INVESTIGATION OF AN APPARENT INCREASED PREVALENCE OF BRAIN TUMORS IN A U. S. PETROCHEMICAL PLANT

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Twenty primary brain cancer deaths have occurred among workers at one U. S. petrochemical plant in Texas. A joint investigation by federal occupational health scientists with company cooperation is nearing completion. Results from this case-series and neuropathological confirmation of the observed cases are provided in this report. These studies are part of a more complete occupational health evaluation of the plant which includes a cohort mortality study and a brain tumor case–control study. We believe this group of 20 brain tumor deaths is the largest single series of presumably occupationally related brain cancers reported to date in the medical literature.

In November 1978, the Occupational Safety and Health Administration (OSHA), the federal occupational health enforcement agency of the U.S. Department of Labor, received an employee complaint that work-related chemical exposures might have caused his recently diagnosed brain cancer as well as brain tumors in fellow workers.

OSHA's office in Clear Lake City, Texas began an investigation of brain cancer mortality at the employee's worksite, a moderate-sized petrochemical production facility in Texas City, located in Galveston County south of Houston. Workers, surviving family members, union officials, local physicans and hospital staff, Texas state health officials and company personnel were interviewed. Four primary brain tumor deaths were discovered among former employees in this way. It is ironic that the worker who filed the original complaint with OSHA was found to have a metastatic carcinoma to the brain, and is not counted among the cases. The plant physician subsequently reviewed death information maintained by the company medical department, primarily covering workers who died while employed as well as those who, by virtue of 15 years of company service, were eligible for death benefits. Ten deaths from primary brain cancer were thus identified, including the four previously found. OSHA then requested technical assistance from the National Institute for Occupational Safety and Health (NIOSH), its companion research agency in the U.S. Department of Health and Human Services.

In February 1979, OSHA, NIOSH, and the company established a collaborative study plan to investigate the apparent excess of brain cancers. A historical prospective cohort mortality study was begun to determine more exactly the risk for brain cancer and the existence of any other unusual mortality patterns among plant employees. Also included is a case–control study of all primary brain cancer cases to

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ascertain whether a particular job or chemical exposure at the plant is associated with an excess risk of brain cancer. Finally, a reference neuropathology laboratory agreed to examine autopsy and surgical pathology specimens to provide histologic confirmation of the cause of death in each case where suitable material could be obtained. Reports from the cohort mortality study and the case–control study are in preparation, and the results of the pathology confirmation are included in this paper.

To assist in the early ascertainment of the total number of brain tumors at the plant, an experimental case-finding technique was used, details of which have been previously published.[1] Use of this method with further investigation of company records revealed the current total of 20 cases which are the subject of this report. All those affected were deceased by March 1980.

Work history data for the 20 cases are provided in TABLE 1. The average age at death was 55; the youngest died at age 30, and there were six deaths after age 60. Of the deaths, 45% occurred between ages 50 and 59. The pattern of age at death observed in this brain tumor series does not differ substantially from the patterns previously reported for adults of employment age in other series.[2–4]

Total length of employment at the plant ranged from 1 month to slightly more than 35 years, with a median value of 19 years. Two cases had short periods of employment, 38 and 29 days, respectively. Median length of employment excluding these two cases was 21 years. The interval from first employment to death, which provides an estimate of latency, varied from as few as 3 1/2 years to nearly 36 years, with a median of 24 years.

TABLE 1

WORK HISTORY DATA FOR 20 PRIMARY BRAIN CANCER CASES IN A TEXAS PETROCHEMICAL PLANT

Case	Date of Hire	Date of Death	Age at Death	Length of Employment (years-months)	Job Title	Department
1	12/16/40	05/15/64	51	3-6	Operator	Production
2	05/18/41	02/19/66	56	24-8	Operator	Production
3	07/29/41	05/18/76	66	31-8	Foreman	Maintenance
4	11/30/41	12/13/65	55	20-4	Operator	Production
5	07/09/44	10/28/79	59	35-0	Boilermaker	Structural Shop
6	09/18/44	05/21/74	55	0-1	Operator	Production
7	09/18/46	03/07/79	55	32-3	Laborer/Oiler	Maintenance
8	09/26/46	03/22/73	63	26-6	Operator	Production
9	09/21/48	07/02/75	49	2-1	Pipefitter	Maintenance
10	03/02/49	06/05/71	61	22-3	Operator	Production
11	01/25/50	01/13/68	66	16-7	Equip. Operator	Maintenance
12	10/19/50	05/14/74	59	17-1	Operator	Energy Systems
13	10/23/50	02/18/80	57	28-10	Operator	Production
14	09/19/51	01/08/74	52	22-3	Machinist	Machine Shop
15	04/27/53	10/03/56	33	0-1	Machinist	Maintenance
16	08/17/53	04/05/62	30	8-7	Weighmaster	Shipping
17	08/21/53	05/05/71	44	17-3	Operator	Production
18	10/30/53	12/21/78	49	24-8	Weighmaster	Shipping
19	10/08/45	10/15/70	70	2-4	Painter	Maintenance
20	03/12/47	06/28/74	61	10-0	Laborer	Maintenance

No particular trend or clustering by hire date among the cases has been identified as compared to the general plant population. One case was hired in late 1940 as part of a small plant start-up crew. Three more were hired in 1941 during the first year of plant operation, and the others at fairly regular intervals until the last group of four started work during 1953. The first death occurred in 1956, followed by five others during the 1960s. Fourteen of the deaths occurred after 1970, three of them during 1979–1980. No established pattern is revealed by this distribution of the years of death, but there is no evidence that the rate of appearance of cases is declining.

The plant has a current workforce of slightly more than 2,200, including nearly 1,500 hourly employees. The average age is 44, and approximately 1,050 current employees have 25 or more years of company service. Since the plant began operation in 1941, there have been a total of 8,850 employees. These include 6,802 white males, 884 black males, 1,083 white females, and 81 black females as of April, 1979. The distribution by county of residence for current workers in provided in TABLE 2. The plant also engages a temporary independent contractor workforce of 100–250

TABLE 2

CURRENT PLANT WORKFORCE BY COUNTY OF RESIDENCE*

County of Residence	Type of Employee			
	Hourly	Salaried	Total	Percent
Galveston	1,389	609	1,998	90.0
Harris	44	110	154	66.9
Brazoria	41	15	56	2.5
Other	7	4	11	0.5
Total	1,481	738	2,219	100.0

* Data provided by company.

daily, mostly for construction and irregular maintenance jobs. Unfortunately, no employment records are available for this latter group and we have been unable to study their health status further.

Demographic and cause-of-death data from death certificates, and cause-of-death data from medical records are provided in TABLE 3. All cases occurred among male employees, 18 whites and 2 blacks. The mortality rate for primary brain cancer in Texas among black males is about one-half that for white males.[5] However, no conclusions can be drawn regarding the racial distribution of cases, since it appears that a relatively small number of black employees worked at the plant until recent years.

All but one of the cases were native-born Americans; the lone exception was a Norwegian. The great majority of the cases were born in Texas, two were from Louisiana, and one each was from New Mexico, Arkansas, and Missouri. None of the U.S. states of origin has a particularly high risk for brain cancer compared to the U.S. national average.

Eighteen of the cases lived in Texas at the time of their death; 15 were Galveston County residents and the other 3 lived in Harris County. The possibility of

TABLE 3

DEATH CERTIFICATE AND MEDICAL RECORDS DATA FOR 20 PRIMARY BRAIN CANCER CASES IN A TEXAS PETROCHEMICAL PLANT

Case	Race, Sex	Residence	Place of Birth	Cause of Death	
				Death Certificate	Medical Records*
1	WM	Galveston	Texas	Carcinoma of Brain	Glioblastoma (MR)
2	WM	Galveston	Missouri	Malignant Brain Tumor	Meningioma (A)
3	WM	Harris	Texas	Brain Tumor	Glioblastoma (A)
4	WM	Galveston	Texas	Brain Tumor-Meningioma	Meningioma (MR)
5	WM	Galveston	Louisiana	Glioblastoma	Glioblastoma (SP)
6	WM	Galveston	Texas	Brain Tumor-Glial IV†	No Records Available
7	BM	Galveston	Texas	Glioblastoma	Glioblastoma (MR)
8	WM	Galveston	Texas	Glioblastoma	Glioblastoma (SP)
9	WM	Harris	Texas	Astrocytoma	Astrocytoma-Grade I (SP)
10	WM	Galveston	Texas	Malignant Glioma	Glioblastoma (MR)
11	WM	Galveston	New Mexico	Glioblastoma	Glioblastoma (A)
12	WM	Galveston	Norway	Glioblastoma	Glioblastoma (SP)
13	WM	Galveston	Texas	Glioma-Grade III	Astrocytoma-Grade IV† (MR)
14	WM	Galveston	Texas	Glioblastoma	Glioblastoma (A)
15	WM	Harris	Texas	Glioblastoma	No Records Available
16	WM	Galveston	Louisiana	Brain Tumor	Glioblastoma (A)
17	WM	Galveston	Texas	Malignant Glioma	Glioblastoma (SP)
18	WM	Galveston	Texas	Brain Tumor	Glioblastoma (A)
19	WM	Arkansas	Arkansas	Cerebral Carcinoma	Glioblastoma (SP)
20	BM	California	Texas	Meningeal Sarcoma	Meningeal Sarcoma (A)

* Source: MR, Medical Records; A, Autopsy; SP, Surgical Pathology.

† Astrocytoma Grade IV and Glial IV are equivalent terms for glioblastoma multiforme.

an environmental etiology related to Galveston County was considered. Data from the National Cancer Institute for brain cancer mortality rates for Galveston and Harris counties from 1950–1969 are in the mid-range for Texas county and U.S. state-wide values as shown in TABLE 4. Surveys made by the Texas State Department of Health for the years 1975 through 1978 show that the Galveston County annual brain cancer crude mortality rates were, respectively, 4.4, 4.2, 3.6, and 4.5 per 100,000. There is no evidence from these data that local environmental factors outside the plant are responsible for the apparent excess of brain cancer.

To obtain an initial estimate of the brain cancer risk, deaths among adult white

TABLE 4

BRAIN AND OTHER CNS CANCER MORTALITY, 1950–1969: AVERAGE ANNUAL AGE-ADJUSTED RATES PER 100,000*

Location	White Male	White Female	Black Male	Black Female
United States	4.4	2.9	2.3	1.5
Texas	4.3	2.9	1.9	1.5
Galveston County	4.5	2.9	2.5	2.1
Harris County	4.5	3.6	2.0	1.9

* The range of U.S. rates for white males for states with >10 deaths from 1950–1969 was 3.1–5.4. The range of Texas rates for white males for counties with >10 deaths from 1950–1969 was 2.3–10.8. Data from Mason & McKay.[5]

males in Galveston County were analyzed using the county-based list prepared for us by the M.D. Anderson Tumor Institute and described elsewhere.[1] A total of 47 primary brain cancer deaths occurred in the county from 1956 through 1977 among white males aged 20 through 64. Ten of these decedents were plant employees. To permit a rough comparison between the plant and overall county populations, information from the U.S. Census and the Health Services Administration was used.[6,7] In 1970 the Galveston County white male population aged 20 through 64 was 35,988. This number represents a conservative estimate of the adult white male county population during the period 1956 through 1977 since no allowance has been made for migration or for population growth after 1970. The white male population of employment age at risk in the plant from 1956 through 1977 is estimated as 3,700.* Thus, the plant population at risk represented somewhat less than 10.3% (3,700/35,988) of the county-wide adult white male population during the period 1956 through 1977. Yet during this same period, 10 of 47 brain tumor deaths among white male Galveston residents aged 20 through 64 occurred in plant employees, slightly more than 21% of the total. This suggests an approximate plant-wide risk about twice that of the county as a whole.

The underlying causes of death as recorded on the death certificates are listed in TABLE 3. Nine cases of glioblastoma multiforme were recorded directly on the

* This estimate is based on the following assumptions: 77% of the plant population have been white males; 90% lived in Galveston County; and except for 1,050 long-term employees (>25 years) turnover from 1941 through 1979 was roughly constant at 158 white males per year.

certificates. Further investigation of hospital and physician's records provided evidence that there were seven additional cases of glioblastoma multiforme among the total of 20. Preliminary medical evidence thus suggested that 80% (16/20) of the tumors were glioblastomas. Because this type of tumor usually accounts for 25%–50% of deaths in reported brain cancer series, this would indicate an excess of glioblastoma multiforme among these cases.[2–4, 8, 9]

The inherent difficulty in obtaining precise neuropathological diagnosis for cases of central nervous system malignancies is well recognized. Further, an additional possible source of error in epidemiological studies is the necessary reliance upon death certificate data. For these reasons careful review of all available medical records, autopsy reports, operative notes, and consultation with attending physicians was performed to the extent possible for each case to establish a best-evidence diagnosis and confirm the fact that each case represented a primary brain tumor. The Armed Forces Institute of Pathology (AFIP) Neuropathology Department agreed to review autopsy or surgical pathology slides and tissue blocks from all available cases in a blind fashion to establish the histologic diagnosis. We were able to obtain such material for 11 cases. In the other cases either no such material was ever prepared or the material had been lost or discarded in the past. The results of the AFIP review are presented in TABLE 5. Allowing for the slight differences in nomenclature for classifying glioblastoma multiforme, there were 10 exact matches in 11 cases. The sole exception was a surgical pathology specimen in which AFIP could not identify any tumor cells. On review of the case history it was found that the biopsy was obtained when the patient was *in extremis* and a final attempt was made to confirm the clinical diagnosis of malignant brain tumor.

The plant is a diversified petrochemical manufacturing facility with a large number of major product lines which over the years have included ethylene, butadiene, naptha, ethylene dichloride, diethyl sulfate, glycols, aldehydes, acetates, alco-

TABLE 5

NEUROPATHOLOGY CASE REVIEW

Case	Best-Evidence Diagnosis Death Certificate-Medical Records*	A.F.I.P. Pathology Review
2	Meningioma (A)	Meningioma
3	Glioblastoma Multiforme (A)	Glioblastoma Multiforme
5	Glioblastoma Multiforme (SP)	Glioblastoma Multiforme
6	Brain Tumor-Glial IV (DC)†	Glioblastoma Multiforme
9	Astrocytoma-Grade I (SP)‡	Astrocytoma-Grade II‡
10	Glioblastoma Multiforme (MR)	No Neoplasm
11	Glioblastoma Multiforme (A)	Astrocytoma-Grade III†
12	Glioblastoma Multiforme (SP)	Anaplastic Astrocytoma-III†
13	Astrocytoma-Grade IV (MR)†	Anaplastic Astrocytoma-III†
14	Glioblastoma Multiforme (A)	Glioblastoma Multiforme
18	Glioblastoma Multiforme (A)	Anaplastic Astrocytoma†

* Source: DC, Death Certificate; MR, Medical Records; A, Autopsy; SP, Surgical Pathology.

† Astrocytoma-Grades III and IV are generally considered highly aggressive anaplastic glial lesions and are equivalent to glioblastoma multiforme.

‡ Astrocytoma-Grades I and II are generally considered less aggressive glial lesions with lower malignant potential.

hols, amines, organic acids, and plastics and resins (polyethylene, vinyl chloride–vinyl acetate co-polymers, phenolformaldehyde resin). Review of the plant's chemical inventory reveals the presence of at least 10 recognized or suspect carcinogens in qunatities greater than one million pounds per year as raw materials, reaction byproducts, or manufactured compounds. These compounds include benzene, diethyl sulfate, dioxane, ethylene dichloride, hydrazine, isopropyl oils, trichloroethane, trichloroethylene, vinyl chlorides, and vinylidene chloride.

Careful preliminary examination of the work histories of affected employees does not yet establish any common job title, department code, or chemical exposure. Eight of the men were chemical operators in production departments but they were spread throughout the plant, and worked on different chemical processes. Seven others were maintenance workers who may have had the opportunity for plant-wide exposures over the years. Two worked in the chemical shipping department as weighmasters with likely multiple exposures, and three worked in various construction trades. Detailed work histories for the cases are limited to employment by the company with two exceptions. Case 1 was a salaried employee at a nearby petrochemical plant from 1948–1964, and Case 6 worked as a pipefitter from 1952–1974 in the same nearby plant. The extensive examination of work histories undertaken in the case–control study offers the best opportunity to establish a connection between a particular chemical exposure or type of work and an excess risk of brain cancer.

Experimental induction of brain cancer has been achieved with a number of viruses[10–15] and chemicals. Investigation of chemically induced brain cancer in animals has been the subject of experimental study for some 40 years. Much of the early work involved direct pellet implantation and later transplacental carcinogenesis, but more recently standard bioassay methods have been successful as well. TABLE 6 provides a listing of 26 chemicals which have been reported to cause brain tumors in experimental animals.

A detailed computer-assisted literature search was undertaken to identify previous epidemiologic investigations of brain cancer and occupation. This was supplemented by a review of a number of occupational cancer studies where brain cancer was not the original focus of investigation, but a possible association was

TABLE 6

EXPERIMENTAL BRAIN CARCINOGENS*

2-Acetylaminofluorene (16)	Elaiomycin (24)
Acrylonitrile (17)	Ethyl methanesulphonate (25)
1-Aryl-3,3-dialkyltriazenes (18)	Ethylnitrosobiuret† (19)
Azoethane† (19)	Ethylnitrosourea* (26)
Azoxyethane† (19)	1-Methyl-2-benzyl-hydrazine† (18)
Azoxymethane (18)	Methyl methanesulphonate (27)
Butylnitrosourea (20)	Methylnitrosourea† (28)
Cycasin (21)	Methylnitrosourethane (intraplacental) (29)
1,2-Diethylhydrazine (18)	Procarbazine† (26)
Diethylnitrosamine† (18)	Propane sultone (30)
Diethyl sulfate† (22)	Propylene imine (30)
Dimethylbenzanthracene† (23)	Pyrrolizidine alkaloids (31)
Dimethyl sulfate† (22)	Vinyl chloride (32)

* Numbers in paretheses indicate reference sources.

† Transplacental carcinogenesis.

TABLE 7

EPIDEMIOLOGICAL STUDIES:
CLUES TO HUMAN BRAIN CANCER ETIOLOGY*

Aluminum workers (33,34)	Machinists (45)
Anti-Convulsant use (35–37)	Oil refinery workers (46)
Chemists (38,39)	Petrochemical workers (47)
Farm/Rural residents (4)	Pharmaceutical workers (48)
Geographic clustering	Rubber workers (49–51)
Kentucky (40,41), Rhone Valley (42)	
Halomethanes in drinking water (43)	Toxoplasmosis (52)
Lead smelter workers (44)	Veterinarians (53)
Vinyl chloride workers (54–57)	

* Numbers in parentheses indicate reference sources.

uncovered. Results of this review are found in TABLE 7. It is important to note that in most cases the evidence is not conclusive, as the studies suffer, to a greater or lesser degree, from the all-too-frequent epidemiologic difficulties of limited numbers of cases and/or use of Proportionate Mortality Ratio (PMR) methodology. In several instances the authors did not specifically comment on the data in the report indicating an elevated brain cancer risk, or they commented that an apparent excess risk was present but no occupational etiology was evident. In one particular case, the author specifically rejected the implications of his own data.[35, 36] Nevertheless, review of the studies offers several intriguing leads to the further study of occupationally related brain tumors.

Mortality studies using either Standardized Mortality Ratio (SMR) or Proportionate Mortality Ratio (PMR) analysis have revealed an excess brain cancer risk among rubber workers, pharmaceutical workers, vinyl chloride workers, chemists, and petrochemical and oil-refinery workers—all occupational groups with significant potential chemical exposures. In addition, an elevated risk has been observed among veterinarians, machinists, lead smelter workers, and aluminum reduction plant workers who may all have opportunity for chemical exposures on the job. Data from studies of anticonvulsant medication users also suggest an increased risk, though the presence of pre-existing neurological disease as a confounding factor in the etiology of brain tumors in this group cannot be entirely ruled out.

No specific causative agents have been clearly identified in these studies, with the exception of vinyl chloride. In at least four separate investigations a consistent association of vinyl chloride exposure and increased brain cancer risk has been found.[54–57]

A cross-comparison of the large volume of compounds in the plant's chemical inventory, the results of experimental studies in animals, and the available epidemiologic data shows that vinyl chloride and diethyl sulfate are potential suspect agents which may be responsible for the unusual occurrence of brain cancer at this plant. Based on our prior knowledge of the results of animal studies and exposure effects in humans, and its presence in the work environment of this plant under poorly controlled conditions in the past, vinyl chloride must be the first agent investigated. To date, however, examination of the detailed work histories of the 20 cases does not support a significant positive association with vinyl chloride exposure, and other chemicals must therefore be very carefully evaluated.

All of the information available indicates that finding 20 brain tumors in this

plant population strictly by chance is unlikely. There is no good evidence to implicate nonplant, general environmental factors as the cause of a brain cancer excess. We believe these tumors are the likely result of occupational chemical exposures. It is necessary to complete the most thorough possible investigation of this situation, since a previously unsuspected chemical exposure may be responsible for this striking appearance of brain cancer among petrochemical workers.

References

1. Alexander, V., S. S. Leffingwell, J. W. Lloyd, R. J. Waxweiler & R. L. Miller. 1980. Brain cancer in petrochemical workers: A case series report. Am. J. Ind. Med. **1**:115–123.
2. Fan, K. J., J. Kovi & K. M. Earle. 1977. The ethnic distribution of primary central nervous system tumors: AFIP, 1958 to 1970. J. Neuropathol. Exp. Neurol. **36**:41–49.
3. Schoenberg, B. S., B. W. Christine & J. P. Whisnant. 1976. The descriptive epidemiology of primary intracranial neoplasms: the Connecticut experience. Am. J. Epidemiol. **104**:499–510.
4. Choi, N. W., L. M. Schuman & W. H. Gullen. 1970. Epidemiology of primary central nervous system neoplasms. Am. J. Epidemiol. **91**:238–259.
5. Mason, T. J. & F. W. McKay. 1974. U.S. cancer mortality by county, 1950–1969. DHEW Publication no. [NIH] 74-615. National Cancer Institute, Bethesda, Md.
6. Texas Department of Health and the University of Texas System Cancer Center, M. D. Anderson Hospital and Tumor Institute. 1978. Impact of cancer on Texas. p. 99. Houston, Tex.
7. U.S. Bureau of the Census. 1973. County and City Data Book, 1972 (A statistical abstract supplement). p. 450. U.S. Government Printing Office, Washington, D.C.
8. Zimmerman, H. M. 1969. Brain tumors: Their incidence and classification in man and their experimental production. Ann. N.Y. Acad. Sci. **159**:337–359.
9. Percy, A. K., L. R. Elveback, H. Okazaki & L. T. Kurland. 1972. Neoplasms of the central nervous system. Neurology **22**:40–48.
10. Swenberg, J. A. 1977. Chemical and virus-induced brain tumors. Natl. Cancer Inst. Monogr. **46**:3–10.
11. Rubenstein, L. J. 1976. Current concepts in neuro-oncology. Adv. Neurol. **15**:1–25.
12. Ahlstrom, C. G., T. Olin & B. Smitterberg. 1974. Intracranial tumors induced in guinea pigs with Rous sarcoma virus. Acta Path. Microbiol. Scand. Section A **82**:326–336.
13. Bigner, D. D. & C. B. Wilson. 1977. Workshop on cancer of the brain. J. Neurosurg. **47**:923–932.
14. Ida, N., Y. Ikawa, K. Ogawa, M. Takada & H. Sugano. 1974. Cell culture from a rat brain tumor induced by intracerebral inoculation with murine sarcoma virus. J. Natl. Cancer Inst. **53**:431–447.
15. Yung, W. K., N. K. Blank & N. A. Vick. 1976. Glioblastoma. Neurology **26**:76–83.
16. Vasquez, L. 1945. Gliomas in a rat fed with 2-acetyl-aminofluorene. Nature **156**:296–297.
17. Maltoni, C., A. Ciliberti & V. DiMaio. 1977. Carcinogenicity bioassays on rats of acrylonitrile administered by inhalation and by ingestion. Med. Lav. **68**:401–411.
18. Druckrey, H. 1973. Specific carcinogenic and teratogenic effects of 'indirect' alkylating methyl and ethyl compounds, and their dependency on stages of ontogenic developments. Xenobiotica **3**:271–303.
19. Zulch, K. J. & H. D. Mennel. 1973. Recent results in new models of transplacental carcinogenesis in rats. In Transplacental Carcinogenesis. L. Tomatis, U. Mohr & W. Davis, Eds. pp. 29–44. IARC, Lyon, France.
20. Takizawa, S. & H. Nisihara. 1971. Induction of tumors in the brain, kidney, and other extra-mammary gland organs by a continuous oral administration of *N*-nitrosobutylurea in Wistar/Furth rats. Gann **62**:495–503.
21. Hirono, I., G. L. Laqueur & M. Spatz. 1978. Tumor induction in Fischer and Osborne-Mendel rats by a single adminstration of cycasin. J. Natl. Cancer Inst. **40**:1003–1010.

22. DRUCKREY, H., H. KRUSE, R. PREUSSMANN, S. IVANKOVIC & C. LANDSCHUTZ. 1970. Cancerogene alkylierende substanzen. III. Alkyl-halogenide, -sulfate, -sulfonate und ringgespannte heterocyclen. Z. Krebsforsch. **74**:241.
23. ALEXANDROV, V. A. 1976. Some results and prospects of transplacental carcinogenesis studies. Neoplasma **23**:285–299.
24. SCHOENTAL, R. 1969. Carcinogenic action of elaiomycin in rats. Nature **221**:765–766.
25. SWANN, P. F. & P. N. MAGEE. 1969. Induction of rat kidney tumours by ethyl methanesulphonate and nervous tissue tumours by methyl methanesulphonate and ethyl methanesulphonate. Nature **223**:947–949.
26. IVANKOVIC, S. 1973. Experimental prenatal carcinogenesis. *In* Transplacental Carcinogenesis. L. Tomatis, U. Mohr & W. Davis, Eds. pp. 92–99. IARC, Lyon, France.
27. MAGEE, P. N. 1973. Mechanisms of transplacental carcinogenesis by nitroso compounds. *In* Transplacental Carcinogenesis. L. Tomatis, U. Mohr & W. Davis, Eds. pp. 143–148. IARC, Lyon, France.
28. ALEXANDROV, V. A. 1969. [Transplacental blastomogenic action of *N*-nitroso methylurea on rat offspring]. Vopr. Onkol. **15**:55–61.
29. NAPALKOV, N. P. 1973. Some general considerations on the problem of transplacental carcinogenesis. *In* Transplacental Carcinogenesis. L. Tomatis, U. Mohr & W. Davis, Eds. pp. 1–13, IARC, Lyon, France.
30. ULLAND, B., M. FINKELSTEIN, E. K. WEISBURGER, J. M. RICE & J. H. WEISBURGER. 1971. Carcinogenicity of industrial chemicals propylene imine and propane sultone. Nature **230**:460–461.
31. SCHOENTAL, R. & J. B. CAVANAGH. 1972. Brain and spinal cord tumors in rats treated with pyrrolizidine alkaloids. J. Natl. Cancer. Inst. **49**:655–671.
32. MALTONI, C. 1976. Predictive value of carcinogenesis bioassays. Ann. N.Y. Acad. Sci. **271**:431–443.
33. MILHAM, S. 1976. Cancer mortality patterns associated with exposure to metals. Ann. N.Y. Acad. Sci. **271**:243–249.
34. MILHAM, S. 1979. Mortality in aluminum reduction plant workers. J. Occup. Med. **21**:475–480.
35. CLEMMESEN, J. 1974. Are anticonvulsants oncogenic? Lancet (1):705–707.
36. CLEMMESEN, J. & S. HJALGRIM-JENSEN. 1977. On the absence of carcinogenicity to man of phenobarital. Acta Pathol. Microbiol. Scand. (Suppl). **261**:38–50.
37. GOLD, E., L. GORDIS, J. TONASCIA & M. SZKLO. 1978. Increased risk of brain tumors in children exposed to barbiturates. J. Natl. Cancer. Inst. **61**:1031–1034.
38. OLIN, G. R. 1978. The hazards of a chemical laboratory environement—A study of the mortality in two cohorts of Swedish chemists. Am. Ind. Hyg. Assoc. J. **39**:557–562.
39. OLIN, G. R. & A. AHLBOM. 1980. The cancer mortality among Swedish chemists graduated during three decades. Environ. Res. **22**:154–161.
40. BROOKS, W. H. 1972. Geographic clustering of brain tumors in Kentucky. Cancer **30**:923–926.
41. CREAGAN, E. T. & J. F. FRAUMENI. 1973. Deaths from brain tumors in eastern Kentucky 1950–69. J. Natl. Cancer Inst. **51**:1717–1718.
42. TROUILLAS, P., G. MENAUD, G. DETHE, G. AIMARD & M. DEVIC. 1975. Etude epidemiologique des tumeurs primitives du nevraxe dans la region Rhone-Alpes. Rev. Neurol. **131**:691–708.
43. CANTOR, K. P., R. HOOVER, T. J. MASON & L. J. MCCABE. 1978. Associations of cancer mortality with halomethanes in drinking water. J. Natl. Cancer Inst. **61**:979–985.
44. COOPER, W. C. 1976. Cancer mortality patterns in the lead industry. Ann. N.Y. Acad. Sci. **271**:250–259.
45. DECOUFLE, P. 1978. Further analysis of cancer mortality patterns among workers exposed to cutting oil mists. J. Natl. Cancer Inst. **61**:1025–1030.
46. THERIAULT, G. & L. GOULET. 1979. A mortality study of oil refinery workers. J. Occup. Med. **21**:367–370.
47. THOMAS, T. L., P. DECOUFLE & R. MOURE-ERASO. 1980. Mortality among workers employed in petroleum refining and petrochemical plants. J. Occup. Med. **22**:97–103.
48. THOMAS, T. L. & P. DECOUFLE. 1979. MORTALITY among workers employed in the pharmaceutical industry: A preliminary investigation. J. Occup. Med. **21**:619–623.

49. MANCUSO, T. F., A. CIOCCO & A. A. EL-ATTAR. 1968. An epidemiological approach to the rubber industry. J. Occup. Med. **10**:213–232.
50. MCMICHAEL, A. J., R. SPIRTAS & L. L. KUPPER. 1974. An epidemiologic study of mortality within a cohort of rubber workers, 1964–72. J. Occup. Med. **16**:458–464.
51. MONSON, R. R. & L. J. FINE. 1978. Cancer mortality and morbidity among rubber workers. J. Natl. Cancer Inst. **61**:1047–1053.
52. SCHUMAN, L. M., N. W. CHOI & W. H. GULLEN. 1967. Relationship of central nervous system neoplasms to *Toxoplasma gondii* infection. Am. J. Public Health **57**:848–856.
53. BLAIR, A. & H. M. HAYES. 1980. Cancer and other causes of death among U.S. veterinarians, 1966–1977. Int. J. Cancer. **25**:181–185.
54. TABERSHAW, I. R. & W. R. GAFFEY. 1974. Mortality study of workers in the manufacture of vinyl chloride and its polymers. J. Occup. Med. **16**:509–518.
55. WAXWEILER, R. J., W. STRINGER, J. K. WAGONER & J. JONES. 1976. Neoplastic risk among workers exposed to vinyl chloride. Ann. N.Y. Acad. Sci. **271**:40–48.
56. MONSON, R. R. & J. M. PETERS. 1974. PROPORTIONAL mortality among vinyl chloride workers. Lancet (2):397–398.
57. BYREN, D., G. ENGHOLM, A. ENGLUND & P. WESTERHOLM. 1976. Mortality and cancer morbidity in a group of Swedish VCM and PVC production workers. Environ. Health Perspect **17**:167–170.