

TUMORS AND CANCER; THE DELANEY AMENDMENT

“By far the most mutagenic agents known to man are chemicals, not radiation. And in regard, food additives rather than fallout at present levels may present a greater danger.”

Dr. Richard Caldecott (1961)

(Atomic Energy Commission)

Heavy consumers of aspartame products appear to be increased for developing tumors in the brain (see below) and elsewhere. The author initially considered “anecdotes” about cancer involving organs other than the brain in aspartame reactors to be coincidental. AS the number increased, however, a relationship could not be ignored.

Reference was made in Chapter IX to aspartame-induced vaginal bleeding, breast tenderness, and changes involving blood cells and lymph nodes.

Admittedly, this realm remains controversial. The Bressler Report (1977) underscored the numerous shortcomings of aspartame studies in rats, especially tumor induction. Dr. M. Adrian Gross, a senior FDA pathologist-scientist, stated

“In view of all these indications that the cancer-causing potential of aspartame is a matter that had been established way beyond any reasonable doubt, one can ask: “What is the reason for the apparent refusal by the FDA to invoke for this food additive the so-called Delaney Amendment to the Food, Drug, and Cosmetic Act?” (Congressional Record-Senate August 1, 1985, p. S10837).

There may be a long hiatus between the introduction of a drug or chemical and awareness of its link to cancer. This is illustrated by phenolphthalein, the main ingredient of several popular laxatives. Nearly a century lapsed before documentation of its carcinogenic activity in rodents – including tumors of the ovaries, kidneys, adrenal glands and thymus (McGinley 1997).

Selected Tumors

Dr. George Schwartz (1999) suggested a connection between aspartame consumption and breast cancer and prostate cancer. Both markedly increased following the release of aspartame in 1981, based on governmental surveillance statistics.

There are suggestive anecdotal reports in this series.. For example, a diabetic male developed retinopathy and joint pain while consuming diet colas, and then cancer of the breast.

The puzzling rise of certain cancers over the past decade, especially among younger weight-conscious women, warrants consideration of the contributory role of aspartame products.

- Ductal breast carcinoma in situ rose 52 percent from 1983-1989; during this period the use of aspartame products quadrupled. The numbers subsequently rose to 23,000 case in 1992 and 36,000 in 1998, 200 persons higher than had been projected.
- A fourfold increase in adenocarcinoma of the cervix in England's East Anglia region, most notably in the 30- to 39-year-age group was reported in 1997 b Diane Stockton of the Institute of Public health at Cambridge University.

The Delaney Amendment

Congress included the Delaney clause in the 1958 Food Additives Amendment. Its intent was to ban the ingestion of cancer-causing chemicals.

The circumstances surrounding the adoption of its Federal law may be of interest to "Trivia" buffs. Representative James Delaney of New York unsuccessfully tried to obtain its passage for five years. Delaney's staff then briefed actress Gloria Swanson, a health food advocate, in 1956. She enlisted sympathetic wives of congressmen, who in turn encouraged their husbands to support the bill.

Unfortunately, the Delaney clause was emasculated by the Senate's Comprehensive Regulatory Reform Act of July 19, 1995. Without defining the terms "negligible" or "insignificant," it stated that a substance or product shall not be prohibited or refused approval when it "presents a negligible or insignificant foreseeable risk to human health."

The Author's Perspective

Having monitored the controversy about saccharin and urinary bladder tumors (see below). The following revelations proved troublesome: (a) deficiencies involving comparable testing with aspartame; (b) ignored reports of brain tumors in mice given aspartame; and (c) reluctance of governmental agencies to invoke the Delaney Amendment.

In prior publications, the author reported increased tumor rates attributable to divers influenced to which the population is exposed. They include

- The ability of insulin to enhance the action of male hormone (testosterone) on prostatic growth (Sirek 1953; Calame 1964; Roberts 1966a, 1967c).
- Diaz-Sanchez et al (1999) demonstrated enhancement of insulin biosynthesis and secretion by testosterone, consistent with the hyperinsulinemia encountered in hyper androgenic syndromes.
- A variety of tumors caused by exposure to the pesticide pentachlorophenol - especially lymphoma, sarcoma, leukemia and other blood disorders (Roberts 1990b, 1997d).
- Breast enlargement/tumors in persons taking mega doses of vitamin E (Roberts 1994c).
- Prostate cancer after vasectomy (Roberts 1993d).

Aspartame as a Co-Carcinogen

A potentiated carcinogenic effect by aspartame in our increasingly complex environment demands study. Others share a similar orientation.

- Dr. Samuel S. Epstein (199) (Professors of Environmental and Occupational Medicine, University of Illinois) stated, “Much cancer is avoidable and due to past exposure to chemical and physical carcinogens in the air, water and food and the workplace.”
- Huff, Haseman and Rall (1991) offered this summary concerning chemical carcinogens.

“We believe our scientific and public responsibility must continue to be directed toward identifying those chemicals, mixtures of chemicals, and exposure circumstances that present potentially the most predictable carcinogenic (and other toxicological) hazards to humans... The important issue is not whether we are undeniably correct in extrapolating carcinogenic responses in laboratory animals up the evolutionary trail to humans, but rather to concentrate our vigilance to assure and improve the entrusted public health.”

Possible Carcinogenic Mechanisms

Several of the potential cancer-inducing properties of aspartame, its three components (phenylalanine; aspartic acid; and a methyl ester that promptly becomes free methanol after ingestion), and the many breakdown products on exposure to heat and storage are cited here and in the ensuing discussion of brain tumors.

- Many constituents in the human diet are nitrosated within the gastrointestinal tract to form potentially carcinogenic nitroso compounds. Shephard et al (1993) reported mutagenic activity by aspartame after nitrosation, using *Salmonella typhimurium* as the test organism.
- The diketopiperazine derivative of aspartame (Chapter XXV) has been incriminated as a tumor-causing chemical.

- Formaldehyde released from the breakdown of methyl alcohol (Chapter XXI) is known to be carcinogenic.
- The potential carcinogenic effects of chronic hyperinsulinemia (Chapter XIV) has been discussed in prior publications, with special reference to the prostate (Roberts 1967d). Others have implicated hyperinsulinemia in the pathogenesis of breast cancer (Diamanti-Kandarakis 1999).
- Alteration of glucose transport is a characteristic of experimental tumors. Reporting on this phenomenon, and the dramatic increase in total cellular glucose transporter protein, Birenbaum et al (1987) emphasized the induction of such transformation when fibroblasts are starved for glucose.
- Increased phenylalanine may play a role. Animal and human studies indicate that restricting dietary phenylalanine decreases tumor growth and metastases (Norris 1990).
- Several investigators have implicated prolactin (Chapter XXIV) as a tumor-promoting substance in various organs – including the pituitary (Oliveira 1999), endometrium (Brosens 1999), and human breast (Maus 1999).
- The brown substances created by the heating of amino acids during cooking may be mutagenic and carcinogenic (Abelson 1983). They include a number of DNA-damaging agents.
- The causation or enhancement of brain and other tumors in persons consuming aspartame products may summate upon a hyper immune state induced by early and multiple immunizations with vaccines whose long-term safety is being increasingly challenged (Section 6-D). A number contain formaldehyde (Chapter XXI) and mercury as preservatives.

The mutagenic and carcinogenic potential of other chemicals might intensify under the influence of aspartame and its breakdown products. The ability of aspartame to induce or aggravate the multiple chemical sensitivity syndrome, including pesticide reactions, was discussed in Chapter VIII-E.

The Issue of Gender

The agencies responsible for approving aspartame apparently overlooked an important gender-related detail in experimental studies. The assessment for potential urinary bladder cancer following administration of aspartame and its diketopiperazine derivative was studied only in female mice. Professor George T. Brian (1984) noted that female Swiss albino mice were used for “all” such studies.

The author expressed reservations about limiting the testing to female animals at the First International Meeting On Dietary Phenylalanine and Brain Function held on May 10, 1987 in Washington, D.C. Information to the contrary from those present – including at least five professionals and scientific consultants for the manufacturer – was specifically solicited. No verbal or written response, then or since, has been received.

The subject of urinary bladder tumors induced by saccharin will be discussed below. There is little doubt, however, that it is largely a phenomenon of male rats. Miller and Howe (1977) asserted. “For bladder cancer, the distinction between males and females seems to us to be fundamental.”

BRAIN TUMORS

Pre-Approval Perspectives

On September 60, 1980 a Public Broad Of Inquiry (PBI) unequivocally advised against the approval of aspartame owing to the high incidence of brain tumors among animals receiving this chemical. It did not mince words: “The Board has not been presented with proof of a reasonable certainty that aspartame (NutraSweet) is safe for use as a food additive under is intended conditions of use.”

The observations of Dr. John Olney concerning aspartame-related brain tumors are detailed below. Other investigators also reported increased rates of brain tumors (gliomas) in rats given aspartame (Congressional Record-Senate 1985a, b). Cornell, Wolfe and Sanders (1984) reviewed the data. Dr. M. Adrian Gross stated, “At least one of those studies has established beyond any reasonable doubt that aspartame is capable of inducing brain tumors in experimental animals” (Congressional Record-Senate 1985b).

Professor Walle Nauta (Massachusetts Institute of Technology) chaired the Public Board of Inquiry (PBOI) convened by the FDA in 1980 to evaluate the issue of aspartame-related brain tumors. This Board recommended that aspartame NOT be approved. It

concluded that the evidence from the Lifetime Rat Study and the Two Year Rat Study "...appeared to suggest the possibility that aspartame, at least when administered in the huge quantities employed in the studies, may contribute to the development of brain tumors" (United States General Accounting Office 1987). The carcinogenic potential of aspartame was further suggested by early occurrence of tumors in dosed animals.

The Board's recommendation was overruled, however, by the FDA Commissioner Nauta emphasized that he had been under the clear impression aspartame would be excluded from soft drinks! He asserted that the inquiry would have been conducted differently had he known otherwise (Congressional Record-Senate 1985, p.S5503).

Dr. Douglas L. Park (Staff Science Advisor, Office of Health Affairs of the Department of Health & Human Services) submitted his analysis of the hearing by this PBOI in 1981. He pointed out that his interpretation of the term "authentic," as used by the Universities Associated for Research and Education in Pathology (URAEP), was primarily that the experiments "had indeed been done." Park then explained his concerns about the occurrence of brain tumors in the treated rats. "I believe that aspartame has not been shown to be safe for the proposed food additive uses. Along with the Board of Inquiry, I must recommend, therefore, that aspartame not be approved until additional studies are carried out using proper experimental designs," (Italics supplied)

The FDA was influenced by the Ishii (1981) report. These investigators administered aspartame and its diketopiperazine to SLC Wistar rats for 104 weeks at the Ajinomoto Company's research laboratories. Although two astrocytomas, two oligodendrogliomas and one ependymoma were found among the four test groups, it was concluded that neither agent cause brain tumors.

The same gender difference noted above for urinary bladder tumors is again suggested by a higher incidence of brain tumors among male rats given aspartame. (The incidence rates in female rats and controls were the same.)

Does Aspartame Cause Human Brain Cancer?

The author's initial report on this topic (Roberts 1991a) was published a decade ago. Since then, more than a score of reports have been personally received about patients who developed brain tumors after consuming considerable aspartame. They included astrocytoma, oligodendroglioma, other gliomas, meningioma, and hypothalamic tumors.

Examples of the prodigious consumption of aspartame are cited.

- A 19-year-old woman developed an acoustic neuroma after prolonged use of five to six cans diet soda daily.
- The husband of a woman who died of a brain tumor at the age of 37, leaving an 8-year-old daughter, wrote this poignant note:

“She was a heavy user of aspartame. On a typical day, she would consume 6-12 cans of diet cola. I used to joke to her about drinking so much diet cola that she could cut out the middleman by having them deliver the stuff right to our house. She also consumed it in many products every day because, like most women, she was obsessed with watching her weight.”

- The wife of a man who died of glioblastoma wrote of his addiction to a diet cola. “He drank gallons of this soda each week. I personally saw our 20-gallon trash cans filled each week to the brim with his empty large diet cola bottles. He was obsessed intense thirst for the diet cola.
- A man who developed an astrocytoma had been putting 20 aspartame tablets in each cup of coffee, along with consuming from two to three 2-liter bottles of diet soda daily.
- A 49-year-old woman attempted drastic reduction of weight. She developed a large glioblastoma in the posterior fossa within several months after “ingesting massive quantities of aspartame.” In addition to various diet sodas, ice cream and puddings, she drank “tons of coffee,” adding six packets of a tabletop sweetener to each cup.
- A 43-year-old woman developed severe depression, a 60-pound weight gain, and a subsequent brain tumor after consuming diet colas for many years. On learning about aspartame disease, she commented, “This supposed miracle sweetener of the century turns out to be the silent killer of my life.”

Dr. Lennart Hardell (2000) (Department of Oncology, Orebro Medical Center, Orebro, Sweden) found an odds ratio of 1.24 patients with malignant brain tumors who consumed low-calorie drinks, compared to controls. Furthermore, this risk increased among persons exposed to radiation.

Representative Case Reports

Case XXVII-F-1

A 41-year-old woman had consumed at least two to three cans of aspartame soft drinks more than 11 years. She developed a grand mal seizure. A brain tumor (oligodendroglioma) was found. Surgery was followed by radiation therapy. Her previous non-neurologic complaints included palpitation, abdominal pain, blood in the stools, severe itching without rash, a gain of ten pounds, and unexplained discomfort in the knuckles and elbows.

Case XXVII-F-2

A 62-year-old manager switched to aspartame products in the wake of publicity about the tumor-causing effects of saccharin. He averaged six packets of an aspartame tabletop sweetener in his coffee daily, and also added it to iced tea.

The patient experienced decreased vision in both eyes, partial loss of hearing, headaches, mild confusion, slurring of speech and leg cramps. His granddaughter developed hives from aspartame sodas.

A diagnosis of primary brain lymphoma was later made by biopsy. There was no evidence for immunosuppression or overt exposure to environmental carcinogens. As with aspartame consumers who developed brain tumors, this patient had difficulty in determining whether his neurological manifestations were primarily due to a brain tumor evolving over several years, or aspartame disease which was then complicated by the tumor.

Case XXVII-F-3

A diabetic man was advised to drink a minimum of one gallon liquid daily because of concomitant high uric acid levels. He did so by using aspartame sodas.

Within several months, he experienced persistent headaches, “zoning out”, and a striking decline in his body temperature to 95.6 degrees. An MRI of the brain ten years before was normal. He consulted an endocrinologist. A repeat study revealed a large tumor (hamartoma) in the hypothalamus.

The Rising Incidence Of Primary Brain Cancer

The incidence rates for primary malignant brain tumors have increased by 2.5 percent annually since 1980 according to a National Cancer Institute registry, particularly among older persons. This phenomenon cannot be attributed solely to better diagnostic technology.

The National Cancer Institute’s Surveillance Epidemiology and End Results (SEER) statistics (Cancer Statistics Review 1973-87, NIH Publication No. 89-2789) indicate an impressive increase in the age-adjusted incidence rates of primary brain cancer since 1985 – possible as early as 1984. This phenomenon was documented in the categories “All Races, Males and Females,” “All Races, Males,” and “All Races, Females,” “All Races, Males” and “All Races, Females.”

Statistically significant rises in brain cancer also were found in the Estimated Annual Percent Change (EAPC) over the 1983-1987 period. SEER Table II-34, containing the five-year trends for all races, indicated that the annual percent change rose from 2.1 in 1975-1979 to 8.7 in 1983-1987 for males; for females; it increased from 2.1 in 1975-1979 to 11.7 in 1983-1987.

It has been argued that such increases reflect more accurate diagnosis by recent scanning and other procedures. In rebuttal, these considerations are germane.

- Adequate brain scanning devices had been widely available for at least one decade previously.
- The rise of primary brain tumors was quantitative.
- The incidence rates for cancer involving most other systems either remaining stable or declined during the 1983-1987 period.

Recent data continue to confirm that the incidence rates for brain cancer in the United States have increased in both adults (Devesa 1995) and children (Gurney 1996). In fact, the increased reporting of brain tumors among young persons causes children with headache to worry about a tumor as the cause!

The Rising Incidence Of Primary Brain Lymphoma

The subset of primary brain lymphoma is of unique interest.

- Eby et al (1988) reported a nearly threefold rise in incidence of this previously-rare tumor among immunologically normal persons in the 1982-1984 SEER data. Specifically, the rate increased from 2.7 cases per ten million population in 1973-1975 to 7.5 cases per ten million in 1982 through 1984 ($P=0.001$). The age-adjusted rise was more striking among women – from 4.9 per ten million in 1979-1981 to 8.9 per ten million in 1982-1984. This could not “be explained completely by confounding effects.”
- Yau et al (1996) reported a steep rise in the incidence of primary lymphoma of central nervous system in non-immunocompromised patients between 1981 and 1991 in southeast Scotland. Primary brain lymphoma accounted for 7.6 percent of all gliomas managed by the median of 1.5 percent for the previous decade. These investigators noted similar increases of primary brain lymphoma in other European centers.

The foregoing phenomenon assumes considerable pertinence in light of these facts: (a) the formal approval of aspartame in July 1981, and (b) the 3:1 preponderance of women

with reactions to aspartame (Section 1). Eby and al (1988) commented: “A possible explanation of the increased incidence might be other noninfectious environmental exposures. One could conjecture that primary brain lymphomas may have a long latency period and are the result of occupational or other chemical exposures. However, the similar increases in incidence in both men and women, particularly in older persons, make occupational exposures an unlikely cause.

Experimental Aspartame-Associated Brain Tumors

Prior experimental evidence corroborates this association. An unexpected high incidence of primary brain tumors was found experimentally in rats during the 1970s. Although FDA scientists and others expressed considerable concern, the statutes of limitations on two such studies were allowed to expire before the Delaney Amendment (XXVII-E) could be invoked. The details appear in the Congressional Record-Senate hearings of May 7, 1985 and August 1, 1985, and in prior text (Roberts 1989a).

Even though aspartame continues to be touted as “the most thoroughly testes additive in history,” there remains a paucity of corporate-neutral studies aimed at proving or disproving carcinogenesis in rats and other species.

Related Criticisms Of The FDA

A. Dr. M. Adrian Gross

Dr. Gross a senior FDA pathologist, told the Senate hearing held on August 1, 1985

(pp. S108220- 10847)

“In view of all these indications that the cancer-causing potential of aspartame is a matter that has 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 Delaney Amendment to the Food, Drug, and Cosmetic Act?’” (Italics supplied)

In a subsequent stinging rebuke of the FDA, Dr. Gross stated in his sworn analysis of corporate experimental studies (November 3, 1987)

“At least one of those studies had revealed 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 in 1974; moreover, as a review of that study in the FDA was so flawed, the Agency apparently did not even realize it at the time that only a portion of the observations on brain tumors had in fact been submitted by G. D. Searle & Co. in their petition for approval.”

B. Dr. John Olney

Dr. Olney (Professor of Psychiatry and Neuropathology, Washington University School of Medicine) wrote the following statement to Senator Howard Metzenbaum, dated December 8, 1987 concerning aspartame-related brain tumors.

“This is an exceedingly complex topic which, unfortunately, has a history riddled with appearance of fraudulent practices by the manufacturer of NutraSweet and ineptitude and/or malfeasance on the part of the FDA officials. In the mid 1970’s, when I reviewed the NutraSweet record in preparation for the hearing I had promised, I came upon a peculiar study which the manufacturer had submitted to the FDA and which FDA had unquestioningly accepted as evidence for the safety of NutraSweet. The study showed that in 320 NutraSweet-fed rats there were 12 brain tumors, whereas in a group of concurrent control rats which were not exposed to NutraSweet-fed is 3.75%, this suggests the need for additional in-depth research to rule out the possibility...

“I seriously doubt whether this method of data analysis would stand the scrutiny of competent disinterested statisticians. Even more seriously I wonder why FDA allows microscopic slides to disappear (while I supposedly impounded) and why they do not question the de novo emergence of a brain tumor among the controls when the slides reappear.

“The PBOI panel member who was primarily responsible for reviewing the brain tumor issue was Peter Lampert, M.D., Neuropathologist and chairman of the pathology department at Univ, of Calif. San Diego. Dr. Lampert personally examined the microscopic slides pertaining to the brain tumor studies, and told me a year or so after the PBOI report was completed that he had been surprised at the large size of the brain tumors in the NutraSweet-fed rats.” (Italics supplied)

C. Senator Howard Metzenbaum

Senator Metzenbaum offered this commentary at the May 7, 1985 Senate hearing.

“I do not claim children will develop brain tumors. I do not know that. I do know that the FDA was worried about it. I do know that three of the six FDA scientists advising the FDA Commissioner on final approval were sufficiently worried about it that they were not willing to approve the product. The FDA’s own scientists were split on the issue.” (P.S5492)

D. The Community Nutrition Institute

The Community Nutrition Institute and others filed a petition on August 8, 1983 seeking (a) a public hearing by the FDA concerning its approval of aspartame in liquids (“wet use”) because one had not been held, and (b) a stay of such approval pending the hearing due to concern over neurotoxicity. The United States Court of Appeals for the District of Columbia Circuit (9) denied both requests (No. 84- 1153 and No. 84-5253 [D.C. Civil Action No. 83-03846, decided September 24. 1985].)

This court was aware of prior misgivings by scientists and the Public Board of Inquiry convened in January 1980, including the Board’s plea for “further study to establish whether or not a relationship existed between the ingestion of aspartame and brain tumors.” (In the three years since the Board’s recommendation, G. D. Searle & Co. “chose not to conduct cancer studies on aspartame... and the FDA failed to require such studies.”) The Court made the following pertinent comment (p.14):

“Our scope of review, the exactitude of the fit that we require between the agency’s conclusions and the germane facts is investigated, is necessarily deferential. The judiciary is ill-equipped to conduct investigation and analyze facts of the type involved in this case. Because of the agency’s expertise and broad discretion in ensuring the safety of food additives, we cannot substitute our judgement for the agency’s. The Commission’s finding that there were no material issues of fact can be overturned only if an examination of the record discloses that material issues of fact are apparent to any reasonable examiner.” (Italics supplied)

Brain Cancer in Females

The apparent rise of these tumors in women is noteworthy. The threefold higher incidence of severe reactions to aspartame products in females (Section 1) is germane.

Malignant brain tumors in adults previously occurred more often among men (Salcman 1985, Cole 1989). Older male rats also develop more spontaneous brain tumors (chiefly granular-cell meningiomas) than females (Krinke 1985)

The increase of fatal brain cancer among women is illustrated by the following death rates (per 100,000 population) among females of all ages (kindly supplied by Mr. Edwin Silverberg, Department of Epidemiology & Statistics, American Cancer Society): 1979 – 3.4; 1980- 3.5; 1981 – 3.5; 1982 – 4.0. These increases were more striking among white women than non-white women. (Socioeconomic and cultural factors pertaining to the consumption of “diet” drinks during the early 1980s in part explains these discrepancies.)

Pathogenetic Insights

The following newer concepts concerning the etiology and pathogenesis of primary brain tumors are pertinent.

- Aspartame and its components or metabolites might activate some proto-oncogene, such as the epidermal growth factor-receptor (EGF-R) gene (Hoy Sang 1989)

– either directly or indirectly (e.g., by tissue glucopeia or the influence of uncommon amino acids dextroisomers.)

- The substitution of no-calorie or low-calorie products for conventional foods and beverages, whether as meals or snacks, can have serious sequelae in the brain (Chapter IV). Under usual circumstances, this organ is almost totally dependent upon glucose for optimal function. This point is emphasized relative to the pathogenesis of multiple sclerosis (Roberts 1966).
- The initial rise of primary brain lymphoma in 1982 – when the consumptions of aspartame was much less than after its approval of “wet” use during 1983 – might be explained by the need for a less intense biophysiological or toxic stimulus than the more common types of brain tumor.
- The unchecked hyperinsulinized state (Chapter XIV) may be critical.

The author is impressed by the prolonged use of aspartame gum in some of these patients. The ability of small molecules to enter the brain directly from the oropharynx was described in Chapter II-E.

Primary Tumors

Pituitary tumors occurred in patients who had consumed considerable aspartame for years, and evidenced other clinical features of aspartame disease. For example, one female aspartame reactor developed a pituitary tumor in 1992, which recurred in 1995. She had continued consuming six diet colas, and aspartame yogurt and hot chocolate daily.

Attention is directed to several prolactin-secreting pituitary tumors encountered (see Chapter XXVII-F-5). The stimulation of prolactin by phenylalanine was discussed in Chapters IX-E and XXIV.

Animal studies validate this association. Multiple instances of pituitary tumors were cited in the Bressler Report – e.g., the following female rats:

No. M15CF – pituitary adenoma

No. H18HF – pituitary adenoma

No. K18HF – pituitary adenoma

No. M17LF – marked enlargement of pituitary and both adrenal glands

No. J30HM – marked enlargement of pituitary

Representative Case Reports

Case XXVII-F-4

A 35-year-old man with longstanding diabetes had been consuming considerable diet cola since its availability. In recent years, he suffered severe unexplained headaches, numbness of the hands, and intermittent diarrhea. He felt “my mind was in a fog,” and gained 80 pounds. A pituitary tumor enveloping the optic nerve was found and removed. Continuing to drink diet cola, his blood glucose did “some weird things.” He then learned about aspartame disease, and improved after stopping the diet soda.

Case XXVII-F-5

A female aspartame reactor repeatedly developed repeatedly developed “horrible headaches whenever I knowingly or unknowingly consume aspartame.” As a teenager, she “literally existed on diet sodas and a low caloric intake because I was so very body conscious.” She then developed a prolactin-secreting pituitary tumor. This caused her to focus on aspartame disease because “I come from an incredibly healthy stock, and live a healthy life style in a reasonably uncontaminated environment.”

G. OCCUPATIONAL EXPOSURE THROUGH INHALATION

The author initially reports of aspartame disease caused by exposure in the manufacturing environment with skepticism. As more were received from perspective professionals, the association seemed more plausible.

These findings are relevant.

- The Material Safety Data Sheet on aspartame lists its potential adverse effects on the eyes, skin and respiratory tract, along with required personnel protective equipment (including an approved air purifying or mist respirator) and first aid measures
- Visitors to an aspartame manufacturing plant are advised to wear protective clothing in order to avoid hazardous exposure.
- There have been related instances of non-occupational exposure. One woman reported “I am allergic to aspartame. If I break open a packet containing it, and inhale the powder, I instantly develop a headache.”

Representative Case Reports

Case XXVII-13

The head of an engineering firm wrote the author after reading about aspartame disease. He described the problem of a friend, the installation engineer of more than a dozen automatic centrifuges used in the manufacture of aspartame. After exposure to the dry aspartame powder as these machines were started up, he suffered multiple symptoms – “hot flashes,” marked weakness and insomnia. They slowly disappeared after completion of the installations, and without further exposure.

Case XXVII-14

A 21-year-old man was exposed over one year to a fine dust of aspartame at the packaging plant where he worked. He complained of blurred vision, headache, dizziness

and depression. An autopsy following his sudden death revealed degenerative changes in the liver, kidneys, heart and lungs. The cardiac abnormalities suggested alcoholic beverages.

Case XXVII-15

A 33-year-old worker at a plant manufacturing aspartame developed progressive dizziness, palpitations, a rapid heart rate, intermittent “fuzzy vision” with a “sparkly light,” “needles” over the right face, and leg weakness. He blended aspartame with citric acid, with or without an acidulent containing phosphoric acid. (He would cut the bags, and slowly pour the chemical in 140-degree water.) Any exposed skin was covered with a fine talc. He could detect the sweetness through his mask.

The author saw him in consultation because prior neurologic and psychiatric evaluations failed to uncover another cause. One neurologist began his report by indicating the patient’s concern over occupational exposure to aspartame, but made no further reference to it in his three-page analysis.

Commentary

Sensational but premature exposes of diseases in workers and their communities have been attributed to chemicals used in industry.

This apparently was the case with problems affecting residents in Hinkley (California), a desert town. They were ascribed to the chromium-6 used in a Pacific Gas & Electric plant manufacturing a rust inhibitor. On the other hand, this scenario may apply to exposed personnel through the manufacture of aspartame.

This story formed the basis for a hit movie Erin Brockovich. A huge settlement was made before the publication of scientific information indicating that this substance is a toxin and carcinogen only when inhaled during production (The Wall Street Journal March 28, 2000, p. A-30).

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Reference was made in Chapter IX to aspartame-induced vaginal bleeding, breast tenderness, and changes involving blood cells and lymph nodes.

Admittedly, this realm remains controversial. The Bressler Report (1977) underscored the numerous shortcomings of aspartame studies in rats, especially tumor induction. Dr. M. Adrian Gross, a senior FDA pathologist-scientist, stated

“In view of all these indications that the cancer-causing potential of aspartame is a matter that had been established way beyond any reasonable doubt, one can ask: “What is the reason for the apparent refusal by the FDA to invoke for this food additive the so-called Delaney Amendment to the Food, Drug, and Cosmetic Act?” (Congressional Record-Senate August 1, 1985, p. S10837).

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Having monitored the controversy about saccharin and urinary bladder tumors (see below). The following revelations proved troublesome: (a) deficiencies involving comparable testing with aspartame; (b) ignored reports of brain tumors in mice given aspartame; and (c) reluctance of governmental agencies to invoke the Delaney Amendment.

In prior publications, the author reported increased tumor rates attributable to divers influenced to which the population is exposed. They include

- The ability of insulin to enhance the action of male hormone (testosterone) on prostatic growth (Sirek 1953; Calame 1964; Roberts 1966a, 1967c).
- Diaz-Sanchez et al (1999) demonstrated enhancement of insulin biosynthesis and secretion by testosterone, consistent with the hyperinsulinemia encountered in hyper androgenic syndromes.
- A variety of tumors caused by exposure to the pesticide pentachlorophenol - especially lymphoma, sarcoma, leukemia and other blood disorders (Roberts 1990b, 1997d).
- Breast enlargement/tumors in persons taking mega doses of vitamin E (Roberts 1994c).
- Prostate cancer after vasectomy (Roberts 1993d).

Aspartame as a Co-Carcinogen

A potentiated carcinogenic effect by aspartame in our increasingly complex environment demands study. Others share a similar orientation.

- Dr. Samuel S. Epstein (199) (Professors of Environmental and Occupational Medicine, University of Illinois) stated, “Much cancer is avoidable and due to past exposure to chemical and physical carcinogens in the air, water and food and the workplace.”
- Huff, Haseman and Rall (1991) offered this summary concerning chemical carcinogens.

“We believe our scientific and public responsibility must continue to be directed toward identifying those chemicals, mixtures of chemicals, and exposure circumstances that present potentially the most predictable carcinogenic (and other toxicological) hazards to humans... The important issue is not whether we are undeniably correct in extrapolating carcinogenic responses in laboratory animals up the evolutionary trail to humans, but rather to concentrate our vigilance to assure and improve the entrusted public health.”

Possible Carcinogenic Mechanisms

Several of the potential cancer-inducing properties of aspartame, its three components (phenylalanine; aspartic acid; and a methyl ester that promptly becomes free methanol after ingestion), and the many breakdown products on exposure to heat and storage are cited here and in the ensuing discussion of brain tumors.

- Many constituents in the human diet are nitrosated within the gastrointestinal tract to form potentially carcinogenic nitroso compounds. Shephard et al (1993) reported mutagenic activity by aspartame after nitrosation, using *Salmonella typhimurium* as the test organism.
- The diketopiperazine derivative of aspartame (Chapter XXV) has been incriminated as a tumor-causing chemical.

- Formaldehyde released from the breakdown of methyl alcohol (Chapter XXI) is known to be carcinogenic.
- The potential carcinogenic effects of chronic hyperinsulinemia (Chapter XIV) has been discussed in prior publications, with special reference to the prostate (Roberts 1967d). Others have implicated hyperinsulinemia in the pathogenesis of breast cancer (Diamanti-Kandarakis 1999).
- Alteration of glucose transport is a characteristic of experimental tumors. Reporting on this phenomenon, and the dramatic increase in total cellular glucose transporter protein, Birenbaum et al (1987) emphasized the induction of such transformation when fibroblasts are starved for glucose.
- Increased phenylalanine may play a role. Animal and human studies indicate that restricting dietary phenylalanine decreases tumor growth and metastases (Norris 1990).
- Several investigators have implicated prolactin (Chapter XXIV) as a tumor-promoting substance in various organs – including the pituitary (Oliveira 1999), endometrium (Brosens 1999), and human breast (Maus 1999).
- The brown substances created by the heating of amino acids during cooking may be mutagenic and carcinogenic (Abelson 1983). They include a number of DNA-damaging agents.
- The causation or enhancement of brain and other tumors in persons consuming aspartame products may summate upon a hyper immune state induced by early and multiple immunizations with vaccines whose long-term safety is being increasingly challenged (Section 6-D). A number contain formaldehyde (Chapter XXI) and mercury as preservatives.

The mutagenic and carcinogenic potential of other chemicals might intensify under the influence of aspartame and its breakdown products. The ability of aspartame to induce or aggravate the multiple chemical sensitivity syndrome, including pesticide reactions, was discussed in Chapter VIII-E.

The Issue of Gender

The agencies responsible for approving aspartame apparently overlooked an important gender-related detail in experimental studies. The assessment for potential urinary bladder cancer following administration of aspartame and its diketopiperazine derivative was studied only in female mice. Professor George T. Brian (1984) noted that female Swiss albino mice were used for “all” such studies.

The author expressed reservations about limiting the testing to female animals at the First International Meeting On Dietary Phenylalanine and Brain Function held on May 10, 1987 in Washington, D.C. Information to the contrary from those present – including at least five professionals and scientific consultants for the manufacturer – was specifically solicited. No verbal or written response, then or since, has been received.

The subject of urinary bladder tumors induced by saccharin will be discussed below. There is little doubt, however, that it is largely a phenomenon of male rats. Miller and Howe (1977) asserted. “For bladder cancer, the distinction between males and females seems to us to be fundamental.”

BRAIN TUMORS

Pre-Approval Perspectives

On September 60, 1980 a Public Broad Of Inquiry (PBI) unequivocally advised against the approval of aspartame owing to the high incidence of brain tumors among animals receiving this chemical. It did not mince words: “The Board has not been presented with proof of a reasonable certainty that aspartame (NutraSweet) is safe for use as a food additive under is intended conditions of use.”

The observations of Dr. John Olney concerning aspartame-related brain tumors are detailed below. Other investigators also reported increased rates of brain tumors (gliomas) in rats given aspartame (Congressional Record-Senate 1985a, b). Cornell, Wolfe and Sanders (1984) reviewed the data. Dr. M. Adrian Gross stated, “At least one of those studies has established beyond any reasonable doubt that aspartame is capable of inducing brain tumors in experimental animals” (Congressional Record-Senate 1985b).

Professor Walle Nauta (Massachusetts Institute of Technology) chaired the Public Board of Inquiry (PBOI) convened by the FDA in 1980 to evaluate the issue of aspartame-related brain tumors. This Board recommended that aspartame NOT be approved. It

concluded that the evidence from the Lifetime Rat Study and the Two Year Rat Study "...appeared to suggest the possibility that aspartame, at least when administered in the huge quantities employed in the studies, may contribute to the development of brain tumors" (United States General Accounting Office 1987). The carcinogenic potential of aspartame was further suggested by early occurrence of tumors in dosed animals.

The Board's recommendation was overruled, however, by the FDA Commissioner Nauta emphasized that he had been under the clear impression aspartame would be excluded from soft drinks! He asserted that the inquiry would have been conducted differently had he known otherwise (Congressional Record-Senate 1985, p.S5503).

Dr. Douglas L. Park (Staff Science Advisor, Office of Health Affairs of the Department of Health & Human Services) submitted his analysis of the hearing by this PBOI in 1981. He pointed out that his interpretation of the term "authentic," as used by the Universities Associated for Research and Education in Pathology (URAEP), was primarily that the experiments "had indeed been done." Park then explained his concerns about the occurrence of brain tumors in the treated rats. "I believe that aspartame has not been shown to be safe for the proposed food additive uses. Along with the Board of Inquiry, I must recommend, therefore, that aspartame not be approved until additional studies are carried out using proper experimental designs," (Italics supplied)

The FDA was influenced by the Ishii (1981) report. These investigators administered aspartame and its diketopiperazine to SLC Wistar rats for 104 weeks at the Ajinomoto Company's research laboratories. Although two astrocytomas, two oligodendrogliomas and one ependymoma were found among the four test groups, it was concluded that neither agent cause brain tumors.

The same gender difference noted above for urinary bladder tumors is again suggested by a higher incidence of brain tumors among male rats given aspartame. (The incidence rates in female rats and controls were the same.)

Does Aspartame Cause Human Brain Cancer?

The author's initial report on this topic (Roberts 1991a) was published a decade ago. Since then, more than a score of reports have been personally received about patients who developed brain tumors after consuming considerable aspartame. They included astrocytoma, oligodendroglioma, other gliomas, meningioma, and hypothalamic tumors.

Examples of the prodigious consumption of aspartame are cited.

- A 19-year-old woman developed an acoustic neuroma after prolonged use of five to six cans diet soda daily.
- The husband of a woman who died of a brain tumor at the age of 37, leaving an 8-year-old daughter, wrote this poignant note:

“She was a heavy user of aspartame. On a typical day, she would consume 6-12 cans of diet cola. I used to joke to her about drinking so much diet cola that she could cut out the middleman by having them deliver the stuff right to our house. She also consumed it in many products every day because, like most women, she was obsessed with watching her weight.”

- The wife of a man who died of glioblastoma wrote of his addiction to a diet cola. “He drank gallons of this soda each week. I personally saw our 20-gallon trash cans filled each week to the brim with his empty large diet cola bottles. He was obsessed intense thirst for the diet cola.
- A man who developed an astrocytoma had been putting 20 aspartame tablets in each cup of coffee, along with consuming from two to three 2-liter bottles of diet soda daily.
- A 49-year-old woman attempted drastic reduction of weight. She developed a large glioblastoma in the posterior fossa within several months after “ingesting massive quantities of aspartame.” In addition to various diet sodas, ice cream and puddings, she drank “tons of coffee,” adding six packets of a tabletop sweetener to each cup.
- A 43-year-old woman developed severe depression, a 60-pound weight gain, and a subsequent brain tumor after consuming diet colas for many years. On learning about aspartame disease, she commented, “This supposed miracle sweetener of the century turns out to be the silent killer of my life.”

Dr. Lennart Hardell (2000) (Department of Oncology, Orebro Medical Center, Orebro, Sweden) found an odds ratio of 1.24 patients with malignant brain tumors who consumed low-calorie drinks, compared to controls. Furthermore, this risk increased among persons exposed to radiation.

Representative Case Reports

Case XXVII-F-1

A 41-year-old woman had consumed at least two to three cans of aspartame soft drinks more than 11 years. She developed a grand mal seizure. A brain tumor (oligodendroglioma) was found. Surgery was followed by radiation therapy. Her previous non-neurologic complaints included palpitation, abdominal pain, blood in the stools, severe itching without rash, a gain of ten pounds, and unexplained discomfort in the knuckles and elbows.

Case XXVII-F-2

A 62-year-old manager switched to aspartame products in the wake of publicity about the tumor-causing effects of saccharin. He averaged six packets of an aspartame tabletop sweetener in his coffee daily, and also added it to iced tea.

The patient experienced decreased vision in both eyes, partial loss of hearing, headaches, mild confusion, slurring of speech and leg cramps. His granddaughter developed hives from aspartame sodas.

A diagnosis of primary brain lymphoma was later made by biopsy. There was no evidence for immunosuppression or overt exposure to environmental carcinogens. As with aspartame consumers who developed brain tumors, this patient had difficulty in determining whether his neurological manifestations were primarily due to a brain tumor evolving over several years, or aspartame disease which was then complicated by the tumor.

Case XXVII-F-3

A diabetic man was advised to drink a minimum of one gallon liquid daily because of concomitant high uric acid levels. He did so by using aspartame sodas.

Within several months, he experienced persistent headaches, “zoning out”, and a striking decline in his body temperature to 95.6 degrees. An MRI of the brain ten years before was normal. He consulted an endocrinologist. A repeat study revealed a large tumor (hamartoma) in the hypothalamus.

The Rising Incidence Of Primary Brain Cancer

The incidence rates for primary malignant brain tumors have increased by 2.5 percent annually since 1980 according to a National Cancer Institute registry, particularly among older persons. This phenomenon cannot be attributed solely to better diagnostic technology.

The National Cancer Institute’s Surveillance Epidemiology and End Results (SEER) statistics (Cancer Statistics Review 1973-87, NIH Publication No. 89-2789) indicate an impressive increase in the age-adjusted incidence rates of primary brain cancer since 1985 – possible as early as 1984. This phenomenon was documented in the categories “All Races, Males and Females,” “All Races, Males,” and “All Races, Females,” “All Races, Males” and “All Races, Females.”

Statistically significant rises in brain cancer also were found in the Estimated Annual Percent Change (EAPC) over the 1983-1987 period. SEER Table II-34, containing the five-year trends for all races, indicated that the annual percent change rose from 2.1 in 1975-1979 to 8.7 in 1983-1987 for males; for females; it increased from 2.1 in 1975-1979 to 11.7 in 1983-1987.

It has been argued that such increases reflect more accurate diagnosis by recent scanning and other procedures. In rebuttal, these considerations are germane.

- Adequate brain scanning devices had been widely available for at least one decade previously.
- The rise of primary brain tumors was quantitative.
- The incidence rates for cancer involving most other systems either remaining stable or declined during the 1983-1987 period.

Recent data continue to confirm that the incidence rates for brain cancer in the United States have increased in both adults (Devesa 1995) and children (Gurney 1996). In fact, the increased reporting of brain tumors among young persons causes children with headache to worry about a tumor as the cause!

The Rising Incidence Of Primary Brain Lymphoma

The subset of primary brain lymphoma is of unique interest.

- Eby et al (1988) reported a nearly threefold rise in incidence of this previously-rare tumor among immunologically normal persons in the 1982-1984 SEER data. Specifically, the rate increased from 2.7 cases per ten million population in 1973-1975 to 7.5 cases per ten million in 1982 through 1984 ($P=0.001$). The age-adjusted rise was more striking among women – from 4.9 per ten million in 1979-1981 to 8.9 per ten million in 1982-1984. This could not “be explained completely by confounding effects.”
- Yau et al (1996) reported a steep rise in the incidence of primary lymphoma of central nervous system in non-immunocompromised patients between 1981 and 1991 in southeast Scotland. Primary brain lymphoma accounted for 7.6 percent of all gliomas managed by the median of 1.5 percent for the previous decade. These investigators noted similar increases of primary brain lymphoma in other European centers.

The foregoing phenomenon assumes considerable pertinence in light of these facts: (a) the formal approval of aspartame in July 1981, and (b) the 3:1 preponderance of women

with reactions to aspartame (Section 1). Eby and al (1988) commented: “A possible explanation of the increased incidence might be other noninfectious environmental exposures. One could conjecture that primary brain lymphomas may have a long latency period and are the result of occupational or other chemical exposures. However, the similar increases in incidence in both men and women, particularly in older persons, make occupational exposures an unlikely cause.

Experimental Aspartame-Associated Brain Tumors

Prior experimental evidence corroborates this association. An unexpected high incidence of primary brain tumors was found experimentally in rats during the 1970s. Although FDA scientists and others expressed considerable concern, the statutes of limitations on two such studies were allowed to expire before the Delaney Amendment (XXVII-E) could be invoked. The details appear in the Congressional Record-Senate hearings of May 7, 1985 and August 1, 1985, and in prior text (Roberts 1989a).

Even though aspartame continues to be touted as “the most thoroughly testes additive in history,” there remains a paucity of corporate-neutral studies aimed at proving or disproving carcinogenesis in rats and other species.

Related Criticisms Of The FDA

A. Dr. M. Adrian Gross

Dr. Gross a senior FDA pathologist, told the Senate hearing held on August 1, 1985

(pp. S108220- 10847)

“In view of all these indications that the cancer-causing potential of aspartame is a matter that has 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 Delaney Amendment to the Food, Drug, and Cosmetic Act?’” (Italics supplied)

In a subsequent stinging rebuke of the FDA, Dr. Gross stated in his sworn analysis of corporate experimental studies (November 3, 1987)

“At least one of those studies had revealed 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 aspartame in 1974; moreover, as a review of that study in the FDA was so flawed, the Agency apparently did not even realize it at the time that only a portion of the observations on brain tumors had in fact been submitted by G. D. Searle & Co. in their petition for approval.”

B. Dr. John Olney

Dr. Olney (Professor of Psychiatry and Neuropathology, Washington University School of Medicine) wrote the following statement to Senator Howard Metzenbaum, dated December 8, 1987 concerning aspartame-related brain tumors.

“This is an exceedingly complex topic which, unfortunately, has a history riddled with appearance of fraudulent practices by the manufacturer of NutraSweet and ineptitude and/or malfeasance on the part of the FDA officials. In the mid 1970’s, when I reviewed the NutraSweet record in preparation for the hearing I had promised, I came upon a peculiar study which the manufacturer had submitted to the FDA and which FDA had unquestioningly accepted as evidence for the safety of NutraSweet. The study showed that in 320 NutraSweet-fed rats there were 12 brain tumors, whereas in a group of concurrent control rats which were not exposed to NutraSweet-fed is 3.75%, this suggests the need for additional in-depth research to rule out the possibility...

“I seriously doubt whether this method of data analysis would stand the scrutiny of competent disinterested statisticians. Even more seriously I wonder why FDA allows microscopic slides to disappear (while I supposedly impounded) and why they do not question the de novo emergence of a brain tumor among the controls when the slides reappear.

“The PBOI panel member who was primarily responsible for reviewing the brain tumor issue was Peter Lampert, M.D., Neuropathologist and chairman of the pathology department at Univ, of Calif. San Diego. Dr. Lampert personally examined the microscopic slides pertaining to the brain tumor studies, and told me a year or so after the PBOI report was completed that he had been surprised at the large size of the brain tumors in the NutraSweet-fed rats.” (Italics supplied)

C. Senator Howard Metzenbaum

Senator Metzenbaum offered this commentary at the May 7, 1985 Senate hearing.

“I do not claim children will develop brain tumors. I do not know that. I do know that the FDA was worried about it. I do know that three of the six FDA scientists advising the FDA Commissioner on final approval were sufficiently worried about it that they were not willing to approve the product. The FDA’s own scientists were split on the issue.” (P.S5492)

D. The Community Nutrition Institute

The Community Nutrition Institute and others filed a petition on August 8, 1983 seeking (a) a public hearing by the FDA concerning its approval of aspartame in liquids (“wet use”) because one had not been held, and (b) a stay of such approval pending the hearing due to concern over neurotoxicity. The United States Court of Appeals for the District of Columbia Circuit (9) denied both requests (No. 84- 1153 and No. 84-5253 [D.C. Civil Action No. 83-03846, decided September 24. 1985].)

This court was aware of prior misgivings by scientists and the Public Board of Inquiry convened in January 1980, including the Board’s plea for “further study to establish whether or not a relationship existed between the ingestion of aspartame and brain tumors.” (In the three years since the Board’s recommendation, G. D. Searle & Co. “chose not to conduct cancer studies on aspartame... and the FDA failed to require such studies.”) The Court made the following pertinent comment (p.14):

“Our scope of review, the exactitude of the fit that we require between the agency’s conclusions and the germane facts is investigated, is necessarily deferential. The judiciary is ill-equipped to conduct investigation and analyze facts of the type involved in this case. Because of the agency’s expertise and broad discretion in ensuring the safety of food additives, we cannot substitute our judgement for the agency’s. The Commission’s finding that there were no material issues of fact can be overturned only if an examination of the record discloses that material issues of fact are apparent to any reasonable examiner.” (Italics supplied)

Brain Cancer in Females

The apparent rise of these tumors in women is noteworthy. The threefold higher incidence of severe reactions to aspartame products in females (Section 1) is germane.

Malignant brain tumors in adults previously occurred more often among men (Salcman 1985, Cole 1989). Older male rats also develop more spontaneous brain tumors (chiefly granular-cell meningiomas) than females (Krinke 1985)

The increase of fatal brain cancer among women is illustrated by the following death rates (per 100,000 population) among females of all ages (kindly supplied by Mr. Edwin Silverberg, Department of Epidemiology & Statistics, American Cancer Society): 1979 – 3.4; 1980- 3.5; 1981 – 3.5; 1982 – 4.0. These increases were more striking among white women than non-white women. (Socioeconomic and cultural factors pertaining to the consumption of “diet” drinks during the early 1980s in part explains these discrepancies.)

Pathogenetic Insights

The following newer concepts concerning the etiology and pathogenesis of primary brain tumors are pertinent.

- Aspartame and its components or metabolites might activate some proto-oncogene, such as the epidermal growth factor-receptor (EGF-R) gene (Hoy Sang 1989)

– either directly or indirectly (e.g., by tissue glucopeia or the influence of uncommon amino acids dextroisomers.)

- The substitution of no-calorie or low-calorie products for conventional foods and beverages, whether as meals or snacks, can have serious sequelae in the brain (Chapter IV). Under usual circumstances, this organ is almost totally dependent upon glucose for optimal function. This point is emphasized relative to the pathogenesis of multiple sclerosis (Roberts 1966).
- The initial rise of primary brain lymphoma in 1982 – when the consumptions of aspartame was much less than after its approval of “wet” use during 1983 – might be explained by the need for a less intense biophysiological or toxic stimulus than the more common types of brain tumor.
- The unchecked hyperinsulinized state (Chapter XIV) may be critical.

The author is impressed by the prolonged use of aspartame gum in some of these patients. The ability of small molecules to enter the brain directly from the oropharynx was described in Chapter II-E.

Primary Tumors

Pituitary tumors occurred in patients who had consumed considerable aspartame for years, and evidenced other clinical features of aspartame disease. For example, one female aspartame reactor developed a pituitary tumor in 1992, which recurred in 1995. She had continued consuming six diet colas, and aspartame yogurt and hot chocolate daily.

Attention is directed to several prolactin-secreting pituitary tumors encountered (see Chapter XXVII-F-5). The stimulation of prolactin by phenylalanine was discussed in Chapters IX-E and XXIV.

Animal studies validate this association. Multiple instances of pituitary tumors were cited in the Bressler Report – e.g., the following female rats:

No. M15CF – pituitary adenoma

No. H18HF – pituitary adenoma

No. K18HF – pituitary adenoma

No. M17LF – marked enlargement of pituitary and both adrenal glands

No. J30HM – marked enlargement of pituitary

Representative Case Reports

Case XXVII-F-4

A 35-year-old man with longstanding diabetes had been consuming considerable diet cola since its availability. In recent years, he suffered severe unexplained headaches, numbness of the hands, and intermittent diarrhea. He felt “my mind was in a fog,” and gained 80 pounds. A pituitary tumor enveloping the optic nerve was found and removed. Continuing to drink diet cola, his blood glucose did “some weird things.” He then learned about aspartame disease, and improved after stopping the diet soda.

Case XXVII-F-5

A female aspartame reactor repeatedly developed repeatedly developed “horrible headaches whenever I knowingly or unknowingly consume aspartame.” As a teenager, she “literally existed on diet sodas and a low caloric intake because I was so very body conscious.” She then developed a prolactin-secreting pituitary tumor. This caused her to focus on aspartame disease because “I come from an incredibly healthy stock, and live a healthy life style in a reasonably uncontaminated environment.”

G. OCCUPATIONAL EXPOSURE THROUGH INHALATION

The author initially reports of aspartame disease caused by exposure in the manufacturing environment with skepticism. As more were received from perspective professionals, the association seemed more plausible.

These findings are relevant.

- The Material Safety Data Sheet on aspartame lists its potential adverse effects on the eyes, skin and respiratory tract, along with required personnel protective equipment (including an approved air purifying or mist respirator) and first aid measures
- Visitors to an aspartame manufacturing plant are advised to wear protective clothing in order to avoid hazardous exposure.
- There have been related instances of non-occupational exposure. One woman reported “I am allergic to aspartame. If I break open a packet containing it, and inhale the powder, I instantly develop a headache.”

Representative Case Reports

Case XXVII-13

The head of an engineering firm wrote the author after reading about aspartame disease. He described the problem of a friend, the installation engineer of more than a dozen automatic centrifuges used in the manufacture of aspartame. After exposure to the dry aspartame powder as these machines were started up, he suffered multiple symptoms – “hot flashes,” marked weakness and insomnia. They slowly disappeared after completion of the installations, and without further exposure.

Case XXVII-14

A 21-year-old man was exposed over one year to a fine dust of aspartame at the packaging plant where he worked. He complained of blurred vision, headache, dizziness

and depression. An autopsy following his sudden death revealed degenerative changes in the liver, kidneys, heart and lungs. The cardiac abnormalities suggested alcoholic beverages.

Case XXVII-15

A 33-year-old worker at a plant manufacturing aspartame developed progressive dizziness, palpitations, a rapid heart rate, intermittent “fuzzy vision” with a “sparkly light,” “needles” over the right face, and leg weakness. He blended aspartame with citric acid, with or without an acidulent containing phosphoric acid. (He would cut the bags, and slowly pour the chemical in 140-degree water.) Any exposed skin was covered with a fine talc. He could detect the sweetness through his mask.

The author saw him in consultation because prior neurologic and psychiatric evaluations failed to uncover another cause. One neurologist began his report by indicating the patient’s concern over occupational exposure to aspartame, but made no further reference to it in his three-page analysis.

Commentary

Sensational but premature exposes of diseases in workers and their communities have been attributed to chemicals used in industry.

This apparently was the case with problems affecting residents in Hinkley (California), a desert town. They were ascribed to the chromium-6 used in a Pacific Gas & Electric plant manufacturing a rust inhibitor. On the other hand, this scenario may apply to exposed personnel through the manufacture of aspartame.

This story formed the basis for a hit movie Erin Brockovich. A huge settlement was made before the publication of scientific information indicating that this substance is a toxin and carcinogen only when inhaled during production (The Wall Street Journal March 28, 2000, p. A-30).

TUMORS AND CANCER; THE DELANEY AMENDMENT

“By far the most mutagenic agents known to man are chemicals, not radiation. And in regard, food additives rather than fallout at present levels may present a greater danger.”

Dr. Richard Caldecott (1961)

(Atomic Energy Commission)

Heavy consumers of aspartame products appear to be increased for developing tumors in the brain (see below) and elsewhere. The author initially considered “anecdotes” about cancer involving organs other than the brain in aspartame reactors to be coincidental. AS the number increased, however, a relationship could not be ignored.

Reference was made in Chapter IX to aspartame-induced vaginal bleeding, breast tenderness, and changes involving blood cells and lymph nodes.

Admittedly, this realm remains controversial. The Bressler Report (1977) underscored the numerous shortcomings of aspartame studies in rats, especially tumor induction. Dr. M. Adrian Gross, a senior FDA pathologist-scientist, stated

“In view of all these indications that the cancer-causing potential of aspartame is a matter that had been established way beyond any reasonable doubt, one can ask: “What is the reason for the apparent refusal by the FDA to invoke for this food additive the so-called Delaney Amendment to the Food, Drug, and Cosmetic Act?” (Congressional Record-Senate August 1, 1985, p. S10837).

There may be a long hiatus between the introduction of a drug or chemical and awareness of its link to cancer. This is illustrated by phenolphthalein, the main ingredient of several popular laxatives. Nearly a century lapsed before documentation of its carcinogenic activity in rodents – including tumors of the ovaries, kidneys, adrenal glands and thymus (McGinley 1997).

Selected Tumors

Dr. George Schwartz (1999) suggested a connection between aspartame consumption and breast cancer and prostate cancer. Both markedly increased following the release of aspartame in 1981, based on governmental surveillance statistics.

There are suggestive anecdotal reports in this serious. For example, a diabetic male developed retinopathy and joint pain while consuming diet colas, and then cancer of the breast.

The puzzling rise of certain cancers over the past decade, especially among younger weight-conscious women, warrants consideration of the contributory role of aspartame products.

- Ductule breast carcinoma in situ rose 52 percent from 1983-1989; during this period the use of aspartame products quadrupled. The numbers subsequently rose to 23,000 case in 1992 and 36,000 in 1998, 200 persons higher than had been projected.
- A fourfold increase in adenocarcinoma of the cervix in England's East Anglia region, most notably in the 30- to 39-year-age group was reported in 1997 b Diane Stockton of the Institute of Public health at Cambridge University.

The Delaney Amendment

Congress included the Delaney clause in the 1958 Food Additives Amendment. Its intent was to ban the ingestion of cancer-causing chemicals.

The circumstances surrounding the adoption of its Federal law may be of interest to "Trivia" buffs. Representative James Delaney of New York unsuccessfully tried to obtain its passage for five years. Delaney's staff then briefed actress Gloria Swanson, a health food advocate, in 1956. She enlisted sympathetic wives of congressmen, who in turn encouraged their husbands to support the bill.

Unfortunately, the Delaney clause was emasculated by the Senate's Comprehensive Regulatory Reform Act of July 19, 1995. Without defining the terms "negligible" or "insignificant," it stated that a substance or product shall not be prohibited or refused approval when it "presents a negligible or insignificant foreseeable risk to human health."

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Having monitored the controversy about saccharin and urinary bladder tumors (see below). The following revelations proved troublesome: (a) deficiencies involving comparable testing with aspartame; (b) ignored reports of brain tumors in mice given aspartame; and (c) reluctance of governmental agencies to invoke the Delaney Amendment.

In prior publications, the author reported increased tumor rates attributable to divers influenced to which the population is exposed. They include

- The ability of insulin to enhance the action of male hormone (testosterone) on prostatic growth (Sirek 1953; Calame 1964; Roberts 1966a, 1967c).
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- Formaldehyde released from the breakdown of methyl alcohol (Chapter XXI) is known to be carcinogenic.
- The potential carcinogenic effects of chronic hyperinsulinemia (Chapter XIV) has been discussed in prior publications, with special reference to the prostate (Roberts 1967d). Others have implicated hyperinsulinemia in the pathogenesis of breast cancer (Diamanti-Kandarakis 1999).
- Alteration of glucose transport is a characteristic of experimental tumors. Reporting on this phenomenon, and the dramatic increase in total cellular glucose transporter protein, Birenbaum et al (1987) emphasized the induction of such transformation when fibroblasts are starved for glucose.
- Increased phenylalanine may play a role. Animal and human studies indicate that restricting dietary phenylalanine decreases tumor growth and metastases (Norris 1990).
- Several investigators have implicated prolactin (Chapter XXIV) as a tumor-promoting substance in various organs – including the pituitary (Oliveira 1999), endometrium (Brosens 1999), and human breast (Maus 1999).
- The brown substances created by the heating of amino acids during cooking may be mutagenic and carcinogenic (Abelson 1983). They include a number of DNA-damaging agents.
- The causation or enhancement of brain and other tumors in persons consuming aspartame products may summate upon a hyper immune state induced by early and multiple immunizations with vaccines whose long-term safety is being increasingly challenged (Section 6-D). A number contain formaldehyde (Chapter XXI) and mercury as preservatives.

The mutagenic and carcinogenic potential of other chemicals might intensify under the influence of aspartame and its breakdown products. The ability of aspartame to induce or aggravate the multiple chemical sensitivity syndrome, including pesticide reactions, was discussed in Chapter VIII-E.

The Issue of Gender

The agencies responsible for approving aspartame apparently overlooked an important gender-related detail in experimental studies. The assessment for potential urinary bladder cancer following administration of aspartame and its diketopiperazine derivative was studied only in female mice. Professor George T. Brian (1984) noted that female Swiss albino mice were used for “all” such studies.

The author expressed reservations about limiting the testing to female animals at the First International Meeting On Dietary Phenylalanine and Brain Function held on May 10, 1987 in Washington, D.C. Information to the contrary from those present – including at least five professionals and scientific consultants for the manufacturer – was specifically solicited. No verbal or written response, then or since, has been received.

The subject of urinary bladder tumors induced by saccharin will be discussed below. There is little doubt, however, that it is largely a phenomenon of male rats. Miller and Howe (1977) asserted. “For bladder cancer, the distinction between males and females seems to us to be fundamental.”

BRAIN TUMORS

Pre-Approval Perspectives

On September 60, 1980 a Public Broad Of Inquiry (PBI) unequivocally advised against the approval of aspartame owing to the high incidence of brain tumors among animals receiving this chemical. It did not mince words: “The Board has not been presented with proof of a reasonable certainty that aspartame (NutraSweet) is safe for use as a food additive under is intended conditions of use.”

The observations of Dr. John Olney concerning aspartame-related brain tumors are detailed below. Other investigators also reported increased rates of brain tumors (gliomas) in rats given aspartame (Congressional Record-Senate 1985a, b). Cornell, Wolfe and Sanders (1984) reviewed the data. Dr. M. Adrian Gross stated, “At least one of those studies has established beyond any reasonable doubt that aspartame is capable of inducing brain tumors in experimental animals” (Congressional Record-Senate 1985b).

Professor Walle Nauta (Massachusetts Institute of Technology) chaired the Public Board of Inquiry (PBOI) convened by the FDA in 1980 to evaluate the issue of aspartame-related brain tumors. This Board recommended that aspartame NOT be approved. It

concluded that the evidence from the Lifetime Rat Study and the Two Year Rat Study "...appeared to suggest the possibility that aspartame, at least when administered in the huge quantities employed in the studies, may contribute to the development of brain tumors" (United States General Accounting Office 1987). The carcinogenic potential of aspartame was further suggested by early occurrence of tumors in dosed animals.

The Board's recommendation was overruled, however, by the FDA Commissioner Nauta emphasized that he had been under the clear impression aspartame would be excluded from soft drinks! He asserted that the inquiry would have been conducted differently had he known otherwise (Congressional Record-Senate 1985, p.S5503).

Dr. Douglas L. Park (Staff Science Advisor, Office of Health Affairs of the Department of Health & Human Services) submitted his analysis of the hearing by this PBOI in 1981. He pointed out that his interpretation of the term "authentic," as used by the Universities Associated for Research and Education in Pathology (URAEP), was primarily that the experiments "had indeed been done." Park then explained his concerns about the occurrence of brain tumors in the treated rats. "I believe that aspartame has not been shown to be safe for the proposed food additive uses. Along with the Board of Inquiry, I must recommend, therefore, that aspartame not be approved until additional studies are carried out using proper experimental designs," (Italics supplied)

The FDA was influenced by the Ishii (1981) report. These investigators administered aspartame and its diketopiperazine to SLC Wistar rats for 104 weeks at the Ajinomoto Company's research laboratories. Although two astrocytomas, two oligodendrogliomas and one ependymoma were found among the four test groups, it was concluded that neither agent cause brain tumors.

The same gender difference noted above for urinary bladder tumors is again suggested by a higher incidence of brain tumors among male rats given aspartame. (The incidence rates in female rats and controls were the same.)

Does Aspartame Cause Human Brain Cancer?

The author's initial report on this topic (Roberts 1991a) was published a decade ago. Since then, more than a score of reports have been personally received about patients who developed brain tumors after consuming considerable aspartame. They included astrocytoma, oligodendroglioma, other gliomas, meningioma, and hypothalamic tumors.

Examples of the prodigious consumption of aspartame are cited.

- A 19-year-old woman developed an acoustic neuroma after prolonged use of five to six cans diet soda daily.
- The husband of a woman who died of a brain tumor at the age of 37, leaving an 8-year-old daughter, wrote this poignant note:

“She was a heavy user of aspartame. On a typical day, she would consume 6-12 cans of diet cola. I used to joke to her about drinking so much diet cola that she could cut out the middleman by having them deliver the stuff right to our house. She also consumed it in many products every day because, like most women, she was obsessed with watching her weight.”

- The wife of a man who died of glioblastoma wrote of his addiction to a diet cola. “He drank gallons of this soda each week. I personally saw our 20-gallon trash cans filled each week to the brim with his empty large diet cola bottles. He was obsessed intense thirst for the diet cola.
- A man who developed an astrocytoma had been putting 20 aspartame tablets in each cup of coffee, along with consuming from two to three 2-liter bottles of diet soda daily.
- A 49-year-old woman attempted drastic reduction of weight. She developed a large glioblastoma in the posterior fossa within several months after “ingesting massive quantities of aspartame.” In addition to various diet sodas, ice cream and puddings, she drank “tons of coffee,” adding six packets of a tabletop sweetener to each cup.
- A 43-year-old woman developed severe depression, a 60-pound weight gain, and a subsequent brain tumor after consuming diet colas for many years. On learning about aspartame disease, she commented, “This supposed miracle sweetener of the century turns out to be the silent killer of my life.”

Dr. Lennart Hardell (2000) (Department of Oncology, Orebro Medical Center, Orebro, Sweden) found an odds ratio of 1.24 patients with malignant brain tumors who consumed low-calorie drinks, compared to controls. Furthermore, this risk increased among persons exposed to radiation.

Representative Case Reports

Case XXVII-F-1

A 41-year-old woman had consumed at least two to three cans of aspartame soft drinks more than 11 years. She developed a grand mal seizure. A brain tumor (oligodendroglioma) was found. Surgery was followed by radiation therapy. Her previous non-neurologic complaints included palpitation, abdominal pain, blood in the stools, severe itching without rash, a gain of ten pounds, and unexplained discomfort in the knuckles and elbows.

Case XXVII-F-2

A 62-year-old manager switched to aspartame products in the wake of publicity about the tumor-causing effects of saccharin. He averaged six packets of an aspartame tabletop sweetener in his coffee daily, and also added it to iced tea.

The patient experienced decreased vision in both eyes, partial loss of hearing, headaches, mild confusion, slurring of speech and leg cramps. His granddaughter developed hives from aspartame sodas.

A diagnosis of primary brain lymphoma was later made by biopsy. There was no evidence for immunosuppression or overt exposure to environmental carcinogens. As with aspartame consumers who developed brain tumors, this patient had difficulty in determining whether his neurological manifestations were primarily due to a brain tumor evolving over several years, or aspartame disease which was then complicated by the tumor.

Case XXVII-F-3

A diabetic man was advised to drink a minimum of one gallon liquid daily because of concomitant high uric acid levels. He did so by using aspartame sodas.

Within several months, he experienced persistent headaches, “zoning out”, and a striking decline in his body temperature to 95.6 degrees. An MRI of the brain ten years before was normal. He consulted an endocrinologist. A repeat study revealed a large tumor (hamartoma) in the hypothalamus.

The Rising Incidence Of Primary Brain Cancer

The incidence rates for primary malignant brain tumors have increased by 2.5 percent annually since 1980 according to a National Cancer Institute registry, particularly among older persons. This phenomenon cannot be attributed solely to better diagnostic technology.

The National Cancer Institute’s Surveillance Epidemiology and End Results (SEER) statistics (Cancer Statistics Review 1973-87, NIH Publication No. 89-2789) indicate an impressive increase in the age-adjusted incidence rates of primary brain cancer since 1985 – possible as early as 1984. This phenomenon was documented in the categories “All Races, Males and Females,” “All Races, Males,” and “All Races, Females,” “All Races, Males” and “All Races, Females.”

Statistically significant rises in brain cancer also were found in the Estimated Annual Percent Change (EAPC) over the 1983-1987 period. SEER Table II-34, containing the five-year trends for all races, indicated that the annual percent change rose from 2.1 in 1975-1979 to 8.7 in 1983-1987 for males; for females; it increased from 2.1 in 1975-1979 to 11.7 in 1983-1987.

It has been argued that such increases reflect more accurate diagnosis by recent scanning and other procedures. In rebuttal, these considerations are germane.

- Adequate brain scanning devices had been widely available for at least one decade previously.
- The rise of primary brain tumors was quantitative.
- The incidence rates for cancer involving most other systems either remaining stable or declined during the 1983-1987 period.

Recent data continue to confirm that the incidence rates for brain cancer in the United States have increased in both adults (Devesa 1995) and children (Gurney 1996). In fact, the increased reporting of brain tumors among young persons causes children with headache to worry about a tumor as the cause!

The Rising Incidence Of Primary Brain Lymphoma

The subset of primary brain lymphoma is of unique interest.

- Eby et al (1988) reported a nearly threefold rise in incidence of this previously-rare tumor among immunologically normal persons in the 1982-1984 SEER data. Specifically, the rate increased from 2.7 cases per ten million population in 1973-1975 to 7.5 cases per ten million in 1982 through 1984 ($P=0.001$). The age-adjusted rise was more striking among women – from 4.9 per ten million in 1979-1981 to 8.9 per ten million in 1982-1984. This could not “be explained completely by confounding effects.”
- Yau et al (1996) reported a steep rise in the incidence of primary lymphoma of central nervous system in non-immunocompromised patients between 1981 and 1991 in southeast Scotland. Primary brain lymphoma accounted for 7.6 percent of all gliomas managed by the median of 1.5 percent for the previous decade. These investigators noted similar increases of primary brain lymphoma in other European centers.

The foregoing phenomenon assumes considerable pertinence in light of these facts: (a) the formal approval of aspartame in July 1981, and (b) the 3:1 preponderance of women

with reactions to aspartame (Section 1). Eby and al (1988) commented: “A possible explanation of the increased incidence might be other noninfectious environmental exposures. One could conjecture that primary brain lymphomas may have a long latency period and are the result of occupational or other chemical exposures. However, the similar increases in incidence in both men and women, particularly in older persons, make occupational exposures an unlikely cause.

Experimental Aspartame-Associated Brain Tumors

Prior experimental evidence corroborates this association. An unexpected high incidence of primary brain tumors was found experimentally in rats during the 1970s. Although FDA scientists and others expressed considerable concern, the statutes of limitations on two such studies were allowed to expire before the Delaney Amendment (XXVII-E) could be invoked. The details appear in the Congressional Record-Senate hearings of May 7, 1985 and August 1, 1985, and in prior text (Roberts 1989a).

Even though aspartame continues to be touted as “the most thoroughly testes additive in history,” there remains a paucity of corporate-neutral studies aimed at proving or disproving carcinogenesis in rats and other species.

Related Criticisms Of The FDA

A. Dr. M. Adrian Gross

Dr. Gross a senior FDA pathologist, told the Senate hearing held on August 1, 1985

(pp. S108220- 10847)

“In view of all these indications that the cancer-causing potential of aspartame is a matter that has 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 Delaney Amendment to the Food, Drug, and Cosmetic Act?’” (Italics supplied)

In a subsequent stinging rebuke of the FDA, Dr. Gross stated in his sworn analysis of corporate experimental studies (November 3, 1987)

“At least one of those studies had revealed 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 aspartame in 1974; moreover, as a review of that study in the FDA was so flawed, the Agency apparently did not even realize it at the time that only a portion of the observations on brain tumors had in fact been submitted by G. D. Searle & Co. in their petition for approval.”

B. Dr. John Olney

Dr. Olney (Professor of Psychiatry and Neuropathology, Washington University School of Medicine) wrote the following statement to Senator Howard Metzenbaum, dated December 8, 1987 concerning aspartame-related brain tumors.

“This is an exceedingly complex topic which, unfortunately, has a history riddled with appearance of fraudulent practices by the manufacturer of NutraSweet and ineptitude and/or malfeasance on the part of the FDA officials. In the mid 1970’s, when I reviewed the NutraSweet record in preparation for the hearing I had promised, I came upon a peculiar study which the manufacturer had submitted to the FDA and which FDA had unquestioningly accepted as evidence for the safety of NutraSweet. The study showed that in 320 NutraSweet-fed rats there were 12 brain tumors, whereas in a group of concurrent control rats which were not exposed to NutraSweet-fed is 3.75%, this suggests the need for additional in-depth research to rule out the possibility...

“I seriously doubt whether this method of data analysis would stand the scrutiny of competent disinterested statisticians. Even more seriously I wonder why FDA allows microscopic slides to disappear (while I supposedly impounded) and why they do not question the de novo emergence of a brain tumor among the controls when the slides reappear.

“The PBOI panel member who was primarily responsible for reviewing the brain tumor issue was Peter Lampert, M.D., Neuropathologist and chairman of the pathology department at Univ, of Calif. San Diego. Dr. Lampert personally examined the microscopic slides pertaining to the brain tumor studies, and told me a year or so after the PBOI report was completed that he had been surprised at the large size of the brain tumors in the NutraSweet-fed rats.” (Italics supplied)

C. Senator Howard Metzenbaum

Senator Metzenbaum offered this commentary at the May 7, 1985 Senate hearing.

“I do not claim children will develop brain tumors. I do not know that. I do know that the FDA was worried about it. I do know that three of the six FDA scientists advising the FDA Commissioner on final approval were sufficiently worried about it that they were not willing to approve the product. The FDA’s own scientists were split on the issue.” (P.S5492)

D. The Community Nutrition Institute

The Community Nutrition Institute and others filed a petition on August 8, 1983 seeking (a) a public hearing by the FDA concerning its approval of aspartame in liquids (“wet use”) because one had not been held, and (b) a stay of such approval pending the hearing due to concern over neurotoxicity. The United States Court of Appeals for the District of Columbia Circuit (9) denied both requests (No. 84- 1153 and No. 84-5253 [D.C. Civil Action No. 83-03846, decided September 24. 1985].)

This court was aware of prior misgivings by scientists and the Public Board of Inquiry convened in January 1980, including the Board’s plea for “further study to establish whether or not a relationship existed between the ingestion of aspartame and brain tumors.” (In the three years since the Board’s recommendation, G. D. Searle & Co. “chose not to conduct cancer studies on aspartame... and the FDA failed to require such studies.”) The Court made the following pertinent comment (p.14):

“Our scope of review, the exactitude of the fit that we require between the agency’s conclusions and the germane facts is investigated, is necessarily deferential. The judiciary is ill-equipped to conduct investigation and analyze facts of the type involved in this case. Because of the agency’s expertise and broad discretion in ensuring the safety of food additives, we cannot substitute our judgement for the agency’s. The Commission’s finding that there were no material issues of fact can be overturned only if an examination of the record discloses that material issues of fact are apparent to any reasonable examiner.” (Italics supplied)

Brain Cancer in Females

The apparent rise of these tumors in women is noteworthy. The threefold higher incidence of severe reactions to aspartame products in females (Section 1) is germane.

Malignant brain tumors in adults previously occurred more often among men (Salcman 1985, Cole 1989). Older male rats also develop more spontaneous brain tumors (chiefly granular-cell meningiomas) than females (Krinke 1985)

The increase of fatal brain cancer among women is illustrated by the following death rates (per 100,000 population) among females of all ages (kindly supplied by Mr. Edwin Silverberg, Department of Epidemiology & Statistics, American Cancer Society): 1979 – 3.4; 1980- 3.5; 1981 – 3.5; 1982 – 4.0. These increases were more striking among white women than non-white women. (Socioeconomic and cultural factors pertaining to the consumption of “diet” drinks during the early 1980s in part explains these discrepancies.)

Pathogenetic Insights

The following newer concepts concerning the etiology and pathogenesis of primary brain tumors are pertinent.

- Aspartame and its components or metabolites might activate some proto-oncogene, such as the epidermal growth factor-receptor (EGF-R) gene (Hoy Sang 1989)

– either directly or indirectly (e.g., by tissue glucopeia or the influence of uncommon amino acids dextroisomers.)

- The substitution of no-calorie or low-calorie products for conventional foods and beverages, whether as meals or snacks, can have serious sequelae in the brain (Chapter IV). Under usual circumstances, this organ is almost totally dependent upon glucose for optimal function. This point is emphasized relative to the pathogenesis of multiple sclerosis (Roberts 1966).
- The initial rise of primary brain lymphoma in 1982 – when the consumptions of aspartame was much less than after its approval of “wet” use during 1983 – might be explained by the need for a less intense biophysiological or toxic stimulus than the more common types of brain tumor.
- The unchecked hyperinsulinized state (Chapter XIV) may be critical.

The author is impressed by the prolonged use of aspartame gum in some of these patients. The ability of small molecules to enter the brain directly from the oropharynx was described in Chapter II-E.

Primary Tumors

Pituitary tumors occurred in patients who had consumed considerable aspartame for years, and evidenced other clinical features of aspartame disease. For example, one female aspartame reactor developed a pituitary tumor in 1992, which recurred in 1995. She had continued consuming six diet colas, and aspartame yogurt and hot chocolate daily.

Attention is directed to several prolactin-secreting pituitary tumors encountered (see Chapter XXVII-F-5). The stimulation of prolactin by phenylalanine was discussed in Chapters IX-E and XXIV.

Animal studies validate this association. Multiple instances of pituitary tumors were cited in the Bressler Report – e.g., the following female rats:

No. M15CF – pituitary adenoma

No. H18HF – pituitary adenoma

No. K18HF – pituitary adenoma

No. M17LF – marked enlargement of pituitary and both adrenal glands

No. J30HM – marked enlargement of pituitary

Representative Case Reports

Case XXVII-F-4

A 35-year-old man with longstanding diabetes had been consuming considerable diet cola since its availability. In recent years, he suffered severe unexplained headaches, numbness of the hands, and intermittent diarrhea. He felt “my mind was in a fog,” and gained 80 pounds. A pituitary tumor enveloping the optic nerve was found and removed. Continuing to drink diet cola, his blood glucose did “some weird things.” He then learned about aspartame disease, and improved after stopping the diet soda.

Case XXVII-F-5

A female aspartame reactor repeatedly developed repeatedly developed “horrible headaches whenever I knowingly or unknowingly consume aspartame.” As a teenager, she “literally existed on diet sodas and a low caloric intake because I was so very body conscious.” She then developed a prolactin-secreting pituitary tumor. This caused her to focus on aspartame disease because “I come from an incredibly healthy stock, and live a healthy life style in a reasonably uncontaminated environment.”

G. OCCUPATIONAL EXPOSURE THROUGH INHALATION

The author initially reports of aspartame disease caused by exposure in the manufacturing environment with skepticism. As more were received from perspective professionals, the association seemed more plausible.

These findings are relevant.

- The Material Safety Data Sheet on aspartame lists its potential adverse effects on the eyes, skin and respiratory tract, along with required personnel protective equipment (including an approved air purifying or mist respirator) and first aid measures
- Visitors to an aspartame manufacturing plant are advised to wear protective clothing in order to avoid hazardous exposure.
- There have been related instances of non-occupational exposure. One woman reported “I am allergic to aspartame. If I break open a packet containing it, and inhale the powder, I instantly develop a headache.”

Representative Case Reports

Case XXVII-13

The head of an engineering firm wrote the author after reading about aspartame disease. He described the problem of a friend, the installation engineer of more than a dozen automatic centrifuges used in the manufacture of aspartame. After exposure to the dry aspartame powder as these machines were started up, he suffered multiple symptoms – “hot flashes,” marked weakness and insomnia. They slowly disappeared after completion of the installations, and without further exposure.

Case XXVII-14

A 21-year-old man was exposed over one year to a fine dust of aspartame at the packaging plant where he worked. He complained of blurred vision, headache, dizziness

and depression. An autopsy following his sudden death revealed degenerative changes in the liver, kidneys, heart and lungs. The cardiac abnormalities suggested alcoholic beverages.

Case XXVII-15

A 33-year-old worker at a plant manufacturing aspartame developed progressive dizziness, palpitations, a rapid heart rate, intermittent “fuzzy vision” with a “sparkly light,” “needles” over the right face, and leg weakness. He blended aspartame with citric acid, with or without an acidulent containing phosphoric acid. (He would cut the bags, and slowly pour the chemical in 140-degree water.) Any exposed skin was covered with a fine talc. He could detect the sweetness through his mask.

The author saw him in consultation because prior neurologic and psychiatric evaluations failed to uncover another cause. One neurologist began his report by indicating the patient’s concern over occupational exposure to aspartame, but made no further reference to it in his three-page analysis.

Commentary

Sensational but premature exposes of diseases in workers and their communities have been attributed to chemicals used in industry.

This apparently was the case with problems affecting residents in Hinkley (California), a desert town. They were ascribed to the chromium-6 used in a Pacific Gas & Electric plant manufacturing a rust inhibitor. On the other hand, this scenario may apply to exposed personnel through the manufacture of aspartame.

This story formed the basis for a hit movie Erin Brockovich. A huge settlement was made before the publication of scientific information indicating that this substance is a toxin and carcinogen only when inhaled during production (The Wall Street Journal March 28, 2000, p. A-30).

TUMORS AND CANCER; THE DELANEY AMENDMENT

“By far the most mutagenic agents known to man are chemicals, not radiation. And in regard, food additives rather than fallout at present levels may present a greater danger.”

Dr. Richard Caldecott (1961)

(Atomic Energy Commission)

Heavy consumers of aspartame products appear to be increased for developing tumors in the brain (see below) and elsewhere. The author initially considered “anecdotes” about cancer involving organs other than the brain in aspartame reactors to be coincidental. AS the number increased, however, a relationship could not be ignored.

Reference was made in Chapter IX to aspartame-induced vaginal bleeding, breast tenderness, and changes involving blood cells and lymph nodes.

Admittedly, this realm remains controversial. The Bressler Report (1977) underscored the numerous shortcomings of aspartame studies in rats, especially tumor induction. Dr. M. Adrian Gross, a senior FDA pathologist-scientist, stated

“In view of all these indications that the cancer-causing potential of aspartame is a matter that had been established way beyond any reasonable doubt, one can ask: “What is the reason for the apparent refusal by the FDA to invoke for this food additive the so-called Delaney Amendment to the Food, Drug, and Cosmetic Act?” (Congressional Record-Senate August 1, 1985, p. S10837).

There may be a long hiatus between the introduction of a drug or chemical and awareness of its link to cancer. This is illustrated by phenolphthalein, the main ingredient of several popular laxatives. Nearly a century lapsed before documentation of its carcinogenic activity in rodents – including tumors of the ovaries, kidneys, adrenal glands and thymus (McGinley 1997).

Selected Tumors

Dr. George Schwartz (1999) suggested a connection between aspartame consumption and breast cancer and prostate cancer. Both markedly increased following the release of aspartame in 1981, based on governmental surveillance statistics.

There are suggestive anecdotal reports in this serious. For example, a diabetic male developed retinopathy and joint pain while consuming diet colas, and then cancer of the breast.

The puzzling rise of certain cancers over the past decade, especially among younger weight-conscious women, warrants consideration of the contributory role of aspartame products.

- Ductule breast carcinoma in situ rose 52 percent from 1983-1989; during this period the use of aspartame products quadrupled. The numbers subsequently rose to 23,000 case in 1992 and 36,000 in 1998, 200 persons higher than had been projected.
- A fourfold increase in adenocarcinoma of the cervix in England's East Anglia region, most notably in the 30- to 39-year-age group was reported in 1997 b Diane Stockton of the Institute of Public health at Cambridge University.

The Delaney Amendment

Congress included the Delaney clause in the 1958 Food Additives Amendment. Its intent was to ban the ingestion of cancer-causing chemicals.

The circumstances surrounding the adoption of its Federal law may be of interest to "Trivia" buffs. Representative James Delaney of New York unsuccessfully tried to obtain its passage for five years. Delaney's staff then briefed actress Gloria Swanson, a health food advocate, in 1956. She enlisted sympathetic wives of congressmen, who in turn encouraged their husbands to support the bill.

Unfortunately, the Delaney clause was emasculated by the Senate's Comprehensive Regulatory Reform Act of July 19, 1995. Without defining the terms "negligible" or "insignificant," it stated that a substance or product shall not be prohibited or refused approval when it "presents a negligible or insignificant foreseeable risk to human health."

The Author's Perspective

Having monitored the controversy about saccharin and urinary bladder tumors (see below). The following revelations proved troublesome: (a) deficiencies involving comparable testing with aspartame; (b) ignored reports of brain tumors in mice given aspartame; and (c) reluctance of governmental agencies to invoke the Delaney Amendment.

In prior publications, the author reported increased tumor rates attributable to divers influenced to which the population is exposed. They include

- The ability of insulin to enhance the action of male hormone (testosterone) on prostatic growth (Sirek 1953; Calame 1964; Roberts 1966a, 1967c).
- Diaz-Sanchez et al (1999) demonstrated enhancement of insulin biosynthesis and secretion by testosterone, consistent with the hyperinsulinemia encountered in hyper androgenic syndromes.
- A variety of tumors caused by exposure to the pesticide pentachlorophenol - especially lymphoma, sarcoma, leukemia and other blood disorders (Roberts 1990b, 1997d).
- Breast enlargement/tumors in persons taking mega doses of vitamin E (Roberts 1994c).
- Prostate cancer after vasectomy (Roberts 1993d).

Aspartame as a Co-Carcinogen

A potentiated carcinogenic effect by aspartame in our increasingly complex environment demands study. Others share a similar orientation.

- Dr. Samuel S. Epstein (199) (Professors of Environmental and Occupational Medicine, University of Illinois) stated, “Much cancer is avoidable and due to past exposure to chemical and physical carcinogens in the air, water and food and the workplace.”
- Huff, Haseman and Rall (1991) offered this summary concerning chemical carcinogens.

“We believe our scientific and public responsibility must continue to be directed toward identifying those chemicals, mixtures of chemicals, and exposure circumstances that present potentially the most predictable carcinogenic (and other toxicological) hazards to humans... The important issue is not whether we are undeniably correct in extrapolating carcinogenic responses in laboratory animals up the evolutionary trail to humans, but rather to concentrate our vigilance to assure and improve the entrusted public health.”

Possible Carcinogenic Mechanisms

Several of the potential cancer-inducing properties of aspartame, its three components (phenylalanine; aspartic acid; and a methyl ester that promptly becomes free methanol after ingestion), and the many breakdown products on exposure to heat and storage are cited here and in the ensuing discussion of brain tumors.

- Many constituents in the human diet are nitrosated within the gastrointestinal tract to form potentially carcinogenic nitroso compounds. Shephard et al (1993) reported mutagenic activity by aspartame after nitrosation, using *Salmonella typhimurium* as the test organism.
- The diketopiperazine derivative of aspartame (Chapter XXV) has been incriminated as a tumor-causing chemical.

- Formaldehyde released from the breakdown of methyl alcohol (Chapter XXI) is known to be carcinogenic.
- The potential carcinogenic effects of chronic hyperinsulinemia (Chapter XIV) has been discussed in prior publications, with special reference to the prostate (Roberts 1967d). Others have implicated hyperinsulinemia in the pathogenesis of breast cancer (Diamanti-Kandarakis 1999).
- Alteration of glucose transport is a characteristic of experimental tumors. Reporting on this phenomenon, and the dramatic increase in total cellular glucose transporter protein, Birenbaum et al (1987) emphasized the induction of such transformation when fibroblasts are starved for glucose.
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BRAIN TUMORS

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The observations of Dr. John Olney concerning aspartame-related brain tumors are detailed below. Other investigators also reported increased rates of brain tumors (gliomas) in rats given aspartame (Congressional Record-Senate 1985a, b). Cornell, Wolfe and Sanders (1984) reviewed the data. Dr. M. Adrian Gross stated, “At least one of those studies has established beyond any reasonable doubt that aspartame is capable of inducing brain tumors in experimental animals” (Congressional Record-Senate 1985b).

Professor Walle Nauta (Massachusetts Institute of Technology) chaired the Public Board of Inquiry (PBOI) convened by the FDA in 1980 to evaluate the issue of aspartame-related brain tumors. This Board recommended that aspartame NOT be approved. It

concluded that the evidence from the Lifetime Rat Study and the Two Year Rat Study "...appeared to suggest the possibility that aspartame, at least when administered in the huge quantities employed in the studies, may contribute to the development of brain tumors" (United States General Accounting Office 1987). The carcinogenic potential of aspartame was further suggested by early occurrence of tumors in dosed animals.

The Board's recommendation was overruled, however, by the FDA Commissioner Nauta emphasized that he had been under the clear impression aspartame would be excluded from soft drinks! He asserted that the inquiry would have been conducted differently had he known otherwise (Congressional Record-Senate 1985, p.S5503).

Dr. Douglas L. Park (Staff Science Advisor, Office of Health Affairs of the Department of Health & Human Services) submitted his analysis of the hearing by this PBOI in 1981. He pointed out that his interpretation of the term "authentic," as used by the Universities Associated for Research and Education in Pathology (URAEP), was primarily that the experiments "had indeed been done." Park then explained his concerns about the occurrence of brain tumors in the treated rats. "I believe that aspartame has not been shown to be safe for the proposed food additive uses. Along with the Board of Inquiry, I must recommend, therefore, that aspartame not be approved until additional studies are carried out using proper experimental designs," (Italics supplied)

The FDA was influenced by the Ishii (1981) report. These investigators administered aspartame and its diketopiperazine to SLC Wistar rats for 104 weeks at the Ajinomoto Company's research laboratories. Although two astrocytomas, two oligodendrogliomas and one ependymoma were found among the four test groups, it was concluded that neither agent cause brain tumors.

The same gender difference noted above for urinary bladder tumors is again suggested by a higher incidence of brain tumors among male rats given aspartame. (The incidence rates in female rats and controls were the same.)

Does Aspartame Cause Human Brain Cancer?

The author's initial report on this topic (Roberts 1991a) was published a decade ago. Since then, more than a score of reports have been personally received about patients who developed brain tumors after consuming considerable aspartame. They included astrocytoma, oligodendroglioma, other gliomas, meningioma, and hypothalamic tumors.

Examples of the prodigious consumption of aspartame are cited.

- A 19-year-old woman developed an acoustic neuroma after prolonged use of five to six cans diet soda daily.
- The husband of a woman who died of a brain tumor at the age of 37, leaving an 8-year-old daughter, wrote this poignant note:

“She was a heavy user of aspartame. On a typical day, she would consume 6-12 cans of diet cola. I used to joke to her about drinking so much diet cola that she could cut out the middleman by having them deliver the stuff right to our house. She also consumed it in many products every day because, like most women, she was obsessed with watching her weight.”

- The wife of a man who died of glioblastoma wrote of his addiction to a diet cola. “He drank gallons of this soda each week. I personally saw our 20-gallon trash cans filled each week to the brim with his empty large diet cola bottles. He was obsessed intense thirst for the diet cola.
- A man who developed an astrocytoma had been putting 20 aspartame tablets in each cup of coffee, along with consuming from two to three 2-liter bottles of diet soda daily.
- A 49-year-old woman attempted drastic reduction of weight. She developed a large glioblastoma in the posterior fossa within several months after “ingesting massive quantities of aspartame.” In addition to various diet sodas, ice cream and puddings, she drank “tons of coffee,” adding six packets of a tabletop sweetener to each cup.
- A 43-year-old woman developed severe depression, a 60-pound weight gain, and a subsequent brain tumor after consuming diet colas for many years. On learning about aspartame disease, she commented, “This supposed miracle sweetener of the century turns out to be the silent killer of my life.”

Dr. Lennart Hardell (2000) (Department of Oncology, Orebro Medical Center, Orebro, Sweden) found an odds ratio of 1.24 patients with malignant brain tumors who consumed low-calorie drinks, compared to controls. Furthermore, this risk increased among persons exposed to radiation.

Representative Case Reports

Case XXVII-F-1

A 41-year-old woman had consumed at least two to three cans of aspartame soft drinks more than 11 years. She developed a grand mal seizure. A brain tumor (oligodendroglioma) was found. Surgery was followed by radiation therapy. Her previous non-neurologic complaints included palpitation, abdominal pain, blood in the stools, severe itching without rash, a gain of ten pounds, and unexplained discomfort in the knuckles and elbows.

Case XXVII-F-2

A 62-year-old manager switched to aspartame products in the wake of publicity about the tumor-causing effects of saccharin. He averaged six packets of an aspartame tabletop sweetener in his coffee daily, and also added it to iced tea.

The patient experienced decreased vision in both eyes, partial loss of hearing, headaches, mild confusion, slurring of speech and leg cramps. His granddaughter developed hives from aspartame sodas.

A diagnosis of primary brain lymphoma was later made by biopsy. There was no evidence for immunosuppression or overt exposure to environmental carcinogens. As with aspartame consumers who developed brain tumors, this patient had difficulty in determining whether his neurological manifestations were primarily due to a brain tumor evolving over several years, or aspartame disease which was then complicated by the tumor.

Case XXVII-F-3

A diabetic man was advised to drink a minimum of one gallon liquid daily because of concomitant high uric acid levels. He did so by using aspartame sodas.

Within several months, he experienced persistent headaches, “zoning out”, and a striking decline in his body temperature to 95.6 degrees. An MRI of the brain ten years before was normal. He consulted an endocrinologist. A repeat study revealed a large tumor (hamartoma) in the hypothalamus.

The Rising Incidence Of Primary Brain Cancer

The incidence rates for primary malignant brain tumors have increased by 2.5 percent annually since 1980 according to a National Cancer Institute registry, particularly among older persons. This phenomenon cannot be attributed solely to better diagnostic technology.

The National Cancer Institute’s Surveillance Epidemiology and End Results (SEER) statistics (Cancer Statistics Review 1973-87, NIH Publication No. 89-2789) indicate an impressive increase in the age-adjusted incidence rates of primary brain cancer since 1985 – possible as early as 1984. This phenomenon was documented in the categories “All Races, Males and Females,” “All Races, Males,” and “All Races, Females,” “All Races, Males” and “All Races, Females.”

Statistically significant rises in brain cancer also were found in the Estimated Annual Percent Change (EAPC) over the 1983-1987 period. SEER Table II-34, containing the five-year trends for all races, indicated that the annual percent change rose from 2.1 in 1975-1979 to 8.7 in 1983-1987 for males; for females; it increased from 2.1 in 1975-1979 to 11.7 in 1983-1987.

It has been argued that such increases reflect more accurate diagnosis by recent scanning and other procedures. In rebuttal, these considerations are germane.

- Adequate brain scanning devices had been widely available for at least one decade previously.
- The rise of primary brain tumors was quantitative.
- The incidence rates for cancer involving most other systems either remaining stable or declined during the 1983-1987 period.

Recent data continue to confirm that the incidence rates for brain cancer in the United States have increased in both adults (Devesa 1995) and children (Gurney 1996). In fact, the increased reporting of brain tumors among young persons causes children with headache to worry about a tumor as the cause!

The Rising Incidence Of Primary Brain Lymphoma

The subset of primary brain lymphoma is of unique interest.

- Eby et al (1988) reported a nearly threefold rise in incidence of this previously-rare tumor among immunologically normal persons in the 1982-1984 SEER data. Specifically, the rate increased from 2.7 cases per ten million population in 1973-1975 to 7.5 cases per ten million in 1982 through 1984 ($P=0.001$). The age-adjusted rise was more striking among women – from 4.9 per ten million in 1979-1981 to 8.9 per ten million in 1982-1984. This could not “be explained completely by confounding effects.”
- Yau et al (1996) reported a steep rise in the incidence of primary lymphoma of central nervous system in non-immunocompromised patients between 1981 and 1991 in southeast Scotland. Primary brain lymphoma accounted for 7.6 percent of all gliomas managed by the median of 1.5 percent for the previous decade. These investigators noted similar increases of primary brain lymphoma in other European centers.

The foregoing phenomenon assumes considerable pertinence in light of these facts: (a) the formal approval of aspartame in July 1981, and (b) the 3:1 preponderance of women

with reactions to aspartame (Section 1). Eby and al (1988) commented: “A possible explanation of the increased incidence might be other noninfectious environmental exposures. One could conjecture that primary brain lymphomas may have a long latency period and are the result of occupational or other chemical exposures. However, the similar increases in incidence in both men and women, particularly in older persons, make occupational exposures an unlikely cause.

Experimental Aspartame-Associated Brain Tumors

Prior experimental evidence corroborates this association. An unexpected high incidence of primary brain tumors was found experimentally in rats during the 1970s. Although FDA scientists and others expressed considerable concern, the statutes of limitations on two such studies were allowed to expire before the Delaney Amendment (XXVII-E) could be invoked. The details appear in the Congressional Record-Senate hearings of May 7, 1985 and August 1, 1985, and in prior text (Roberts 1989a).

Even though aspartame continues to be touted as “the most thoroughly testes additive in history,” there remains a paucity of corporate-neutral studies aimed at proving or disproving carcinogenesis in rats and other species.

Related Criticisms Of The FDA

A. Dr. M. Adrian Gross

Dr. Gross a senior FDA pathologist, told the Senate hearing held on August 1, 1985

(pp. S108220- 10847)

“In view of all these indications that the cancer-causing potential of aspartame is a matter that has 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 Delaney Amendment to the Food, Drug, and Cosmetic Act?’” (Italics supplied)

In a subsequent stinging rebuke of the FDA, Dr. Gross stated in his sworn analysis of corporate experimental studies (November 3, 1987)

“At least one of those studies had revealed 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 aspartame in 1974; moreover, as a review of that study in the FDA was so flawed, the Agency apparently did not even realize it at the time that only a portion of the observations on brain tumors had in fact been submitted by G. D. Searle & Co. in their petition for approval.”

B. Dr. John Olney

Dr. Olney (Professor of Psychiatry and Neuropathology, Washington University School of Medicine) wrote the following statement to Senator Howard Metzenbaum, dated December 8, 1987 concerning aspartame-related brain tumors.

“This is an exceedingly complex topic which, unfortunately, has a history riddled with appearance of fraudulent practices by the manufacturer of NutraSweet and ineptitude and/or malfeasance on the part of the FDA officials. In the mid 1970’s, when I reviewed the NutraSweet record in preparation for the hearing I had promised, I came upon a peculiar study which the manufacturer had submitted to the FDA and which FDA had unquestioningly accepted as evidence for the safety of NutraSweet. The study showed that in 320 NutraSweet-fed rats there were 12 brain tumors, whereas in a group of concurrent control rats which were not exposed to NutraSweet-fed is 3.75%, this suggests the need for additional in-depth research to rule out the possibility...

“I seriously doubt whether this method of data analysis would stand the scrutiny of competent disinterested statisticians. Even more seriously I wonder why FDA allows microscopic slides to disappear (while I supposedly impounded) and why they do not question the de novo emergence of a brain tumor among the controls when the slides reappear.

“The PBOI panel member who was primarily responsible for reviewing the brain tumor issue was Peter Lampert, M.D., Neuropathologist and chairman of the pathology department at Univ, of Calif. San Diego. Dr. Lampert personally examined the microscopic slides pertaining to the brain tumor studies, and told me a year or so after the PBOI report was completed that he had been surprised at the large size of the brain tumors in the NutraSweet-fed rats.” (Italics supplied)

C. Senator Howard Metzenbaum

Senator Metzenbaum offered this commentary at the May 7, 1985 Senate hearing.

“I do not claim children will develop brain tumors. I do not know that. I do know that the FDA was worried about it. I do know that three of the six FDA scientists advising the FDA Commissioner on final approval were sufficiently worried about it that they were not willing to approve the product. The FDA’s own scientists were split on the issue.” (P.S5492)

D. The Community Nutrition Institute

The Community Nutrition Institute and others filed a petition on August 8, 1983 seeking (a) a public hearing by the FDA concerning its approval of aspartame in liquids (“wet use”) because one had not been held, and (b) a stay of such approval pending the hearing due to concern over neurotoxicity. The United States Court of Appeals for the District of Columbia Circuit (9) denied both requests (No. 84- 1153 and No. 84-5253 [D.C. Civil Action No. 83-03846, decided September 24. 1985].)

This court was aware of prior misgivings by scientists and the Public Board of Inquiry convened in January 1980, including the Board’s plea for “further study to establish whether or not a relationship existed between the ingestion of aspartame and brain tumors.” (In the three years since the Board’s recommendation, G. D. Searle & Co. “chose not to conduct cancer studies on aspartame... and the FDA failed to require such studies.”) The Court made the following pertinent comment (p.14):

“Our scope of review, the exactitude of the fit that we require between the agency’s conclusions and the germane facts is investigated, is necessarily deferential. The judiciary is ill-equipped to conduct investigation and analyze facts of the type involved in this case. Because of the agency’s expertise and broad discretion in ensuring the safety of food additives, we cannot substitute our judgement for the agency’s. The Commission’s finding that there were no material issues of fact can be overturned only if an examination of the record discloses that material issues of fact are apparent to any reasonable examiner.” (Italics supplied)

Brain Cancer in Females

The apparent rise of these tumors in women is noteworthy. The threefold higher incidence of severe reactions to aspartame products in females (Section 1) is germane.

Malignant brain tumors in adults previously occurred more often among men (Salcman 1985, Cole 1989). Older male rats also develop more spontaneous brain tumors (chiefly granular-cell meningiomas) than females (Krinke 1985)

The increase of fatal brain cancer among women is illustrated by the following death rates (per 100,000 population) among females of all ages (kindly supplied by Mr. Edwin Silverberg, Department of Epidemiology & Statistics, American Cancer Society): 1979 – 3.4; 1980- 3.5; 1981 – 3.5; 1982 – 4.0. These increases were more striking among white women than non-white women. (Socioeconomic and cultural factors pertaining to the consumption of “diet” drinks during the early 1980s in part explains these discrepancies.)

Pathogenetic Insights

The following newer concepts concerning the etiology and pathogenesis of primary brain tumors are pertinent.

- Aspartame and its components or metabolites might activate some proto-oncogene, such as the epidermal growth factor-receptor (EGF-R) gene (Hoy Sang 1989)

– either directly or indirectly (e.g., by tissue glucopeia or the influence of uncommon amino acids dextroisomers.)

- The substitution of no-calorie or low-calorie products for conventional foods and beverages, whether as meals or snacks, can have serious sequelae in the brain (Chapter IV). Under usual circumstances, this organ is almost totally dependent upon glucose for optimal function. This point is emphasized relative to the pathogenesis of multiple sclerosis (Roberts 1966).
- The initial rise of primary brain lymphoma in 1982 – when the consumptions of aspartame was much less than after its approval of “wet” use during 1983 – might be explained by the need for a less intense biophysiological or toxic stimulus than the more common types of brain tumor.
- The unchecked hyperinsulinized state (Chapter XIV) may be critical.

The author is impressed by the prolonged use of aspartame gum in some of these patients. The ability of small molecules to enter the brain directly from the oropharynx was described in Chapter II-E.

Primary Tumors

Pituitary tumors occurred in patients who had consumed considerable aspartame for years, and evidenced other clinical features of aspartame disease. For example, one female aspartame reactor developed a pituitary tumor in 1992, which recurred in 1995. She had continued consuming six diet colas, and aspartame yogurt and hot chocolate daily.

Attention is directed to several prolactin-secreting pituitary tumors encountered (see Chapter XXVII-F-5). The stimulation of prolactin by phenylalanine was discussed in Chapters IX-E and XXIV.

Animal studies validate this association. Multiple instances of pituitary tumors were cited in the Bressler Report – e.g., the following female rats:

No. M15CF – pituitary adenoma

No. H18HF – pituitary adenoma

No. K18HF – pituitary adenoma

No. M17LF – marked enlargement of pituitary and both adrenal glands

No. J30HM – marked enlargement of pituitary

Representative Case Reports

Case XXVII-F-4

A 35-year-old man with longstanding diabetes had been consuming considerable diet cola since its availability. In recent years, he suffered severe unexplained headaches, numbness of the hands, and intermittent diarrhea. He felt “my mind was in a fog,” and gained 80 pounds. A pituitary tumor enveloping the optic nerve was found and removed. Continuing to drink diet cola, his blood glucose did “some weird things.” He then learned about aspartame disease, and improved after stopping the diet soda.

Case XXVII-F-5

A female aspartame reactor repeatedly developed repeatedly developed “horrible headaches whenever I knowingly or unknowingly consume aspartame.” As a teenager, she “literally existed on diet sodas and a low caloric intake because I was so very body conscious.” She then developed a prolactin-secreting pituitary tumor. This caused her to focus on aspartame disease because “I come from an incredibly healthy stock, and live a healthy life style in a reasonably uncontaminated environment.”

G. OCCUPATIONAL EXPOSURE THROUGH INHALATION

The author initially reports of aspartame disease caused by exposure in the manufacturing environment with skepticism. As more were received from perspective professionals, the association seemed more plausible.

These findings are relevant.

- The Material Safety Data Sheet on aspartame lists its potential adverse effects on the eyes, skin and respiratory tract, along with required personnel protective equipment (including an approved air purifying or mist respirator) and first aid measures
- Visitors to an aspartame manufacturing plant are advised to wear protective clothing in order to avoid hazardous exposure.
- There have been related instances of non-occupational exposure. One woman reported “I am allergic to aspartame. If I break open a packet containing it, and inhale the powder, I instantly develop a headache.”

Representative Case Reports

Case XXVII-13

The head of an engineering firm wrote the author after reading about aspartame disease. He described the problem of a friend, the installation engineer of more than a dozen automatic centrifuges used in the manufacture of aspartame. After exposure to the dry aspartame powder as these machines were started up, he suffered multiple symptoms – “hot flashes,” marked weakness and insomnia. They slowly disappeared after completion of the installations, and without further exposure.

Case XXVII-14

A 21-year-old man was exposed over one year to a fine dust of aspartame at the packaging plant where he worked. He complained of blurred vision, headache, dizziness

and depression. An autopsy following his sudden death revealed degenerative changes in the liver, kidneys, heart and lungs. The cardiac abnormalities suggested alcoholic beverages.

Case XXVII-15

A 33-year-old worker at a plant manufacturing aspartame developed progressive dizziness, palpitations, a rapid heart rate, intermittent “fuzzy vision” with a “sparkly light,” “needles” over the right face, and leg weakness. He blended aspartame with citric acid, with or without an acidulent containing phosphoric acid. (He would cut the bags, and slowly pour the chemical in 140-degree water.) Any exposed skin was covered with a fine talc. He could detect the sweetness through his mask.

The author saw him in consultation because prior neurologic and psychiatric evaluations failed to uncover another cause. One neurologist began his report by indicating the patient’s concern over occupational exposure to aspartame, but made no further reference to it in his three-page analysis.

Commentary

Sensational but premature exposes of diseases in workers and their communities have been attributed to chemicals used in industry.

This apparently was the case with problems affecting residents in Hinkley (California), a desert town. They were ascribed to the chromium-6 used in a Pacific Gas & Electric plant manufacturing a rust inhibitor. On the other hand, this scenario may apply to exposed personnel through the manufacture of aspartame.

This story formed the basis for a hit movie Erin Brockovich. A huge settlement was made before the publication of scientific information indicating that this substance is a toxin and carcinogen only when inhaled during production (The Wall Street Journal March 28, 2000, p. A-30).

