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Increasing brain tumor rates: is there a link to aspartame?

Olney JW, Farber NB, Spitznagel E, Robins LN.

Department of Psychiatry, Washington University Medical School, St. Louis, MO 63110, USA.

In the past two decades brain tumor rates have risen in several industrialized countries, including the United States. During this time, brain tumor data have been gathered by the National Cancer Institute from catchment areas representing 10% of the United States population. In the present study, we analyzed these data from 1975 to 1992 and found that the brain tumor increases in the United States occurred in two distinct phases, an early modest increase that may primarily reflect improved diagnostic technology, and a more recent sustained increase in the incidence and shift toward greater malignancy that must be explained by some other factor(s). Compared to other environmental factors putatively linked to brain tumors, the artificial sweetener aspartame is a promising candidate to explain the recent increase in incidence and degree of malignancy of brain tumors. Evidence potentially implicating aspartame includes an early animal study revealing an exceedingly high incidence of brain tumors in aspartame-fed rats compared to no brain tumors in concurrent controls, the recent finding that the aspartame molecule has mutagenic potential, and the close temporal association (aspartame was introduced into US food and beverage markets several years prior to the sharp increase in brain tumor incidence and malignancy). We conclude that there is need for reassessing the carcinogenic potential of aspartame.

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Increasing Brain Tumor Rates: Is There a Link to Aspartame?

JOHN W. OLNEY, MD, NURI B. FARBER, EDWARD SPITZNAGEL, AND LEE N. ROBINS

Abstract. In the past two decades brain tumor rates have risen in several industrialized countries, including the United States. During this time, brain tumor data have been gathered by the National Cancer Institute from catchment areas representing 10% of the United States population. In the present study, we analyzed these data from 1975 to 1992 and found that the brain tumor increases in the United States occurred in two distinct phases, an early modest increase that may primarily reflect improved diagnostic technology, and a more recent sustained increase in the incidence and shift toward greater malignancy that must be explained by some other factor(s). Compared to other environmental factors putatively linked to brain tumors, the artificial sweetener aspartame is a promising candidate to explain the recent increase in incidence and degree of malignancy of brain tumors. Evidence potentially implicating aspartame includes an early animal study revealing an exceedingly high incidence of brain tumors in aspartame-fed rats compared to no brain tumors in concurrent controls, the recent finding that the aspartame molecule has mutagenic potential, and the close temporal association (aspartame was introduced into US food and beverage markets several years prior to the sharp increase in brain tumor incidence and malignancy). We conclude that there is need for reassessing the carcinogenic potential of aspartame.

Key Words: Aspartame; Brain tumors; Human; Increased incidence; Increased malignancy; Mutagenesis.

INTRODUCTION

Recent epidemiological surveys have identified a pattern of increasing brain tumor rates in several industrialized countries, including the United States, Canada, West Germany, France, Italy, England and Wales (1–3). The increases identified in these surveys occurred between the early 1970s and mid 1980s and were particularly striking in the age group over 55. Although a detailed analysis according to brain tumor type was not conducted, glioblastomas were tentatively identified as the primary category accounting for the increases (2, 3). The cause of the increases remains unknown; some have suggested that more complete ascertainment due to improved diagnostic technology may provide an explanation (4, 5), but others have argued that this cannot be a complete explanation (1–3), especially since highly malignant glioblastomas are readily ascertained with or without recent advances in diagnostic methology.

Environmental factors peculiar to industrialized societies that have been studied in relation to the increased brain tumor rates include ionizing radiation (6), smoke inhalation (7), pesticides (8) various industrial chemicals (9, 10) and electromagnetic fields (11, 12). One other factor that has been briefly mentioned in the literature but not seriously evaluated is the artificial sweetener aspartame. Roberts (13) mentioned aspartame as a candidate based on the observation that brain tumor rates rose sharply in the United States over a three-year period (1984–1987) following approval by the Food and Drug Administration (FDA) in 1981 of aspartame for marketing in the United States. Also highly relevant is the fact that in 1980 FDA convened a Public Board of Inquiry (PBOI) where a panel of scientists, including prominent neuroscientists (Walle J.H. Nauta and Peter W. Lampert), were asked to evaluate evidence from two animal studies potentially linking aspartame to malignant astrocytic brain tumors. The PBOI panel concluded (14) that evidence from one study was "bizarre" and totally unreliable, and evidence from the other study appeared to show that "aspartame may contribute to the development of brain tumors." Therefore, it was recommended (14) that additional research be performed to rule out brain tumor risk and that approval of aspartame be withheld pending the outcome of such studies. The FDA Commissioner who received the PBOI report referred it to additional expert FDA consultants who concurred with the PBOI panel's recommendations. However, in 1981 a newly appointed FDA Commissioner approved aspartame on the basis of his judgment that brain tumor risk was minimal and further research was not necessary (15). As a consequence, specific studies recommended by the PBOI panel were never done. However, Shephard and colleagues (16) recently reported that if aspartame is nitrosated in vitro to simulate the nitrosation that is believed to occur in the stomach, the nitrosated product has substantial mutagenic activity.

To fully evaluate the potential complicity of aspartame in rising brain tumor rates it would be important to analyze in detail the brain tumor trends in numerous industrialized societies over a wide span of years both predating and postdating the introduction of aspartame into each society. To initiate this assessment, we have analyzed data available from the United States National Cancer Institute pertaining to the incidence in the United

Departments of Psychiatry (JWO, NBF, LNR) and Biostatistics (ES), Washington University Medical School, St. Louis, MO 63110.

Correspondence to: John W. Olney, MD, Department of Psychiatry, Washington University School of Medicine, 4940 Childrens Place, St. Louis, MO, 63110.

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TABLE 1
Morphological Types of CNS Tumors

Astrocytomas: Astrocytoma, NOS (9400); Protoplasmic astrocytoma (9410); Gemistocytic astrocytoma (9411); Fibrillary astrocytoma (9420); Astroblastoma (9430).
Anaplastic astrocytoma (9401).
Pilocytic astrocytoma (9421).
Glioblastomas: Glioblastoma, NOS (9440); Giant cell glioblastoma (9441); Gliosarcoma (9442).
Miscellaneous gliomas: Glioma, malignant (9380); Gliomatosis cerebri (9381); Mixed glioma (9382).
Oligodendrogliomas: Oligodendroglioma, NOS (9450); Oligodendroglioma, anaplastic (9451); Oligodendroblastoma (9460).
Medulloblastomas: Medulloblastoma, NOS (9470); Desmoplastic medulloblastoma (9471); Medullomyoblastoma (9472).
Primitive neuroectodermal tumor (9473).
Ependymomas: Ependymoma, NOS (9391); Ependymoma, anaplastic (9392).

States of primary tumors of the central nervous system (CNS), including both the brain and spinal cord, for the period from 1975 to 1992 (the last year for which such data are available). This analysis differs from those previously reported in that it is substantially more current and provides previously unavailable information detailing striking recent changes in the incidence rates for specific types of brain tumors. In addition, this analysis uncovers specific information pertaining to the temporal pattern of changes in brain tumor rates that is important for interpreting the potential role of environmental agents in brain tumorigenesis.

METHODS

All of the data analyzed in this study were obtained from the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) Program, which provides for the collection (and dissemination for research purposes) of data pertaining to all types of cancer from 9 different catchment areas across the United States (17). These catchment areas collectively comprise approximately 10% of the United States population and are distributed so as to provide a representative sampling of various demographic segments of the population. Audits are performed to help achieve complete ascertainment of cases in each cachment area and to document consistency of diagnosis (1, 17). We included in our analysis all cases that were recorded with a "Site Recode" of 31010 (brain) or 31040 (meninges, spinal cord, cranial nerves, and miscellaneous CNS), and one of the "histology codes" of interest (9380, 9381, 9382, 9391, 9392, 9400, 9401, 9410, 9411, 9420, 9421, 9430, 9440, 9441, 9442, 9450, 9451, 9460, 9470, 9471, 9472, 9473) for the years of interest (1975–1992). The histological types and code numbers (ICD-O-2, 1992) for the CNS tumors included in our analysis are listed in Table 1. All rates were age-adjusted using the population figures supplied with the SEER data set and the 1970 US standard population.

In prior studies, the focus has been primarily on total tumor incidence without adequate attention to individual tumor types, and there has been a tendency to assess the magnitude of overall change in incidence from one extreme time point to another (e.g. from the early 1970s to the mid-1980s) without determining whether the increases occurred episodically or on a steadily progressive basis. Because increases attributable to aspartame would be expected to have a unique temporal pattern corresponding to the pattern of public exposure to this agent, and might be limited to increases in only specific tumor types, we plotted the incidence rate for each year and each tumor type from 1975 to 1992, thereby generating curves optimally useful for evaluating whether aspartame is a logical candidate to explain the observed changes in brain tumor incidence. Analyzing the data in this manner also provided the important advantage of allowing a determination of changes in malignancy of astrocytic tumors (e.g. dedifferentiation of astrocytomas to gliobastomas) as well as incidence of brain tumors over the time period evaluated.

Regarding reliability of diagnosis, the SEER database provides comprehensive information pertaining to the morphological type of tumor, and for most types of brain tumors, approximately 95% of the diagnoses are confirmed microscopically. An exception is the nondescript "malignant glioma" category, a category that tends to be used in cases that lack microscopic confirmation of the diagnosis. While about 65% of the tumors assigned this diagnosis are lacking microscopic confirmation, including this diagnostic category in our overall tracking of CNS tumor incidence did not confound the results of our analysis because this category accounted for only 8% of all CNS tumor diagnoses and the incidence in this category remained almost unchanged over the entire period from 1975 to 1992 (it actually showed a slight decrease, presumably because more tumors were being microscopically confirmed in recent years). Another exception is that glioblastomas in the elderly have a lower-than-95% rate of microscopic confirmation, but most of those that lack microscopic confirmation have been diagnosed radiographically and there is little basis for believing that sophisticated radiographic imaging plus clinical observations would not provide the correct diagnosis in a high percentage of these cases.

RESULTS

The annual incidence rates for all CNS tumors combined (Table 1) for consecutive years from 1975 to 1992 are plotted in Figure 1. A striking feature of the incidence curve is that it has a biphasic character, with phase 1 lasting from 1975 to 1984 and phase 2 from 1985 to

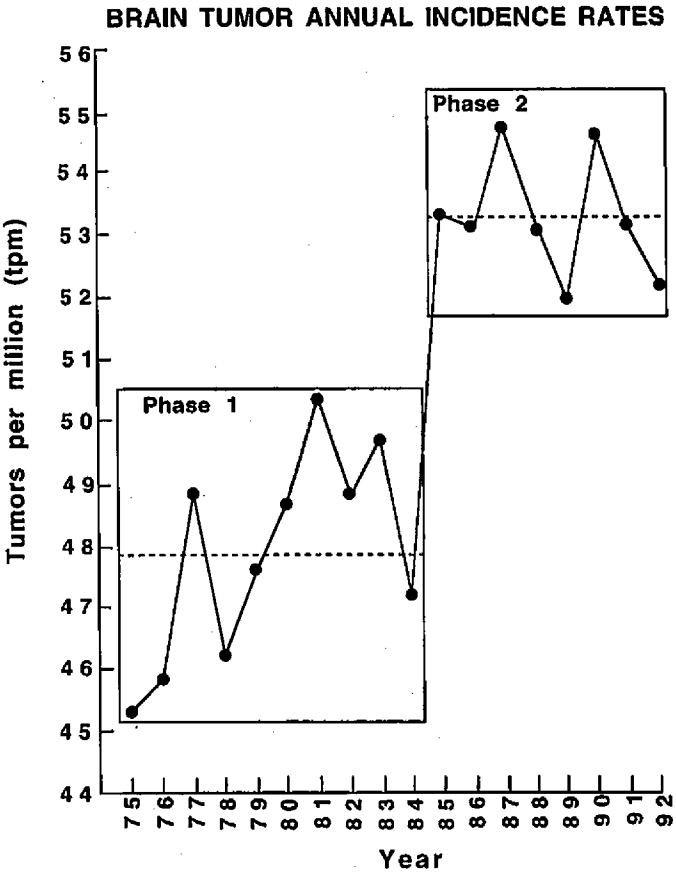

Fig. 1. This graph derived from SEER data depicts the reported incidence in the United States of malignant CNS tumors (all types listed in Table 1 combined) for consecutive years from 1975 to 1992. The curve is biphasic. The mean annual incidence of brain tumors in each phase is indicated by the dashed line (47.89 tpm for phase 1 and 53.26 tpm for phase 2). To confirm the biphasic nature of the curve, a nonlinear least squares regression test was applied. The point estimate divided by the standard error gives a z score of 7.6, $p<0.0000$. The jump = 5.37 tumors per million, with 95% confidence limits of 3.86 to 6.88. The point estimate for when the changeover occurs is between 1984 and 1985, when aspartame had been on the market for about 3 years.

1992. In phase 1, the tumor incidence rose in the 1975 to 1977 interval from 45 to 49 tumors per million (tpm), then fluctuated at a mean level of 48 tpm for 8 years (1977 to 1984). Phase 2 began in the 1984 to 1985 interval with a striking jump from 47 to 53 tpm, then remained at a sustained mean level of 53 tpm for 8 consecutive years (1985 to 1992). The data in Figure 1 pertain to total CNS tumor incidence for both sexes. When analyzed for males and females separately, more tumors occurred in males but the shape of the CNS tumor incidence curves (not shown) was almost identical for the two sexes and each was similar to the curve shown in Figure 1.

The incidence of astrocytomas (Fig. 2A) increased by 50% over a two-year period from 1975 to 1977, then remained at an elevated plateau until 1987, after which it dropped precipitously and progressively so that by 1992 the reported incidence was reduced to approximately 53% of that reported in 1987. Interestingly, the shape of the curve for glioblastomas (Fig. 2B) is almost an exact reciprocal of the curve for astrocytomas. Anaplastic astrocytomas (Fig. 2C) rose from a very low incidence in 1975 to a moderately higher level in 1977 and then leveled off until 1984, after which they rose steadily for 8 consecutive years to a level in 1992 more than 3 times higher than in 1984.

The curves for several types of tumors (oligodendrogliomas, mixed gliomas, pilocytic astrocytomas, ependymomas, primitive neuroectodermal tumors, and gliomatosis cerebri) were similar to one another in that all showed a pattern of moderate increases partially counterbalanced by decreases in the 1970s and then a leveling trend until the mid-1980s when there was a sustained upswing lasting for a series of consecutive years from about 1986 to 1992. Because several different types of tumors showed this pattern, we grouped the data for all such tumors to permit the shape of their curve to be examined as a composite (Fig. 3). Medulloblastomas showed an aberrant increase for one specific year (1977), but a level incidence for all other years (not illustrated). Malignant gliomas, an ill-defined category, fluctuated widely from year to year, but the mean incidence remained level across the period from 1975 to the late 1980s, then showed a slight downward trend (not illustrated).

Because the shape of the curve for the total brain tumor incidence (Fig. 1) is strikingly biphasic, with the crossover between the two phases occurring in the interval from 1984 to 1985, we separated the data into phase 1 (1975 to 1984) and phase 2 (1985 to 1992) for further analysis. In table 2, mean annual tumor incidence data for phase 1 years are compared with those for phase 2 years. The data are given for total CNS tumors and for each of the tumor subtypes either individually or in certain groupings. Glioblastomas and anaplastic astrocytomas combined accounted for the bulk of the increases (mean annual increase of 5.65 tpm) and the group of other tumors presented as a composite in Figure 3 accounted for the remainder of the increases (mean annual increase of 2.91 tpm). Subtracting from these increases the decreases for astrocytomas (2.81 tpm), medulloblastomas (0.17 tpm), and malignant gliomas (0.21 tpm) results in 5.37 tpm as the net mean annual increase in total CNS tumors in phase 2 compared to phase 1. This represents 1310 new brain tumors per year (for the years 1985–1992) in the United States (calculated on the basis of a mean US population of 244 million for those years).

We also performed an analysis to determine how the increased incidence of various brain tumors shown in Table 2 distributed over different age groups (0 to 19, 20

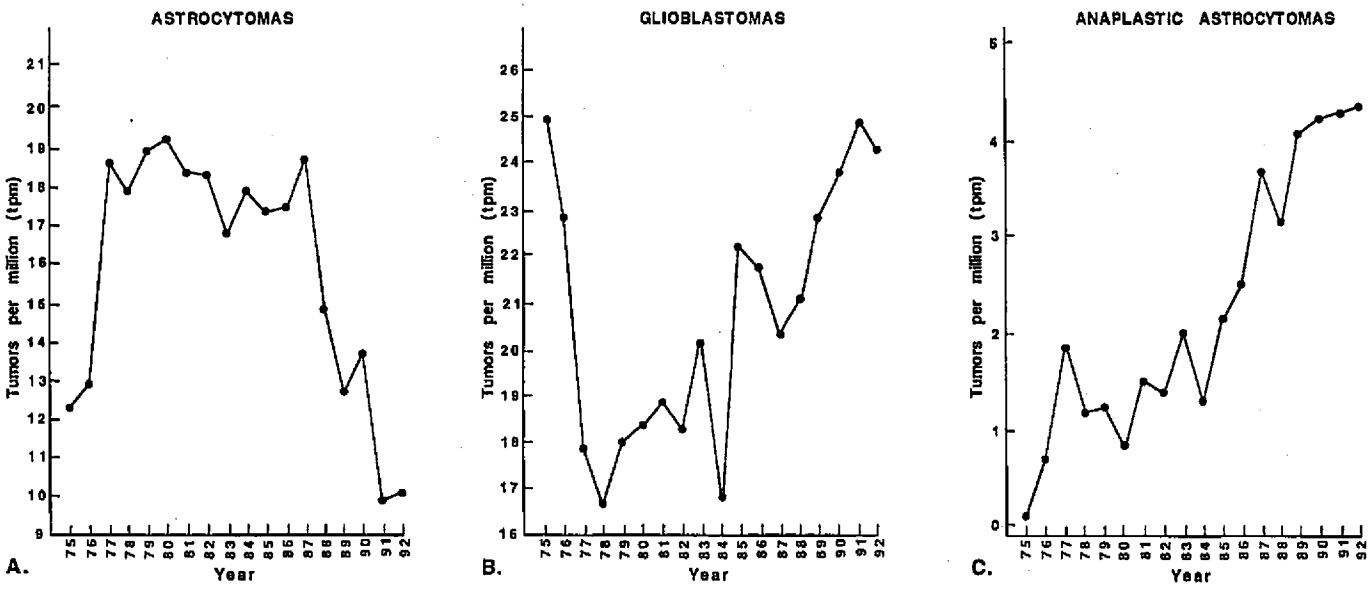

Fig. 2. In these graphs the annual incidence of different histological types of CNS tumors is illustrated. A. The tumors grouped under the heading "astrocytomas" in Table 1. Note the sharp increase in the period from 1975 to 1977 which is counterbalanced by an equally sharp drop in the period from 1987 to 1992. B. The tumors grouped under the heading "glioblastomas" in Table 1. This curve appears to be almost an exact reciprocal of the curve for astrocytomas (A) except that in the 1980s the upswing in the glioblastoma incidence began to occur earlier than the decline in astrocytomas. C. Anaplastic Astrocytomas. There is an increase between 1975 and 1977, then no net change until a progressive increase that began in 1984 and continued until 1992.

to 44, 45 to 69 and 70+). The results of this analysis are shown in Figure 4. The composite tumors, which include tumors that occur most frequently in young people, showed the most striking increases in patients aged 0 to 19 and the second most striking increases in the 20 to 44-year-old age group. The glioblastoma plus anaplastic astrocytoma category showed the largest increases in the 45 to 69 and 70+ groups. Astrocytomas were decreased across all age groups, but the decreases were most pronounced among the 45- to 69-year-old age group and were much smaller in the 70+ group.

To determine whether the shift from astrocytomas to glioblastomas that occurred in the mid-to-late 1980s influenced clinical outcome, we studied the <2 year death rate associated with each of these tumor types in an early period (1975 to 1982) before the shift occurred, compared to a later period (1985 to 1990) when the shift was occurring. The years 1991 and 1992 were excluded from the analysis because accurate 2-year survival data were not available for these years. The analysis was applied to four age groups (0 to 19, 20 to 44, 45 to 69 and 70+). We found (Table 3) that for each age group each tumor type has its own characteristic <2 year death rate, and this death rate did not change appreciably from the early period (1975 to 1982) to the later period (1985 to 1990) for either astrocytomas or glioblastomas in any of the four age groups. However, since glioblastomas have a substantially worse 2-year death rate than astrocytomas, the increase in glioblastomas coupled with a decrease in astrocytomas would result in an overall worsening of clinical outcome. In addition, there was an apparent small increase in the <2 year death rate for both astrocytomas and glioblastomas in the 0- to 19-year-old age group; however, because of the small numbers of patients having either astrocytomas or glioblastomas in this age group, this observation should be interpreted cautiously.

DISCUSSION

The trends observed for astrocytomas and glioblastomas are complex and require careful analysis. It is generally believed that well-differentiated astrocytomas can dedifferentiate into more highly malignant glioblastomas. Our findings are consistent with this view if one takes into consideration the introduction of improved methods for detecting brain tumors (computerized tomography, CT) in the early-to-mid 1970s. We propose that in the era before improved detection methods, hesitancy to perform invasive diagnostic procedures resulted in a large number of astrocytic tumors progressing through an early stage of low malignancy to a later stage of high malignancy before they were diagnosed; hence, a large number of glioblastomas were reported in 1975 (Fig. 2B) compared to a low number of astrocytomas (Fig. 2A). Improved detection methods (circa 1976–1977) caused an upward shift in the detection of astrocytomas (before they progressed to glioblastomas) and a corresponding downward shift in the diagnosis of glioblastomas. In the mid-to-late 1980s, despite availability of increasingly more

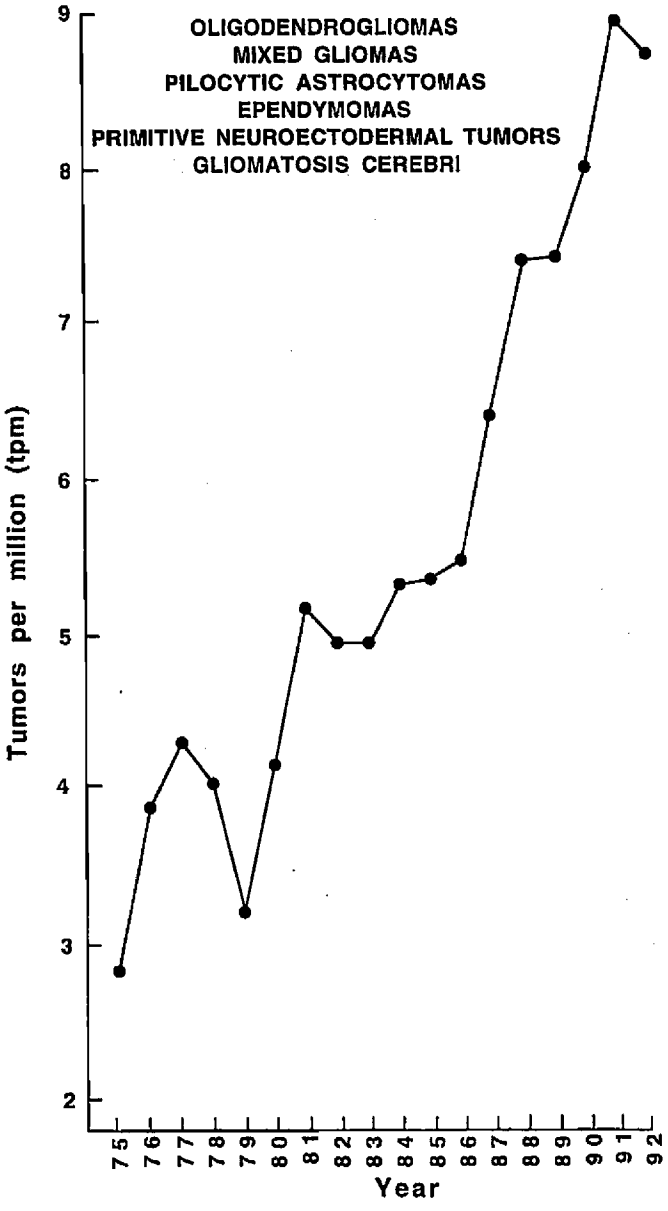

Fig. 3. A composite curve was generated by grouping the incidence data for various types of CNS tumors that showed a sustained upward swing in incidence rates beginning in the mid-1980s. The categories included in this grouping are: oligodendrogliomas, mixed gliomas, pilocytic astrocytomas, ependymomas, primitive neuroectodermal tumors, and gliomatosis cerebri. The shape of this composite curve suggests that it was influenced by factors that caused the incidence to rise eratically from 3 tpm in 1975 to 5 tpm in 1981, then to stabilize at the 5 tpm level for 6 years. This was followed by a new phase in which the incidence steadily climbed from 5 tpm in 1986 to 9 tpm in 1992. This surge in the incidence of these several types of tumors appears to have commenced about 2 years later than the surge in glioblastomas (Fig. 2B) and anaplastic astrocytomas (Fig. 2C).

TABLE 2
Mean Annual Incidence of Brain Tumors in Phases 1 and 2

	Mean annual incidence (age adjusted) Tumors per million (tpm)		Increase or (Decrease)
	Phase 1 (1975–1984)	Phase 2 (1985-1992)	
Glioblastomas + anaplastic astrocytomas	20.55	26.20	5.65
Composite*	4.31	7.22	2.91
Astrocytoma	17.12	14.31	(2.81)
Medulloblastoma	1.74	1.57	(0.17)
Malignant glioma	4.17	3.96	(0.21)
Total CNS Tumors	47.89	53.26	5.37

* Oligodendrogliomas, Mixed Gliomas, Pilocytic Astrocytomas, Ependymomas, Primitive Neuroectodermal Tumors, Gliomatosis Cerebri.

sophisticated detection methods (magnetic resonance imaging [MRI] was introduced in the early to mid-1980s), the shift was in the opposite direction (fewer astrocytomas and more glioblastomas). This suggests the important possibility that some new factor(s) might have overpowered and reversed the artefactual effect of improved detection, and produced a real increase in the malignancy of astrocytic brain tumors at the same time that a substantially larger number of these and other types of malignant brain tumors were being induced, including oligodendrogliomas, mixed gliomas, ependymomas and primitive neuroectodermal tumors (Fig. 3 and Table 2).

We performed a limited analysis to determine how the astrocytoma-to-glioblastoma shift that occurred in the mid-to-late 1980s influenced clinical outcome. One reason for performing this analysis was to clarify whether this shift signified a real increase in the malignancy of astrocytic tumors, or whether it reflected an artefact of diagnosis related to the fact that in the mid-1980s new criteria were introduced (18) for distinguishing glioblastomas from astrocytomas. If the shift were artefactual (i.e. assignment of a glioblastoma diagnosis to tumors which in the prior era would have been considered astrocytomas), it should cause the <2 year death rate for glioblastomas to drop substantially, especially in younger age groups in which the characteristic <2 year death rate is much lower for astrocytomas than for glioblastomas. We found that the <2 year death rate did not change appreciably from the early period to later period for either astrocytomas or glioblastomas in any of the four age groups. Thus, tumors diagnosed as astrocytomas in either time period behaved as astrocytomas and those diagnosed as glioblastomas behaved as glioblastomas. These results

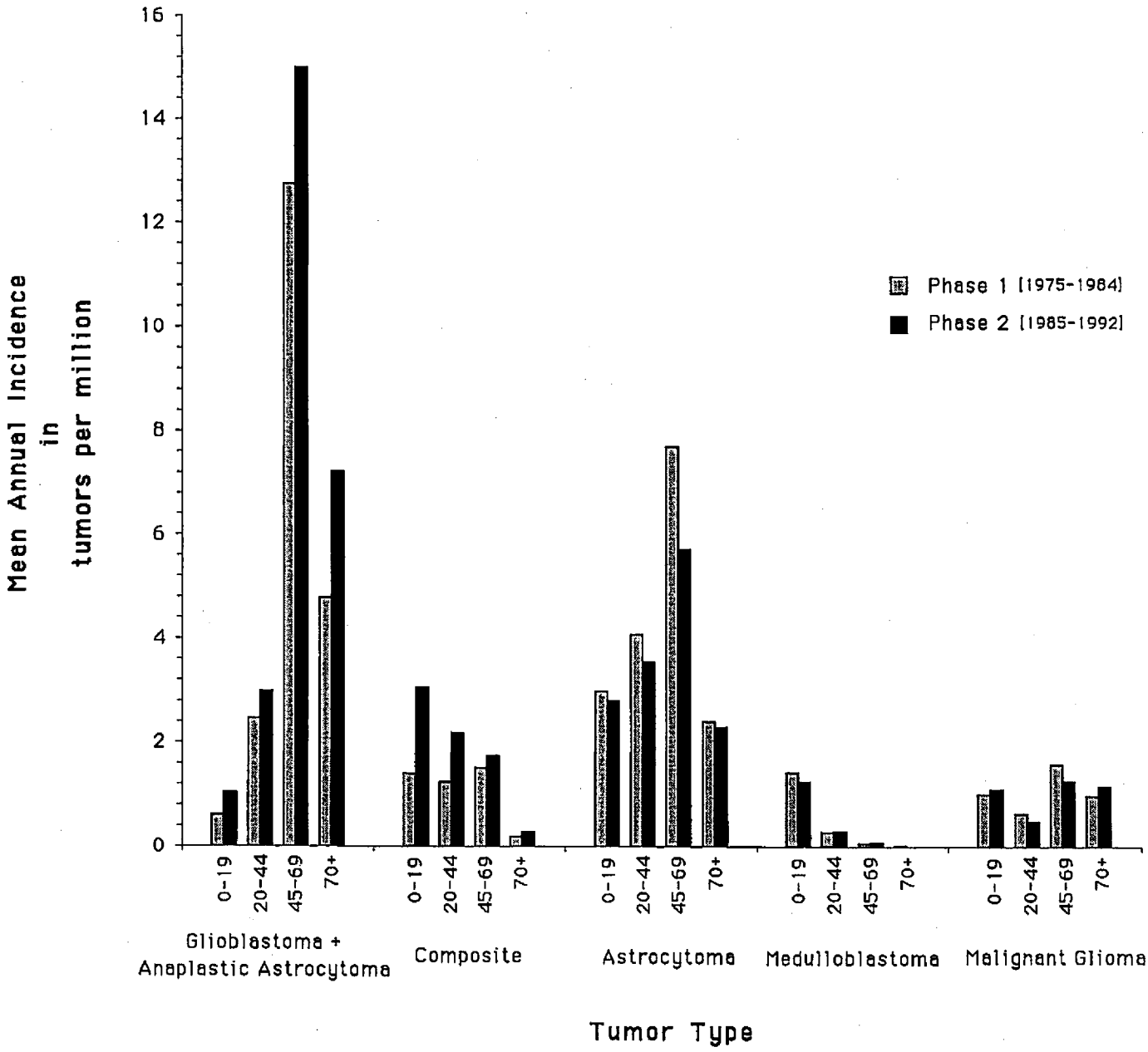

Fig. 4. A histographic presentation of the age distribution of the incidence of various types of brain tumors in phase 1 (1975 to 1984) compared to phase 2 (1985 to 1992). The composite group was comprised of oligodendrogliomas, mixed gliomas, pilocytic astrocytomas, ependymomas, primitive neuroectodermal tumors, and gliomatosis cerebri. The increased incidence of composite tumors in phase 2 was most heavily concentrated in the 0 to 19 and 20 to 44 age groups. The glioblastoma + anaplastic astrocytoma increases occurred primarily in the 45 to 69 and 70+ age groups. These increases were almost completely counterbalanced by a decrease in astrocytomas in the 45 to 69 age group but not in the 70+ age group.

favor the interpretation that the shift reflects a real increase in the rate of conversion of astrocytic tumors from a lower to higher grade of malignancy rather than a mere change in diagnostic assignment practices. Also supporting this interpretation is the fact that the sharp increase in glioblastomas began in the interval from 1984 to 1985 (Fig. 2B) and the drop in astrocytomas did not begin until the interval from 1987 to 1988 (Fig. 2A). A shift in the astrocytoma/glioblastoma ratio based on a switch in diagnostic practices would involve a reciprocal decrease in one category and increase in the other in any given year, but it should not cause a shift where one category is three years out of synchrony with the other.

The curve for anaplastic astrocytomas requires separate analysis. Anaplastic astrocytomas have a reputation for developing slowly at first, then suddenly becoming

TABLE 3
Astrocytoma and Glioblastoma Two-Year Outcome by Age Group

Age group	Astrocytoma percent dead within 2 years		Glioblastoma percent dead within 2 years	
	Period 1 (1975–1982)	Period 2 (1985–1990)	Period 1 (1975–1982)	Period 2 (1985–1990)
0 to 19 years	21.2%	26.4%	66.6%	70.4%
20 to 44 years	28.2%	26.6%	70.7%	69.7%
45 to 69 years	77.5%	73.4%	93.4%	92.8%
≥70 years	90.0%	93.0%	97.3%	96.2%

transformed into a much more malignant and rapidly growing tumor. Therefore, improved detection methods that permitted more of these tumors to be detected in their slow growth phase is a logical explanation for the increase in their reported incidence in the mid-1970s. However, if they were detectable by new sophisticated methods as anaplastic (undifferentiated) astrocytomas in their early slow growth phase, this would suggest that they may be an independent neoplastic species that originates de novo in undifferentiated form rather than by dedifferentiation of a preexisting astrocytoma. Thus, at least part of the rapidly climbing incidence of these tumors in the period from 1985 to 1992 may reflect de novo tumor induction.

Our observations pertaining to age-specific trends (Fig. 4) revealed that the increases in composite tumors (Fig. 3, Table 2) were concentrated in the younger age groups and the glioblastoma increase was concentrated in the older groups. It is noteworthy that although there was a large increase in glioblastomas and anaplastic astrocytomas in both the 45 to 69 and 70+ age groups, this increase was counterbalanced by a correspondingly large decrease in astrocytomas in only the 45 to 69 age group. We interpret these changes as follows: in both the 45 to 69 and 70+ age groups there was a marked increase in the rate of conversion of astrocytomas to glioblastomas and this resulted in a similarly increased incidence of glioblastomas in both age groups. In addition, in the 70+ (but not the 45 to 69) age group, the rate of induction of new astrocytomas was almost strong enough to keep pace with the astrocytoma to glioblastoma conversion rate; hence, there was a smaller reduction in the reported incidence of astrocytomas in the 70+ than 45 to 69 age group.

Our analysis identifies two broad categories of brain tumors that showed striking increases in the phase 2 period, the first being highly malignant astrocytic tumors (glioblastomas and anaplastic astrocytomas) and the second being a composite grouping (Fig. 3 and Table 2), that vary in malignancy from moderately high for most types to relatively low for pilocytic astrocytomas. It is reasonable to question whether the steady increase in these tumors occurring in phase 2 could be explained in terms of MRI (introduced circa 1983) being able to detect additional tumors not detectable by CT. We consider this unlikely for the following reasons: Sophisticated detection methods are not used for general screening, but rather for diagnosis of conditions that are producing clinical symptoms. Most if not all of these tumors are malignant enough so that when they begin to produce symptoms they are already large enough (or soon will be) to be detected by either MRI or CT. Certain occult, benign, very slow growing tumors (e.g. gangliogliomas) can be detected earlier and more effectively by MRI than CT, but the tumors in question would effectively be detected in a relatively short time by either technology. Therefore, we question whether a substantially higher percentage of these tumors was detected by MRI in phase 2 than was already being detected by CT in phase 1.

Our analysis of United States CNS tumor data differs from other recent CNS tumor analyses pertaining either to the United States or other countries (1–3) in that prior analyses focused on a time interval (early 1970s to the mid-1980s) that included about 12 years from phase 1 and only 1 to 3 years of phase 2. In essence, when these analyses were performed it was too early to detect or analyze the pattern that we are identifying as a bimodal pattern. Based on prior observations pertaining primarily to phase-1 years, several authors (1, 4, 5) have suggested that at least some of the reported increases may not signify a true increase in tumor incidence; rather it may reflect more complete ascertainment due to the introduction of improved CT diagnostic methods in the early-to-mid-1970s, and perhaps improved health care attention, especially for senior citizens. Our analysis of the SEER data for phase-1 years is consistent with this interpretation in that our total CNS tumor curve (Fig. 1) shows an appreciable jump coincidental with the introduction of CT technology. This was followed by a leveling-off for the remainder of phase 1, which suggests that the maximum potential impact of CT technology was realized within phase 1, and that there may not have been any other major factors promoting an increased brain tumor incidence in the phase-1 period.

Our findings signify that the sharp increase in brain tumor incidence noted by Roberts (13) in the mid-1980s was not a fleeting phenomenon. Rather, it was the initial phase of an upward swing in the brain tumor incidence which evolved into a sustained increase in both the per capita number and malignancy of brain tumors, a phenomenon that has endured for at least 8 years. The observation by Davis et al (1) that a sharp upward trend in deaths from brain tumors was detectable in the mid 1980s in the United Kingdom, France, Germany and Italy suggests the need for an evaluation of the most recent brain

tumor data in these countries to determine whether, regarding incidence, temporal profile, tissue diagnosis and degree of malignancy, they parallel the trends detected in our analysis of the United States SEER data.

Compared to other environmental factors, aspartame appears to be a promising candidate for explaining the surge in brain tumors in the mid-1980s. Other factors that are putatively relevant (6–12, 19) were introduced gradually over recent decades rather than all at once in the early 1980s. Most of these factors are occupationally linked and could not explain a pattern of increases affecting males and females in even distribution. Moreover, with the exception of ionizing radiation (which could not explain more than a small fraction of the brain tumor increases), there is no convincing evidence to support an etiological role for any of these factors (20). The electromagnetic field issue was recently reviewed comprehensively by Heath (12) and by Inskip et al (20), who concluded that the evidence linking this factor to brain tumors is weak and inconclusive. In particular, it was noted that there is no experimental evidence that this mechanism can cause in vitro mutagenesis or in vivo carcinogenesis. Adding substantial strength to the potential complicity of aspartame is the fact that there is evidence on file at FDA (21) documenting an unexplained high incidence of brain tumors in aspartame-fed rats, and it was recently demonstrated by Shephard et al (16) that if aspartame is nitrosated in vitro to simulate the nitrosation that might be expected to occur in the stomach, the nitrosated product shows a substantial degree of mutagenic activity.

The study revealing a high incidence of brain tumors in aspartame-fed rats (21) is one submitted to FDA in the early 1970s by the manufacturer of aspartame. This study was carefully reviewed by the PBOI panel of judges, including examination of the microscopic slides pertaining to brain tumors by Drs Walle J. H. Nauta and Peter W. Lampert (14). In this study, Sprague Dawley rats received aspartame in their feed for 2 years from weaning to 104 weeks of age. The most striking finding was that the 320 aspartame-fed rats developed 12 malignant brain tumors and the 120 concurrent control rats had no brain tumors. Absence of brain tumors in the concurrent control group is consistent with a large body of literature documenting that spontaneous brain tumors in laboratory rats are quite rare. For example, in a comprehensive review of experimental brain tumors in laboratory animals, Bigner and Swenberg (22) cited seven normative studies collectively pertaining to 59,812 rats (mostly of the Sprague Dawley strain) studied from infancy to late adulthood, in which only 49 brain tumors were found. It might be argued that this incidence (less that 1 brain tumor per thousand rats) is unrealistically low and may reflect failure in some of these studies to section the brain meticulously at multiple levels. However, PBOI panel members (Nauta and Lampert) who personally examined the records and histological slides pertaining to the aspartame-feeding study found that these brain tumors could not be considered inconspicuous or occult; rather, 90% of them were gliomas (primarily astrocytic) and 8 out of 12 were so large they could be detected by gross inspection. Moreover, they tended to be early of onset and were rapidly growing tumors that caused the animals to die at periodic intervals over both the first and second years of the 2-year study (14). In addition, they were dose related, with higher doses of aspartame being associated with a higher tumor incidence.

The recent study (16) showing that the aspartame molecule acquires mutagenic activity when nitrosated provides a clue to a possible mechanism by which aspartame could cause brain tumors. Nitrosation of aspartame or its diketopiperazine breakdown product could result in a nitrosourea-like molecule, and nitrosoureas are the most effective agents known for producing malignant brain tumors in experimental animals (20, 22–25). Some nitrosoureas have broad spectrum carcinogenicity and can induce cancer in both the CNS and several other organs, but other members of this family, particularly alkylated nitrosoureas, are organo-specific for the CNS. These agents can act by a direct and relatively rapid mechanism to induce brain tumors when administered systemically to adult rats (22, 24). In addition, they are particularly potent in acting by a delayed mechanism involving in utero exposure of the fetus and resulting in a high incidence of malignant brain tumors which do not manifest until adulthood (22, 23, 25). The malignant tumors induced by either the direct or delayed mechanism are not typically of the childhood type (i.e. medulloblastoma), but rather are predominantly adult tumors (e.g. astrocytomas, glioblastomas, mixed gliomas, oligodendrogliomas). Thus, it may be significant that the recent surge in human brain tumor rates involved these various adult types of tumors, whereas childhood medulloblastoma was the singular tumor type that showed no increase.

Regarding the mechanism by which a mutagenic agent can trigger in vivo carcinogenesis, it is currently believed that multiple separate mutations involving several types of proteins (oncogenes, growth factors, tumor suppression factors) must occur to cause normal cells to become carcinogenic. However, an environmental mutagen need not contribute all of the required mutations; a single mutation would be sufficient if it were of a kind that could act in concert with other existing mutations to tip the balance in favor of tumor induction. Thus, in human adult or aging populations the accumulation of spontaneous mutations may be sufficient to set the stage for an environmental agent to provide a single critical factor required to trigger carcinogenesis. Alternatively, the environmental agent may cause a particular type of mutation

to occur in the fetus that has the potential to trigger carcinogenesis only on a delayed basis because it requires a substantial delay interval for the right number and kind of other mutations to accumulate. An additional alternative to explain delayed tumor expression following fetal exposure is that on a programmed basis the immature organism possesses tumor suppression factors that the adult organism lacks.

Aspartame was initially approved in the United States in 1981 (15) for limited uses; however, one of these uses was "free flowing" table top use, i.e. pills or powder packets for such beverages as coffee, tea and lemonade. In 1983 approval was extended to much larger markets, including essentially all foods and beverages. Proposing that aspartame could be linked either to the onset in 1985 of a sustained increase in the rate of highly malignant brain tumors (Figs. 2B, C) in aging populations, or to the onset in 1987 (Fig. 3) of a steady climb in the incidence of various brain tumors that occur predominantly in young to middle-aged people may not be unreasonable in view of the large number of people in either age group who drink considerable amounts of coffee, tea or "diet" soft drinks on a daily basis. The earlier onset of the highly malignant tumors in the older age groups could relate to the fact that they have had more years to accumulate spontaneous mutations for the proposed aspartame-linked mutations to interact with. If exposure of in utero fetuses to aspartame can cause brain tumors on a delayed basis, tumors induced by this mechanism may not become evident for another 20 or 30 years.

In summary, there are three major criteria that are usually invoked in evaluating the potential of an environmental agent to behave as a human carcinogen: (a) Does the agent have in vitro mutagenic potential? (b) Do experimental animals show an increased incidence of specific types of cancer when exposed to the agent? (c) Do humans show an increased incidence of the same types of cancer when exposed to the agent? Based on the limited evidence available, aspartame appears to meet all three criteria. Therefore, although our analysis does not establish definitive proof of a causal link between aspartame and the recent increase in incidence and shift in malignancy of brain tumors that occurred in the United States several years after aspartame was introduced, it does indicate the need for a reassessment of the carcinogenic potential of this agent which is currently being ingested widely throughout many parts of the world.

REFERENCES

1. Davis DL, Ahlbom A, Hoel D, Percy C. Is brain cancer mortality increasing in industrial countries? Am J Indust Med 1991;19:421–31
2. Greig NH, Ries LG, Yancik R, Rapoport, SI. Increasing annual incidence of primary malignant brain tumors in the elderly. J Natl Cancer Inst 1990;82:1621–23
3. Mao Y, Desmeules M, Semenciw RM, Hill G, Gaudette L, Wigle DT. Increasing brain cancer rates in Canada. Can Med Assoc J 1991;145:1583–90
4. Levi F, La Vecchia C. Trends in brain cancer. Lancet 1989;2:917
5. Kurland LT, Schoenberg BS, Annegers JF, Okazaki H, Molgaard C. Brain tumors in the chemical industry. Ann NY Acad Sci 1982;381: 6–16
6. Alexander V. Brain tumor risk among United States nuclear workers. Occup Med 1991;6(4):695–711
7. Demers PA, Heyer NJ, Rosenstock L. Mortality among firefighters from three northwestern United States cities. Brit J Indust Med 1992;49:664–70
8. Brownson RC, Reif, JS, Chang JC, Davis JR. An analysis of occupational risks for brain cancer. Am J Pub Health 1990;80:169–72
9. Thomas TL, Waxweiler RJ. Brain tumors and occupational risk factors. Scand J Work Environ Health 1986;12:1–15
10. Hagmar L, Akesson B, Nielsen J, Andersson C, Linden K, Attewell R, Moller T. Mortality and cancer morbidity in workers exposed to low levels of vinyl chloride monomer at a polyvinyl chloride processing plant. Am J Indust Med 1990;17:553–65
11. Savitz DA, Loomis DP. Magnetic field exposure in relation to leukemia and brain cancer mortality among electric utility workers. Am J Epidemiol 1995;141:123–34
12. Heath CW. Electromagnetic field exposure and cancer: A review of epidemiologic evidence. CA 1996;46:29–45
13. Roberts HJ. Does aspartame cause human brain cancer? J Advancement Med 1991;4:231–41
14. Nauta Walle JH, Lampert Peter W, Young Vernon. Aspartame: Decision of the public board of inquiry (FDA Docket No. 75F-0355.) Available through US Government Printing Office, see Federal Register 1980;45:69558
15. Hayes AH. Aspartame: Commissioner's final decision, Federal Register 1991;46:38284–38308
16. Shephard SE, Wakabayashi K, Nagao M. Mutagenic activity of peptides and the artificial sweetener aspartame after nitrosation. Fd Chem Toxic 1993;31:323–29
17. Kosary CL, Ries LAG, Miller BA, Hankey BF, Harras A, Edwards BK, eds. SEER cancer statistics review, 1973–1992. Bethesda, MD: NIH Publications, 1995
18. Nelson J, Tsukada Y, Schoenfeld D, Fulling K, Lamarche J, Peress N. Necrosis as a prognostic criterion in malignant supratentorial, astrocytic gliomas. Cancer 1983;52:550–54
19. Wrensch M, Bondy, ML, Wiencke J, Yost M. Environmental risk factors for primary malignant brain tumors: A review. J Neuro Oncol 1993;17:47–64
20. Inskip PD, Linet MS, Heineman EF. Etiology of brain tumors in adults. Epidemiologic Reviews 1995;17:382–414
21. Study E33-34 in Master File 134 on aspartame, on file at the FDA Hearing Clerk's Office
22. Bigner DD, JA Swenberg JA. Experimental tumors of the central nervous system. Upjohn Company, Kalamazoo, Michigan, 1977
23. Druckrey H, Ivankovic S, Preussmann R. Teratogenic and carcinogenic effects in the offspring after a single injection of ethylnitrosourea to pregnant rats. Nature 1966;210:1378–79
24. Wechsler W, Kleihues P, Matsumoto S, Zulch KJ, Ivankovic S, Preussmann R, Druckrey H. Pathology of experimental neurogenic tumors chemically induced during prenatal and postnatal life. Ann NY Acad Sci 1969;159:360–480
25. Swenberg JA, Koestner A, Wechsler W, Denlinger RH. Quantitative aspects of transplacental tumor induction with ethylnitrosourea in rats. Cancer Res 1972;32:2656–60

Quick Review of Monsanto/NutraSweet's PR Statements Regarding the Aspartame / Brain Cancer Research Published by Dr. John W. Olney, et al. in the Journal of Neuropathology and Experimental Neurology (Nov. 1996)

by Mark Gold

mgold@holisticmed.com

http://www.holisticmed.com/aspartame/

(See web page for more information and sweetener resources.)

Dr. Dimitrio Trichopoulos

According the "The Observer" of London, Dr. Trichopoulos was approached by the manufacturer, Monsanto/NutraSweet, to write a critique of the study for them. Therefore, his statements are obviously not the statements of an independent scientist.

> "This paper has a misleading title. The 'Results' section which, as
> a rule, addresses the original contribution of the paper, does not
> even include the word 'aspartame' that nevertheless figures
> prominently in the title and the running title."

The title of the paper is: "Increasing Brian Tumor Rates: Is There a Link to Aspartame?" The title is clearly intended to show that the paper examines the increasing brain tumors rates and tries to determine if aspartame is a possible cause. It is hardly misleading.

The "Results" section is the results of the analysis of the rates of various types of brain tumors. The "Discussion" section is used to discuss whether aspartame may play a part in the increasing rates of certain types of brain tumors.

Such comments are really silly and have no place in a serious discussion of the aspartame / brain cancer link.

> "Instead, the paper examines time trends of brain tumor incidence and
> mortality in the United States, as many other authors have
> previously done, with a twist that is methodologically so unsound as
> to make the conclusions of the paper clearly untenable."

Given that Dr. Trichopoulos was reviewing this study at the request of the manufacturer, it may not surprise some that he made this comment. However, this statement contains no discussion of why the methodology was unsound -- it is just the opinion of someone reviewing the study for the industry.

> "Therefore, the arguments presented by Olney et al. fly in the face
> of the ecological evidence that they invoke. The introduction and
> widespread use of aspartame coincides in time with a *deceleration of
> an increasing trend that has been apparent well before aspartame was
> introduced. No one could seriously claim that this deceleration is

> due to aspartame, but the suggestion that aspartame causes brain
> cancer on the basis of these data is even more preposterous."

A common trick of aspartame industry PR is to argue against a point that no one (including Dr. Olney) is trying to make. The above comment is looking at the *overall* brain cancer incidence rates over the past 15-20 years. It is clear that brain cancer incidence rates have been climbing rapidly since the 1970s. Dr. Trichopoulos may be correct that *overall* brain cancer incidence rates are not increasing quite as rapidly as they did before aspartame was approved.

However, all of this seems to have little to do with Dr. Olney's research. Dr. Olney points out that it is the rates of the extremely deadly forms of brain cancer (e.g., glioblastoma and anaplastic astrocytoma) in the most susceptible populations that went up significantly not long after aspartame's approval. The rates of the much less deadly brain cancer (i.e., astrocytoma) went down not long after aspartame approval. It is the increase in the rate of conversion of astrocytic tumors from a lower to higher grade (i.e., more deadly) that Dr. Olney, et al. focused on, not simply the change in overall brain tumor rates.

>"The arguments of Olney et al. implicitly require two biologically

>indefensible assumptions: that a certain factor (aspartame) could
>cause a solid tumor (brain cancer) with a latency period of less than
>four years and that subsequent widespread exposure to this factor
>would cause no further increase in the incidence of that cancer.
>These assumptions are preconditions in their futile effort to
>explain, in causal terms, an arbitrarily chosen and improperly
>illustrated transient shift in the secular incidence of brain
>tumors."

As you can see, Dr. Trichopoulos once again seems to avoid discussing the large shift of brain tumor rates to much more deadly forms of brain tumors. He seems set on discussion overall brain cancer rates despite the fact that it is only briefly discussed in Dr. Olney's paper. Dr. Olney quite clearly expresses in the "Method" section of the paper that he will be discussing specific tumor types in relation to aspartame:

"In prior studies, the focus has been primarily on total tumor incidence without adequate attention to individual tumor types, and there has been a tendency to assess the magnitude of overall change in incidence from one extreme time point to another (e.g., from the early 1970s to the mid 1980s) without determining whether the increases occurred episodically or on a steadily progressive basis. Because increases attributable to aspartame would be expected to have

a unique temporal pattern corresponding to the pattern of public exposure to this agent, and might be limited to increases in only specific tumor types, we plotted the incidence rate for each year and each tumor type from 1975 to 1992...."

Dr. Olney points out that "it is currently believed that multiple separate mutations involving several types of proteins must occur to cause normal cells to become carcinogenic. Thus, in human adult or aging populations the accumulation of spontaneous mutations may be sufficient to set the stage for an environmental agent to provide a single critical factor required to trigger carcinogenesis."
Therefore, in the population group that is, by far, the most susceptible to glioblastomas and anaplastic astrocytomas -- the late middle aged and elderly -- it would certainly be possible for brain tumors to progress after 4-5 years that aspartame was on the market. It is the less susceptible populations that would likely see a longer time period (on average) before the tumor develops.

Dr. Paul Levy

Dr. Levy has cowritten with Monsanto/NutraSweet a defense of aspartame (Neurology 45:1631). That, by itself, doesn't prove that Dr. Levy's statements are inaccurate, but it does show that Dr. Levy was not an independent researcher who happened to write comments

about this study.

> "...this statistical and epidemiological treatment of the SEER data
> is seriously flawed and furnishes no evidence to justify the
> conclusion of an association between aspartame use and increased
> brain tumor incidence rates."

Again, nothing but opinion. It is interesting that Monsanto/NutraSweet would approach their friends in the scientific community to comment on the study, but would quite often quote statements such as that above that have no facts or reasonining associated with them. We will just have to wait until the responses are published in the Journal of Neuropathology and Experimental Neurology before we see what (if anything) they are basing these statements on.

> "When the same analysis is performed separately in age groups 0-19
> years, 20-39 years, 40-64 years, and 65 plus years, the only
> significant increase with time is in the 65 plus age group which can
> be explained, at least in part, by the increased access to health
> care including diagnostic procedures among the elderly."

Once again, it appears that Dr. Levy is now discussing *overall* brain tumor rates. Dr. Olney shows that the much more deadly types of brain cancer (glioblastoma and anaplastic astrocytoma) increased

substantially in the 45-69 age group and the 70+ age group. As Dr. Olney stated, "the earlier onset of the highly malignant tumors in the older age groups could relate to the fact that they have had more years to accumulate spontaneous mutations for the proposed aspartame-linked mutations to interact with." If exposure of in utero fetuses to aspartame can cause brain tumors on a delayed basis, tumors induced by this mechanism may not become evident for another 20 or 30 years."

Dr. Olney also discusses the effect of the changes in diagnostic procedures on cancer incidence rates. Here is an excerpt from Dr. Olney's paper that should help put to rest Dr. Levy's unsubstantiated statement about diagnostic procedures:

> "It is reasonable to question whether the steady increase in these tumors occurring in phase 2 [1985-1992] could be explained in terms of MRI (introduced circa 1983) being able to detect additional tumors not detectable by CT [technology]. We consider this unlikely for the following reasons: Sophisticated detection methods are not used for general screening, but rather for diagnosis of conditions that are producing clinical symptoms. Most if not all of these tumors are malignant enough so that when they begin to produce symptoms they are already large enough (or soon will be) to be detected by either MRI or CT. Certain occult, benign, very slow growing tumors (e.g.,

gangliogliomas) can be detected earlier and more effectively by MRI than CT, but the tumors in question would effectively be detected in a relatively short time by either technology."

Dr. Adalbert Koestner

Dr. Koestner wrote a chapter about aspartame and brain tumors for the manufacturer's aspartame book in 1984. Once again, this shows that Dr. Koestner just didn't happen to read the study and respond as might an independent researcher.

> "Dr. Olney states, 'The most striking finding was that the 320
> aspartame-fed rats developed 12 malignant brain tumors and 120
> concurrent controls had not brain tumors.' This statement is a
> misrepresentation of the facts."

It amazes me that Dr. Koestner could question Dr. Olney's statements on this fact since Dr. Olney was an active participant in the pre-approval hearings when the number of tumors was discussed. It is clear that Dr. Koestner inappropriately received his tumor figures from UAREP, an organization that was reportedly paid $500,000 to "review" studies for the manufacturer. (See the footnote at the

bottom of the second page of Dr. Koestner's article in "Aspartame: Physiology and Biochemistry" published by Marcel Dekker, page 447.) The *original* record clearly shows 12 brain tumors in the test animals and zero in the controls as stated by Dr. Olney:

> "There were other problematic aspects of the brain tumor data. In the pre-1975 records that I reviewed, it was clear that several competent pathologists had carefully examined the original microscopic slides from the first study and agreed that there were 12 brain tumors in the NutraSweet-fed rats and zero brain tumors in the controls. When the FDA conducted a task force investigation of these laboratories in 1975, they singled out these studies for further investigation and ordered that all laboratory records, including microscopic slides etc. be impounded under FDA seal. Several years later when a group of pathologists (UAREP) was sent to authenticate these studies, they could not find the microscopic slides. The UAREP pathologists were finally taken to a laboratory where the slides were not supposed to be and there they found some but not all of the original slides. Clearly they had not been kept

under FDA seal and by mysterious coincidence the slides that were finally presented to the UAREP pathologists contained evidence for 11 brain tumors in Nutrasweet-fed rats and 1 tumor in controls. It is important to recognize that if there are zero tumors in the controls, it is very difficult to argue that the tumor incidence in the control and Nutrasweet-fed rats is the same. But if there is 1 tumor in the control group, it is possible with statistical acrobatics to reach the conclusion that the incidence is the same. And, indeed, this is exactly the argument that the manufacturer and the FDA Bureau of Foods pressed at the Public Board of Inquiry. They accepted the finding of 1 brain tumor among the controls even though the authentic record showed zero brain tumors in the controls, then they proceeded to break down the animals into smaller and smaller sub groups according to sex, dose level etc. and finally the 1 brain tumor in one sub group of control animals appeared to be not significantly different from 2 or 3 tumors in each of the experimental sub groups. 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 supposedly
impounded) and why they do not question the de
novo emergence of a brain tumor among the controls
when the slides reappear."

> "Since aspartame in the two Searle-Hazelton studies did not fulfill
> any of the criteria established for neurocarcinogenic agents and
> since the incidence of brain tumors was well within the range of
> spontaneous brain tumors in 2-year-old Sprague Dawley rats, there can
> be no causal link between aspartame and brain tumors observed in the
> Searle-Hazelton studies."

Dr. Koestner is arbitrarily stating that aspartame does not meet the criteria established for neurocarcinogenic agents. He goes into detail in the chapter from the book mentioned above. His arguments in that chapter are badly flawed as I discuss in detail in the draft scientific/history review of aspartame ("Aspartylphenylalanine Diketopiperazine (DKP)" chapter) on my web page:
< http://www.holisticmed.com/aspartame/ >

Twelve brain tumors in the aspartame-fed rats was well outside the spontaneous brain tumor rates for 2-year-old Sprague Dawley rats. He

is just making up statements out of the blue now. The Public Board of Inquiry which included the President of the American Association of Neuropathologists (and which unanimously voted *against* aspartame approval because of the brain tumors) found that the spontaneous brain tumor rate would be somewhere around 0.7% -- many times below the brain tumor rate of 3.75% found in one pre-approval study and over 3% in another pre-approval study. The FDA Commissioners own scientists were against approval and worried because of this brain tumor rate.

The FDA Commissioner used a study that *did not* discuss methodology at all to guess that the spontaneous brain tumor rate was 2.2% (still below what was found in the pre-approval experiments). But he apparently felt it was close enough and decided to approve aspartame. And as is well-known, he became a high-paid consultant for the manufacturer's PR firm shortly thereafter.

Dr. Gary Flamm

> "The paper misstates critical facts and totally ignores important
> facts such as the third carcinogenicity study conducted on aspartame
> in rats which confirmed earlier findings that aspartame is not

> carcinogenic."

As is discussed in the draft review on my web page, Dr. Olney points out that 1) this study was not used in the determination for aspartame approval (as admitted to by the FDA Commissioner), 2) it appeared in a poor quality journal, 3) the report was sketchy (i.e., not detailed), and 4) the type of rats used was different than in the pre-approval studies.

I further point out that the study was conducted by a close business partner of the manufacture, Ajinomoto (who is now producing aspartame). Ajinomoto was a major part of the International Glutamate Technical Committee (IGTC). During that period of time, the IGTC funding "research" that including hiding aspartame in the drink mix of MSG experiments, using a brain protective substance on animals before giving the animals the test substances (including aspartame and MSG), and recropping a picture from an old experiment to show "no damage" in a newer experiment. One has to be unbelievably gullible to accept any sketchy study from Ajinomoto during this period of time.

> "I also deeply resent the insinuation that the FDA Commissioner
> approved aspartame on the basis of his judgment alone with no support
> from experts in carcinogenesis. This charge is clearly contradicted

> by the written record...."

As Dr. Olney points out:

"Also highly relevant is the fact that in the 1980 FDA convened a Public Board of Inquiry (PBOI) where a panel of scientists, including prominent neuroscientists (Walle J.H. Nauta and Peter W. Lampert), were asked to evaluate evidence from two animal studies potentially linking aspartame to malignant astrocytic brain tumors. The PBOI panel concluded that evidence from one study was 'bizarre' and totally unreliable, and evidence from the other study appeared to show that 'aspartame may contribute to the development of brain tumors.' .... The FDA Commissioner who received the PBOI report referred it to additional expert FDA consultants who concurred with the PBOI panel's recommendations."

Please note that Dr. Peter W. Lampert was, at that time, the President of the American Association of Neuropathologists and, by far, the most qualified member of the PBOI to judge whether aspartame had the potential to cause brain tumors. He never waivered from his position that more studies were needed before approval should be allowed.

From the FDA Commissioner's statement approving aspartame in 1981

(Federal Register, Vol. 46, No 142., 7/24/81) one can see that he relied only on his own judgment (or lack thereof) and a review performed by the FDA Bureau of Foods. It is surprising to say the least that the FDA Commissioner would ignore the PBOI suggestions, the suggestion of the FDA Commissioner's review team and instead accept a report from the FDA Bureau of Foods.

> "While nitrosation of aspartame or DKP is theoretically possible as
> discussed in the paper cited by Shephard et al., the product would
> not be nitrosourea as was incorrectly stated by the authors. The
> formation of nitrosamides would, if it occurred, proceed through
> nitrosation of the peptide bond. The quantity of nitrosated product
> produced with aspartame would be minuscule compared to that which
> would form with dietary protein and peptides. Reaction of peptide
> bonds proceed very slowly and are not considered to be a public
> health problem."

As Olney pointed out, the Shephard paper showed that "if aspartame is nitrosated in vitro to simulate the nitrosation that is believed to occur in the stomach, the nitrosated product has substantial mutagenic activity." That is what Shephard et al. found. If Dr. Flamm believes that the conversion of DKP to other chemicals does not create a mutagenic compound, then he should push for completely independent research to address this issue (as should have been done

many years ago before approval was granted). Dr. Olney points to this as a possibility as to how aspartame may contribute to brain cancer.

As I point out in my draft review, one cannot discount the effects of other breakdown products of aspartame contributing to the increase in the deadlier forms of brain cancer without adequate research.

> "In conclusion, I am in deep despair over the damage the subject
> paper may do to the credibility of science and to the FDA. The paper
> has replaced proper scientific analysis of all relevant data with a
> selective picking of just that which might support their groundless
> speculation."

The manufacturer of aspartame, Monsanto/NutraSweet has long since begun the destruction of the scientific process by conducting experiments on aspartame that can generously be described as "deceptive." The fact that several officials at the FDA obtained key positions in the aspartame industry and that since that time the FDA has done everything possible (including banning safe sweeteners) to help the manufacturer push aspartame on the public only serves to dig a deeper hole for the FDA. If the FDA reputation is irreparably damaged, the FDA officials need only look in the mirror to discover the cause of the problem. Then they should look at the large and growing number of serious toxicity reactions caused by aspartame.

(See samples on my web page.)

In conclusion, Dr. Olney is correct in his call for independent studies to look at the aspartame and brain cancer issue. He points out that aspartame meets the three main criteria usually invoked in evaluating the potential of an environmental agent to behave as a human carcinogen.

a. Aspartame has been shown to have in vitro mutagenic potential.

b. There was an increased in incidence of specific types of cancer when animals were exposed to aspartame.

c. Humans have shown an increase (especially susceptible populations) in the same types of cancer since not long after aspartame has been approved.

Dr. Olney is not asserting that he proved that aspartame causes brain cancer. However, he is calling for independent research to settle the matter before it is too late.

Obviously, there are many reasons why one would not choose to slowly poison oneself with chronic, long-term aspartame use, even if aspartame didn't cause brain cancer. See the web page address below

for more information.

- Mark Gold

mgold@holisticmed.com

http://www.holisticmed.com/

http://www.holisticmed.com/aspartame/