspartame which had been convened following the request of Dr. John W. Olney of the Washington University School of Medicine in St. Louis, Mo. and Mr. James Turner, a Washington, 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 evidence (or lack of it) for the safety of aspartame;

Although largely as a result of the findings arising from the 1975 investigation at G.D. Searle & Co., the U.S. Congress appropriated an additional $16,000,000 or so to the FDA for the express purpose to do a better job at monitoring the quality of studies carried out by the regulated industry and although the FDA took this money and recruited a large number of investigators *allegedly to devote to this program*, other than the limited audits carried out in 1977 by the FDA with respect to aspartame, apparently nothing more in the way of such 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 1975 were eventually unsealed 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.

This kind of track record on the part of the FDA does not seem to me to inspire much confidence that the health of the people of this country is in fact adequately protected by its regulatory 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 that participated in that 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 presence of tissue masses likely to be tumors (e.g., animal No. F6HF;

—Grossly detected pathological changes in general for the experimental animals;

—Records of ophthalmoscopic examinations for those animals;

—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;

—Excision of tissue masses likely to be tumors from live animals in this study;

—Absence of batch records and records for the mixing of the test 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 assay for the actual DKP that 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 experimental rats;

—Failure to report to the FDA of all internal tumors present in the experimental rats, e.g., polyps in the uterus (Animal K9MF, ovarian neoplasms (Animals H10CF, H19CF, and H7HF) as well as other lesions (Animal D29CF);

—Inconsistencies between different parts of the report on this study submnitted 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 group 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 obtaned direct evidence that in fact the distrbution of the test agent in that diet was clearly not homogeneous due to failure to have the test agent ground in a sufficiently fine manner. A Polaroid photograph of a sample of that diet obtained by the investigative team actually shows the test agent in the form of coarse particles within the diet. It follows that the experimental rats could eat 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 may recall that amongst the material that I had given you there was a rather extensive prepared statement by Dr. Olney before the Scientific Board of Inquiry. 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 only one aspect discussed by him there—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 animals with any brain tumors were noted amongst 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 such as this is observed is quite simple:—did the agent on test, aspartame in this case, *cause* the brain tumors noted amongst the animals exposed to it, or rather can one view the occurence of such tumors only in the two groups of rats exposed to aspartame as merely a "chance" event, an occurence 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 policy in scientific circles is to state that the result observed has achieved "high statistical significance". What this implies is that 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 *not* be justified in concluding that the test agent was *not* a factor causing such incidences.

In other words whenever the results of an appropriate statistical test for significance yields a p (for probability) value equal to or less than 0.5 or 5%, *the policy in the FDA and in any other scientific or regulatory 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 the exposed animals by comparison 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 scientist or 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"; rather, the decision is made by 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, or 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...	0.005,891
Standard error of this slope.....	0.003,046
Chi square for significance of this slope.....	3.724
"p" or probability of this chi square	0.027

The entry in the last row above, p = 0.027, indicates that the results on the incidence of brain tumors that were tabulated by Dr. Olney, had in fact achieved rather high statistical significance since p = 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 what he had gleaned from the world literature on this subject—the "historical control rate" for such tumors amongst large populations of rats indicates that no more than 49 animals afflicted with them have been found amongst nearly 60,000 rats, an incidence rate of less than one tenth of 1 percent.

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; a recent example of this can be given in their decision concerning the carcinogenicity or cancer-induction propensities of a number of color additives, a matter that arose as recently as last year. One cannot help wondering just 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:—that the significance that attaches to those tumors amongst the rats exposed to aspartame increases many-fold over the already high significance mentioned above when what was observed merely in this particular study is considered.

In view of 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:—What 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 clear beyond any shadow of a doubt that aspartame had caused brain tumors or brain cancer in animals, and is this not sufficient to satisfy the 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 aspartame causes cancer) how would the FDA justify its position that it views a

certain amount of aspartame (50 mgm/kgm body-weight) as consituting an ADI (Allowable Daily Intake) or "safe" level of it? Is that position in effect not equivalent to setting a "tolerance" for this food additive and thus a violation of that law? And if the FDA itself elects to violate the law, who is left to protect the health of the public?

(c) Precisely how safe is the FDA's estimate of the Allowable Daily Intake (ADI) of 50 mgm/kgm body-weight for aspartame?

Even though the FDA seemingly declined to apply the provisions of the Delaney Amendment in this case, they could have still elected to subject the data on brain tumors to a formal Risk Assessment or Risk Analysis; this is a procedure on which they have a regulation and FDA policy is to carry out such formal Risk Assessment in the case of suspected carcinogenic agents which find their way into human food through exposure to them by food-producing animals. In other words, this is not some kind of technique that would be new or unfamiliar to that regulatory agency. And yet, it appears that either that specific procedure was not attempted at all in the FDA as far as aspartame is concerned, or, if attempted, its results were set aside or ignored.

In this section I shall present the results of my own computations involving the risks of brain tumors; the specific set of data analyzed has been given in the previous section here—the incidences of such tumors as tabulated by Dr. Olney in his presentation before the Scientific Board of Inquiry with respect to aspartame.

The first item to be considered is that if one wishes to extend safety data from small laboratory rodents such as rats to much larger mammals such as humans, the exposure rates expressed in grams per body-weight must be modified or corrected by a certain adjustment.

The reason for this is that relatively small animals have, per unit body-weight or mass, a much larger body-surface. It is well known that most metabolic functions are better related to body-surface than they are to body-weight. For example, if one were to provide general anesthesia, say, for an elephant, and one were to select the same dose in mgm/kgm body-weight of a general anesthetic which is used in humans, chances are excellent that the animal will promptly die due to a drug-overdose; the reason for this is the same—for a given unit of body-weight, the elephant has a much smaller total surface area than the human and, therefore, a much lower tolerance for any drug given on a basis of body-weight.

The usual adjustment aimed at correcting this problem is to find what dose in humans is equivalent to a certain dose given to rats (expressed in grams per kgm body-weight). In the particular study of Searle where the brain tumors were found, the average adult weight of male rats was 506 gms. and that for female rats was 331 gms, for an average weight for the two sexes of 418.5 gms. A 60 kgm adult human is "worth" on a weight or mass basis 60,000/418.5=143.37 such rats. On a body-surface basis, however, that same 60 kgm. human would be "worth" only the two-thirds power of 143.37 i.e., only 27.39 rats of an identical average weight. Thus, in order to have equivalence between humans and rats, doses expressed in grams/kgm body-weight for the rate must be divided by the one-third power of 143.37 i.e., by 5.23. It is clear that 5.23×27.39 is 143.37, the ratio of the body-weights for the two species.

The formal risk assessment was carried out by utilizing two separate techniques: one was the Mantel-Bryan approach (also known as the log-probit method) while the other was the so-called One-Hit procedure. The latter is defined as $P(d) = 1 - \exp(-\lambda d)$ where P stands for probability, d for dosage, $\exp(-\lambda d)$ indicates e, the well-known mathematical constant, 2.718, raised to the power of $-\iota$, and λ stands for a constant to be estimated from the observed experimental results.

The Mantel-Bryan procedure, published nearly a quarter century ago in 1961 in the Journal of the National Cancer Institute (Vol. 27, page 455, under the title "Safety Testing of Carcinogenic Agents") represents the first rational and formal approach at risk analysis; in the time elapsed since its publication it has gained extremely widespread recognition and acceptance. Such regulatory agencies as the FDA and the EPA use it routinely in their risk assessment procedures inasmuch as it is being generally regarded as a "classic" method.

I have used here both of these extrapolating techniques with a confidence interval of 90 percent, and in either case the Abbott Correction was utilized.

The table that follows presents the "virtually" safe levels of aspartame expressed in mgm/kgm body-weight corresponding to a variety of upper limits on the risk with the data derived, as explained, from the observations on brain tumors in rats as tabulated by Dr. Olney. The results for each of the two methods of extrapolation (the log-probit and the one-hit procedures) are presented for either rats or humans; as explained on the previous page here, the estimates for the human are 5.23 times smaller than those for the rat due to the necessary correction for the relative body-surface of the two species.

RESULTS OF THE FORMAL RISK ASSESSMENT

[Based on data for brain tumors in rats]

Extrapolating procedure: Upper limit on brain tumor risk	"Virtually safe" levels of aspartame expressed in mgm/kgm body-weight			
	Mantel-Bryan or log-probit method		One-hit method	
	For rats	For humans	For rats	For humans
1/100,000,000	0.380	0.072.6	0.000,731	0.000,140
5/100,000,000	0.733	0.140	0.003,66	0.000,699
1/10,000,000	0.983	0.188	0.007,31	0.001,40
5/10,000,000	2.00	0.382	0.036,5	0.006,99
1/1,000,000	2.74	0.524	0.073,1	0.014,0
5/1,000,000	5.95	1.14	0.366	0.069,9
1/100,000	8.45	1.61	0.731	0.140
5/100,000	28.0	3.82	3.66	0.699
1/10,000	29.7	5.67	7.31	1.40
5/10,000	79.6	15.2	36.6	6.99
1/1,000	126	24.1	73.1	14.0
5/1,000	412	78.7	366	69.9
1/100	733	140	735	140

Examination of the entries in the table just above reveals that for very small upper limits on the risk, the one-hit procedure yields estimates much smaller than those generated by the log-probit method: For an upper limit on the risk as small as 1/100,000,000, the one-hit estimates are some 526 times smaller than the corresponding ones resulting from the log-probit approach. However, for larger upper limits on the risk, this difference between the two kinds of estimates gradually disappears—thus, for an upper limit on the risk as high as 1/100 the estimates generated by each of these two separate methods of extrapolation appear to be virtually identical.

If we now wish to enquire on the upper limit for the brain tumor risk associable with 50 mgms/kg body-weight for aspartame (the level that the FDA views as constituting an Allowable Daily Intake or ADI), we may consult the table on the previous page here; 50 mgms/kg body-weight for humans would fall between the entries in the third-last and the second-last row in that table; the upper limit on the risk would, therefore, be between 1 and 5 per thousand population for each of the two extrapolating procedures. More exact interpolation would yield for 50 mgm/kg body-weight for humans (equivalent to 261.69 mgm/kg body-weight for rats) an upper limit on the risk of 2.27/1,000 population under the log-probit kind of extrapolation and 3.57/1,000 population for the one-hit kind.

It is clear that risks of this magnitude for what the FDA regards as a "safe" level of exposure to aspartame represent an outright calamity or disaster. In fact, were the Allowable Daily Intake of aspartame be only *one-tenth* as large as decreed by the FDA, i.e., in the neighborhood of merely 5 mgm/kgm body-weight, the table on the previous page reveals the upper limit on the brain tumor risk would still be as large as approximately 1/10,000 population for the log-probit method and almost 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-hundred times smaller (i.e., no more than 0.5 mgm/kgm body-weight) 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 communication.

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. Environmental Protection Agency where I am currently employed; that agency has no regulatory jurisdiction or interest in food-additives such as 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. ADRIAN GROSS,
Senior Science Advisor,
Benefits and Use Division,
Office of Pesticide Programs.

STATEMENTS FROM COMMUNITY NUTRITION INSTITUTE

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 founding members announced that a lawsuit would be filed against G. D. Searle and Company, makers of aspartame under the trade name NutraSweet.

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 hot line.

A founding member of the organization, Mrs. Shannon Roth, 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.

Roth said she is filing a personal injury lawsuit against Searle in Florida, and that she is joining with several other members of "Victims" to file a personal injury claim against the Food and Drug Administration (FDA). James Turner, an attorney and consumer activist, said that an administrative petition is being filed with the Justice Department as the preliminary step toward the eventual personal injury lawsuit against FDA.

CNI's Executive Director, Rod Leonard, said the new organization would provide a link between aspartame users who have experienced adverse reactions and have suffered injury and economic loss. He described

the symptoms which include grand mal seizures, severe suicidal depression, temporary and permanent blindness, menstrual problems and other severe disorders.

Leonard said that he and Turner also are filing a request with FDA to create a national surveillance program on aspartame complaints. He said FDA Commissioner Frank Young had told 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 reports will be a charade," Leonard said, "unless the FDA also sends a memorandum to physicians, health clinics, psychologists, allergists and other specialists informing them of the plan by FDA to collect information on adverse reports." He and Turner said a national monitoring program must include notification of physicians.

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

COMMUNITY NUTRITION INSTITUTE,
Washington, DC, September 13, 1984.

Dr. Frank E. Young,
Commissioner, Food and Drug Administration, Rockville, MD.

DEAR MR. COMMISSIONER: This letter is a request for the Food and Drug Administration to establish and maintain a surveillance program to monitor the complaints of all consumers regarding aspartame, a sweetener product that is marketed as NutraSweet by Searle and Company. When FDA approved in July 1983 the use of aspartame in liquids, the agency was aware of health concerns expressed both 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 some action be taken by FDA to fulfill its July pledge. We proposed that 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—including a CDC evaluation.

We now 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 and others that it has received some 680 complaints that were forwarded to CDC, with the implied conclusion that this is the total number of complaints. However, in discussions with the staff in the Freedom of Information Office (FIO) at FDA, we now learn that those complaints were all received prior to February or March of this year, and do not include any complaints received subsequently.

In addition, the FIO office said that regional FDA 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, no effort has been made since April to determine the actual extent of consumer reactions to NutraSweet, or to analyze and categorize the complaints. In at least one 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 complaints of 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 now seems self-serving 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 self-fulfilling 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 physicians to its need for information, but instead waits on consumers who seek medical advice about their complaints to make a special effort to alert 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 want 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 from physicians.

This episode illuminates a darker problem within FDA and the procedures now employed in the regulation of food additives. Had aspartame been introduced as a drug, physicians would be routinely monitoring the reaction of their patients when prescribing the substance for use in weight control or for other special dietary 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 had 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 American food supply. Subsequent studies and further analysis of the data have served only to raise additional questions that preclude a finding that the product is safe. Only last week, for example, D. Jeffrey Bada of Scripps Institution in La Jolla, CA, found that potentially harmful chemical changes occur when NutraSweet is heated in liquid form. Your agency said it is reviewing 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 NutraSweet. 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 FDA should be doing is carefully monitoring the effects of aspartame on its consumers.

Thus far, FDA has spurned its responsibilities, and has no monitoring strategy. As the newly appointed Commissioner, you have the opportunity to take a more responsible stance than did your predecessor, and I urge you to develop and make public an effective and intensive surveillance program to monitor the health consequences of the consumption of aspartame. We stand ready to 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 issues raised concerning the safety of 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 constituents on the chemical composition of the brain, and on various brain functions and types of behavior. I have studied these effects in experimental animals, normal people, and people with brain disorders. My interest in aspartame derives from the fact that it contains two amino acids, phenylalanine and aspartic acid. Aspartame's consumption raises the 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 to believe 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 phenylalanine in aspartame, especially if—as 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 Diseases and Stroke to extend these studies.

I believe that the information now available about aspartame warrants the following conclusions about its possible effects on the brain:

1. 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 alters 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. These changes are enhanced when the aspartame is consumed along with a food that is rich in carbohydrate (as happens, for example, when someone eats a jelly sandwich or cookies or pasta along with diet soda). The changes in neurotransmitter release are likely to affect nu-

numerous brain functions (like the control of blood pressure, or the appetite) and aspects of behavior.

2. When normal human volunteers consume aspartame in doses that are high—but within the FDA's estimates of 90th percentile intakes—blood amino acid levels change in ways that almost certainly produce corresponding alterations in the chemical composition of their brains (especially if the aspartame has been ingested along with carbohydrate-rich foods). However the particular changes that occur in the human's brain are likely to be different from those occurring in the rat's. (This is because the rat's liver destroys the phenylalanine in aspartame very quickly, while the human's liver destroys the phenylalanine much more slowly. The predominant effect of aspartame on the human's brain is likely to be an increase in its phenylalanine levels; the predominant effect on the rat's brain has been shown to be an increase in its levels of tyrosine, another amino acid that is formed when the liver metabolizes phenylalanine.) Hence, while it seems likely that aspartame, in doses of sufficient size, will affect brain functions and behavior in people, the precise nature of its effects cannot necessarily be predicted using data from experiments on rats. It is necessary also to do functional and behavioral studies on people—normal people; people with metabolic disorders that impair their ability to metabolize phenylalanine; and people with brain disorders that might sensitize them to whatever changes in brain chemistry the aspartame might produce.

3. Such studies are essential before we can state categorically that aspartame does not affect the brain. However—in the absence of positive evidence that aspartame produces deleterious effects, their performance would not seem to be a prerequisite to the continued general use of aspartame. Of greater concern are the numerous anecdotal reports, written by consumers (and, in some cases, physicians), suggesting a relationship between their consumption of aspartame-sweetened foods and the subsequent appearance of various neurological and behavioral sequellae. A recent report prepared by the Center for Disease Control for the Food and Drug Administration summarized the contents of several hundred such letters; it concluded that the question of whether the sweetener can cause the signs and symptoms that have been ascribed to it can be resolved only by "controlled clinical studies" carried out in medical research centers. (In such studies, patients would alternately receive aspartame and a placebo, double-blind, while their physical condition was being carefully monitored.) I agree with the CDC and the FDA that it is imperative that such studies now be done. I also agree that, even though the evidence for a causal relationship (between aspartame consumption and subsequent behavioral or neurological symptoms, as described by some patients) is, in some cases, highly suggestive, such uncontrolled, anecodotal case reports provide an insufficient basis for limiting aspartame's use.

4. If aspartame does produce side-effects involving the brain, and if these side-effects result from the sweetener's phenylalanine content, then their production almost certainly requires that large amounts of aspartame—probably several grams—be consumed. The problem at present is that it is difficult if not impossible for the patient or his physician to know how much aspartame he has eaten or drunk. A can of diet soda is required to indicate that it contains aspartame, but nowhere on the can need it be stated how much aspartame it contains. I doubt that one consumer (or physician) in a thousand now realizes, for example, that a can of TAB provides less than one-fourth as much aspartame as a can of DIET-PEPSI or DIET-COKE. The unavailability of this information causes countless people to worry about aspartame who should not (because they consume only tiny amounts of it). Moreover it deprives consumers (or their physicians) of the ability to calculate how much aspartame they have drunk on days when they think the sweetener might have caused side-effects; and it deprives them of the opportunity to set reasonable limits on their aspartame intake. I believe it is essential that companies which include aspartame in their products be required to indicate on the labels (in readable print) how much of the sweetener is present in each can or serving. This simple change in labeling practice would, I believe, sharply reduce the number of consumers who believe without probable foundation that they have suffered aspartame related side-effects. Perhaps more importantly, it would also enable physicians to identify those patients who might really have had such responses, so that such people might then undergo controlled clinical testing.

Thank you again for giving me this opportunity to express these views.

STATEMENT OF DR. LOUIS J. ELSAS II

Thank you for your inquiry regarding the Phenylalanine containing sweeteners Nutrasweet, Aspartame, and Equal. All are dipeptides composed of two amino acids, aspartate and L-Phenylalanine. The following are responses to several inquiries like your own.

First let me allay your anxieties by saying that there have been no documented side effects from L-Phenylalanine-containing sweeteners.

1. I have no insight into alleged "victims" of aspartame, but suggest that after eating or drinking aspartame-containing food stuffs and while symptomatic, the blood concentrations of L-Phenylalanine be quantiated. Inquire where and how from your local physician or University medical center. Human biochemical geneticists usually can provide this service. A comparative repeat sample should be quantitated when symptoms are no longer present.

2. From my own and others studies, high blood concentrations of L-Phenylalanine are harmful to human brains in at least three situations:

a. In older than 6 months old children and adults with mature brains high blood concentrations will prolong performance time, slow brain wave cycles (EEG) and reduce neurotransmitter production in a reversible manner.

b. In newborns to 6 months old with rapidly growing brains elevated blood phenylalanine produces irreversible brain damage by slowing migration of oligodendroglia (brain cells) and altering myelin (nerves' insulation) formation.

c. In pregnancy, if the mother's blood phenylalanine is raised to high concentrations, her child's brain development can be irreversibly damaged.

No one has determined "how high" the blood phenylalanine must be elevated to produce any of these bad effects under any of these conditions or age groups. It has not been proven that "all people can take as much aspartame without fear of ill effects as they desire." In fact there are many genetically susceptible people: affected patients with phenylketonuria (about 20,000) and their asymptomatic parents (about 4,800,000 based on a U.S. Population of 240,000,000) who should not take unlimited amounts of aspartame until this information is available.

Several 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. In the interim I would suggest moderation particularly if you are pregnant, breast feeding or have had symptoms directly related to ingesting phenylalanine-containing sweeteners.

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

(A Model for the Study of Phenylalanine and Brain Function in Man)

ABSTRACT

Phenyletonuria provides a human model for the study of the effect of phenylalanine on brain function. Although irreversible mental retardation is preventable through newborn diagnosis and dietary phenylalanine restriction, controversy exists regarding the effects of increased concentrations of phenylalanine in older patients. We have studied ten older, treated, phenylketonuric patients using a triple-blind, multiple trials, crossover design. Each patient was tested at the end of each of three 1-wk periods of high or low phenylalanine intakes. Tests included a repeatable battery of neuropsychological tests, analysis of plasma amino acids, and measurement of urine amino acids, phenyl organic acids, dopamine, and serotonin. In all 10 patients, plasma phenylalanine rose (900—4,000 μM). In 9 of 10 patients there was an inverse relationship between plasma phenylalanine and urine dopamine excretion. When blood phenylalanine was elevated, these patients had prolonged performance times on neuropsychological tests of higher but not lower integrative function. Urinary serotonin fell during phenylalanine loading in six patients. The concentration of phenylacids in the urine was not proportional to the plasma phenylalanine at concentrations below 1.5 mM. In one patient, neither performance time nor dopamine excretion varied as blood phenylalanine rose or fell. We interpret these data as follows: blood phenylalanine above 1.3 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 Folling (1) attributed a syndrome of mental retardation and aberrant behavior to an inherited metabolic error. Since then, phenylketonuria (PKU) [1] 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 producing this permanent structural damage remain unclear, but several hypotheses have developed. Decreased or abnormal myelin formation and/or impaired oligodendroglial migration during the first 6 mo of postpartum brain development are the most probable mechanisms.

Controversy persists regarding possible effects of elevated phenylalanine on brain function when development is nearly complete in older, treated patients with PKU. Whether or not elevated concentrations of phenylalanine disturb central nervous system function in these patients is un-

[1] *Abbreviations used in this paper:* PKU, phenylketonuria; WISC, Wechsler Intelligence Scale; WRAT, Wide Range Achievement Tests.

known. Since ~1 in 16,000 Caucasian newborns (Georgia statistics) is affected with PKU, and effective newborn screening has prevented permanent brain damage since 1970 in the newborn screenee, an answer to the question of whether high plasma phenylalanine affects mental function becomes more urgent for this accumulating population.

Silverman and Guthrie (unpublished observations) approached the question by administering one loading dose of phenylalanine to control subjects, heterozygotes, and homozygous affected patients with PKU and compared errors in response time among the three groups. Their results suggested a difference among the three groups which related directly to the concentrations of plasma phenylalanine achieved.

In 1980, Waisbren 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 reports. The PKU Collaborative Study began a prospective study in 1967. Results of achievement tests (Stanford Binet, Wechsler Intelligence Scale (WISC), Wide Range Achievement Tests [WRAT]) on 81 children, 38 of whom had continued the diet beyond 6 yr of age and 43 of whom had discontinued at 6 yr of age, 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 (1983) reported a negative correlation between performance on neuropsychological tests and serum phenylalanine concentration on the day of testing in a group of early treated patients age 6–13 yr. Neither of these studies used the patient as his/her own control. Interindividual variation, differences in phenylalanine concentrations achieved and in techniques used by collaborating centers have hindered interpretation of results.

In in vitro systems, phenylalanine influences the synthesis of two biogenic amines, dopamine and serotonin, which are critical compounds in neurotransmission. Both tyrosine-3-hydroxylase (E.C.C.1.14.16.2) and tryptophan-5-hydroxylase (E.C.C.1.14.16.4) are rate-limiting enzymes in the synthesis of dopamine and serotonin, respectively, and are competitively inhibited by phenylalanine at millimolar concentrations. Another potential inhibitory effect of phenylalanine on biogenic amine synthesis is through impaired uptake of tyrosine and tryptophan across the blood-brain barrier. Phenylalanine, tyrosine, and tryptophan share the same transport system and compete for a common transport function at physiologic concentrations. Since transport of amino acids across the blood-brain barrier is the rate limiting step in the movement of amino acids from plasma to brain, and since their plasma concentration is near saturation of their transporter proteins, increased concentrations of plasma phenylalanine could limit the transport of tyrosine and tryptophan and thus their availability to the brain cell membrane for neuropeptide synthesis or conversion to biogenic amines.

The current study compares specific neuropsychological tests with changes in plasma phenylalanine and biogenic amine production in young adults and older children with PKU. Although the dopamine excreted in the urine is a reflection of multiple sources of dopamine synthesis, 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 made of competitive inhibition by phenylalanine of tyrosine and tryptophan transport by kidney tubule. We use a triple/blinded, crossover, clinical protocol to circumvent the influence of individual variations in this disorder.

METHODS

Study design. 10 patients with PKU, aged 6–24 yr, were admitted on a 21-d protocol to the Emory University Clinical Research Facility. Informed consent was obtained from adult patients or from the parents of patients <21 yr of age. Each patient served as his or her own control. Each patient was 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 I dietary phenylalanine. Past plasma concentrations of phenylalanine on known intake and genotyping of parents were used to determine the amount of phenylalanine added to patient formulation for restriction and loading (23,24). Patients whose entering concentration of plasma phenylalanine was high either because of poor control or because of diet discontinuation for several years were on the high-low-high 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 source. A specified amount of tasteless l-phenylalalanine was added to the formula during the loading phases. The study was triple-blinded: neither the patients nor their parents could taste the difference in formula and were unaware of their experimental condition: the psychologist administering the neuropsychologic tests was uninformed of the patients' blood phenlyalanine concentration; and the laboratory personnel performing amino acid, organic acid, and amine analyses did not know the condition under which sample were obtained.

Biochemical tests. Blood and urine samples were obtained on all patients at the beginning of the first week as a baseline and at the new equilibria achieved at the end of each 7-d interval.

Plasma and urine amino acids were analyzed by ion exchange chromatography on the Beckman model 119 CL using lithium buffers (Beckman Instruments Inc., Palo Alto, CA). Because tryptophan is somewhat labile in extraction from blood, recovery of "spiked" standards from whole blood and urine was quantitated to determine losses. In the physiological ranges measured from 50 to 200 μM, recovery was 82–90% efficient. Data are presentred normalized to an internal standard without correction for these specific losses which are in the range for the internal standard, *S*-2-aminoethyl-L-cysteine.

Dopamine assays were performed using the single isotope radioenzymatic assay developed by Peuler and Johnson. This method used catechol-*o*-methyl transferase from rat liver to transfer a radioactive methyl group from *S*-adenosyl methionine to catecholamine, forming methyl catecholamine derivatives which were then characterized by radiochromatographic analysis. The assay was sensitive in urine to 120 pg/ml for dopamine.

Serotonin was determined by a radioimmunoassay developed by Peskar and Spector (26) using rabbit antibody prepared by coupling serotonin to bovine serum albumin. The antibody bound 50 percent of ^{3}H-serotonin in the absence of free serotonin. Less than 1 ng of free serotonin was detected by standard displacement methods.

Urine organic acids were analyzed by gas chromatography on a HP 5992 gas chromatograph/mass spectroscope and quantitated on a HP 5790 gas chromatograph. Organic acids were extracted with ethyl acetate and ether and derivatized with trimethylsilane and *bis*-(trimethysilyl)trifluoracetamide (27). The level of sensitivity for phenylacids in urine was ~5 pg. Specific recovery of phenyllactic, phenylacetic, and phenylpyruvic acids were 68, 91, and 58 percent, respectively. All calculations are corrected for these losses by parallel external and internal standards used during extraction, derivatization, and quantitation.

Renal clearances were calculated for phenylalanine, tyrosine, and tryptophan, from timed 24-h urine collections and midpoint plasma collections. Both specimens were quantitated for concentrations of amino acids and creatinine. The glomerular filtration rate (GFR) was calculated from the creatinine clearance, as were the rates of a specific amino acid filtration, excretion, and reabsorption using the following formulation: $F_{AA} = GFR \times P_{AA}$, $E_{AA} = U_{AA} \times V$, $T_{AA} = F_{AA} - E_{AA}$, where U was urinary amino acid concentration in mg-ml, V (urine volume) in ml/min, and P_{AA} the plasma amino acid concentration in mg/ml. The F_{AA} (filtered aminoacid), E_{AA} (excreted aminoacid), and T_{AA} (reabsorbed aminoacid) were expressed in mg/min. Percent reabsorption was calculated as $T_{AA}/E_{AA} \times 100$.

Neuropsychological tests. Measurements of general intelligence and achievement were based on the Wechsler Intelligence Scales. (The Wechsler Adult Intelligence Scale for adults and the WISC for children) and the WRAT. 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 tests given multiple times is subject learning. Two procedures were incorporated in the study design to reduce the artifacts due to learning. For one group of test (type 1, Table I), the subject was allowed 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 2, Table I). Because of this limitation, equivalent forms of this latter group tests 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 measured.

Interpretation of data. Data are arrayed for all subjects in tabular form (Tables II, III, IV, and V) to emphasize intraindividual 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.

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

Test name	Type [1]	Age [2]	Variables
Tests of higher integrative function			
Choice reaction time:			
Figures	1	≥6	Visual-perceptual discrimination and associated latency.
Letters	1	≥6	
Rhymes	1	≥6	
Trails B	2	≥8	Complex visual-motor coordination. Maintaining a set. Following instructions.
Digit span	2	≥8	Short-term auditory memory. Concentration.
Benton visual retention	1	≥8	Visual memory.
Benziko-Morgan	2	≥8	Attention. Short-term auditory memory.
Symbol digit	2	≥6	Visual-motor speed. Concentration.
Tests of lower integrative function			
RAN	2	≥6	Verbal visual integration.
Trails A	2	≥6	Visual-motor coordination.
Grooved pegboard	1	≥5	Visual-spatial-tactile coordination. Visual-motor speed.
Halstead finger tapping	1	≥5	Fine motor skill.

[1] 1. A test which can be repeated over several testing sessions. 2. A test which cannot be repeated and must be presented as equivalent forms over several testing sessions.
[2] The age listed in years plus greater ages.

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 mo of age, respectively. K.K. is the older brother of T.K. Both D.A. and W.J. 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 results. Plasma and urine amino acid and urine 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 stabilizating the plasma phenylalanine concentration on a constant diet was determined by sampling one subject daily. A new plateau of blood phenylalanine concentration was achieved on the sixth to seventh day after each diet change. The plasma phenylalanine reflected the diet changes, and the relationship between intake and plasma concentration demonstrated interindividual variation between ingested phenylalanine ranging from 36 to 130 mg-kg per d and plasma phenylalanine concentration ranging from 800 to 4,400 μM.

Urinary phenyl acids are not detected in the urine of normal subjects. Four of the five patients who were on the High-low-high protocol and had not recently been on restricted phenylalanine intake were excreting large amounts of phenylpyruvate and phenyllocate at the end of the first week of high phenylalanine intake. Excretion of both fell dramatically after 1 wk of restricted phenylalanine intake. However, excretion reached the original high levels at the end of the third week (high dietary phenylalanine). In the low-high-low group who had been on continuous dietary control before entry into this study, excretion of organic acids never reached the high levels of the other group despite comparable plasma phenylalanine levels. In general, <50 mg of phenylacids per gram creatinine were excreted until the plasma phenylalanine rose above 1,500 μM. Those with the highest plasma phenylalanine did not consistently excrete the greatest amount of derived organic acids.

The results of dopamine and serotonin excretion are arrayed in Table III. Results were normalized to creatinine excretion. Interindividual variation in dopamine excretion was great. In general, the patients who were on the low-high-low protocol and had been on consistent dietary management before the study achieved higher levels of dopamine excretion than did those patients in the high-low-high group who were not well controlled immediately before the study. This kind of separation was not seen for serotonin excretion. Changes in dopamine excretion varied inversely with changes in plasma phenylalanine in 9 of 10 patients. The inverse relationship of changes in plasma phenylalanine concentrations and urinary dopamine excretion are graphed in Fig. 2. Solid symbols represent patients on the high-low-high protocol. Open symbols represent patients on low-high-low protocols. Results from all patients cluster in quadrants I and III regardless of the protocol (high-low-high or low-high-low) where quadrants I and III circumscribe an inverse relationship between plasma phenylalanine and urinary dopamine concentrations. Symbols in quadrant I show an increase in urine dopamine with decrease in plasma phenylalanine, those in quadrant III show a decrease in urine dopamine with an increase in plasma phenylalanine. Serotonin excretion did not vary directly with changes in phenylalanine.

TABLE II.—EFFECTS OF DIETARY MANIPULATION OF PHENYLALANINE (PHE) ON CONCENTRATIONS OF PHE, TYROSINE (TYR), AND TRYPTOPHAN (TRP) IN PLASMA AND URINE AND ON EXCRETION OF THREE ORGANIC ACIDS

Patient	Wk	Dietary PHE (mg/kg/d)	Plasma PHE (μM)	Plasma TYR (μM)	Plasma TRP (μM)	Urine PHE (mg/g creatinine)	Urine TYR (mg/g creatinine)	Urine TRP (mg/g creatinine)	Urine organic acids (mg/g creatinine)		
									Phenylpyruvate	Phenylacetate	Penyllactate
B.R.	1	36	1,255	46	46	192	16	4.6	68	np	203
	2	4	252	65	66	99	8.5	2.4	28	np	36
	3	36	797	33	46	22	7.1	10.7	35	np	21
W.J.	1	105	1,790	33	24	155	6	2	639	150	950
	2	7	197	26	36	40	6	19	17	nd	37
	3	105	1,303	29	23	375	7	16	1,057	377	872
K.K.	1	82	2,317	37	34	256	5	6	597	87	1,233
	2	7.5	1,426	24	52	114	4	7	55	38	87
	3	81	3,296	49	58	295	6	10	1,126	103	2,143
T.K.	1	74	2,058	28	42	850	14	37	787	128	1,179
	2	8	753	35	63	88	6	3	59	63	56
	3	74	2,647	35	53	313	8	8	1,217	152	1,776
A.S.	1	69	4,405	33	36	496	14	20	877	79	689
	2	8	441	22	45	74	7	9	36	10	23
	3	69	3,900	26	35	178	6	15	894	94	515
D.A.	1	10	668	65	117	18	6	3	13	1	22
	2	100	3,260	85	94	361	18	11	179	71	329
	3	10	1,632	78	113	44	5	2	34	103	118
M.B.	1	17	304	46	65	38	20	8	nd	nd	15
	2	94	1,549	57	43	166	14	3	69	84	110
	3	16	634	51	63	76	6	7	34	5	71
M.F.	1	19	199	37	68	13	5	7	12	nd	12
	2	95	1,402	87	80	195	13	19	15	175	nd
	3	18	329	28	50	50	8	17	18	28	nd
M.K.	1	38	793	58	93	112	25	14	19	38	50
	2	130	2,460	62	43	367	22	11	791	130	751
	3	40	577	47	41	94	20	10	9	58	45
T.W.	1	17	352	45	40	48	9	26	nd	nd	nd
	2	100	2,290	32	33	509	15	32	464	273	450
	3	15	536	32	40	104	7	29	nd	nd	nd

Np, not processed; Nd, none detected. Data are single measurements. The space between patients A.S. and D.A. separates the patients on the high-low-high protocol above from those on the low-high-low protocol below

Studies of membrane transport. To explore the possibility that increased concentration of phenylalanine might competitively inhibit tyrosine or tryptophan uptake by the only plasma membrane transport function available for study in children, we quantitated their renal tubular transport. Renal tubular reabsorption data were obtained on eight 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 rate of filtered phenylalanine (45 mg/min/M2 in patient A.S.), we observed no less than 99% reabsorption of tyrosine. Maximum renal uptake of tryptophan was also seen at these filtered loads of phenylalanine. These findings differ from earlier results reported by Lines and Waisman, who reported a generalized aminoaciduria in PKU patients and suggested the possibility of competitive inhibition of reabsorption by high filtered loads of phenylalanine. However, their data were not adjusted for surface 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