EVIDENCE FOR ASPARTAME

Betty Martini's debate with Dr. R. Fink on Brain Tumor List:

Scientific Evidence For Aspartame (NutraSweet/Equal, Canderel, etc.)
Triggering Brain Tumors

FDA Toxicologist, Dr. Adrian Gross' Letters To Senator Howard Metzenbaum

Note to the Reader: Dr. Fink is on the MIT Brain Tumor List and refuses to allow aspartame information to be posted on the list. Keep in mind that Dr. Richard Wurtman of MIT at one time was a critical opponent of NutraSweet. If you read the UPI Investigation on www.dorway.com you will see that he was threatened by Searle that if he did seizure studies on aspartame he no longer would get research funds, and they were rejected. Today, MIT does get research funds and Dr. Wurtman no longer speaks out about aspartame. However, he left a paper trail including the book: Dietary Phenylalanine and Brain Function, Edited by Richard J. Wurtman, and Eva Ritter-Walker, Birkhauser. Phenylalanine is 50% of aspartame and Dr. Wurtman told Congress that as an isolate it is neurotoxic and goes directly in the brain. It lowers the seizure threshold and depletes serotonin. Aspartame breaks down into diketopiperazine (DKP) - a known brain tumor agent. There is a river of information and government documents on www.dorway.com We are now taking case histories for class action having to do with aspartame triggered brain tumors, seizures, blindness and eye deterioration. If you are a victim please email me with contact information.

There was a great attempt to get information to brain tumor victims on MIT's brain tumor list of over 1000. This was blocked by Dr. Fink, and I was refused posting privileges. Here is the debate below. Betty Martini, Founder, Mission Possible International (770 242-2599).

Dear Dr. Fink:

You said: "But until someone shows me scientific evidence that aspartame causes brain tumors, long winded postings on aspartame do not belong on this Brain tumor list, in my opinion."

First of all, nobody could put long winded statements about anything on this list because there is a 250 word limit. Secondly, you want someone to show you scientific evidence that aspartame causes brain tumors, but when I do you don't look at the research and disregard everything I say. You said in one post that the information on www.dorway.com was unscientific. I asked you to explain how peer reviewed research is "unscientific". I notice you refrain from answering such questions when you're wrong. Peer reviewed research is listed under the name of Dr. Ralph Walton who showed this research on 60 Minutes in l996 when the famed Dr. John Olney who founded the field of neuroscience called excitotoxicity made world news on the brain tumor/aspartame association. Dr. Olney is probably one of the most famous neuroscientists on the planet today. Look at his curriculum vitae on www.dorway.com and you'll see its one of the most prestigious you've ever seen. He was the one who did the studies on aspartic acid in l970 (40% of aspartame) and found that it caused lesions in the brains of mice. He told Searle, the original manufacturer, but they did not tell the FDA until after it was approved.

Dr. Olney update is also on this web site. And you'll find a journal article on brain tumors by Dr. H. J. Roberts, peer reviewed. When 2/3rds of the population is using a product that breaks down to a brain tumor agent (DKP) and triggered brain tumors in original studies, do you not think its important enough to investigate as I asked? Why would you turn away from this research.

Below are three reports from the FDA toxicologist on site having to do with aspartame studies, Dr. Adrian Gross. The last two letters to Senator Metzenbaum were written after he left the FDA, although he testified in Congress and said that aspartame violated the Delaney Amendment because "without a shadow of a doubt" it can trigger brain tumors. The Delaney Amendment forbid putting anything in food you know will cause cancer. In the second letter he lists all the brain tumors. Obviously, you've seen this report and have known all along. After all how can you say you know what is on www.dorway.com if you've never been there? Notice brain tumor after brain tumor, astrocytoma,

meningeal sarcoma, medulloblastoma, etc. Dr. Gross' last words to Congress were "And if the FDA violated its own law who is left to protect the public?" Quote taken directly from the Congressional Record. Now remember the FDA violated the law because it approved aspartame even though without a shadow of a doubt it triggers brain tumors. And Dr. Gross was there!!!!!!!!!!

And in the end the finest scientists the FDA had to offer set up a Board of Inquiry and it was their decision that the petition of Searle should be revoked and aspartame not approved for two reasons, that aspartame had not been proven safe and because it had triggered brain tumors. The summation is on the web site and soon the entire report will be scanned in.

I wrote you about the new medical text that goes into the brain tumors and seizures triggered by aspartame. Aspartame Disease: An Ignored Epidemic, www.sunsentpress.com or 1 800 814 - 9800 I explained how important it was because there are so many people on this list who are having seizures and taking such drugs as Dilantin, and aspartame interacts with Dilantin. A physician concerned with the consumer would want those brain tumor victims warned so they wouldn't use this neurotoxic drug with Dilantin and like drugs. But instead of being concerned you simply didn't want to discuss it. Why would you shrug off something as important as drug interaction when so many people on this list are using such drugs. Why are you not concerned about them having reactions?

Even a former FDA Investigator wrote you about the seriousness of this issue, and still you're not concerned.

Then you have the gall to lie about me on this list saying about when I lectured for the World Environmental Conference "There is evidence that she never attended the meeting, and that the allegations she made are totally false (in a message from the person who allegedly make the statements." You've been on www.dorway.com so you've seen my invitation to speak for the World Environmental Conference and my correspondence with Dr. Gaylord who gave the keynote address. (www.dorway.com/nomarkle.html) And when you mentioned this Jay Reynolds who has tried to cover it up, I sent you a post from Dr. Gaylord to myself admitting I was there and lectured. Finding out you were wrong rather than apologize and put it on the list so they won't think your misinformation was correct, you continue to complain about my posting of it. If you're wrong, be man enough to admit it.

And you say: "Betty Martini is not benign or sincere. Her entire "crusade" is based on her reported attendance at a meeting (years ago) in which aspartame was being discussed." Another lie. I founded Mission Possible International before I ever lectured for the World Environmental Conference. The reason it is so well known is that Nancy Markle picked up a post I had written about it from www.dorway.com published it under her name, and then a global networker put it on 450 global networks and it made world news. Why did she do it? I didn't know her at the time, but Shoshanna had just gotten a divorce because her husband got lupus from aspartame with the usual mood swings, and she didn't want it to happen to anyone else. Monsanto set up front groups on the Internet and did everything possible to put out the fire but couldn't and sold the NutraSweet Company.

I have received at least 10 calls about it today, and this is the year 2002 and I lectured in l995. Some call it a fluke, but I know exactly why they can't put out the fire. I mentioned so many problems triggered by aspartame that anyone who saw it who was using it, saw their symptoms no physician could diagnose and got off of it. When they got well they made 5000 more copies. It continues to be published in countries all over the world. We had to set up 4 support groups just to handle the victims and today there are 5 aspartame detoxification centers in the United States. Even if people saw the post and didn't use aspartame they knew many people with those symptoms. It is a crime against humanity to cover up such symptoms because it ties the hands of physicians who then can't diagnose their patients. And aspartame interacts with just about every drug used to treat the problems it causes as outlined in the medical text, and the reason it was written was so that finally physicians would have the facts instead of fantasy that looks like it was written by little Red Riding Hood.

Neurosurgeon Russell Blaylock, M.D., author of 'Excitotoxins: The Taste That Kills'
says about aspartame and brain tumors on page 212 - 213:

"It is interesting to note that the first experiments done to test the safety of aspartame before its final approval in l981 disclosed a high incidence of brain tumors in the animals fed NutraSweet. In fact, this study was done by the manufacturer of NutraSweet, G. D. Searle. In this study 320 rats were fed aspartame and 120 rats were fed a normal diet and used as controls. The study lasted two years. At the end of the study twelve of the aspartame fed rats had developed brain tumors (astrocytomas), while none of the control rats had. This represented a 3.75% incidence of brain tumors in the rats fed aspartame, which was twenty-five times higher than the incidence of spontaneous brain

tumors developing in rats (0.15%). "

"The study divided the rats into those exposed to low doses of aspartame and those exposed to a high dose. In the low dose group five of the rats developed brain tumors for and incidence of 3.13%. In the high dose group, seven developed brain tumors (4.38%). This indicates a dose related incidence of brain tumors. The higher the dose of aspartame, the more brain tumors were induced. "

"When Dr. John Olney pointed out these findings to the FDA "Aspartame Board of Inquiry" he was told that the high incidence of tumors was the result of spontaneous development of brain tumors in rats. That is, that some rats develop brain tumors naturally, just as humans do. Dr. Olney is a trained neuropathologist as well as a neuroscientist. He reviewed the incidence of spontaneously occurring brain tumors in rats and found that out of seven studies using a total of 59,000 rats and only 0,08% developed brain tumors - the aspartame fed rats had a forty-seven fold higher incidence. But to be fair, he even accepted G. D. Searle's references for spontaneously developing brain tumors in rats and arrives at a figure of 0.15%. This was still a twenty-five fold higher incidence in the aspartame fed rats than in the controls. "

"It was then observed that when brain tumors develop spontaneously in rats, the rate at which they appear begins to accelerate after two years of age, exactly when the Searle's study ended. Importantly, brain tumors are extremely rare before age one and one-half in the rat. So in truth the incidence of spontaneously occurring brain tumors would be even less than cited above. Yet, the aspartame fed rats developed two tumors by sixty weeks of age and five tumors by seventy weeks."

"In a collective study of 41,000 rats no tumors were seen to occur before sixty weeks and only one by seventy weeks. The fact that 320 aspartame fed rats developed six brain tumors by seventy-six weeks indicates an "incredible and unprecedented" occurrence. Within the final twenty-eight weeks of the study six more brain tumors occurred in the aspartame fed group. Dr. Olney notes that "one must assume that many more (brain tumors) would have occurred after 104 weeks. "

"It became obvious that the G. D. Searle Company was trying desperately to protect their potential billion dollar plus money maker. They claimed that more brain tumors were found because they searched the pathological slides so diligently. But, they searched just as diligently in the control rats and found none. Besides, neuropathologists examining the slides later stated that the tumors were large enough to be seen with the naked eye. "

"Because of the criticism submitted by Dr. Olney, the G. D. Searle company conducted a second study which was designed to be more comprehensive. Instead of a two-year study, this would span the entire lifetime of the rats, from intrauterine life to death. The results of this study can only be characterized as bizarre. This time they reported five brain tumors in 120 control rats (an incidence of 3.13%) and four brain tumors in 120 control rats (an incidence of 3.33%). While this was designed to show that aspartame was not the cause of the brain tumors, if accepted, the study would indicate that both groups had a brain tumor incidence thirty times higher than the known rate of spontaneous brain tumor occurrence in rats."

"But the story gets even more interesting, Dr. Olney hypothesized that one possible cause of the tumor induction was a by-product of aspartame metabolism called diketopiperazine (DKP). When nitrosated by the gut it produces a compound closely resembling a powerful brain tumor causing chemical - N-nitrosourea. "

"The G. D. Searle company conducted a separate study to test the carcinogenicity of diketopiperazine (DKP). The results of this study were not submitted to the FDA until after aspartame had already been approved for general use by the American population. This study was not a lifetime study but rather a 115 week study which consisted of feeding rats their normal feed mixed with DKP. There were 114 control animals and 216 that supposedly ate the DKP. (Not all of the animals were even examined for tumors.) There were two brain tumors in the controls (1.62% incidence) and three (1.52% in the DKP groups. But strangely enough, the incidence of brain tumors found in both groups were sixteen times higher than would be expected from spontaneous occurring tumors. That did not make sense."

"So how can we explain these strange findings? It is instructive at this point to know that in l975 the drug enforcement division of the Bureau of Foods investigated the G. D. Searle company as part of an investigation of "apparent irregularities in data collection and reporting practices." The director of the FDA at that time stated that they found "sloppy" laboratory techniques and "clerical errors, mixed-up animals, animals not getting the drugs they were

supposed to get, pathological specimens lost because of improper handling, and a variety of other errors, (which) even if innocent, all conspire to obscure positive findings and produce falsely negative results."

"The drug enforcement division carried out a study under the care of agent Jerome Bressler concerning Searle's laboratory practices and data manipulation (known as the Bressler Report ("Note from Martini - this FDA audit is on www.dorway.com ") He found that the feed used to test DKP had been improperly mixed so that the animals would receive only small doses of the chemical to be tested. (I have seen a photograph of the feed mix and can attest to the "sloppy" method used.) The commissioner also charged G. D. Searle company with "failure to maintain control and experimental animals on separate racks and failure to mark animals to ensure against mix-ups between experiments (animals fed aspartame and DKP) and controls." This vital and telling report was buried in a file cabinet, never to be acted on by the FDA."

"Such poor techniques would explain why both control animals and those eating aspartame had exceptionally high brain tumor rates, since they, most likely, were both eating the aspartame feed. What is ironic is that the FDA would accept studies from a company with an obvious heavy financial interesting in having aspartame approved. But even more amazing is that they would depend on the same company to provide studies that they, FDA, knew beforehand were highly questionable and possibly fraudulent upon which they would make such an important public safety decision."

"Thus far, no independent studies have been done to examine this vital issue. As a neurosurgeon I see the devastating effects a brain tumor has, not only on its victim, but on the victim's family as well. To think that there is even a reasonable doubt that aspartame can induce brain tumors in the American population is frightening. And to think that the FDA has lulled them into a false sense of security is a monumental crime." (end of quotes from book)

I'm going to stop at this point from quoting the book although it goes on, and even discusses the association of primary brain lymphoma and aspartame, a particularly nasty tumor with a high mortality rate. He discusses Dr. Roberts research in this issue and you can read the peer reviewed journal article on web.

Now you can tell me I'm long winded, because I had to bring you information on brain tumors because of your lack of interest and constant denials. When there is even the suspicion that a product being used by 2/3rds of the population triggers brain tumors, it should be your first concern. And after I told you about the interaction of anti-seizure medication with aspartame and the fact that it is documented in Dr. Roberts new medical text, did you not feel the people on this list had the right to know?

And it doesn't stop here. We have the secret trade information on web as well which was volunteered during congressional hearings. It reads like psychomanipulation to get aspartame approved but in the last paragraph Searle mentions they have to consider almost complete conversion to DKP and if they tell the FDA they are not going to get it approved, and of course, DKP is the brain tumor agent.

And what about human studies? Can you imagine people signing up for a study on aspartame to see if they would develop a brain tumor? So Searle decided not to let them know. They carried out studies in six countries and sacrificed people in poor villages that would not be missed. They just lied to the people and told them that NutraSweet was simply made out of papaya, a lie, and it was perfectly safe to use. The studies lasted 18 months and many of the people developed all kinds of seizures and astrocytomas, glioblastomas, etc. Some of them died just so Searle would know for sure! And when they found out that aspartame is a killer rather than publish the studies they simply sold the company to Monsanto in l985. Studies completed in l984. You will find the affidavit of the translator on web, N. Vera But the studies showed other things like the fact aspartame destroys the brain and the central nervous system. And just recently in Norway a new study has shown that aspartame destroys the brain.

The FDA never wanted aspartame approved, they wanted Searle indicted for fraud. Searle was even excising these brain tumors from the rats and then putting them back in study. When the rats died they simply resurrected them on paper. Want it from the record?

FDA Toxicologist and Task Force member, Dr. Adrian Gross stated (Wilson l985):

"They (G. D. Searle) 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. 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."

FDA Lead Investigator and Task Force Team Leader, Phillip Brodsky described the l975 FDA Task Force members as some of the most experienced drug investigators. He went on to state that he had never seen anything as bad as G. D. Searle's studies (Graves 1984; page S5499 of Congressional Record l985a).

And don't think that Searle didn't get caught. When they were found removing the brain tumors their excuse was that the rats couldn't breathe well. But how many brain tumors did they remove before they were caught? FDA toxicologist, Dr. Adrian Gross, gave several reasons why Searle's misconduct invalidated their experiments and one was: "It is highly unlikely that the FDA Investigative teams found all of the problems with G. D. Searle's studies. G. D. Searle seemed so intent on covering up their misconduct, that it is quite likely that they were able to hide many of the problems from the FDA."

But Searle needed help to coverup the issue so on August 4, l976 they met with the FDA and convinced them to allow them to hire a private agency, University Associated for Education in Pathology (UAREP). As described by Florence Graves (l984, page s5500 of Congressional Record l985a):

"The pathologists were specifically told that they were not to make a judgment about aspartame's safety or to look at the designs of the tests. Why did the FDA choose to have pathologists conduct an investigation when even some FDA officials acknowledged at the time that UAREP had a limited task which would only partially shed light on the validity of Searle's testing? The answer is not clear."

In other words, UAREP was sworn to silence, and how much did they get to be quiet? They received a half a million dollars!!!

Searle was intent on getting aspartame approved. They had invested 19.7 million dollars in an incomplete production facility and 9.2 million dollars in aspartame inventory. On Dec 8, l975, stockholders filed a class action lawsuit alleging that G. D. Searle had concealed information from the public regarding the nature and quality of animal research at G. D. Searle in violation of the Securities and Exchange Act (Farber l989, page 48).

Now Dr. Fink you do know a little about aspartame. Because you not only refused to take an interest in this issue, but also tried to make it look insignificant, I'm sending a copy of this to the list by blind copy. How dare you say to the group that I am insincere. I don't get paid for warning the world and educating them. Mission Possible International, a worldwide volunteer force, warning consumers off aspartame is funded by my husband's retirement funds. I don't sell anything. I'm sincere enough to care about the lives of the people. Because you have refused to tell them that aspartame interacts with anti-seizure medication I've had to write privately to each person and warn them. I'm the one taking case histories all day and have for years. I'm the one that gets the calls when a mother who didn't know aspartame is a teratogen gives birth to a baby with a brain tumor. I'm the one who Kelli Motluck, a heavy user of aspartame, called when she developed glioblastomas. She said I want to live, I want to live, I want to live and if I die you tell the world Monsanto Chemical Company murdered me. When I lectured to the press, the regulatory people and industry in London (filmed) I complied with Kelli's request. Cyndi Veth cried, I'm so very young to have a brain tumor. She drank lots of Diet Coke.

And the issue is so well documented that we are now taking case histories for class action having to do with the brain tumors, seizures and blindness triggered by aspartame. A 52 week oral toxicity infant monkey study used pivotal in the approval of aspartame, showed that out of 7 infant monkeys fed aspartame, 5 had grand mal seizures and one died.

Today, Dr. Peter Nunn in London is doing research on aspartame and brain tumors. Be assured that anyone who has posted in the last year will get a copy of this note. And even though you owe me an apology more importantly these people on the list have the right to know that a product estimated to be in 9000 products and climbing and 100 countries of the world triggers brain tumors. Now they will know to avoid it, and they will know what went on in the approval process and they can check out www.dorway.com And if you consider all these government records, the damning Center for Disease Control investigation, secret trade information, peer reviewed research, and a river of information from physicians unscientific, I don't think they will. They can even go to the Aspartame Toxicity Center, www.holisticmed.com/aspartame and read the horror stories that pour in from the victims. They can also read the archives of the Aspartame Support Groups.

And for your information aspartame also triggered mammary, uterine, ovarian, pancreatic, testicular and thyroid tumors just for starters, not just brain tumors. There were also pituitary adenomas. There is one lady on this list who wrote me about her aspartame brain tumor before she got on this list. Her boyfriend served in the Persian Gulf where diet sodas sat on pallets for as long as 8 weeks at a time, and the troops drank them all day. She was in a support group with 70 of those vets - all with brain tumors. If they had only had the research on web they never would have used the product.

I read every email on this list and many people are using drugs that interact with aspartame. They have the right to know. Now read on for Dr. Adrian Gross' letters, on-site FDA toxicologist. And I hope you took the note from the former FDA Investigator very seriously.

And as to the herb situation, a man who grows them was visited by government officials about even growing or selling these three herbs mentioned. However, I am grateful for someone finding where they can be attained. They are getting a thank you by copy of this note. Physicians mentioned in this report are also getting a copy as well. Dr. Fink, the coverup is over - period.

Betty Martini, Founder, Mission Possible International, 770 242-2599 www.dorway.com,
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See Dr. Gross' letters below...

Note: This is in three parts:

Dr. Gross 1976 DHHS/FDA memo to Dr. Sharp on irregular proposal
Dr. Gross 1987 Oct. Letter (reply) to Senator Metzenbaum
Dr. Gross 1987 Nov. Letter (follow-up) to Senator Metzenbaum

(Note: This memo is on DHHS stationary)

To: Mr. Carl Sharp
Date: Nov. the 4th, 1976
From : M. Adrian Gross
Subject : Draft Agreement for Validation of Searle Aspartame Studies.

The following are some comments which you requested on the document under reference as well as on the cover memorandum Wylie/Gardner dated November 1, 1976.

I must confess that I became deeply disturbed on reading this effort - last July 14th in a telephone conversation I had with Commissioner Schmidt during which I stated my reservations about this entire plan, he assured me that whatever is being contemplated in this area will be undertaken in full knowledge of and consultation with some of us who were intimately involved with the Searle investigations and that whatever is finally accepted will be of such nature as not to jeopardize or undermine all of our previous work. Given this kind of background I suffered a rude shock by the proposed plan in front of us at this time.

Let us put this matter in some perspective by establishing the basic facts here. The Searle investigation which started in the Fall of 1975 can be viewed as an investigation "for cause" following the discovery of certain improprieties in the conduct of animal studies during preliminary inspections in the 1974 and in the first half of 1975. The report of the Task Force submitted i March of 1976 in essence constituted a stinging indictment of Searle and it contained various recommendations for regulatory action including referral to the Justice Department for review of possible criminal violations of the law.

The Aspartame studies to which we have reference here are nothing but an extension of the studies which were reviewed by the Task Force. I see no essential difference between them and any of the studies already investigated. In the meantime this Agency as received a substantial amount of additional funding for the express purpose of monitoring the quality of research carried out by regulated industry in a much expanded fashion. As part of this program, there has been a marked degree of effort, time and money expended on setting up sundry task forces, steering committees, training courses for investigators, "surveillance" inspections, regulations for good laboratory

practices, compliance programs, etc.

Yet, notwithstanding any of this, now that the Agency is confronted with the need of completing what it started out to do in this Searle matter, we seem to be turning to an outside group of questionable capability in this area:- the UAREP. I know absolutely nothing of the past experience of this outfit to carry out investigations of this sort - perhaps, whoever it was that selected this group to carry out our responsibilities for us might be as kind as to enlighten us on this point. I noted the name of Dr. Stowell associated with this organization - I have known Dr. Stowell for many years now from the time he was Scientific Director of the Armed Forces Institute of Pathology and I can readily agree that he has impeccable credentials and a remarkable achievement in his own field of pathology; as far as investigations of the sort that we are concerned with here, however, I would judge him to be a complete neophyte in this particular area. I also know nothing of the others at UAREP to do the actual "hands-on" part of the investigation - we need additional details here but I would doubt very much that UAREP could come up with a number of workers who are both experienced and competent in matters of this sort.

Speaking as a pathologist, I seriously question the wisdom of selecting a group of pathologist to oversee the kind of investigations that are called for here; pathology problems do not constitute but a small part of the difficulties involved in situations such as these. My own experience is that, as a rule, controversial technical aspects in pathology proper (such as whether any particular characterization of any given lesion is a proper one or not) are \seldom an important factor in a determination whether any study contains serious flaws. this has been amply demonstrated in the extensive Searle investigation as well as in other investigations currently under way in the Bureau of Drugs. I have great difficulties in visualizing pathologist conducting a searching examination of a variety of records which have nothing to do with pathology or closely question a number of administrators, laboratory technicians or aids, animal caretakers, etc., on their practices, on detail of their tasks, adequacy of their observations and so on.

I would not like to generate the impression here that scientific expertise in pathology or in any other scientific field associated with studies like these could or should be totally ignored. Far from it. However, the concept under which we have operated ever since I can remember is that investigations are best handled by trained and experienced investigators. Where there is a need to address certain scientific problems which transcend the capabilities of the investigators, the practice has always been for the appropriately qualified specialists from the various Bureaus of the FDA to assist the investigators; in those few cases where outstanding technical difficulties beyond the capabilities of Agency scientists are required, we have not refrained in the past from using help from outside and I should hope we shall continue to do so in the future. But this help provided by scientists on an ad-hoc basis and only where it is required is an entirely different matter than having scientists direct the actual course of the investigation. While I believe it is entirely proper (in fact preferable) to have scientists evaluate the scientific impact of a set of findings, I cannot see professional scientists do the job of professional investigators any more than I could see members of a legal society doing the work of detectives or policemen in investigating various aspects of a specific crime.

It disturbs me to see from the draft we have here that the role of what is termed the "FDA Monitor" will be reduced to little more than having this person be present during communications between UAREP and Searle; I find this kind of prospect ludicrous and I do not understand the need for it.

What I understand even less is why Searle should offer or be asked to pay the cost of this entire operation to the investigative agent in a direct manner; why is there a necessity for this body, UAREP, to enter into any kind of formal contract with Searle and why are we expected to co-sign such a contract? The fact that Searle will pay for this cannot but give them some kind of decision-making role as is evident from merely reading the terms of this proposed contract. It seems to me that no-one except the FDA can have the responsibility for undertaking this kind of work - this is our mission and we are being paid from public funds to carry it out.

Although, as expressed above, there is much I do not understand about this entire plan, particularly its basic raison d'etre, there is something here that I appreciate fully:- this is the statement at the top of page two of Wylie's memorandum:- "Searle understandably continues to press for the expediting of this agreement."

I would suggest that implementation of this contract can have only one of two predictable outcomes which are mutually exclusive:-

a) There are serious improprieties in the conduct of these studies. If this is the case, I would submit that inexperienced outside scientists selected by an outside agency under contract to the firm which is the object of the investigation, will have a markedly reduced probability of detecting such improprieties;

b) There are no serious improprieties in the conduct of these studies. IF this is the case, it would necessarily follow that any report written by the "investigators" would not signal the presence of any such improprieties. But, if so, for exactly the same reasons as listed above, such a report may well be interpreted as being nothing short of an improper whitewash.

My recommendation is simply that this entire plan be aborted forthwith, and that we proceed with this matter in a way we are supposed to; this is the way we have handled things like this in the past and the way we anticipate to operate in the future. M. Adrian Gross HFD-108 ---

(Note from Martinti: What happened after this memo. On January 10, 1977 in a 33 page letter, FDA Chief Counsel Richard Merrill recommended to U.S. Attorney Sam Skinner that a grand jury investigate Searle for the apparent violations of the Federal Food, Drug and Cosmetic Act 21 USC 331 (e) and the False Reports to the Government Act 18 U.S.C. 1001 for "their willful and knowing failure to make reports to the Food and Drug Administration required by the Act 21 USC 355 (i) and for concealing material facts and making false statements in reports of annual studies conducted to establish the safety of (aspartame)." The FDA called special attention to studies investigating the effect of NutraSweet on monkeys and hamsters.

U.S. Attorneys Sam Skinner and William Conlon both hired on with the defense team and the statute of limitations expired. No FDA Commission would allow aspartame to be on the market for 16 years. Then Don Rumsfeld who was working for Searle said he would call in his markers and get aspartame approved anyway. He was on Reagan's Transition Team, and the day after President Reagan took office he appointed Dr. Arthur Hull Hayes to do the deadly deed. A Board of Inquiry was set by the best scientists the FDA had who said aspartame had not been proven safe and caused brain tumors. Dr. Hayes over-ruled the Board of Inquiry and approved it anyway and then went to work for the PR Agency of the manufacturer and has refused to talk to the press ever since.

With regard to the UAREP mentioned in this memo, Searle paid them $500,000. They got that money for being sworn to silence. From Aspartame (NutraSweet) Is It Safe? by H. J. Roberts, M.D., Charles Press, in a chapter titled "The Myth of 'The Most Thoroughly Tested Additive in History', under Shortcomings:

"The failure to challenge the manufacturer's contract with Universities Associated for Research and Education in Pathology (UAREP), This private group was engaged to determine the factual accuracy of prior aspartame articles - BUT with the stipulation that UAREP "shall not express an opinion" regarding either the design or safety significance of these studies, nor make recommendations about the safety of aspartame for human use! Dr. M. Adrian Gross also challenged the credentials of UAREF relative to its ability to assess prior aspartame studies."

Searle sold the NutraSweet Company to Monsanto in l985 and they have since sold it to several including Ajinomoto who claims the UAREP were an outside independent firm. See my letter to Ajinomoto on www.dorway.com and they refuse to answer it. Also on this site you can read the UPI investigation documenting Rumsfeld's part in getting aspartame approved even though it is a deadly chemical poison that makes brain tumors. Aspartame Disease is now a global plague and the 1000 page medical text, Aspartame Disease: An Ignored Epidemic (www.aspartameispoison.com or www.sunsentpress.com or 1 800 814 - 9800 lists all types of neurodegenerative diseases, diabetes and other tumors triggered by this neurotoxin. It is also a baby killer, an abortifacient and teratogen (triggers birth defects). It interacts with drugs and as a chemical hypersensitization agent interacts with other toxins, additives and vaccines.)

(Note: This letter is on EPA Stationary)

Senator Howard M. Metzenbaum
United States Senate
140 Russell Senate Office Building
Washington, DC, 20510

(Dated 30 October, 1987)

Dear Senator Metzenbaum:

The following is in response to a request for comments addressed to me by Mr. James C. Wagoner of your Office in reference to the safety of the artificial sweetener aspartame, known commercially as Nutrasweet.

As you may know, during my service with the FDA from 1964 to 1979 I participated along with others in the extensive investigation of the quality of experimental studies carried out by or for the G.D. Searle& Co. of Skokie, Ill. Inasmuch as I had participated both in the "on-site" investigations as G.D. Searle & Co., as well as in the evaluation of the findings that emerged, my signature along with those of others appears on the final report of that FDA investigations (known also as the Searle Task Force Report) which was dated March the 24th, 1976.

In early 1979 I was transferred fro duty from the FDA to the EPA to assume a position involving a promotion for me. My comments here ought not to be taken to imply in any way that they represent the views of the EPA since this agency has no regulatory concerns whatsoever in the area of food additives; rather, such comments of mine represent strictly my own views.

During that 1975 FDA investigation at G.D. Searle & Co. and at a number of their contractors, a total of 25 distinct experimental studies were intensively audited. Almost half of those 25 studies (11, to be exact) were carried out for aspartame with the remaining 14 studies having been distributed amongst 6 drug products manufactured by G.D. Searle & Co. It is worthy of note that the conduct of all experimental studies by that firm, regardless whether they entailed food additives or drug products, was the responsibility of a single group in the G.D. Searle & Co.'s organization:- the Pathology-Toxicology or Path-Tox Department. Practices that were noted in connection with any given such study were quite likely to have been noted also for other studies that were audited, and this was a situation which was in no way unexpected:- after all, the set of all such studies executed by that firm from about 1968 to the mid 1970's were conducted in essentially the same facilities, by virtually the same technicians, professional workers and supervisors, and the nature of such studies does not differ much whether a food additive or a drug product is being tested for safety in laboratory animals. It is in this sense, therefore, that the overall conclusions summarized at the beginning of the Searle Task Force Report have relevance to a all the studies audited in 1975 (whether they had reference to aspartame or to any of the six drug products of Searle's) and, by extension, to the totality of experimental studies carried out by that firm around that time - 1968 to 1975.

The FDA's Task Force Report starts at the top of its page 1 with:-

"At the heart of the 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 of 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 error blur the differences between treated and control animals and in- crease 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 those general comments and references to no basis for reliance on reports generated by the GD Searle Company, serious deficiencies in Searle's operations and practices, Searle's integrity, Searle's selectively reporting the results, poorly conceived, carelessly executed and inaccurately analyzed or reported experiments at Searle's, a pattern of conduct which compromises the scientific integrity of the studies, pervasive problems in the Searle studies, their unreliability, etc., which apply across the board to all studies investigated, there are a number of additional problems that attach specifically to the aspartame studies. These are discussed in the FDA's Searle Task Force Report in its
page 25 - paragraph 1 - on the identity of the material tested;

page 26 - last paragraph - on the excision of tumor masses ante-mortem and writing the protocol after the start of a study;

page 31 - paragraph 2 - on Searle tactics designed to obtain FDA approval for aspartame;

page 32 - last paragraph - on continuity of personnel at Searle and on the adequacy of their training and supervision of such personnel;

page 33 - paragraph 2 - on practices which could compromise the study;

- paragraph 3 - on improper departure from protocol specifications on age of the
animals used;

page 34 - paragraph 2 - on deviations from protocol at Hazleton Laboratories;

page 36 - paragraph 3 - on the lack of concern both at Searle and at Hazleton Laboratories over the homogeneity, or stability of the ingredient-diet mixture; subsequent paragraphs deal with the same sort of problems at Hazleton Laboratories and it is concluded that "there is no way in which it can be assured that animals received the intended dosage.";

page 39 - paragraph 1 - on the improper use of pesticides in the areas where the studies were carried out; on the condition of the blenders used to mix the test agent in the diet; on the lack of records on mixing operations; on the conditions of the labels of the mixtures; on the lack of inventories of the test substance;

page 42 - paragraph 1 - on the records kept of the observations made and on the numerous errors and inconsistencies amongst observations and findings;

page 47 - near bottom - on the impact of the errors in the records of observations;

page 51 - paragraph 1 - on the excision of tumor masses; see also page 52, paragraph 1 there for the impropriety of this practice;

page 52 - last paragraph - on the "substantial" loss in pathology information due to autolysis, fixation "in toto", etc.

page 55 - top - on the impropriety of changing a prosector's observations by others who did not participate in examining the carcasses of the animals;

page 57 - paragraph 2 - on the poor quality of material prepared for microscopic examination of the tissues;

page 60 - paragraph 3 - on observations being reported for material that never existed; this problem was noted at both Searle and Hazleton Laboratories;

page 62 - paragraph 2 - on the lack of training by the "professional" scientists making observations in teratogenicity studies;

page 64 - paragraph 3 - on the abysmal quality of the aspartame teratology and reproduction studies and on an evaluation of these by a leading international British expert in this area;

page 66 - paragraph 3 - on the serious problems with the Waisman study of Aspartame in monkeys;

page 80 - top - on the false values presented by Searle on observations collected during the aspartame studies in hamsters, with reference to blood, clinical chemistry, etc., and the improper filtering of results from the 115 week rat study with aspartame.

It should be pointed out that the Task Force Report detailing those general conclusions as well as those that relate specifically to the aspartame studies are not merely the views of the members of the Task Force itself. That Task Force operated under the direction of a Steering Commit- tee composed of a number of FDA Bureau Directors as well as others and the Chairman of that Committee was none other then the FDA Commissioner himself. In fact the Task Force Report was addressed to the Commissioner in his capacity as Chairman of the Steering Committee, and, it seems clear that both the Committee and the Commissioner accepted that report and transmitted it to the United States Senate as an institutional FDA report without changing in it as much as a semicolon. The following are quotes from pages 3 and 4 of the record of hearings of April 8-9 and July 10, 1976, held by Sen. Edward Kennedy, Chairman, Subcommittee on Administrative Practice and Procedure, Committee on the Judiciary, and Chairman, Subcommittee on Health, Committee on Labor and Public Health:-

page 3 of the record - Commissioner Schmidt of the FDA :- "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 - Senator Kennedy (addressing Commissioner Schmidt):- "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 examinations' 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...

" Given those conclusions reached on the quality of Searle experimental studies in general and of the aspartame studies in particular, as we have seen above, by both the FDA as an institution and its Commissioner in 1976, how is it possible for another Commissioner in July, 1981, to reapprove the use of aspartame being marketed in dry foods? How is it possible for yet another Commissioner two years later, in July, 1983, to have extended such approval for marketing aspartame also in carbonated beverages? Such approvals were based on largely the very same studies that were examined by the Task Force in 1975-76.

It seems to me that no amount of additional examinations of pathology material such as undertaken by the UAREP and others, now additional statistical analyses carried out on the data, and no judgmental evaluations or interpretations of any data arising from those studies can in any way rectify the basic problem expressed by the Task Force, i.e., the FDA itself: in the absence of reasonable expectation that the experimental animals were administered the correct dosages of the test agent, any observational data carried out on those animals must be regarded as questionable or flawed. This is to say nothing of all the myriad of other problems involving the competence of those conducting such studies, and the care they exercised in their execution. Once a study is carried out and the test animals are disposed of, all that remains are the number of tiny bits of fissure preserved from their organs for microscopic examination and the written records of observations made by those who actually carried out that study. While the tissues themselves can be examined by others long after the remains of those animals no longer exist, the

reliability of the written records has already been found to be unacceptable in a great variety of ways. Clearly, there is no way that even the most competent scientists can make any new observations on those animals at a time subsequent to the conduct of the study. Once a study is compromised in its executions, it is beyond salvation by anyone.

Even with respect to those small portions of tissue preserved for microscopic examination for an indefinite period of time after any study is completed there are serious problems as presented in the 1976 FDA report with respect to Searle studies in general and for the aspartame studies in particular:- there is little if any assurance that such samples of tissues as were preserved actually originate from the specific animals said by Searle or Hazleton to have been their source (see the discussion on page 57 paragraph 2 et seq.) Furthermore, due to the unacceptably high rate of post-mortem autolysis, a great many such tissues were not collected at all from the experimental animals. In any such study of even a few hundred test animals, it takes no more than a dozen or so of them to exhibit a particular lesion (such as brain tumors, for instance) where missing no more than one or two animals manifesting such tumors in any given exposure group may well make the difference whether that particular lesion is or is not significantly associated with the test agent, i.e., aspartame or any of its related chemicals.

Following the Senate hearing in the Spring and Summer of 1976, during the winter beginning in that year the FDA began negotiating with GD Searle& Co. on retaining the UAREP (Universities Associated with Research and Education in Pathology), a private organization, on the feasibility of investigating a number of other Searle studies with aspartame. Whin I heard of those negotiating being in effect, I wrote a memorandum to Mr. Carl Sharp, the chairman of the FDA's Searle Task Force, on November the 4th, 1976. a copy of it is given here as Attachment 1, and my apprehensions over such plans is clearly evident there. Basically, they amounted to the fact that the UAREP was totally unsuited for such task since it had never before engaged in anything like it and I also objected to the idea that Searle was to fund that particular activity by the UAREP. As mentioned there, the FDA had just received a supplemental appropriation from the US Congress for the express purpose of expanding its own activities in that very area of investigating the conduct of such experimental studies by the regulated industry. Under that appropriation (which came to some $16,000.000) a great number of additional investigators were hired and trained for this particular task by the FDA.

A few months prior to the UAREP beginning its investigations in August of 1977, in April of that same year, yet another FDA investigation of three aspartame studies conducted at GD Searle & Co. was undertaken. The 76-page report of that investigation (also known as the Bressler report, after the name of the leader of the investigative team, Mr. Jerome Bressler, a compliance officer in the FDA's Chicago District) reveals the reference to a single one of those studies (the 115-week experiment in rats exposed to DKP or diketopiperazine, a breakdown product of aspartame) the following:

- substitutions of some of the animals in that study;

- the presence of intercurrent disease amongst the test animals and the administration of drugs to combat this, neither of which were completely reported to the FDA;

- incomplete examinations of tissues from the experimental animals;

- excision of tissue masses likely to be tumors from live animals during the study;

- absence of batch records for the mixing of the test substance into the diet of the test animals;

- incomplete stability studies for the agent on test;

- absence of homoqeneity 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 the DKP that was given to those rats;

- problems with the fixation-in-toto and autolysis;

- failure to report to the FDA all tissue masses (likely to be tumors) which were found in the experimental rats;

- failure to report to the FDA all internal tumors present in the experimental rats, e.g., polyps in the uterus (animal K9MF), ovary neoplasms (Animals H19CF, H19CF, and H7HF) as well as other lesions (Animal D29CF);

- inconsistencies between different parts of the report on this study submitted by GD Searle & Co. to the FDA on the precise nature of the lesions manifested by the test rats;

- numerous transcription errors in that report.

Interestingly and most important, the Bressler investigating group found not only that no homogeneity test were conducted by GD Searle & Co. on the mixture of the test agent within the animals' diet, but they actually obtained direct evidence that in fact the distribution 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. Descriptive remarks on this issue were found by the FDA investigators in a notebook kept by Searle personnel on observations made during the study, as was a Polaroid photo- graph taken by the same Searle technicians and which clearly shows the test agent in the form of coarse particles with the animals' diet. If follows that the experimental rats could have consumed their feed without actually touching the DKP and, consequently, no-one can state with any assurance whatsoever just how much DKP (if any) those rats were actually exposed to in the course of that study. Evidence such as this obtained by the FDA investigators seems to me to have been crucial to the interpretation of any findings or observations by Searle.

On page 32 of the GAO report one can read the view of the FDA's Center for Food Safety and Applied Nutrition (CFSAN) on the findings of the investigators. To me these read like a script written for Abbott and Costello in the sense of their having their perceptions inside-out or upside-down - "the diets may have been homogeneous because of a dose-related increase in the incidence of uterine polyps and decrease in blood cholesterol levels" (a clear non-sequitur, such as one almost never encounters in real life); on the problem with autolysis of the tissues the CFSAN felt "they could not determine whether the results would have been altered if these tissues had been obtained before autolysis (an obvious instance of placing the burden of proof that a study is unsound on the Government rather then requiring the petitioner for approval of a food additive to demonstrate, as the Law requires, that any study is of sound quality); the observation by the investigators that 329 fetuses were examined in two days by a single person (a clear impossibility) was laid aside by the CFSAN with another non-sequitur:- that "the Searle scientist who performed these examinations estimated that he examined about 30 fetuses a day..."; on the fact that an insufficient number of sections were made out of the heart, the CFSAN observed:- "...while there was no evidence that the study was compromised by this issue, the practice of not making enough sections through the organs, as specified in the protocol, did not preclude a possible failure to observe abnormalities which may have occurred."

Despite all these problems, at least some of which undermined or compromised the study in an unredeeming manner, apparently the CFSAN and the FDA Commissioner found the quality of those three studies reported on by the Bressler investigating group as being in fact of an acceptable nature and GD Searle & Co. were notified to this effect in September, 1977.

The investigation undertaken by the UAREP began in August, 1977. After reading the report of that group, it became painfully clear to me that the misgivings which I foresaw in November 1976 (see Attachment 1 here) were indeed justified and my worst fears were eventually realized. If one compares the kind of detailed and painstaking findings made by the professional investigators from the FDA both in 1975 and in 1977 with the rather amateurish activities by the UAREP outlined in their report, the contrast between these could hardly have been greater. Of course, inasmuch as GD Searle had paid for the UAREP investigation, the cost of it for the FDA was nil; what the FDA got in return for its money, was not worth much more than this.

Perhaps the most disappointing aspect of this entire fiasco with the quality or reliability of the experimental studies with aspartame was the failure of the Public Board of Inquiry (PBOI) to consider these aspects in their deliberations. The PBOI expressly declined to do so even after the principal objectors to the approval of aspartame for marketing, Mr. James Turner and Dr. John Olney, asked for such consideration. To me it seems almost beyond belief that a collection of scientists can sit on judgement over the interpretations to be made on a set of results arising from certain studies, not only failing to consider the adequacy of the conduct of those studies but actually refusing to do so.

Given this sort of circumstance, it should not come as a surprise to anyone that eventually the Commissioner of the FDA finally reapproved aspartame for marketing even though his own panel of experts were divided over the issue

whether this particular food additive had been shown in a reasonable manner to be safe.

As mentioned in the GAO report (page 12 there) "The Federal Food, Drug, and Cosmetic Act does not specifically define 'safety'. However, the legislative history of the Food Additives Amendment indicates that safety means "proof of a reasonable certainty that no harm will result from the proposed use of an additive'." It is intuitively clear to anyone that no "reasonable certainty" can attach to any results emanating from studies as profoundly flawed as the Commissioner of the FDA had determined in 1976 and as amply reconfirmed since then.

This concludes my remarks on the quality or reliability of the experimental studies with aspartame carried out by the GD Searle & Co. or by the contractors working under the direction of that firm.

Since Mr. Wagoner of your Office has requested my comments in a very short period of time, I am expediting this letter to you now; however, I plan to send you in the very near future an additional communications where two other issues are discussed in some detail:- the problem with the brain tumors induced by aspartame and that the FDA's having set a very high (and, to my view, clearly dangerous) level of Acceptable Daily Intake, or ADI, for this particular food additive in the diet of humans.

Finally, I wish to state here that, quite aside from my professional background as a scientist and speaking merely as an individual citizen, I am grateful for the concern you have had over the safety of aspartame for many years now; as such, I wish to thank you for having given me this opportunity of being of some service to you. With best wishes for the future, I remain, Senator Metzenbaum,

Sincerely yours,

M. Adrian Gross
Senior Science Advisor
Benefits and Use Division,
Office of Pesticide Programs

Sworn to be a true copy on 30 Oct, 1987.

(Note: This letter is on EPA Stationary)

Senator Howard M. Metzenbaum
United States Senate
140 Russell Senate Office Building
Washington, DC, 20510

(Dated 3 November, 1987)

Dear Senator Metzenbaum,

The following represents a continuation of my letter to you of last week, October the 30th, 1987. In that letter I discussed the many serious problems with the quality or reliability of the experimental studies with aspartame carried out by or for G.D. Searle & Co.; I noted there that in 1976, the FDA Commissioner at that time, Dr. Alexander Schmidt, speaking for the FDA as an agency, publicly stated that he agreed with a set of conclusions, the first of which was that the FDA had no basis for reliance on the quality of studies generated by or for that firm.

Once such a determination is made at the highest level of the FDA, it seems bizarre, to say the least, that essentially the same set of studies could provide a foundation for the subsequent decision that those studies in fact had demonstrated the safety of aspartame with "reasonable certainty" as required the Food Additive Amendment of the Federal Food, Drugs, and Cosmetics Act. As the television commercials for Weyerheauser, the "tree-growing company", keep telling us:- "once the eagles are gone, they are gone."

Much the same is true also for experimental or laboratory rats:- once they are gone, no one can bring them back for an interview to ask them how much, if any, aspartame or DKP they had ingested while the experimental studies in

which they had participated were in progress and, without such essential information, examination of their preserved tissues by even the most skillful and competent of pathologists becomes largely a meaningless exercise which cannot in any way resurrect in Phoenix-like fashion the value of those studies.

However, having said all of this, let us assume that in fact those studies were of an acceptable quality; let us pretend that the test animals were actually exposed qualitatively and quantitatively to what G. D. Searle & Co. would have us believe that they were exposed; that there was no post-mortem autolysis of their carcasses rendering vast numbers of their tissues to a state unsuitable for pathology examination; that the technicians involved in the conduct of those studies were fully trained, competent, and adequately supervised to make observations on those animals prior to their death; that the same was true with respect to the observations made after their death; that in fact those technicians actually made proper such observations; that the proper samples of tissues with grossly observed lesions were in fact collected for additional microscopic examination; that the identity of such tissue specimens corresponded (as they should) to the identity of each animal that was their source, etc. In short, let us make believe in a spirit of Halloween that nothing which was uncovered for the aspartame studies by the FDA investigations of 1975 and 1977 was actually true, i.e., that in fact we are dealing here with studies of an absolutely perfect quality or reliability. Of course, such assumptions belong to the domain of Fantasyland, but, nevertheless, let us play this little game for awhile.

Under such highly speculative hypothetical conditions, let us now ask again whether aspartame can be viewed as being safe with "reasonable certainty".

To answer this question, let us focus for a moment on the pathology examinations carried out not by the pathologist originally retained by GD Searle & Co. (those of the Experimental Pathology Laboratories, or EPL) who examined the tissues from the rats in the Two-Year Rat Study) but, rather, on the examinations carried out by the expert pathologists in the UAREP. Although in my last letter addressed to you last week I referred to the investigative efforts of the UAREP as being "amateurish" by comparison with those of the professional investigators in the FDA, I have no reason to question or criticize in any way the competence of UAREP pathologists in their own specialty where they had examined first-hand tissue specimens said to gave been collected from the animals in that study.

The UAREP report (Volume 2, Chapter IV, dealing with that particular study, reveals in Appendix IV-21 on its page 393 et seq. the animals which were found by the UAREP pathologist to have harbored brain tumors:

- Group Sex Path.No Animal No. Type of brain tumor Weeks to death

1 M 64-603 83-651 Astrocytoma 104

2 M 64-775 83-745 Astrocytoma 104

3 M 64-764 83-837 Astrocytoma 76

4 M 64-707 83-919 Astrocytoma 104
M 64-712 83-888 Oligodendroglioma 59
M 64-713 83-892 Astrocytoma 49
M 64-715 83-895 Astrocytoma 100

5 M none
Table Continued from previous page

1 F none

2 F 64-989 83-769 Astrocytoma 104
65-011 83-766 Astrocytoma 69

3 F none

4 F 64-925 83-934 Astrocytoma 85

5 F 84-881 84-010 Medulloblastoma/meningeal sarcoma 13

64-888 84-019 Astrocytoma 67

Altogether the table just above lists a total of 12 animals with brain tumors, 7 males and 5 females; for both sexes there are 1 in Group1, 3, in Group 2, 1 in Group 3, 5 in Group 4, and 2 in Group 5 for a total of 12. Note that the GAO report which refers to those animals at the bottom of its page 45 is in error in that it lists 4 (rather than 3) animals with brain tumors in Group 2 (the low dosage group). Because of this error, the GAO's Figure 4.1 on page 46 of its report is somewhat misleading.

The GAO report also indicates under item (2) on its page 34:- "According to UAREP's president at the time of its review"

"...the thing that impressed (UAREP) throughout the study,... which is reflected in our final statements and conclusions, was that the interpretations of the experimental results by previous observers did not really differ very significantly from ours following our review of the material."

Yet, Appendix IV-25 beginning on page 446 of the UAREP report repre- sents a 6-page table entitled "Significant Discrepancies Between Histo- pathologic Diagnoses By UAREP and EPL", the last mentioned having been, as stated above, the "previous observers", i.e., the pathologists originally retained by GD Searle & Co. to examine those tissues and whose report was submitted by that firm to the FDA in support of their petition to have aspartame approved for marketing. In that table I have counted some 207 such "significant discrepancies" between the diagnoses of the UAREP and EPL and these involve some 162 animals or 37% of all the 440 animals in that study. This was not reported by the GAO representatives who apparently were content with merely chatting with the UAREP president about his reminiscences of some 10 years ago.

Moreover, that same UAREP report reveals in that very same Appendix IV-25 as cited above for the 12 animals with brain tumors the characterizations or diagnoses reached by the pathologists from the EPL:

for animal No. 83-651 with an astrocytoma of the brain EPL lists the brain as unremarkable;

for animal No. 83-745 with an astrocytoma of the brain EPL lists no comparable diagnosis;

for animal No. 83-837 with an astrocytoma of the brain EPL lists no comparable diagnosis;

for animal No. 83-919 with an astrocytoma of the brain EPL lists no comparable diagnosis;

for animal No. 83-888 with an Oligodendroglioma of the brain EPL lists no comparable diagnosis;

for animal No. 83-892 with an astrocytoma of the brain EPL lists no comparable diagnosis;

for animal No. 83-895 with an astrocytoma of the brain EPL lists no comparable diagnosis; for animal No. 83-769 with an astrocytoma of the brain EPL lists no comparable diagnosis; for animal No. 83-766 with an astrocytoma of the brain EPL lists no comparable diagnosis; for animal No. 83-934 with an astrocytoma of the brain EPL lists an ependymoma i.e., a different kind of brain tumor;

for animal No. 84-010 with a Medulloblastoma/meningeal sarcoma of the brain, EPL lists a meningioma i.e., a tumor of the membranes covering the brain;

for animal No. 84-019 with an astrocytoma of the brain there was no discrepancy in the EPL diagnosis.

In other words, for the 12 animals identified as having brain tumors in this study by the UAREP pathologists, EPL pathologists (i.e., the "pre- various observers" as the president of the UAREP has it) had completely missed no less than 9 or 75% of these. Such difference between the diagnoses of those two groups cannot by any stretch of the imagination be interpreted by any reasonable person as being "not very significant" as that same president of the UAREP is quoted by the GAO to have stated. Incidentally, the GAO representatives themselves also failed in their report to highlight this tremendous difference between the diagnoses of the UAREP and EPL.

Furthermore, Appendix IV-20 on page 391 of that same UAREP report reveals in the first row of the table on that specific page that GD Searle & Co. or their agents had provided to the subcontracting EPL pathologists, i.e., to those

whose report that firm had originally submitted to the FDA:
- a) only 8 (or only 10%) of the brain sections for the 80 animals in group 2;
b) only 7 (or only less then 9%) of the brain sections for the 80 animals in Group 3;
c) only 5 (or only less than 7%) of the brain sections for the 80 animals in Group 4;

and the UAREP were proved with the brain sections of 2 fewer animals than were provided to the EPL. Again, this is another little wrinkle not high- lighted in the GAO report.

This, quite by itself, is sufficiently eloquent on just how G.D. Searle& Co. saw fit to discharge their responsibilities in reporting fully and completely their results of the Two Year Rat Study with aspartame to the FDA; it is just as eloquent on precisely how thoroughly the Bureau of Foods of the FDA (the predecessor of the CFSAN) had reviewed the data emanating from that study prior to its initial approval in 1974 for the marketing of that food additive.

I note at the bottom of page 54 in the GAO report that CFSAN had objected to the medulloblastoma that was noted in a female rat at the top exposure level on the grounds that "it was unlikely aspartame caused this tumor". Such statement would imply that aspartame had caused all the other tumors (the nine astrocytomas and the solitary oligodendroglioma noted in animals exposed to it) which is vastly more than enough to lead to a conclusion that, because of this, it cannot be regarded as being a safe food additive. The reason for such conclusion by the CFSAN appear in the first paragraph of page 46 of the GAO report. As is also true for many of the other arguments advanced by the CFSAN and by G.D. Searle& Co., those reasons are largely speculative and without much merit. Still, to accom- modate the CFSAN's views regardless of their validity, I am willing to ignore the occurrence of that particular tumor in a female animal at the top exposure level.

If we are to analyze the distribution of the rest of those brain tumors, we ought ignore also the response of any animals at the top level of exposure (Group 5) on the grounds that completing toxicity may well have inhibited the expression of brain tumors in the animals of that group.

Accordingly we have for the male animals with brain tumors:

- in Group 1 i.e., at 0 mcm/kgm body-weight 1/59 = 1.69% positive rats;

in Group 2 i.e., at 1,000 mcm/kgm body-weight 1/36 = 2.78% positive rats;

in Group 3 i.e., at 2,000 mcm/kgm body-weight 1/40 = 2.50% positive rats;

in Group 4 i.e., at 4,000 mcm/kgm body-weight 4/40 = 10.00% positive rats;

This particular distribution yields a dose-response slope as high as 0.000,019,865 with standard error of only 0.000,009,729,2 leading to a chi square with one degree of freedom for slope as high as 4.118, whose one-sided probability is as low as p = 0.021,217; in other words, the dose-dependent increase in frequency of brain tumors for the male rats in that study was highly significant and, therefore, attributable to aspartame, the agent on test.

That particular slope of the dose-response function yields the following expected incidences of brain tumors amongst male animals:

- at 0 mcm/kgm body-weight - 0.867%

at 1,000 mcm/kgm body-weight - 2.854%

at 2,000 mcm/kgm body-weight - 4.840%

at 4,000 mcm/kgm body-weight - 8.813%

Note that the four expected values given just above are fairly close to their respective observed values listed near the bottom of the preceding page, which indicates a close fit of the observations to the dose-response or regression function.

If we have reference to the animals of both sexes with brain tumors, we have:-

in Group 1 i.e., at 0 mcm/kgm body-weight 1/118 = 0.847% positive rats;
in Group 2 i.e., at 1,000 mcm/kgm body-weight 3/ 76 = 3.948% positive rats;
in Group 3 i.e., at 2,000 mcm/kgm body-weight 1/ 80 = 1.250% positive rats;
in Group 4 i.e., at 4,000 mcm/kgm body-weight 5/ 80 = 6.250% positive rats;

This particular distribution yields a dose-response slope as high as 0.000,011,578 with a standard error of only 0.000,005,831,8 leading to a chi square with one degree of freedom for slope almost as high as the one for merely the male animals, 3.920, with one-sided probability almost as low as that for merely the male animals, p = 0.023,860. The conclusion that follows is identical with that reached above for merely the male animals.

The expected incidences for both sexes are:-

at 0 mcm/kgm body-weight - 1.006%
at 1,000 mcm/kgm body-weight - 2.164%
at 2,000 mcm/kgm body-weight - 3.322%
at 4,000 mcm/kgm body-weight - 5.638%

or, again, fairly close agreement to the observed values given just above.

Note that in the analyses outlined above I have not combined the response noted at two or more experimental groups, as was done by the PBOI and as objected to by the CFSAN.

If we now analyze the data in the same "uncombined" fashion, while still excluding from consideration the medulloblastoma manifested by a female in the top exposure level group, and even if we do consider the poor response of the animals in the top exposure level group (which, as noted, may have been due to competing toxicity interfering with the expression of brain tumors), but consider the so-called "historical control" incidence of brain tumors (49/59,812 cited by Dr. Olney in his table 2 on page 2 of Part III of his written statement presented to the PBOI as well as the rate of 4/115 positive control animals noted by both the UAREP and EPL for the Lifetime Toxicity study of aspartame in the rat - see UAREP report, Chapter V, page 559) along with the contemporaneous (local) control rate of 1.118 positive animals of both sexes noted in the Two-Year aspartame study in the rat, we end up with a total of 54/60,045 = 0.090% for the control inci- dence for both sexes. The weighted averages of the exposure level in Group 5 animals was 7,420 mgm/kgm body-weight. Accordingly we would have:

- at 0 mcm/kgm body-weight - 54/60,045 = 0.090% rats with brain tumors;
at 1,000 mcm/kgm body-weight - 3/ 76 = 3.947% rats with brain tumors;
at 2,000 mcm/kgm body-weight - 1/ 80 = 1.250% rats with brain tumors;
at 4,000 mcm/kgm body-weight - 5/ 80 = 6.250% rats with brain tumors;
at 7,420 mcm/kgm body-weight - 1/ 77 = 1.299% rats with brain tumors;

This distribution yields a slope of dose-response function as high as 0.000,005,297 with a standard error of only 0.000,000,423,4, leading to a chi square with one degree of freedom for slope as high as 156 whose one- sided probability is as low as 4.031E-36, i.e., 4 with 35 zeros ahead of it and to the right of the decimal point. This is nothing short of astronomically high significance.

Alternatively, if one considers merely the contemporaneous or local control value in the two-year rat study with aspartame, 1/118 = 0.85% animals positive for brain tumors, the response at the lowest level of exposure, 1000 mgm/kgm body-weight, 3/76 = 3.95% animals similarly positive for brain tumors, is elevated by comparison with that control rate more than 4.5 times which is borderline significance at p = 0.058,674. The response at the next to the highest level of exposure of 4,000 mgm/kgm body-weight, 5/80 = 6.25% animals with brain tumors, is elevated more than 7.3 times over that same control rate of 0.85%, and this is highly significant at the p = 0.009,975 probability level.

Finally in this entire consideration of significance for the brain tumors, one could set up yet another sort of contrast by making believe that all animals exposed to aspartame were in fact exposed to the highest level tried, 7,420 mgm/kgm body-weight. This would extend a great deal of the benefit of doubt to aspartame. that particular contrast of 0.090% the control rate versus 10/313 = 3.195% for all exposed animals (still excluding the medulloblastoma objected to by the CFSAN), leads to a chi square adjusted for continuity and with one degree of freedom as high as 254 which is,

again, of almost astronomical significance.

In other words, even if one is willing to give aspartame a very generous benefit of doubt on the quality or reliability of the two-year study in rats as well as several other considerable benefits of the doubt involved in the test of significance, it still emerges that the rate of brain tumors amongst the animals exposed to it vastly exceeds that for animals not exposed to it and such excess is very highly significant. What this says is that there cannot be any reasonable, or even shadow of a doubt that aspartame had caused such an increase in the incidence of brain tumors.

It follows, therefore, that the conclusion of the PBOI and of several members of the FDA Commissioner's panel of experts is the right conclusion, and that reached by the CFSAN and by the FDA Commissioner who overturned the PBOI view in this respect is the wrong conclusion.

As a result of all the considerations above, I would add my full endorsement to the conclusion of the unidentified statistician mentioned in paragraph 3 on page 56 of the GAO report who apparently reached the same conclusion as I did in an independent manner.

I would also support the views of the similarly unidentified carcinogenicity specialist mentioned in paragraph 2. of that same page in the GAO report who felt that the relatively high exposure rates in the two- year rat study with aspartame were a necessary compensation for the relatively low power of this study to detect as significant increases as high as 5% in the brain tumor rate for humans exposed to aspartame, which would constitute a downright catastrophe.

The Acceptable daily Intake (ADI) of aspartame.

Still under the hypothetical assumption that these experimental studies were of an impeccable quality, let us now turn to a different aspect of the interpretation of results arising from them.

Near the bottom of page 60 of the GAO report it is disclosed that the Acceptable Daily Intake (ADI) of aspartame was raised from 20 mgm/kgm body- weight to 50 mgm/kgm body-weight after aspartame was approved for use in carbonated beverages and after it became evident to the FDA that very young children could potentially consume almost 50 mgm/kgm body-weight of it per day.

It appears that the justification for such sudden and considerable increase of 150% in the ADI for aspartame was provided by the results of five clinical studies as well as five other studies published in the literature; however, it is unclear from the GAO report whether any of those studies were of a long duration (such as a major part of the life-span) - clearly, such studies conducted with humans could not possibly have been of this nature.

To examine whether an ADI of 50 mgm/kgm body-weight can be justifiably regarded as "safe", let us return to the issue of the brain tumors and conduct for these a formal Risk Assessment. Although it has been established here that the incidence of brain tumors in rats was highly significantly related to the dosage of aspartame in the two-year rat study (and, therefore, that aspartame had cause that increase in incidence of brain tumors amongst exposed animals by reference to the rate noted in comparable unexposed ones) such determination of high significance is in fact not a necessary requirement for a formal risk assessment.

I have carried out such risk assessment by utilizing two separate procedures which are widely accepted for this purpose:- the Mantel-Bryan approach (also known as the log-probit method) and the Hone Hit method of extrapolation.

To extend again the benefit of doubt to aspartame, I have had reference in such assessment to the control rate of brain tumors noted merely in the local or contemporaneous control animals (1/118 = 0.847%) rather then to the almost ten times lower rate of the "expanded" control group discussed in the previous section here (54/60.045 = 0.090%); also, I have assumed all non-control rats to have been exposed at the top levels of exposure (7,420 mgm/kgm body-weight) rather then to a series of levels starting at merely 1,000 mgm/kgm body-weight; I have also excluded from consideration the medulloblastoma observed for Animal No. 84-010, but have not excluded the response of any other animal in that study. Each of these features, as mentioned, provides the benefit of doubt to aspartame, i.e., to its "producers" as distinct from its "consumers".

With such additional assumptions, we may tabulate the estimated "virtually safe" levels of aspartame in the mgm/kgm body-weight/day for a variety of upper limits on the risk indicated in the column at the extreme left of the table that

follows here .

Note that for each of the two methods of extrapolation, two estimates are given in the table opposite each upper limit on the risk:- on for rats and one for humans. The estimate for the humans is related to the corresponding one for rats by being 5.23 time smaller then it. This is the factor necessary for "translation" from rats to humans by correcting for the body-area of the two species:- due to its larger size, the human has a body-area per unit mass smaller than does the rat:-

An average male rat in the study considered here weighed 506 Gms., and an average female rat 331 Gms., for a mean weight of 418.5 for the two sexes. This a human of average weight of 60 Kgms., say, is "worth" on a mass or weight basis 60,000/418.5 = 143.37 rats of average weight. But that same human weighing 60 Kgms is worth on a body-area basis only the two-thirds power of 143.37 i.e., only 27 .39 such rats. Thus, to have equivalence for doses expressed in mgm/kgms body-weight rats and humans, the dosage for the rats must be divided by the one-third power of 143.37, i.e., by 5.23. Hence the factor used in the table that follows.

RESULTS EMANATING FROM THE FORMAL RISK ASSESSMENT INVOLVING BRAIN TUMORS

"virtually safe" level of aspartame in mgm/kgm bw/day
Log probit method ----------One Hit method

Upper limit on risk for rats for humans for rats for humans

1/100,000,000 0.700 0.134 0.001,278 0.000,244

5/100,000,000 1.349 0.258 0.006,392 0.001,22

1/ 10,000,000 1.809 0.346 0.012,78 0.002,44

5/ 10,000,000 3.674 0.702 0.063,92 0.012,2

1/ 1,000,000 5.050 0.966 0.127,8 0.024,,4

5/ 1,000,000 10.95 2.09 0.639,2 0.122,

0 1/ 100,000 15.55 2.97 1.278 0.244

5/ 100,000 36.81 7.04 6.392 1.22

1/ 10,000 54.63 10.45 12.78 2.44

5/ 10,000 146.5 28.01 63.93 12.2

1/ 1,000 232.3 44.42 127.9 24.5

5/ 1,000 759.1 145.2 640.8 123.0

It turns out from the entries in the table just above that an ADI of 50 mgm/kgm body-weight for humans is associated by both methods of extrapo- lation with an upper limit on the risk as high as between 1/1,000 and 5/1,000 population exposed to aspartame to develop brain tumors as a result of exposure to that food additive. For this to actually become evident, it would take many years since such tumors have a very long latent period, i.e., it takes a long time for them to become manifest. Thus, it seems to me that we are dealing here with a huge time bomb.

There is hardly any need for me to emphasize here that this represents an unacceptably high risk or hazard posed by aspartame.

SUMMARY AND CONCLUSIONS.

From what has been discussed in my letter addressed to you last week as well as from what has been presented in

the previous pages of this communication, I can conclude the following:-

1. It is impossible for anyone to appreciate just how a determination by the FDA that the G.D. Searle & Co. experimental studies with aspartame were of an unacceptable quality in 1976 can be metamorphosed several years later into a view by that same Agency that essentially the same studies were sufficiently reliable for anyone to assess that this food additive is "reasonably certain" to be safe for consumption by humans.

2. Even if, contrary to the FDA's view in 1976, the quality of the conduct of those studies could be relied upon by the same agency to even begin making such a determination, at least one of those studies had reveled a highly significantly dose-related increase in the incidence of brain tumors as a result of exposure to aspartame.

The full incidence of those brain tumors was not disclosed by G.D. Searle& Co. to the FDA prior to the initial approval for the marketing of aspartame in 1974; moreover, the review of that study in the FDA was so flawed that the Agency apparently did not even realize tat that time that only a portion of the observations on brain tumors had in fact been submit- ted by G.D. Searle & Co. in their petition for that approval.

3. Quite aside from the remarkable significance of the increased incidence with dose of those brain tumors, the ADI of 50 mgm/kgm body- weight recently set by the FDA for the human consumption of aspartame is alarmingly dangerous in that it involves an extremely high and, therefore, a totally unacceptable upper limit on the risk for those consuming aspartame: between 1/1,000 and 5/1,000 population to develop brain tumors as a result of such exposure. 4. Although in their report the GAO express the view that the FDA "followed its required process in approving aspartame (for marketing)" I would sharply disagree with such evaluation. Although the FDA may have gone through the motions or it may have given the appearance of such a process being in place here, the people of this country expect and require a great deal more from that agency charged with protecting their public health:- in addition to mere facade or window-dressing on the part of the FDA, they require a thorough and scientifically based evaluation by the Agency on the safety of the products it regulates.

Unfortunately this has clearly not been the case here. And without this kind of assurance, any such "process: or dance represents no more than a farce and a mockery of what is truly required.

Sincerely yours

M. Adrian Gross, Senior Science Advisor, Benefits and Use Division, Office of Pesticide Programs Sworn to be a true copy on 3 November, 1987.

(Martini Note) There have been three congressional hearings. By this time NutraSweet was owned by Monsanto who paid Senators like Orrin Hatch. One of his press releases said: Hatch says no to congressional hearings on aspartame. So they didn't even happen until l985. Senator Metzenbaum wrote a bill listed as dead bill on www.dorway.com to have independent studies done on the problems being seen in the population. But Monsanto could not allow that to happen. Gregory Gordon who wrote the UPI 8 month investigation on aspartame wrote an article in the Star Tribune on Nov 22, 1996 titled FDA Resisted Proposals To Test Aspartame. He said: "FDA officials have for years resisted proposals from government scientists for comprehensive studies of the safety of the artificial sweetener aspartame, which 100 million Americans consume as NutraSweet."

The FDA who tried for years to prevent the approval of aspartame had now given it's loyalty to industry instead of the consumer public. As I told Acting FDA Commissioner Michael Friedman who was hired by Monsanto in l999: "The FDA no longer needs a revolving door - why not build a bridge to take care of the traffic?" Obviously, this was his reward for defending Monsanto on 60 Minutes in l996.

Never forget the words of FDA toxicologist Dr. Adrian Gross who was a hero of the FDA in his last words to Congress. He said at least one of Searle's 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 .... In view of 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?" ..."Given the cancer causing potential of aspartame how would the FDA justify its position that it views a certain amount of aspartame as constituting an 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?"

The Delaney Amendment made it illegal to allow any residues of cancer causing chemicals in foods. Today it has been repealed. Dr. Adrian Gross has passed on but we will never forget him and his efforts as well as Dr. Jacqueline Verrett, another FDA toxicologist who told Congress that all studies from Searle were built on a foundation of sand and should be thrown out. Aspartame, a deadly chemical poison, that among other things makes brain tumors and kills babies, was marketed for human consumption only because the FDA violated the law. And so operations of Mission Possible International exist the world over, an unpaid volunteer force warning all consumers off aspartame. Take it seriously and save your life.

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