The Significance of Cell Type in the Etiology of Brain Tumors

A CRITICAL REVIEW

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EXECUTIVE SUMMARY

Despite the vast medical literature on brain cancers, little is known about the etiology of these tumors. Brain cancer accounts for only about 2% of all cancers newly diagnosed in the United States; however, the incidence of these malignancies has been increasing steadily over the past several decades, and most strikingly among the elderly. Although some researchers argue that the observed increase in brain cancer is largely due to improved diagnostic technologies, there is substantial evidence that such a "diagnostic sensitivity bias" can account for only a portion of the increase.

As with most cancers, the incidence of many types of brain cancer increases dramatically with age. However, except for age, epidemiological research has identified few if any risk factors for brain cancer. This general lack of useful clues about the causes of brain cancer largely stems from two basic issues:

1.) Brain cancers are rare events (by individual tumor type or collectively), making studies including an adequately large number of cases challenging and often impractical - especially if the study population is relatively small; and

2) Clinically, differential diagnosis and accurate classification of brain tumors is difficult, and this is compounded by complicated and overlapping classification schemes for tumors of the brain.

A majority (between 50% and 70%) of primary tumors of the brain are gliomas. Because of their location and possible function, the cells from which gliomas arise may be most vulnerable to environmental agents which enter the blood system. The subcategories of

gliomas, identified by specific cell type, include astrocytomas (most common), oligodendrogliomas and ependymomas. After gliomas, the second most common category of brain tumors is meningiomas, which comprise about 20% of all brain tumors. All remaining brain tumors (roughly 20%) arise from a variety of cell types, including neuronal cells, blood vessels, nerve roots, pituitary and pineal gland tissue, etc., each of which is extremely rare.

Only a small proportion of published epidemiological studies of brain cancer report results by specific tumor type. As with other cancers, it is conceivable that brain cancers of different cell type have different sets of risk factors. Therefore, it is important for epidemiological studies to identify risk factors for each tumor type separately.

A comprehensive literature search of the National Library of Medicine database MEDLINE was conducted for this report. From about 100 references, thirteen studies were selected for detailed review. Specifically, these studies employed generally sound epidemiological methods; addressed occupational populations potentially exposed to chemical agents; and ideally (though not always possible) identified and considered specific tumor types in the analyses and interpretation. Collectively, these studies provided only suggestive evidence of some weak occupational risk factors for brain cancer. The study with the best methodology (and a focus on astrocytomas) also provided some of the strongest evidence of an association between brain cancer and exposure to agricultural chemicals.

Presently, there are too few high-quality studies available to be able to identify specific agents which might be risk factors for brain cancer. Additional research is needed before occupational and environmental risk factors for brain cancer can be identified. Such research will require the following:

1.) adequately large sample sizes to assure reasonable power to detect modest levels of risk;

2.) clear and accurate tumor diagnosis, including cell type of origin; and

3.) detailed and valid estimates of exposures, measured at an individual level.

Since different histologic types of brain tumors are likely to have different etiologies, categories should not be combined (as they often are to increase sample size) to reduce misclassification and the deleterious effects it has on risk estimation.

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I. INTRODUCTION

I.1. Purpose of this report

The medical literature on human brain cancers is relatively extensive, and addresses broad issues of clinical importance, such as the diagnosis of brain and other central nervous system (CNS) tumors, classification of these lesions (macroscopically, microscopically and cytogenetically), treatment (surgery, chemotherapy, radiation and CNS immunotherapy), and management of the brain cancer patient. However, relatively little is understood regarding the etiology of brain tumors [Ransohoff, 1991]. Much of this uncertainty may be attributed to the difficulties of systematically and reliably categorizing the wide array of brain tumors which are discovered. The lack of more definitive epidemiological studies of risk factors for brain cancers is partially due to the relative rarity of these cancers, which often limits study sample size. The purpose of this report is to comprehensively review the epidemiological literature on brain cancer, with a particular focus on the possible relevance of specific cell types in understanding the etiology of brain cancer.

I.2. Report organization

The report is divided into seven sections, several with subsections. The first four sections provide background information essential in addressing the theme of this report. Following the Introduction (Section I), a brief descriptive review of the epidemiology of brain cancer is presented in Section II. This description includes the distributional patterns of brain tumors by demographic attributes and by type, as well as trends over

time. Section III presents a more detailed summary of the schemes used to classify brain tumors, highlighting the taxonomic complexities.

Section IV constitutes a critical assessment of the key literature addressing brain cancer etiology, with a focus on tumor type. A number of important issues which influence how the scientific studies may be interpreted (or misinterpreted) are raised and discussed in Section V. Most of these issues pertain to the epidemiological methodology, including the relative rarity of brain tumors and resulting small study sizes, and the current diagnostic sensitivity bias debate. Section VI identifies key gaps in the literature, as well as informational needs for future research, and states succinctly the current limits of understanding of brain cancer etiology. The final section is a bibliography of relevant studies, and works cited in this report. Copies of selected articles, marked with an asterisk (*) in the bibliography, are compiled in a separate volume labeled "Source Documents."

I.3. Disclaimer

This report was prepared by Applied Epidemiology, Inc. under contract with and solely for the informational use of Vista Chemical Company. It is intended to serve as an independent scientific review of the published literature. Any opinions expressed are those of the authors and may not necessarily reflect the views of Vista Chemical Company.

II. DESCRIPTIVE EPIDEMIOLOGY OF BRAIN CANCER

II.1. Overview

Brain cancer accounts for approximately 2% of all newly diagnosed malignancies in the United States and in other industrialized countries [Davis et al., 1991; National Cancer Institute, 1988]. The average annual incidence of primary intracranial tumors in the United States is approximately 15,000 [National Cancer Institute, 1988; Berens, 1990]. The incidence of brain tumors increases with age until 65 years or older, and the rate at which incidence increases with age is similar for males and females [Velema and Percy, 1987]. However, several recent reports have noted increases in the incidence and mortality of brain cancer, particularly among the elderly [Grieg et al., 1990; Davis et al., 1990; Kurland et al., 1982]. Gliomas comprise approximately 50% to 70% of all primary intracranial tumors while meningiomas account for about 20% of all primary intracranial tumors [Schoenberg et al., 1976; Berens et al., 1990; Codd and Kurland, 1985]. Most studies of brain cancer have grouped the various cell types together and reported findings based on all malignant brain tumors, despite evidence suggesting that the different histologic types should be treated as separate diseases with possibly distinct etiologies.

Much of the information on the descriptive epidemiology of intracranial neoplasms comes from the following population-based studies: Rochester, Minnesota (1935 to 1977) [Kurland et al., 1982], Connecticut Tumor Registry (1935 to 1964) [Schoenberg et al., 1976], Norway (1955 to 1984) [Helseth et al., 1989], Third National Cancer Survey (1969 to 1971)[Cutler and Young, 1975], and the National Cancer Institute's Surveillance,

Epidemiology and End Results (SEER) (1973 to 1977) [Young et al., 1981]. The descriptive epidemiology of brain cancer is presented below according to age, sex, race, geographic location and temporal trends.

II.2. Age

The incidence of CNS tumors (most of which are located in the brain) increases with age, up until about 65 to 75 years, and the rate of increase with age is similar for males and females [Velema and Percy, 1987]. Recent studies have also documented that the incidence of primary brain tumors is increasing among the elderly, particularly for those over 75 years [Grieg et al., 1990]. However, tumors of different histological type have different age distributions. Medulloblastomas and cerebellar astrocytomas are primarily tumors of children and young people [Walker et al., 1985]. Meningiomas, on the other hand, are infrequent among children, but relatively frequent among adults. The rate at which incidence increases with age is also higher for glioblastomas than for other glial tumors [Velema and Percy, 1982].

II.3. Sex

Several studies have shown higher rates of gliomas for males than for females and higher rates of meningiomas for females than for males [Lovaste et al., 1986; Kurland et al., 1982, Schoenberg et al., 1976; Preston-Martin et al., 1982]. In Los Angeles County from 1972 to 1977, the most common type of glial tumor was astrocytoma for both males and females, followed by glioblastoma [Preston-Martin et al., 1982]. For all types of tumor diagnosed between 1973 and 1982 from nine SEER registries in the United States, the estimated age-adjusted white male to white female ratio was 1.52:1 [Velema and Percy, 1987]. The white male to white female ratio for all glioblastomas over this same time period was 1.61:1. Between 1935 and 1964 in Connecticut, the age-adjusted male to female ratio for glioblastomas was 1.4:1, while the age-adjusted male to female ratio for

meningiomas was 0.7:1 [Schoenberg, 1982]. Similarly, between 1950 and 1977 in Rochester, Minnesota, the average annual age-adjusted incidence rate (per 100,000) was 6.2 among males and 4.9 among females for gliomas and 4.8 among males and 6.1 among females for meningiomas [Kurland et al., 1982].

II.4. Race

In general, whites have higher rates of brain cancer than nonwhites [Schoenberg et al., 1976]. From 1972 to 1977 in Los Angeles County, age-adjusted incidence rates for gliomas were higher for white males than for black males (5.5/100,000 vs. 3.1/100,000) and higher for white females than black females 3.8/100,000 vs. 2.2/100,000) [Preston-Martin et al., 1982]. However, age-adjusted incidence rates for meningiomas were higher for black males than white males (2.8/100,000 vs. 1.8/100,000) and higher for black females than white females (3.4/100,000 vs. 2.7/100,000).

II.5. Geographic location

Between industrialized countries, there are no apparent significant differences in incidence when all brain tumors are examined [Davis et al., 1991; Codd and Kurland, 1985]. Within the United States, the incidence of gliomas and meningiomas in Rochester, Minnesota between 1935 and 1975 differed from the incidence reported for several other U.S. populations. In Rochester, MN, meningiomas accounted for 40% and gliomas accounted for 35% of all primary brain tumors [Codd and Kurland, 1985]. A higher autopsy rate in the Rochester area is a likely explanation for the difference, because 66% of the meningiomas were not diagnosed until the time of autopsy. Meningiomas may be asymptomatic, and are likely to be underreported as a result.

II.6. Temporal trends in incidence

The incidence of brain cancer has been increasing since the 1940s, particularly among the elderly [Grieg et al., 1990; Davis et al., 1991; Garfinkel and Sarokhan, 1982]. It has been speculated that the increase among the elderly is the result of improved diagnostic methods, such as computerized axial tomography (CT), introduced in the mid-1970s, and magnetic resonance imaging (MRI) [Greenwald et al., 1981; Modan et al., 1992; Helseth et al., 1988]. While the mortality rate in whites for all brain cancers was 3.8 per 100,000 in 1940, the mortality rate had increased to 5.8 per 100,000 in 1977 [Garfinkel and Sarokhan, 1982]. These trends were also observed among nonwhites where the mortality rate increased from 2.2 per 100,000 to 3.9 per 100,000 over the same time interval.

III. CLASSIFICATION OF BRAIN TUMORS

III.1. Overview

Brain cancers are notorious for their heterogeneity of clinical presentation. Clinicians often consider each case unique, for there are no known patterns of clinical signs and symptoms, tumor size, or tumor location (in fact, tumors of the entire CNS are often reported as a single site). The lack of useful clinical clues is partly due to the relatively small numbers of brain cancer cases seen by any one clinician over even several years (personal communication, Arthur Frank, M.D., University of Kentucky). Histologic typing of tumors provides somewhat more useful information; however, the completeness of diagnosis and typing is uncertain for any given population, and there are various classification schemes available. Tumor classification schemes differ by degree of specificity, and consequently, comparison of the distribution of tumor types between cases and between epidemiologic studies is complicated. Further, more than one classification scheme might be used to classify the same brain tumor, particularly if it is of glial origin. Most recently, the World Health Organization (WHO) created a classification system for brain tumors [Zülch, 1986] in an effort to provide a uniform nomenclature. Even so, classification of brain tumors may differ between studies, rendering comparisons difficult. Most occupational cohort mortality studies rely solely on information obtained from death certificates, which may describe a brain tumor in terms no more specific than *primary*, *metastatic*, *benign*, or *malignant*.

Brain tumors may be described as *primary* or *secondary*, which is an important distinction because the CNS is a common site for metastatic tumors (most commonly lung, breast, kidney, colon and malignant melanomas) [Larson, 1980; Schoenberg, 1982; Weller, 1986]. In contrast, primary intracranial neoplasms rarely metastasize outside the CNS [Larson, 1980; Schoenberg, 1976; Ransohoff et at., 1991; Yates, 1992].

Brain tumors may also be characterized as *benign* or *malignant.* This distinction primarily describes the biological behavior of the tumor and subsequently, the prognosis for the patient, instead of indicating whether a tumor is likely to metastasize to other organs or systems [Yates, 1992; Schoenberg, 1982]. Generally, all primary brain tumors are malignant; however, tumors which technically are malignant, but which exhibit relatively slow growth rates and respond to therapy - therefore having a better prognosis - are frequently considered benign [Ransohoff et al., 1991]. In general, a histologically malignant brain tumor describes a tumor whose cells are poorly differentiated or anaplastic while a histologically benign brain tumor has well-differentiated cells and increases in size more slowly than a malignant tumor [Weller, 1986]. The location of the brain tumor more often determines the clinical outcome for the patient rather than whether it is considered benign or malignant.

With these distinctions in mind, the most meaningful (and the most specific) system for classifying tumors includes the identification of cell of origin, degree of differentiation, and anatomic site [Yates, 1992].

III.2. Cell type

Primary brain tumors may be broadly classified according to cell type. Tumors by cell type are listed in Table 1 and described further below. Most primary tumors arise from neuroglial (or glial) cells, which in the past have been assumed to function as supporting

TABLE 1: Classification of brain tumors according to cell type

CELL TYPE	TUMOR GROUP	SPECIFIC CELL OF ORIGIN	SPECIFIC TUMOR TYPES	CLASSIFICATION SCHEMES		
Glial	Gliomas	Astrocytes	Astrocytic tumors			
			Astrocytomas	Benign astrocytoma	Astrocytoma	Grade I
				"	"	Grade II
			Glioblastomas	Anaplastic astrocytoma	"	Grade III
				Glioblastoma multiforme	"	Grade IV
		Oligodendrocytes	Oligodendrogliomas	Oligodendroglioma Anaplastic oligodendroglioma		
		Ependymal lining cells	Ependymomas	Epdendymoma Anaplastic ependymoma		
		Mixed glial cells	Mixed gliomas	e.g., Oligo-astrocytoma		
Neuronal			Gangliocytomas	Benign		
Mixed neuronal-glial			Gangliogliomas	Benign Anaplastic		
Cell type unknown (of neuronal or glial origin)	PNET's*		Medulloblastomas Neuroblastomas Ependymoblastomas			
Arachnoidal	Meningiomas		Meningiomas	Benign meningiomas Anaplastic		
Blood vessels	Blood vessels		Hemangioma Hemangioblastoma			
Nerve roots	Nerve roots	Schwann cells	Neurilemmoma Schwannoma			
Pituitary	Pituitary		Chromophobe adenoma			
Pineal	Pineal		Pineal			

* Primitive neuroectodermal tumors

cells to neurons, but are now believed to serve important metabolic functions. Other primary tumors arise from neuronal cells, mixed neuronal-glial, or arachnoidal cells.

III.2.1. Tumors of glial cells

Tumors arising from glial cells are broadly classified as *gliomas.* Gliomas are estimated to account for between 50% and 70% of all primary CNS tumors [Levin, 1989]. There are several different subtypes of gliomas, including astrocytic tumors (astrocytomas and glioblastomas), oligodendrogliomas, ependymomas and mixed gliomas.

The overwhelming majority of gliomas are derived from astrocytes and are classified as either *astrocytomas,* when the tumor shows evidence of well- or moderately differentiated cells, or *glioblastomas,* when the tumor shows highly aggressive and malignant behavior. It should be noted, however, that there is no such cell as a glioblast, and while the vast majority of glioblastomas arise primarily from astrocytes, glioblastomas may also arise from oligodendrocytes or ependymal cells [Yates, 1992; James et al., 1988; Burger and Green, 1987]. Glioblastomas occur mainly in those over 50 years old [Weller, 1986], and while astrocytomas may occur at any age, anaplastic astrocytomas occur primarily in adults [Yates, 1992].

Oligodendrogliomas are generally believed to be derived from oligodendrocytes and may also occur at any age, while *ependymomas* arise from ependymal lining cells and comprise proportionally more of the gliomas in childhood than in adults [Yates, 1992]. Both cell types are much less common than those of the astrocytic tumors [Yates, 1992; Weller, 1986], with oligodendrogliomas accounting for 8% or less of gliomas [Barnard, 1986] and ependymomas accounting for an even smaller proportion of gliomas. The final subclassification of gliomas, mixed gliomas, contain more than one type of neoplastic glial cells (e.g., mixed oligo-astrocytoma).

III.2.2. Tumors of neuronal cells

While gliomas are tumors of glial cells, *gangliocytomas* are tumors of neuronal cells. Neuronal cells are the functional unit of the central nervous system. *Gangliogliomas* and *anaplastic gangliogliomas* are tumors of mixed neuronal-glial cells. Gangliocytomas and gangliogliomas are usually slow-growing tumors and are generally considered benign.

III.2.3. Poorly differentiated tumors of unknown origin

Primitive neuroectodermal tumors (PNETs) are tumors with cells that are poorly differentiated, and subsequently, it is unknown if they are of glial or neuronal origin. These tumors are also frequently classified as *tumors of embryonal origin* [Schoenberg, 1982], and typically arise in the cerebellum and cerebral hemispheres of children and young adults [Weller, 1986]. The most common histological example of a PNET is a *medulloblastoma* [Weller, 1986], a highly aggressive tumor which primarily affects those under the age of five. Less common types include neuroblastomas, which sometimes are classified as PNETs [Weller, 1986], but are classified as a neuronal tumor in the WHO nomenclature [Zülch, 1986]. One major criticism of the classification system advocated by the WHO concerns the classification of glioblastomas, which, because of their poor cellular differentiation, are classified as PNETs [Zülch, 1986]. Thus, this system ignores the cell of origin (glial) for the classification of glioblastomas.

III.2.4. Tumors of arachnoidal cells

Tumors of the meninges or mesodermal tissue are derived from arachnoidal cells [Yates, 1992; Levin, 1989]. Arachnoid cells originate in the arachnoidea, the middle of three membranes covering the brain, and give rise to *meningiomas* and *meningiosarcomas.* Meningiomas typically exhibit relatively benign biological behavior, but a minority of meningiomas (malignant meningiomas and anaplastic meningiomas) invade adjacent tissue and anaplasia may be present [Ransohoff et al., 1991]. Meningiosarcomas are

typically aggressive and behave in a manner that is histologically distinct from other meningiomas [Yates, 1992]. Approximately 20% of all intracranial tumors are meningiomas.

III.2.5. Other cell types

Other tumors which are frequently classified as primary brain tumors include tumors of blood vessel origin (*hemangioma* and *hemangioblastomas*). These tumors usually exhibit benign behavior, as do tumors of nerve roots, arising from Schwann cells (*neurilemmomas*). Because of anatomic proximity, tumors of the pituitary gland (*chromophobe adenoma*), craniopharyngeal duct (*craniopharyngioma*), and pineal body are frequently included with intracranial neoplasms [Schoenberg et al., 1982].

III.3. Degree of differentiation

The degree of cell differentiation in a tumor often describes the degree of malignancy. In general, a well-differentiated tumor describes a tumor whose cells are structurally distinct from the parent cells, which generally indicates a better prognosis and longer survival for the patient. A poorly-differentiated tumor describes a tumor with anaplastic cells, which grow without form or structure.

Tumors are typically assigned a grade which indicates the degree of cell differentiation or biological behavior of the tumor. In a commonly used classification scheme [Kernohan et al., 1949], tumors are graded from one to four with a higher grade indicating increasing cell anaplasia. For example, an astrocytoma grade III or IV describes a tumor with poorly differentiated cells while an astrocytoma grade I or II describes a tumor with well-differentiated or moderately differentiated cells, and therefore indicates a better prognosis. The WHO's classification of brain tumors also grades a brain tumor from one to four, with a higher grade indicating a shorter expected survival time for the patient

[Zülch, 1986]. Daumas-Duport et al. [1988] advocated grading tumors from one to four based on the number of the following criteria present in a tumor: cellular atypism, mitoses, endothelial hyperplasia and cell necrosis. Ringertz [1950] suggested a three-tiered system for grading astrocytic tumors according to the degree of anaplasia, and over time this has evolved into the terms *benign astrocytoma* (equivalent to grade I and grade II astrocytomas under Kernohan et al.), *anaplastic astrocytoma* (equivalent to a grade III astrocytoma under Kernohan et al.) and *glioblastoma multiforme* (equivalent to a grade IV astrocytoma under Kernohan et al.).

III.4. Anatomic site

The three major regions of the brain are the cerebrum, the cerebellum and the brainstem. The two cerebral hemispheres which comprise the cerebrum are further divided into the following four divisions, or lobes: 1) the frontal lobe, which is the anterior division of each cerebral hemisphere; 2) the parietal lobe, which is the middle division of each cerebral hemisphere; 3) the occipital lobe, which is the posterior division of each cerebral hemisphere and closely associated with visual sensory areas of the brain; and 4) the temporal lobe which is the front of the occipital lobe and includes the sensory areas associated with hearing. The cerebellum is also divided into two hemispheres and this region of the brain controls functions associated with muscular activity requiring coordination. The brainstem includes the pons and the medulla oblongata, the latter of which is the lower part of the brain which merges with the spinal cord.

Intracranial neoplasms generally present symptomatically because of irritation or destruction of tissue adjacent to the tumor or because of an increase in intracranial pressure as the mass expands [Schoenberg et al., 1976]. A slow-growing, histologically benign tumor located in a critical anatomic site is more likely to produce clinical symptoms than a fast-growing, histologically malignant tumor located in a less critical

anatomic site [Schoenberg, 1982]. Tumors of the same cell type may produce markedly different symptoms, depending on the location of the tumor. For example, gliomas arising in the temporal lobe produce psychomotor and petit mal seizures while gliomas arising in the sensory motor area may produce grand mal seizures [Ransohoff et al., 1991]. Gliomas located in the occipital and posterior temporal areas may present visual disturbance symptoms.

Astrocytomas can occur anywhere in the brain, but the frequency of occurrence in any anatomical site is generally related to the volume of tissue present [Yates, 1992]. Thus, the majority of malignant brain tumors occur in the cerebral hemispheres [Weller, 1986]. Although the distribution of astrocytomas is random across anatomic sites, other tumors arise in specific sites. For example, medulloblastomas are believed to be sited exclusively in the cerebellum [Barnard, 1986], while ependymomas are typically sited in the cerebral ventricles.

IV. CRITICAL REVIEW OF KEY STUDIES

IV.1. Overview

As part of the review process, over one hundred published scientific papers were searched and identified, many of which are cited in the reference section. Of the relevant articles, thirteen were selected because they additionally met two or more of the following criteria: pertinent to the purpose of this review, specifically, addressing tumor type; employed sound epidemiological research methods; had an adequately large sample size to allow reasonable interpretation; examined occupationally-exposed cohorts; and general overall quality. The individual reviews identify the study type (design), the population studied, whether tumor type was considered, major results or findings, and the study's strengths and weaknesses.

IV.2. Study designs

All of the studies can be classified by design as either cohort mortality studies or case-control studies. In general, occupational cohort mortality studies compare patterns of mortality (by specific causes of death) in the study group to some referent group, usually national or regional populations. This is accomplished by multiplying the mortality rate (i.e., the number of deaths per person-years of observation) for a specific cause of death (for a specific age-race-gender group) from the referent population by the number of comparable individuals (technically the number of person-years contributed) in the occupational cohort. This provides an estimate of the expected number of deaths due to that cause for that specific subgroup. The "expected" number is compared with the actual

number of "observed" deaths due to that cause among the subgroup. The summary measure most often used is the Standardized Mortality Ratio, or SMR, which is simply the ratio of "observed" to "expected" multiplied by 100. Several of the studies were occupational cohort mortality studies in which there was a reasonable number of brain cancer deaths. By nature of the cohort study, only a limited range of risk factors may be examined, and a *nested case-control* study may be helpful for this purpose.

Case-control studies basically compare the prevalence of one or more risk factors between a series of cases (individuals with the condition of interest) and a series of comparable controls (a representative sample from the population base which gave rise to the cases). When the population base is completely defined, that is, when all members of a group can be identified (as in most occupational cohorts), the study is often called a nested case-control study. Case-control studies have the advantage of allowing far more detailed risk factor ascertainment, and, if properly conducted, provide valid results in an efficient manner.

IV.3. Papers reviewed in detail

Reviews are presented in alphabetical order, according to author's last name, as follows:

	AUTHORS	YEAR PUBLISHED
1.	Austin and Schnatter	1983a
2.	Austin and Schnatter	1983b
3.	Bond, Cook et al.	1983
4.	Greenwald, Friedlander et al.	1981
5.	Leffingwell, Waxweiler et al.	1983
6.	Musicco, Sant et al.	1988
7.	Reeve, Bond et al.	1983
8.	Simonato, L'Abbé et al.	1991
9.	Teta, Ott and Schnatter	1991
10.	Thomas, Fontham et al.	1986
11.	Thomas, Stewart et al.	1987
12.	Waxweiler, Alexander et al.	1983
13.	Wong, Whorton et al.	1991

Copies of each of these papers are included in the Source Documents supplement.

1 Austin SG, Schnatter RS. A cohort mortality study of petrochemical workers. Journal of Occupational Medicine 1983;4:304-312.

TYPE OF STUDY
Cohort mortality study

POPULATION
White male employees (n=6,588) who worked between 1941 and 1977 at a Union Carbide petrochemical plant in Texas City, Texas. Comparisons were made to U.S. white male mortality rates, adjusted for age and calendar period.

TUMOR TYPES IDENTIFIED
Of the 16 cases of brain tumors identified through death certificates, clinical or pathological information was available for 13 cases. Fifteen of the sixteen tumor types identified were primary intracranial tumors. The distribution was as follows: 11 glioblastomas (glioblastomas or astrocytomas grade III or IV), 1 astrocytoma grade II, 1 meningiosarcoma, 1 meningioma, 1 malignant brain tumor and 1 metastatic brain tumor.

MAJOR FINDINGS
There were 12 deaths from malignant brain tumors compared to 7.42 expected (SMR=162; 95% CI: 83–283). Among hourly workers who were employed for at least 6 months and with at least 10 years time since hire, there were 10 observed brain cancer deaths compared to 4.03 expected (SMR=248; 95% CI: not reported; $p < 0.05$). The SMR increased to 337 for hourly workers who were employed for at least 6 months and with at least 20 years time since hire, based on 8 observed and 2.37 expected deaths. However, this excess was not statistically significant. Although mortality risk did not appear to increase with increasing duration of employment, risk was elevated for workers with less than five years length of employment and workers with at least 15 years length of employment.

STRENGTHS
Analyses were conducted separately for all workers and hourly workers only, and by length of employment and latency. Death certificate diagnoses of brain cancer were verified using additional diagnostic information (medical and pathology reports) obtained by NIOSH.

WEAKNESSES
Brain cancer mortality was not analyzed by specific cell types. Because an excess of glioblastoma was suspected, the authors compared the proportion of glioblastomas (75%) in the study population to what would be expected in the general population and concluded the proportion in the cases was consistent with the expected proportion. However, this comparison was based on a survey of 126 tumors of the cerebral hemispheres of adults who underwent biopsy at Massachusetts General Hospital, where 77% of the tumors were found to be glioblastomas. This comparison may not be valid because most tumors of the cerebral hemisphere are gliomas, and the anatomic location of the tumors in the cases was not known. A more accurate comparison would be based on the distribution of all cell types in the general population.

2 **Austin SG, Schnatter RS. A case-control study of chemical exposure and brain tumors in petrochemical workers. Journal of Occupational Medicine 1983;4:313-320.**

TYPE OF STUDY
Plant-based case-control study

POPULATION
The cases were comprised of 21 males who died from a primary brain tumor between 1956 and 1980 (all known cases among former plant employees). Two control groups of 80 employees each were randomly selected from among 450 decedents known to the company in June 1979. Group A excluded any employee who had died from any kind of cancer; Group B included both decedents from cancer and noncancer causes.

TUMOR TYPES IDENTIFIED
By definition, all 21 cases were primary brain tumors. The distribution of tumor types was as follows: 14 glioblastomas (includes astrocytomas, grade III and IV), 2 anaplastic astrocytomas (includes 1 astrocytoma grade II), 1 malignant brain tumor not specified, 3 meningiomas and 1 meningiosarcoma. The investigators classified 17 of these cases as gliomas and four as meningiomas (3 benign and one malignant).

MAJOR FINDINGS
When proportions of cases exposed to one of 5 known or suspected carcinogens (benzene, ethylene dichloride, ethylene oxide, diethyl sulfate and vinyl chloride) were compared to the proportions of controls exposed to the same chemical, there were no statistically significant differences. However, when salaried employees were removed from the analysis, there were slight excesses in the proportion of cases with gliomas exposed to ethylene dichloride and vinyl chloride when compared to the proportion of controls exposed to these same chemicals. These excesses persisted when a 15 year latency period was applied. Exposure to an additional 37 chemicals where at least 4 brain tumor cases were exposed showed no significant excesses among the proportion of cases exposed compared to the proportion of controls exposed.

STRENGTHS
Analyses were conducted for all brain tumors and for all gliomas. Cases were initially identified by death certificate, but validated using other sources of information.

Additional analyses were conducted which excluded salaried employees, based on the rationale that salaried employees have a lower risk for exposure to the chemical agents studied than hourly workers (however, this should have been verified with occupational histories).

WEAKNESSES
Controls were selected only from former employees who were known to the company to be deceased.

Exposure to specific chemicals could not be determined for 48% to 57% of the cases and for 56% to 67% of the controls. Although analyses were conducted where those with unknown exposure were considered separately as exposed to all of the chemicals and not exposed to all of the chemicals, the results presented only reflect the analysis which excluded those with unknown exposure. Because of the large proportions of those with unknown exposure, the ability to detect a true association, if one existed, may have been diminished.

3 Bond GG, Cook RR, Wight PC, Flores GH. A case-control study of brain tumor mortality at a Texas chemical plant. Journal of Occupational Medicine 1983;25:377-386.

TYPE OF STUDY
Plant-based case-control study

POPULATION
Cases were 28 white male former workers (employed between 1940 and 1979) who had died of primary intracranial neoplasms. There were two control groups: Group A was selected from all noncancer deaths among white males and matched to each case based on age at death (± 5 years) and year of death. Group B was selected from the 5% sample previously identified [Reeve et al, 1983] and matched to each case on year of birth (± 2 years) and category of duration of employment (≤ 1 year, 1 to 4 years, 5 to 9 years, 10 to 14 years, 15 to 19 years and ≥20 years).

TUMOR TYPES IDENTIFIED
Tumor type was identified for all 28 cases, and clinical and/or pathological information was available for 21 of the cases. The tumor type distribution was as follows: 16 glioblastomas (glioblastomas or astrocytomas grade III or IV), 1 astrocytoma, 1 oligodendroglioma, 1 malignant glioma, 1 medulloblastoma, 3 malignant brain tumors, 2 carcinomas of the brain, 1 brain cancer and 2 brain tumors.

MAJOR FINDINGS
Cases and controls were examined by department assignment and potential exposure to any one of 79 chemical and physical agents. The odds ratio for assignment to the magnesium department was 1.93 (95% CI: 0.95–3.93) when compared to Control Group A and 1.15 (95% CI: 0.56–2.36) when compared to Control Group B. There were no statistically significant associations. When the analysis was restricted to glioblastomas, there were nonsignificantly elevated odds ratios for workers assigned to the magnesium department (OR=1.40) and the machine shop (OR=4.16).

STRENGTHS
Separate analyses were conducted for all intracranial neoplasms and for all glioblastomas. Two control groups allowed comparison of findings; however, this was not used to the fullest extent possible for interpretation.

WEAKNESSES
A selection bias may be present due to incomplete case ascertainment. Cases were determined using death recorded for a four-county area near the plant, deaths known to the company, follow-up based on the 5% sample of the ever-employed population and cases who were reported to NIOSH. Also, one control group was selected from only those former employees whose death was known to the company.

Exposure misclassification was likely because exposure determination was based on company work history records but dichotomized (yes or no). Although it is unlikely that there were systematic differences in exposure classification between cases and controls, non-differential misclassification would result in attenuation of any association. Also, many of the exposures were rare, reducing the statistical power of the analyses.

4 Greenwald P, Friedlander BR, Lawrence CE, Hearne T, Earle K. Diagnostic sensitivity bias: An epidemiologic explanation for an apparent brain tumor excess. Journal of Occupational Medicine 1981;23:690-694.

TYPE OF STUDY
Case-control study

POPULATION
Cases (n=56) were comprised of all Eastman Kodak Rochester employees who had died from primary intracranial neoplasms between 1956 and 1975. Two control groups were selected from Kodak employees: Group A (n=112) consisted of employees who had died from causes not including brain tumors; and Group B (n=62) was drawn from a computerized record system of employees who started working on or after January 1, 1964. A subgroup of cases (n=31) was selected from employees whose hire date was on or after January 1, 1964. Both control groups were matched on sex and five-year age intervals with a 2:1 control:case ratio.

TUMOR TYPES IDENTIFIED
Histological data were available for 51 of the 56 cases. The distribution by tumor type was as follows: 39 glioblastomas, 7 astrocytomas, 1 oligodendroglioma, 1 medulloblastoma, 1 chromophobe adenoma and 2 meningiomas.

MAJOR FINDINGS
Exposures to 18 chemical and physical agents were compared between the cases and controls. There were no statistically significant associations, although risk was elevated among those exposed to solvents other than chlorinated solvents, black-and-white developers and color developers, when either control group was used as the comparison The distribution of tumor types among cases was also compared to the distribution of tumor types among residents of the Rochester area (excluding Kodak employees) and residents of New York state (excluding the Rochester and New York City areas). No differences were found. Glioblastomas accounted for approximately 70% of tumors in the case group and the two comparison groups. The authors concluded that a diagnostic sensitivity bias accounted for the perceived increase in risk from brain cancer.

STRENGTHS
Tumor type was identified and verified for 51 of the 56 cases. Preliminary analyses of the distribution of tumors by cell type were compared with Rochester area and New York State data.

Exposure assessments were made blind to case or control status, preventing information bias. Analyses were conducted which suggested that a diagnostic sensitivity bias might have operated to produce the cluster of cases which led to this investigation.

WEAKNESSES
Although there were a large number of glioblastomas, individual cell types were not analyzed by exposure status.

No direct measures of exposure were available: exposure status was assigned based on "potential for exposure." Random misclassification would reduce the ability to detect any true differences.

5 **Leffingwell SS, Waxweiler R, Alexander V, Ludwig HR, Halperin W. Case-control study of gliomas of the brain among workers employed by a Texas City, Texas chemical plant. Neuroepidemiology 1983;2:179-195.**

TYPE OF STUDY
Nested case-control study

POPULATION
Cases were restricted to the 17 gliomas identified among a possible 23 cases with brain tumors (the six exclusions were 1 metastatic brain tumor, 4 meningiomas, and 1 suspected brain tumor, which was not confirmed at autopsy). Controls were matched to cases on race, sex, year of birth ± 3 years, date of first employment not more than three years earlier than that of the case, and the control's last date of employment must have been later than the case's. In addition, for deceased controls, death must not have been caused by a malignancy.

TUMOR TYPES IDENTIFIED
All 17 cases were gliomas: 15 glioblastomas, 1 astrocytoma grade II and 1 glioblastoma suspected clinically, but a biopsy revealed no tumor.

MAJOR FINDINGS
The greatest apparent risks for brain cancer were associated with exposure (ever exposed) to carbon dioxide, diethyl sulfate, diethylene glycol, ethanol, ethylene, isopropanol, methane, tetraethylene glycol, and vinyl acetate. Among non-maintenance workers who were employed at least 15 years prior to the death of a case, the OR for exposure to diethyl sulfate was 4.87 (90% CI: 1.05–22.53). Risk was also elevated for workers who had ever resided in a nearby community (OR=5.86; 90% CI: 2.25–15.25); however, the average length of residence in the community was shorter for the cases than for the controls.

STRENGTHS
Risk was assessed separately for 33 chemicals to which at least four or more cases had been exposed.

Two analyses were conducted, one which included maintenance workers in the exposed groups and one which excluded maintenance workers from the exposed group.

Associations between residence and brain tumor risk were also examined to determine if the excess among workers at the plant actually reflected an excess in the surrounding communities.

WEAKNESSES
The number of cases finally included in the analysis is fairly small (17), limiting the statistical power of the study.

In the analysis, employees with no exposure were excluded. In the presence of an association between a risk factor and an outcome (i.e., brain cancer), such an exclusion in a case-control study might reduce the strength of the association, leading to a negative bias. Exposure measures were limited to duration of potential exposure (cumulative exposure), which does not account for or approximate exposure dose.

6 **Musicco M, Sant M, Molinari S, Filippini G, Gatta G, Berrino F. A case-control study of brain gliomas and occupational exposure to chemical carcinogens: The risk to farmers. American Journal of Epidemiology 1988;128:778-785.**

TYPE OF STUDY
Case-control study

POPULATION
Cases were comprised of newly diagnosed gliomas (n=240) during 1983 and 1984 in Italy. Controls were comprised of 465 nonglioma nervous system tumors and 277 patients with other neurologic diseases. The 465 tumor controls included 154 meningiomas, 74 brain metastases, 70 pituitary adenomas, 51 neurinomas, 37 malformative neoplasms and 79 other rare brain tumors.

TUMOR TYPES IDENTIFIED
The distribution of tumor types was as follows: 157 glioblastomas (includes astrocytomas grade III or IV), 40 astrocytomas grade I or II, 10 oligendroglioma, 9 ependymoma, 6 medulloblastoma, 1 ganglioglioma and 17 other glioma unspecified.

MAJOR FINDINGS
Study subjects were grouped into one of four occupational categories: white collar workers, sales and service workers, farmers and blue collar workers. A statistically significant increased risk was found for farmers when compared to all controls (RR=1.6; 95% CI: 1.06–2.42) and to tumor controls (RR=1.6; 95% CI: 0.91–2.80). Relative risks were adjusted for age, sex, residence and social class. Among farmers who did not report the use of chemicals the relative risk was 1.2 (95% CI: 0.61–2.51) when compared to all controls and 1.0 (0.12–8.72) when compared to tumor controls. Farmers who reported the use of chemicals experienced relative risks of 1.6 (95% CI: 1.04–2.53) and 2.0 (95% CI. 1.20–3.46) when compared to all controls and only tumor controls, respectively. Risk estimates were highest for farmers who reported using insecticides and fungicides when compared to total controls (OR=2.0; 95% CI: 1.22–3.23) and tumor controls (OR=2.1; 95% CI: 1.27–3.58).

STRENGTHS
Because of the large number of glioma cases, the power of the study was adequate to produce relatively stable estimates of relative risk.

Detailed work history information was obtained by interviewing cases and controls. Because of inclusion of a non-glioma tumor control group, differential recall bias was minimized. The non-glioma tumor controls were comparable to the cases in that they received access to similar diagnostic procedures and experienced similar symptoms. Although these tumors may share a common etiologic agent, brain tumors induced by chemicals in animal studies are mostly gliomas.

Increased risk of brain tumors among farmers who are exposed to agricultural chemicals is biologically plausible. Alkyl-ureas, a common ingredient in fungicide, are precursors of N-nitroso alkyl ureas. These substances have been found to induce brain tumors in rats and their offspring. Increasing relative risks with increasing focus of risk factor measure on pesticides supports the hypothesis of an association.

WEAKNESSES
Duration of employment in farming occupations was used as a surrogate measure of exposure; however, self-reported chemical use was also used.

7 Reeve GR, Bond GG, Lloyd JW, Cook RR, Waxweiler RJ, Fishbeck WA. An investigation of brain tumors among chemical plant employees using a sample-based cohort method. Journal of Occupational Medicine 1983;25:387-393.

TYPE OF STUDY
Sample-based cohort mortality study

POPULATION
Brain tumor deaths (n=25) were identified among former production and nonproduction workers at Dow Chemical, Texas Division. A 5% random sample (n=2,096) of workers ever employed between 1940 and 1977 was drawn. After females and nonwhite males were excluded from the sample, 1,666 white males remained for the analysis. Expected deaths were derived from multiplying the resulting person-years distribution, stratified by duration of employment, time since hire and date of hire, by U.S. age- and calendar year-specific mortality rates for malignant or benign and unspecified brain tumors among white males.

TUMOR TYPES IDENTIFIED
Twenty-five brain tumors were identified within a four-county region near the plant, and clinical or pathological information was available for 19 of the 25 deaths. The distribution of tumors was as follows: 12 glioblastomas (glioblastomas or astrocytomas grade III or IV), 3 malignant and 3 benign brain tumors, not otherwise specified, 1 malignant glioma, 1 medulloblastoma, 1 oligodendroglioma, 1 neurogenic sarcoma, 1 metastatic CNS malignant melanoma, 1 hydrocephalus, and 1 metastatic tumor from the lung. With the exception of the last four types identified, all were primary intracranial tumors.

MAJOR FINDINGS
Although there was no apparent duration-response trend when brain cancer mortality was examined, elevated mortality was reported for workers employed from one to four years and for at least 20 years. Mortality less than or equal to expected was reported for workers employed less than one year and from 5 to 19 years. Workers with at least 20 years or more time since hire, irrespective of duration of employment, also experienced elevated risks. Also, mortality rates were increased for workers first hired before 1945. None of the SMRs reported were statistically significant at alpha = 0.05.

STRENGTHS
Because the 5% sample was not geographically restricted to the same four-county region from which the brain tumor cases were drawn, three different methods were used to estimate expected deaths to allow for migration of former employees out of the region.

WEAKNESSES
A 5% sample of the working population may not be representative of the person-years distribution for the entire workforce. If person-years were underestimated, then mortality risk may be overestimated. If person-years were overestimated, then mortality risk may be underestimated.

The sample also included both production and nonproduction workers which may have underestimated risk if only exposure associated with production workers was present.

Although the distribution of brain tumor types was reported, analyses were conducted on all tumor types (malignant and benign or unspecified tumors were grouped) which does not exclude the possibility that risk was elevated for one or more tumor types.

8 Simonato L, L'Abbé KA, Andersen A, Belli S, Comba P, Engholm G, Ferro G, Hagmar L, Langård S, Lundberg I, Pirastu R, Thomas P, Winkelmann R, Saracci R. A collaborative study of cancer incidence and mortality among vinyl chloride workers. Scandinavian Journal of Work, Environment & Health 1991;17:159-169.

TYPE OF STUDY
Cohort mortality study

POPULATION
12,706 male subjects who had worked at least one year in one of 19 factories that produced vinyl chloride monomer and/or polyvinyl chloride or processed PVC in Italy, Norway, Sweden and the United Kingdom. Mortality rates in the cohort were compared to age- and calendar year-specific national mortality rates.

TUMOR TYPES IDENTIFIED
No histological data were reported. A total of 14 malignant brain neoplasms were reported.

MAJOR FINDINGS
Mortality from brain cancer was near expected (14 observed deaths; 13.1 expected). There were no apparent trends with duration of employment. However, mortality was significantly elevated for workers with at least 30 years since first exposure, based on 4.0 observed brain cancer deaths (1.0 expected; SMR=407; 95% CI: 111–1041). The excess was mostly observed among those hired between 1945 and 1954 and assigned to VCM/PVC production.

STRENGTHS
Job-exposure matrices specific to calendar period were developed by industrial hygienists to provide estimates of cumulative exposure and ranked (low, intermediate, high, unknown) level of exposure. Analyses were conducted by duration of employment, ranked level of exposure and cumulative exposure in parts per million-years to VCM in the air.

Cancer incidence data were included, analysis of which suggested a non-statistically significant increase in brain cancer risk of about 60% (standardized incidence ratio, or SIR = 159) among individuals exposed to VCM from four plants.

WEAKNESSES
A large number of workers were included, thus potentially increasing the power of the study to detect an association; however, only 12 brain cancers were identified. Because the study was a general mortality study, other relevant findings were included (most notably the increased risk of primary liver tumors with VCM exposure), and therefore the focus was not on brain cancer.

Brain tumors were not identified by cell type. The distribution of cell type among workers exposed to VCM/PVC was not compared to the distribution in the general population. The authors concluded that excesses of brain cancer (and lymphoma) were unrelated to exposure, despite the low statistical power to validly conclude this.

9 Teta MJ, Ott MG, Schnatter AR. An update of mortality due to brain neoplasms and other causes among employees of a petrochemical facility. Journal of Occupational Medicine 1991;33:45-51.

TYPE OF STUDY
Cohort mortality study. This study updated the original cohort mortality studies independently conducted by Austin and Schnatter [1983] and Waxweiler et al. [1983].

POPULATION
Male workers at the Union Carbide Texas City, Texas petrochemical plant employed from 1941 through 1983 (n=7,849). Mortality from 1950 to 1983 was examined separately for hourly and salary workers and was compared to U.S. age-, race-, and calendar year-specific mortality rates for males.

TUMOR TYPES IDENTIFIED
Five deaths due to brain neoplasms were identified from 1978 to 1983. The distribution according to the death certificates were as follows: 3 glioblastoma multiforme, 1 malignant astrocytoma and 1 brain tumor unspecified.

MAJOR FINDINGS
Risk was significantly elevated among hourly workers for malignant brain cancer based on 17 observed and 9.4 expected deaths (SMR=181; 95% CI: 106–289) and for benign and unspecified brain tumors based on 7 observed and 2.5 expected (SMR=280; 95% CI: 114–577). For maintenance workers, the SMR was 190, and the excess was greater in nonwhites, whose average employment duration was 16 years (range 6 to 32 years). These excesses are in contrast with an overall deficit of cancer mortality of 11% in the cohort, relative to the U.S. population.

STRENGTHS
Because six years of observation were added (1978-1983), the power of the study was increased over the original studies.

Analyses were conducted by different categories of work area, job titles and potential for working with various compounds.

WEAKNESSES
Separate analyses were conducted for all malignant neoplasms of the brain and all benign and unspecified brain tumors. If these categories do not differentiate tumors etiologically, a loss of statistical power and precision will result, as well as possible bias in the measure of association.

The interpretation, discussion and conclusions in this article downplay the consistency of the excesses seen in the previous studies on this cohort, and the continued observation of excesses, especially among production employees. In fact, no brain neoplasms, malignant or benign, were found among salaried employees, whereas two were expected. This contrast argues against a diagnostic sensitivity bias, in that salaried employees would more likely have access to sophisticated diagnostic equipment and procedures.

10 Thomas TL, Fontham ETH, Norman SA, Stemhagen A, Hoover RN. Occupational risk factors for brain tumors: A case-referent death-certificate analysis. Scandinavian Journal of Work, Environment & Health 1986;12:121-127.

TYPE OF STUDY
Case-control study

POPULATION
Cases (n=718) were white men whose cause of death on their death certificates was brain cancer. Cases and controls were drawn from three geographic areas (northern New Jersey, Philadelphia, and the Gulf Coast of Louisiana). The controls (n=738) were men who had died of other causes, excluding epilepsy and stroke. Usual occupation and industry were abstracted from the death certificates.

TUMOR TYPES IDENTIFIED
The distribution by tumor type was as follows: 201 (51.0 %) glioblastomas (includes astrocytoma grade III or IV), 82 (11.4%) astrocytomas grade I or II, 2 oligodendrogliomas, 4 ependymomas, 77 (10.7%) gliomas unspecified, 28 (3.9%) meningiomas, 4 schwannoma, 2 hemangioblastoma, 1 craniopharyngioma, 2 medulloblastoma, 1 meningiosarcoma, 1 retinoblastoma, 1 sarcoma of the nervous system, 95 (13.2%) malignant brain tumor not specified, 212 (29.5%) unspecified brain tumors and 5 spinal cord tumors, not specified.

MAJOR FINDINGS
There was no excess risk for those decedents whose usual employment (as recorded on the death certificate) was in the chemical industry (OR=1.0; 95% CI: 0.6–1.7). A slight excess risk was reported for those decedents whose usual industry was petroleum refining (OR=1.2; 95% CI: 0.6–2.6). There were statistically significant excesses reported for all white collar professions (OR=1.7; 95% CI: 1.3–2.3), especially among health diagnosing (but not treating, such as physicians) professionals (OR=6.8, 95%CI: 1.4–44.9), who may be exposed to ionizing and nonionizing radiation, as well as chemical substances. Among blue collar professions, precision metal workers showed a moderate excess (OR=2.1; 95% CI: 1.2–3.6). All odds ratios were adjusted for age at death and marital status.

STRENGTHS
This is one of the largest case series included in a case-control study, and information on tumor type is relatively extensive.

WEAKNESSES
Although there were over 200 glioblastoma multiforme tumors, no separate analysis was attempted (nor for other specific tumor types).

Information regarding industry and usual occupation obtained from death certificates is notoriously poor, and may actually reflect the decedent's last job and/or industry instead of the decedent's longest job or usual job. Furthermore, occupation and industry are very crude measures of individual risk factors, and the probability of discovering true associations - unless they are extremely large - is very low in this type of study.

Some death certificate diagnoses of brain tumor may also be misclassified as primary brain tumors when in fact they are metastatic brain tumors.

11 Thomas TL, Stewart PA, Stemhagen A, Correa P, Norman SA, Bleecker ML, Hoover RN. Risk of astrocytic brain tumors associated with occupational chemical exposures: A case-referent study. Scandinavian Journal of Work, Environment and Health 1987;13:417-423.

TYPE OF STUDY
Case-control study. This study is an extension of the previous study by Thomas, Fontham, Norman et al. [1986].

POPULATION
The cases were drawn from a population who were potentially exposed to organic chemicals in petroleum refining or chemical manufacturing in northern New Jersey, Philadelphia and the Gulf Coast of Louisiana. Cases were 300 white men with a confirmed diagnosis of glioblastoma, astrocytoma or a mixed glioma with astrocytic cells between 1979 and 1981 (New Jersey and Philadelphia) or between 1978 and 1980 (Louisiana). Controls were 386 white men who died from causes other than brain tumor, epilepsy, cerebrovascular disease, suicide or homicide and were matched to cases on age at death, year of death and study area.

TUMOR TYPES IDENTIFIED
All tumors were of the astrocytic series: astrocytomas, glioblastomas or mixed glioma with astrocytic cells. The distribution of the 300 tumors among these cell types was not reported. Of these 300 cases, 229 (76%) were pathologically confirmed, and 71 (24%) were diagnosed by physicians using computerized tomography. Of the 483 cases originally identified for the study (death certificate indicating primary brain cancer and having completed an interview with the next-of-kin), 48 (10%) had no brain tumor upon verification, and 135 (28%) had tumors of other origin or unspecified origin.

MAJOR FINDINGS
The odds ratios for astrocytic tumors were 1.5 (95% CI: 0.7–3.2) and 1.2 (95% CI: 0.7–2.0) among those ever employed in the petroleum refining industry and the chemical manufacturing industry, respectively. When production and maintenance workers only were examined, the odds ratios were 1.7 (95% CI: 0.7–4.2) for petroleum refining and 1.2 (95% CI: 0.7–2.2) for chemical manufacturing. The risk of astrocytic brain cancer was inversely related with duration of employment. Subjects who may have been exposed to cutting fluids experienced borderline statistically significant excess mortality from astrocytic brain tumors (OR=1.6; 95% CI: 1.0–2.6). There were also excess risks of astrocytic tumors among men exposed to organic solvents (OR=1.3; 95% CI: 0.8–1.9). Among subject with at least 20 years duration of exposure, astrocytic tumor risk was elevated for workers exposed to lubricating oils (OR=1.4), organic solvents (OR=1.5), and cutting fluids (OR=1.8), although none of the excesses were statistically significant.

STRENGTHS
The study was designed to focus on risk of astrocytic tumors from exposure to petrochemical refining and chemical manufacturing. Few other studies have had such specificity of both risk factor and outcome, in terms of tumor type. Exposure estimates were analyzed both in terms of duration (cumulative exposure) and intensity (low, moderate, high).

WEAKNESSES
Because of the study design requiring data from interviews with next-of-kin, the potential for information bias exists. Only selection (response) bias was examined.

12 Waxweiler RJ, Alexander V, Leffingwell SS, Haring M, Lloyd JW. Mortality from brain cancer and other causes in a cohort of petrochemical workers. Journal of the National Cancer Institute 1983;70:75-81.

TYPE OF STUDY
Cohort mortality study

POPULATION
The cohort was comprised of 7,595 men ever employed at a Union Carbide plant in Texas City, Texas between 1941 and 1977 and followed for mortality through 1977. Comparisons were made to U.S. age-, race-, and calendar year-specific mortality rates for males.

TUMOR TYPES IDENTIFIED
There were 19 deaths from brain tumors in the cohort. Three additional deaths were reported when 3 years were added to the follow-up. Tumor types were identified for men who were employed at least 10 years at the plant. Of the 14 brain tumors in this group, there were 9 glioblastomas (including astrocytomas grade III or IV), 4 meningiomas and 1 glioma unspecified.

MAJOR FINDINGS
The SMR for brain tumors was 206 based on 22 brain tumor deaths (10.7 expected). Mortality from brain cancer also increased with duration of employment for those with at least 15 years time since first employment, and was statistically significant for workers employed between 10 to 19 years (SMR=357; 95% CI: 116–832) and workers employed for at least 20 years (SMR=377; 95% CI: 172–715). No brain tumors were discovered among employees first employed since 1954. Surprisingly, the SMR for all malignant neoplasms showed a strong and statistically significant *deficit* (SMR=80 95% CI: 68–93 for hourly workers), suggesting that the general cancer experience of this group was lower than that of the United States.

STRENGTHS
Determination and verification of tumor type was reasonably successful, although no sub-analyses by type were possible due to small numbers.

The quality of the analysis in this study is good, since several dimensions of risk were explored - including consideration of duration of employment, employment status (hourly versus salaried), years since first employment, and calendar period of risk. Also, temporal changes (increases) in the rates of brain cancer for the referent (United States) were assessed, and estimated to have little if any effect on the study relative risk estimates.

WEAKNESSES
This study is generally free from serious flaws, especially considering that it was published over ten years ago. As the authors point out, one limitation was the selection of controls only from those deaths known to the company (retirees). These individuals may have had disproportionately longer duration of employment, leading to greater opportunity to have had more exposures, including any associated with the cases. A second related weakness, not unique to this study, is the general difficulty in determining exposures among both cases and controls. Lack of precision leading to random measurement error and misclassification reduces a study's ability to detect true risk factors.

13 Wong O, Whorton MD, Foliart DE, Ragland D. An industry-wide epidemiologic study of vinyl chloride workers, 1942-1982. American Journal of Industrial Medicine 1991;20:317-334.

TYPE OF STUDY
Cohort mortality study. This study updates (through 1982) the Chemical Manufacturers Association cohort study previously reported by Tabershaw and Gaffey [1974] and Cooper [1981].

POPULATION
The cohort consisted of 10,173 workers from 37 plants in the United States where vinyl chloride monomer (VCM) or polyvinyl chloride (PVC) was produced, and who had worked for at least one year between 1942 and 1972. Study subjects were followed up for mortality through 1982. Mortality rates in the cohort were compared to U.S. age- and calendar year-specific mortality rates for white males.

TUMOR TYPES IDENTIFIED
Specific cell types for brain tumors were not identified.

MAJOR FINDINGS
A statistically significant excess of cancer of the brain and central nervous system was detected (SMR=180, 95% CI: 114–271), based on 23 observed and 12.8 expected deaths. Although there were no apparent trends with duration of employment, risk was elevated for workers who were exposed to VCM for at least 20 years based on 6 observed and 1.6 expected deaths (SMR=386; 95% CI: not reported; $p < 0.05$). Brain and central nervous system cancer was also significantly elevated for workers hired between 1950 and 1959 (SMR=256; 95% CI: not reported; $p < 0.05$). The authors reported a disproportionately large number of brain cancer cases at two specific PVC plants. This observation was consistent with an excess of liver cancer cases at the same two plants.

STRENGTHS
The study draws on a very large cohort followed over a relatively long period of time, with a total of 23 brain cancer cases observed. This was reported to be consistent with the results from the first analysis of this cohort study by Cooper (SMR=203).

WEAKNESSES
Although this was a general mortality study, analyses were conducted by length of exposure, latency, age at first exposure, calendar year of first exposure and by type of plant (generally a strength). However, these stratified analyses were not particularly helpful in more fully understanding the excess brain cancer risk. It is possible that confounding was present, as SMRs technically are not directly comparable, and are strongly influenced by the distribution of confounders between groups being compared.

The distribution of brain tumors by cell types was not reported.

IV.4. Synthesis and summary

Collectively, the studies reviewed above provide suggestive evidence of occupational (or other environmental) risk factors for brain cancer; however, there is yet inadequate consistency to implicate any specific exposures. Where excesses are noted [Austin and Schnatter, 1983a; Leffingwell et al., 1983; Musicco et al., 1988; Teta et al., 1991; Waxweiler et al., 1983 and Wong et al., 1991], there has been little success in linking these *a priori* with risk factors. One study making a strong case for an association between brain cancer and occupational exposures is the paper by Musicco et al. [1988], in which a dose-response relationship with agricultural chemicals is demonstrated. Furthermore, few studies are able to "explain" these excesses in terms of potential confounding, selection or information bias, although much attention has been paid to the "diagnostic sensitivity bias" [Greenwald et al., 1981; Shah, 1993; Wong and Whorton, 1993].

The next section of this report examines in greater detail the diagnostic sensitivity bias as well as some of the other key issues faced in interpreting the body of epidemiological literature available to date on the etiology of brain cancers.

V. ISSUES AND INTERPRETATION

V.1. Overview

In order to assemble all of the epidemiological information available on brain cancers and to derive valid and useful interpretations, several issues must be addressed. First, and often overlooked, is the biological plausibility of environmental agents inducing *or promoting* brain neoplasms. Secondly, inherent limitations in studying occupational risk factors for brain cancers are explored, including the rarity of these tumors, classification complexities, exposure measurement difficulties, etc. Third, special attention is focused on the issue of diagnostic sensitivity bias, which has been invoked occasionally, but without consideration of the evidence arguing against this bias. Finally, several pieces of evidence supporting an environmental hypothesis are assembled and discussed.

V.2. Biological plausibility

Although it is not strictly necessary to understand the mechanisms of disease process in order to identify risk factors or indicators for disease, evaluation of the biological plausibility of a putative association often adds to or detracts from the credibility of a specific hypothesis. For instance, when cigarettes were first scientifically linked with the occurrence of lung cancer in the 1950s, no mechanism of carcinogenicity was known, and the specific chemical agents involved remained unidentified for years. Nevertheless, the biological plausibility of an inhaled substance causing respiratory cancers was reasonable. From this early notion of plausibility, various components and mechanisms of the actual disease process were identified and refined.

With respect to the chemical induction of brain tumors, biological plausibility considers the bioavailability of a substance or its metabolites to the target tissue, including route of exposure to the substance, metabolic pathways, elimination of the substance, and identification of toxic metabolites, etc. Although this report is not a toxicological review, a few key points warrant mention.

Because the brain is relatively well protected from potential environmental assaults, both physical and chemical, there are limited routes of exposure. One major route of exposure is via the bloodstream, originating from either inhalation or ingestion. Those substances (or metabolites) contacting the brain tissue must first pass the blood-brain barrier, which is impervious to certain chemicals and receptive to others. It has been suggested that the blood-brain barrier may be ineffective in protecting glial cells from blood-borne chemicals, as only a single layer of vascular epithelial cells separate them from the blood [Larson, 1980]. This is important, since more than half of all primary CNS tumors are of glial origin [Levin, 1989; Schoenberg, 1982].

Another approach to understanding the etiology of disease is to study animal models. For chemical exposures, toxicology uses animal systems to elucidate the toxicological properties of these substances. If a specific agent is suspected, a series of tests and studies may help determine whether it is a mutagen, teratogen or carcinogen. For example, if the agent can be shown to act as a carcinogen in an animal species, the finding is often extrapolated to other species, including humans. If an agent can induce tumors in multiple higher-order species, the plausibility that it might act as a human carcinogen may be enhanced more than if tumors are inducible only in a single invertebrate model. Demonstration that various substances can induce tumors (i.e., brain

tumors) in animal models supports, but cannot prove, the hypothesis of environmental risk factors for the tumors in humans.

In 1939, Seligman and Shear were the first to demonstrate that chemicals (specifically methyl-chloranthrene) could induce brain tumors when implanted in the brains of mice [Cusimano, 1989]. Since then, both polycyclic hydrocarbons and aliphatic alkylating agents have been shown to induce CNS tumors, either through direct implantation or administered systemically and passing the blood-brain barrier, although polycyclic aromatic hydrocarbons have not produced brain tumors in laboratory animals exposed via inhalation only [Swenberg, 1977; Cusimano, 1989]. Gliomas, however, have been induced experimentally in laboratory animals by inhalation of both acrylonitrile and vinyl chloride [Maltoni et al., 1982].

Nitrosourea compounds have been studied because of their ability to induce experimentally a consistently high rate of nervous system tumors in laboratory animals. Two specific nitrosamides, N-methyl-N-mtrosourea (MNU) and N-ethyl-N-nitrosourea (ENU), are used extensively in experimental neuro-oncology [Lantos, 1986]. These two compounds exhibit strikingly different modes of action. While ENU injected into gravid rats after day 12 of gestation will produce nearly 100% incidence of neural tumors in offspring, it rarely produces CNS tumors in adult animals. In contrast, MNU produces the highest incidence of tumors in adult animals administered in small, repeated doses [Lantos, 1986].

Although nitrosourea compounds have a half-life of only about 10 minutes, they are metabolized to alkyl cations capable of interacting with nucleophilic groups of deoxyribonucleic acid (DNA), causing nucleotide mispairing and subsequently chromosomal deletions and duplications [Cusimano, 1989]. These chromosomal errors

are believed to remove normal genetic control mechanisms which regulate cell growth and differentiation, leading to malignancy [Kleinhues and Bigner, 1981]. This literature suggests - if the animal models are appropriate - that chemical induction of brain tumors in humans is biologically plausible, and that multiple mechanisms are possible.

V.3. Study limitations

Several issues limit the ability to fully interpret many of the studies which examined brain cancer risk. Some of these limitations are inherent in the methods used to estimate risk, e.g., SMR analysis. Other limitations are potentially the result of information bias, selection bias, and confounding factors which may distort the risk estimates.

Mortality studies typically use information recorded on death certificates to determine disease occurrence. However, the cause of death as recorded on the death certificate may not necessarily be accurate, and for cancers, the death certificate may not specify the histologic cell type of the tumor. For bram cancer, the cause of death may be recorded only as a brain tumor, which would be assigned to the category which includes unspecified brain tumors in a mortality analysis. Thus, malignant forms of brain cancer are likely to be underreported when the underlying cause of death on the death certificate is used to measure disease occurrence. Although many of the studies obtained medical and pathologic reports to confirm the death certificate diagnosis, very few studies analyzed specific cell types separately. Furthermore, cohort mortality studies using SMR analysis are generally unable to estimate risk for specific cell types because data on specific cell types are not routinely collected for the calculation of mortality statistics in the general population. Consequently, analyses are conducted for tumors of different cell types grouped together into broad categories such as malignant, benign and unspecified brain tumors.

Case-control studies, on the other hand, can be used effectively to estimate risk associated with a specific cell type. However, even some case-control studies are limited in their ability to detect true associations between a hypothesized risk factor and brain cancer because of small sample sizes due to the relative rarity of any single type of brain cancer.

In any epidemiologic investigation, it is critical to separate exposed individuals from unexposed individuals for comparative purposes. However, data on individual exposure to specific workplace agents are not available in most occupational studies of brain cancer. In the absence of individual exposure measurements, indirect measures of exposure are used. A frequently used surrogate measure of cumulative exposure in occupational studies is duration of employment in the industry. Standardized mortality ratios which increase with increasing length of employment are frequently cited as evidence supporting a causal relationship between exposure and disease. However, because the mortality rates are standardized according to the underlying person-years distribution, SMRs calculated for different duration of employment strata are not directly comparable to each other. Additionally, a cumulative-exposure model may not always be the appropriate model to describe the exposure-disease relationship, if one exists.

The induction of cancer is believed to be a multistage process with at least two steps. The first step, initiation, occurs when exposure to a carcinogen induces neoplastic changes in the cell. A second step, promotion, occurs when neoplastic development increases in the cell or tissue that has been exposed to the initiating dose [Farber, 1981]. Thus, initiators are agents capable of inducing neoplastic changes in cells, while promoters are agents which encourage the continued proliferation of neoplastic cells. Complete carcinogens are agents which are both initiators and promoters. Recently, several studies have reported elevated risks of brain cancer among workers possibly exposed to electromagnetic fields [Speers et al., 1988; Mack et al., 1991; Preston-Martin et al., 1989;

Lin et al., 1985, Loomis and Savitz, 1989]. While electromagnetic fields have not produced tumors in animal studies, they have been linked with cell growth and replication. This raises additional questions as to whether environmental agents may act as promoters in the genesis of cancer.

Estimates of risk in epidemiologic studies must be interpreted carefully due to the possible presence of bias from potentially confounding variables. These are variables which, by definition, are associated with the exposure under study, are risk factors for the outcome (disease), and are differentially distributed across comparison groups. For example, the risk of gliomas increases with age. However, age may also be related to exposure, because those with the greatest cumulative exposure are generally older. Consequently, the effect of age on glioma risk must be controlled in the analysis. Several other time-dependent variables may potentially confound the relationship between occupational exposure and disease: these variables include interval since hire and duration of employment. Other potential confounding variables include socioeconomic status, race and gender. Although lifestyle factors such as tobacco and alcohol use may also potentially confound the exposure-disease relationship, the effects of these variables on brain cancer risk have not been fully examined.

V.4. Diagnostic sensitivity bias

One of the most intriguing and currently debated issues is the *diagnostic sensitivity bias.* First invoked by Greenwald et al. [1981] as an explanation for the general excess of brain tumors discovered among Eastman Kodak decedents, the diagnostic sensitivity bias results from greater or more "sensitive" scrutiny of particular groups or populations, resulting in a higher proportion of cases coming to diagnostic attention. It is thought to occur most strongly for conditions or cancers which are difficult to diagnose, and which require sophisticated technology not generally available. Thus, Greenwald et al. [1981]

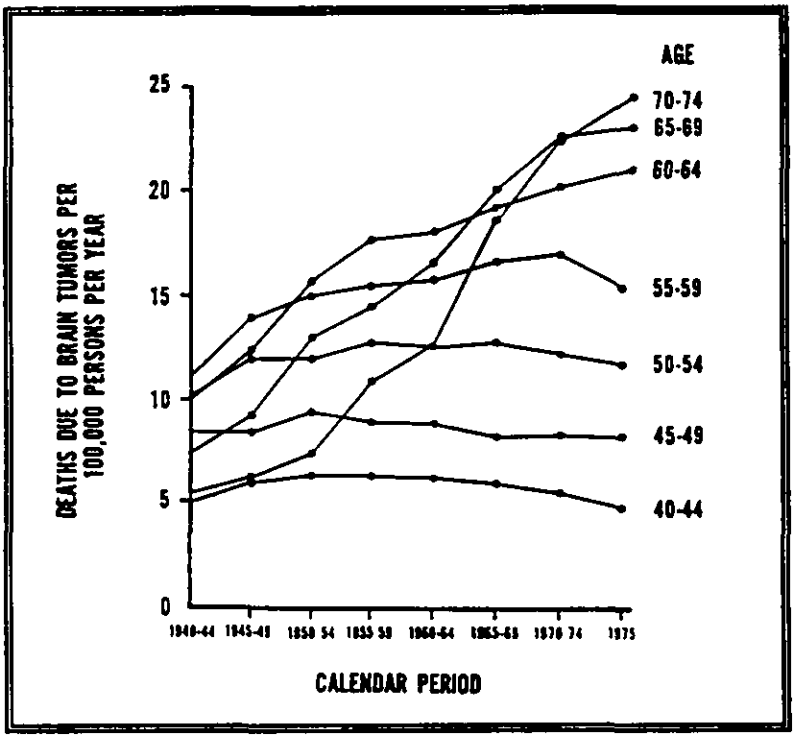
argue that the excess brain cancers among deceased employees, relative to the United States as a whole, resulted from better ascertainment among employees, due to their access to first-rate medical diagnostic technology offered by the company. Their study (reviewed above) showed a higher prevalence of medical tests and interventions among employees than in the State of New York. The prevalence was more comparable to that of Rochester, Minnesota, home of the famous Mayo Clinic [Greenwald et al., 1981]. Theoretically, such a bias is intuitive and attractive; however, there is also conflicting or contradictory evidence.

On a broader scale, brain tumor incidence in the United States and other industrialized nations has been increasing for several decades, with the most striking increases occurring among those over 55 years of age. Modan et al. [1992] show that over the period 1968-1988, the increase in incidence of brain tumors among those 65-74 years of age was about 50%, for those 75-84 there was a 300% increase, and for those over 85, there has been more than an 800% increase. They attribute this observation to changing patterns of diagnosing tumors in the elderly - largely related to changing attitudes toward medical care of the elderly - and introduction of support programs such as Medicare that facilitate access to the diagnostic technologies by the elderly [Modan et al., 1992].

Mao and Desmeules, however, argue that this interpretation is too extreme, citing their own investigation in which they demonstrated that only about 20% of the brain tumors diagnosed among the elderly in Canada were attributable to these diagnostic improvements [Mao and Desmeules, 1993, Desmeules et al., 1992]. Further, they note that the increases in rates have been gradual and constant over several decades; that increases in glioblastomas have been equal to or greater than other histologic types (and due to their severity, would not be dependent on sensitive diagnostic techniques); that prevalence of diagnostic procedures and incidence of related conditions are expected to

be correlated (i.e., diagnostic procedures are required for certain conditions, which might be increasing in incidence); and finally, that Canada has had support programs for decades, and therefore full access to technological developments, yet observe parallel patterns of brain tumor occurrence [Mao and Desmeules, 1993].

Waxweiler et al. [1983] presented a graph of brain tumor mortality rates between 1940 and 1975, a period which mostly predates the introduction of computerized tomography and other diagnostic techniques (see figure below):



Here it can be seen that the increasing mortality rates, presumably paralleling incidence rates, begin as early as 1940. This increase could not be due to technology only introduced since the 1970s. For ages 40 through 54, there is virtually no increase over this time period, not even for the last decade represented, when a diagnostic-related bias would be most likely to appear.

Diagnostic sensitivity bias was cited as an important issue in the interpretation of a brain cancer excess detected in an industry-wide cohort mortality study of vinyl chloride workers. Wong et al. [1991] reported a statistically significant SMR of 180 for brain cancer among the vinyl chloride workers, verifying an apparent excess of brain cancer observed in a previous study of the same cohort. In a letter to the editor, Shah suggested that a diagnostic sensitivity bias may possibly explain the reported results [Shah, 1993]. In their reply, Wong and Whorton concurred that a diagnostic sensitivity bias might have influenced the results, but suggested that the more important issue is whether exposure to vinyl chloride is causally related to brain cancer [Wong and Whorton, 1993]. They cited a detailed analysis performed on excesses of both liver and brain cancer detected in this cohort in the previous analysis in which the investigators were able to demonstrate a statistically significant association with vinyl chloride exposure for liver cancer, but not for brain cancer [Wu et al., 1989]. However, Wu et al. report an excess of brain cancer (SMR=145) among vinyl chloride workers, although due to the reduced sample size the SMR was not statistically significant. For the follow-up period reported by Wong et al., 8 additional brain cancer deaths were reported (3.56 expected; SMR=225), and a statistically significant association with duration of exposure greater than 20 years was found [Wong et al., 1991].

Neither Shah's letter nor Wong and Whorton's reply cites the evidence arguing against a diagnostic sensitivity bias, most notably that summarized by Mao and Desmeules. A re-examination of the data from the Wong and Whorton study may clarify the issue. For example, since the study examined all causes of death, one might look for other causes of death which might behave similarly to brain cancer if a diagnostic sensitivity bias were operating. One such outcome might be cancer of the prostrate, which often was subject to diagnosis only if searched (as it might in a population with a high level of medical service

access and use). In the CMA study, mortality due to prostate cancer was observed as often as expected, using the United States rates as a referent [Wong et al., 1991].

No doubt there are situations in which some cases of brain cancer are detected only because of the availability of diagnostic technology, and these may contribute toward apparent clusters or excesses, especially when external referent groups are used in epidemiological studies. This assessment alone, however, neither supports nor refutes the possible and plausible association of brain cancers with occupational or environmental risk factors. If, as Desmeules et al. [1992] estimate, only 20% of the increase in incidence rates of brain tumors can be attributed to diagnostic sensitivity, a substantial increase remains to be explained. This will only occur if studies of adequate sample size are carefully conducted and fully analyzed and interpreted.

VI. INFORMATIONAL GAPS AND NEEDS

VI.1. Research needs

Despite the wealth of information on brain tumors, and the array of epidemiological and clinical studies in the published literature, understanding of the etiology of brain cancer remains poor. The epidemiological literature on brain cancer suggests that there is evidence of occupational risk factors, but this perspective is clouded by many methodological limitations. Clearly, more research is needed. However, more studies typical of most published to date will not provide the information necessary to improved understanding: in fact, these efforts are likely to lead to further uncertainty and confusion and subjective debates on interpretation.

What is badly needed is more research which has a reasonable probability of producing valid and useful results. First, this will require that the study sample sizes are adequately large to afford the statistical power necessary to detect modest levels of risk. Second, the brain tumor outcome studied should be narrowly defined and ascertained with a high degree of diagnostic accuracy. Since different histologic types of brain tumors are likely to have different etiologies, categories should not be combined (as they often are to increase sample size) to reduce misclassification and the deleterious effects it has on risk estimation. As a few studies have done, the brain tumor types should be limited in any new studies being developed at this time to gliomas [Musicco et al., 1988] or even simply astrocytomas [Thomas et al., 1987]. Third, much greater attention must be paid to the estimation of risk associated with specific factors, including exposure measures. This

will require information on individual study members, rather than crude indicators such as ever vs. never employed in an industry, or usual employment as recorded on death certificates. Until reasonable data are available on risk factors at an individual level, valid assessment is not possible. To reduce the range of possible risk factors which need to be considered, studies should focus on working populations within specific industries.

An industry-based case-control study, or a nested case-control ("nested" in that cases are defined as all cases identified as part of a cohort study, and controls are a random sample of cohort members) would be ideal. The case-control approach is highly efficient, in that it requires smaller total sample sizes (hundreds vs. thousands) and allows more detailed risk factor measurement, leading to enhanced ability to control for confounders. In contrast, cohort mortality studies using U.S. rates as a referent are limited to three factors which can be evaluated and controlled as possible confounding variables: age, sex and race/ethnic group. The case-control study by Musicco et al. [1988] perhaps represents one of the best studies on brain cancer published to date, and should serve as a benchmark for future studies. Research of lesser quality is unlikely to narrow any informational gaps.

VI.2. Data needs

In order for high-quality epidemiological studies to be feasible, certain data resources must be available. As in many occupational epidemiological studies, exposure data of adequate detail and validity are lacking, and often poor surrogate measures are invoked (such as job title, number of years employed in an industry, etc.). What is needed is a more complete characterization of workplace exposures, which includes individual as well as area measures of exposure. When these exposure assessments are combined with individual work histories and information about intervening changes in the manufacturing process, epidemiologists reconstructing exposure histories may then begin to rank, if not

quantify, individual exposure levels, reducing the amount of misclassification bias present (which tends to mask associations).

To identify appropriate cases with brain tumors, histological type of tumor needs to be identified for each potential case, as well as some indication of how the tumor was diagnosed or verified. Ideally, an industry-based brain tumor registry would facilitate the identification of astrocytic brain tumors (as well as other types) for research efforts, as well as enable the monitoring of trends regionally and over time. In many ways, the global registry of cases of angiosarcoma of the liver served a similar purpose, and demonstrated that such a registry was possible.

Provided that the data resources and the research support needed to conduct quality epidemiological studies become available, answers to some of the difficult questions surrounding brain tumor etiology are likely to be forthcoming.

BIBLIOGRAPHY

*Alexander V, Leffingwell SS, Lloyd JW, et al. Brain cancer in petrochemical workers: A case series report. American Journal of Industrial Medicine 1980;1:115-123.

Althouse R, Huff J, Tomatis L, et al. An evaluation of chemicals and industrial processes associated with cancer in humans based on human and animal data: IARC monographs 1-20. Cancer Research 1980;40:1-12.

*Austin SG, Schnatter AR. A case-control study of chemical exposures and brain tumors in petrochemical workers. Journal of Occupational Medicine 1983;25:313-320.

*Austin SG, Schnatter AR. A cohort mortality study of petrochemical workers. Journal of Occupational Medicine 1983;25:304-312.

Barnard RO. The pathology of brain tumors. In: Bleehan NM, ed. Tumours of the Brain. Springer-Verlag: Berlin, Germany, 1986.

Berens ME, Rutka JT, Rosenblum ML. Brain tumor epidemiology, growth, and invasion. Neurosurgery Clinics of North America 1990;1:1-18.

Bertazzi PA, Pesatori AC, Zocchetti C, et al. Mortality study of cancer risk among oil refinery workers. International Archives of Occupational and Environmental Health 1989;61:261-270.

*Bond GG, Cook RR, Wright PC, et al. A case-control study of brain tumor mortality at a Texas chemical plant. Journal of Occupational Medicine 1983;25:377-386.

*Boyle P, Maisonneuve P, Saracci R, et al. Is the increased incidence of primary malignant brain tumors in the elderly real? Journal of the National Cancer Institute 1990;82:1594-1596.

*Brownson RC, Reif JS, Chang JC, et al. An analysis of occupational risks for brain cancer. American Journal of Public Health 1990;80:169-172.

Burch JD, Craib KJP, Choi BCK, et al. An exploratory case-control study of brain tumors in adults. Journal of the National Cancer Institute 1987;78:601-609.

Burger PC, Green SB. Patient age, histologic features, and length of survival in patients with glioblastoma multiforme. Cancer 1987;59:1617-1625.

Codd MB, Kurland LT. Descriptive epidemiology of primary intracranial neoplasms. Progress in Experimental Tumor Research 1985;29:1-11.

Cooper WC. Epidemiologic study of vinyl chloride workers: Mortality through December 31, 1972. Environmental Health Perspectives 1981;41:101.

Cusimano MD. An update on the cellular and molecular biology of brain tumors. The Canadian Journal of Neurological Sciences 1989;16:22-27.

* *References marked with an asterisk (*) are provided in the Source Documents supplement*

Bibliography (continued)

Cutler SJ, Young JL. Third national cancer survey: incidence data. National Cancer Institute Monographs 1975: 41.

Daumas-Duport C, Scheithauer B, O'Fallon J, et al. Grading of astrocytomas: A simple and reproducible method. Cancer 1988,62:2152-2165.

*Davis DL, Ahlbom A, Hoel D, et al. Is brain cancer mortality increasing in industrial countries? American Journal of Industrial Medicine 1991;19:421-431.

*Desmeules M, Mikkelsen T, Mao Y. Increasing incidence of primary malignant brain tumors: Influence of diagnostic methods. Journal of the National Cancer Institute 1992;84:442-445.

Doll R. Effects of exposure to vinyl chloride. An assessment of the evidence. Scandinavian Journal of Work, Environment, and Health 1988;14:61-78.

Editorial. Is pathology dangerous to health? The Lancet 1992;339:277-278.

Enterline PE. Brain tumors in the chemical industry. Journal of Occupational Medicine 1983;25:321.

Farber E. Chemical carcinogenesis. New England Journal of Medicine 1981,305:1379-1389.

Garfinkel L, Sarokhan B. Trends in brain cancer tumor mortality and morbidity in the United States. Annals of the New York Academy of Sciences 1982;381.1-5.

*Greenwald P, Friedlander BR, Lawrence CE, et al. Diagnostic sensitivity bias - An epidemiologic explanation for an apparent brain tumor excess. Journal of Occupational Medicine 1981;23:690-694.

Greig NH, Ries LG, Yancik R, et al. Increasing annual incidence of primary malignant brain tumors in the eldery. Journal of the National Cancer Institute 1990;82:1621-1624.

Hall A, Harrington JM, Aw T-C. Mortality study of British pathologists. American Journal of Industrial Medicine 1991;20:83-89.

Helseth A, Langmark F, Mork SJ. Neoplasms of the central nervous system in Norway. II. Descriptive epidemiology of intracranial neoplasms 1955-1984. APMIS 1988;96:1066-1074.

Helseth A, Mork SJ. Neoplasms of the central nervous system in Norway. III. Epidemiological characteristics of intracranial gliomas according to histology. APMIS 1989,97:547-555.

James CD, Carlbom E, Dumanski JP, et al. Clonal genomic alterations in glioma malignancy stages. Cancer Research 1988;48:5546-5551.

* *References marked with an asterisk (*) are provided in the Source Documents supplement*

Bibliography (continued)

Jones B, Bleasdale C. Exposure to chemical and development of malignant disease (letter to the editor). The Lancet 1992;339:551-552.

*Jones RD. Epidemiology of brain tumors in man and their relationship with chemical agents. Fd Chem Toxic 1986;24:99-103.

Juutilainen J, Laara E, Pukkala E. Incidence of leukaemia and brain tumors in Finnish workers exposed to ELF magnetic fields. International Archives of Occupational and Environmental Health 1990;62:289-293.

Karrh BW, Pell S. Brain cancer in the Du Pont Company. Annals of the New York Academy of Sciences 1982;381:91-96.

Kernohan JW, Mabon RF, Svien JH, et al. A simplified classification of the gliomas. Mayo Clinical Proceedings 1949;24:71-74.

Kessler E, Brandt-Rauf PW. Occupational cancers of the brain and bone. Occupational Medicine: State of the Art Reviews 1987;2:155-163.

Kleinhues P, Bigner DD. Tumors of the nervous system. In: Davison AN, Thompson RH, eds. Molecular Basis of Neuropathology. Arnold Co., London 1981;87-96.

Kurland LT, Schoenberg BS, Annegers JF, et al. The incidence of primary intracranial neoplasms in Rochester, Minnesota, 1935-1977. Annals of the New York Academy of Sciences 1982;381:6-16.

Lantos PL. Development of nitrosourea-induced brain tumours - with a special note on changes occurring during latency. Fd Chem Toxic 1986;24:121-127.

Larson E. The epidemiology of primary brain tumors. Journal of Neurosurgical Nursing 1980;12:121-127.

*Leffingwell SS, Waxweiler R, Alexander V, et al. Case-control study of gliomas of the brain among workers employed by a Texas City, Texas chemical plant. Neuroepidemiology 1983;2:179-195.

*Lin RS, Dischinger PC, Conde J, et al. Occupational exposure to electromagnetic fields and the occurence of brain tumors. An analysis of possible associations. Journal of Occupational Medicine 1985;27:413-419.

Loomis DP, Savitz DA. Mortality from brain cancer and leukaemia among electrical workers. British Journal of Industrial Medicme 1990;47:633-638.

Lovaste MG, Ferrari G, Rossi G. Epidemiology of primary intracranial neoplasms. Experiment in the province of Trento (Italy), 1977-1984. Neuroepidemiology 1986;5:220-232.

* *References marked with an asterisk (*) are provided in the Source Documents supplement*

Bibliography (continued)

*Mack W, Preston-Martin S, Peters JM. Astrocytoma risk related to job exposure to electric and magnetic fields. Bioelectromagnetics 1991;12:57-66.

Maltoni C, Ciliberti A, Carretti D. Experimental contributions in identifying brain potential carcinogens in the petrochemical industry. Annals of the New York Academy of Science 1982;381:216-249.

*Mao Y, Desmeules M. Re: "Increased mortality from brain tumors: A combined outcome of diagnostic technology and change of attitude toward elderly" (letter to the editor). American Journal of Epidemiology 1993;137:1035-1036.

McLaughlin JK, Malker HSR, Blot WJ, et al. Occupational risks for intracranial gliomas in Sweden. Journal of the National Cancer Institute 1987;78:253-257.

Mills PK, Preston-Martin S, Annegers JF, et al. Risk factors for tumors of the brain and cranial meninges in seventh-day adventists. Neuroepidemiology 1989;8:266-275.

*Modan B, Wagener DK, Feldman JJ, et al. Increased mortality from brain tumors: A combined outcome of diagnostic technology and change of attitude toward the elderly. American Journal of Epidemiology 1992;135:1349-57.

*Modan B, Wagener DK, Feldman JJ, et al. Re: "Increased mortality from brain tumors: A combined outcome of diagnostic technology and change of attitude toward elderly" Authors Reply (letter to the editor). American Journal of Epidemiology 1993;137:1036-1037.

*Modan B, Wagener DK, Feldman JJ, et al. Re: "Increased mortality from brain tumors: A combined outcome of diagnostic technology and change of attitude toward elderly" Authors Reply (letter to the editor). American Journal of Epidemiology 1993;138:552.

Morantz RA, Neuberger JS, Baker LH, et al. Epidemiological findings in a brain-tumor cluster in Western Missouri. Journal of Neurosurgery 1985;62:856-860.

*Munasinghe RL, Morris RD. Re: "Increased mortality from brain tumors: A combined outcome of diagnostic technology and change of attitude toward elderly" (letter to the editor). American Journal of Epidemiology 1993;138:551-552.

*Musicco M, Sant M, Molinari S, et al. A case-control study of brain gliomas and occupational exposure to chemical carcinogens: The risk to farmers. American Journal of Epidemiology 1988;128:778-785.

National Cancer Institute. 1987 Annual Cancer Statistics Review, Including Cancer Trends: 1950 - 1985. Bethesda, Maryland: National Instiutes of Health, 1988.

Preston-Martin S, Henderson BE, Peters JM. Descriptive epidemiology of central nervous system neoplasms in Los Angeles County. Annals of the New York Academy of Sciences 1982;381:202-208.

* *References marked with an asterisk (*) are provided in the Source Documents supplement*

Bibliography (continued)

Preston-Martin S, Mack W, Henderson BE. Risk factors for gliomas and meningiomas in males in Los Angeles county. Cancer Research 1989;49:6137-6143.

Preston-Martin S, Paganini-Hill A, Henderson BE, et al. Case-control study of intracranial meningiomas in women in Los Angeles county, California. Journal of the National Cancer Institute 1980;65:67-73.

Preston-Martin S, Yu MC, Henderson BE, et al. Risk factors for meningiomas in men in Los Angeles county. Journal of the National Cancer Institute 1983;70:863-866.

*Ransohoff J, Koslow M, Cooper PR. Cancer of the central nervous system and pituitary. American Cancer Society Textbook of Clinical Onocology 329-337.

*Reeve GR, Bond GG, Lloyd JW, et al. An investigation of brain tumors among chemical plant employees using a sample-based cohort method. Journal of Occupational Medicine 1983;25:387-393.

Reif JS, Pearce N, Fraser J. Occupational risks for brain cancer: A New Zealand cancer registry-based study. Journal of Occupational Medicine 1989;31:863-867.

Ringerz N. Grading of gliomas. Acta Pathol Microbiol Scand 1950;27:51-64

Ronco G, Costa G, Lynge E. Cancer risk among Danish and Italian farmers. British Journal of Industrial Medicine 1992;49:220-225.

Rutty GN, Honavar M, Doshi B. Malignant glioma in laboratory workers. Journal of Clinical Pathology 1991;44:868-869.

Ryan P, Lee MW, North JB, et al. Risk factors for tumors of the brain and meninges: Results from the Adelaide adult brain tumor study. International Journal of Cancer 1992;51:20-27.

Sasco AJ. Cancer risk in laboratory workers (letter to the editor). The Lancet 1992;339:684.

Schoenberg BS. Nervous System. In: Schottenfeld D, Fraumeni JF, eds. Cancer Epidemiology and Prevention. WB Saunders Company: Philadelphia, PA, 1982; 968-983.

Schoenberg BS, Christine BW, Whisnant JP. The descriptive epidemiology of primary intracranial neoplasms: The Connecticut experience. American Journal of Epidemiology 1976;104:499-510.

*Shah HC. Diagnostic bias in occupational epidemiologic studies (letter to the editor). American Journal of Industrial Medicine 1993;24:2490250.

* *References marked with an asterisk (*) are provided in the Source Documents supplement*

Bibliography (continued)

*Simonato L, L'Abbe KA, Andersen A, et al. A collaborative study of cancer incidence and mortality among vinyl chloride workers. Scandinavian Journal of Work, Environment, and Health 1991;17:159-169.

*Speers MA, Dobbins JG, Miller VS. Occupational exposures and brain cancer mortailty: A preliminary study of East Texas residents. American Journal of Industrial Medicine 1988,13:629-638.

Swenberg JA. Chemical- and Virus-Induced brain tumors. National Cancer Institute Mongraph 1977;46:3-10.

Tabershaw JR, Gaffey WR. Mortality study of workers in the manufacture of vinyl chloride and its polymers. Journal of Occupational Medicine 1974;16:509.

*Teta MJ, Ott MG, Schnatter AR. An update of mortality due to brain neoplasms and other causes among employees of a petrochemical facility. Journal of Occupational Medicine 1991;33:45-51.

*Thomas TL, Frontham ETH, Norman SA, et al. Occupational risk factors for brain tumors. Scandinavian Journal of Work, Environment, and Health 1986;12:121-127.

*Thomas TL, Stewart PA, Stemhagen A, et al. Risk of astrocytic brain tumors associated with occupational chemical exposures. Scandinavian Journal of Work, Environment, and Health 1987;13:417-423.

*Thomas TL, Waxweiler RJ. Brain tumors and occupational risk factors. A review. Scandinavian Journal of Work, Environment, and Health 1986;12:1-15.

Tornqvist S, Knave B, Ahlbom A, et al. Incidence of leukaemia and brain tumours in some "electrical occupations". British Journal of Industrial Medicine 1991;48:597-603.

*Velema JP, Percy CL. Age curves of central nervous system tumor incidence in adults: Variation of shape by histologic type. Journal of the National Cancer Institute 1987;79:623-629.

Walker AE, Robins M, Wemfeld FD. Epidemiology of brain tumors: The national survey of intracranial neoplasms. Neurology 1985;35:219-226.

*Waxweiler RJ, Alexander V, Leffingwell SS, et al. Mortality from brain tumor and other causes in a cohort of petrochemical workers. Journal of the National Cancer Institute 1983;70:75-81.

*Weller RO. Brain tumors in man. Food and Chemical Toxicology 1986;24:91-98.

Weller RO. The immunopathology of brain tumors. In: Bleehan NM, ed. Tumours of the Brain. Springer-Verlag: Berlin, 1986.

* *References marked with an asterisk (*) are provided in the Source Documents supplement*

Bibliography (continued)

Wingren G, Axelson O. Cluster of brain cancers spuriously suggesting occupational risk among glassworkers. Scandinavian Journal of Work, Environment, and Health 1992;18:85-89.

*Wong O, Whorton MD. Diagnostic bias in occupational epidemiologic studies: An example based on the Vinyl Chloride literature (letter to the editor). American Journal of Industrial Medicine 1993;24:251-256.

*Wong O, Whorton MD, Foliart DE, Ragland D. An industry-wide epidemiologic study of vinyl chloride workers, 1942-1982. American Journal of Industrial Medicine 1991;20:317-334.

Wu W, Steenland K, Brown D, Wells V, Jones J, Schulte P, Halperin W. Cohort and case-control analyses of workers exposed to vinyl chloride: An update. Journal of Occupational Medicine 1989;31:518-523.

*Yates AJ. An overview of principles for classifying brain tumors. Molecular and Chemical Neuropathology 1992;17:103-120.

Young JL, Percy CL, Asire AJ. Surveillance, Epidemiology and End Results: Incidence and mortality data: 1973-77. National Cancer Institute Monographs 1981:57.

Zülch KJ. Brain Tumors: Their Biology and Pathology. Third revision. Springer-Verlag: Berlin, Germany, 1986.

* *References marked with an asterisk (*) are provided in the Source Documents supplement*