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SCHOOL OF MEDICINE
333 Cedar Street
Department of Internal Medicine
Occupational Medicine Program

February 8, 1983

Attorney Robert Carter
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Dear Mr. Carter:

At your request I have reviewed the records obtained by my colleagues and students in the Occupational Medicine Program regarding Messers Ozolins and Ardis who were evaluated in consultation in 1981. My role in this particular matter has been a somewhat unusual one for me and a somewhat complex one and I will try to elaborate it as I describe the presently available data base. Initial contact with Mr. Ozolins occurred in November of 1980 when his wife called the Occupational Medicine Program for information regarding a possible association between her husband's glioblastoma and his former work as a research organic chemist. To my knowledge she had been referred by a friend.

The basis of the consultation was really quite straight forward as it was related by the patient's wife. Her husband as well as 2 other research chemists with whom he had worked closely, a Dr. Ardis and a Dr. Karabinos had all, within a relatively short period of time, been diagnosed as having malignant glioblastoma multiforme. All 3 men had worked as research chemists in a single relatively small facility dating back to approximately 1960. Because of a spate of epidemiologic and toxicologic literature which had been appearing during the preceeding 12-24 months several members of my staff including Dr. Robins and a senior medical student, Carola Greengard proceeded to attempt to establish some detailed exposure information from Mrs. Ozolins and family members of his two co-workers in the explicit hope that this information could enhance the present state of knowledge available to us about this disease.

Prior to his death in late March of 1981 Ms. Greengard visited Mr. Ozolins on 4 occasions to exchange information. This culminated in the generation of the list of exposures to organic chemicals which you have provided me in your cover letter. In addition, members of my staff were in telephone communication with Mrs. Ardis on at least one occasion in an attempt to establish parallel exposure information. Further, Dr. Robins, during this period of time made contact on several occasions with Dr. Sorensen; then medical director of the Olin-Winchester facility, to assist in the elaboration of exposure data. At no time did I or any other members of my staff participate directly in the medical care of Mr. Ozolins nor did we have opportunity to meet family members of his co-workers.

Subsequent to Mr. Ozlins death and again premised on the distressing and striking coincidence of 3 cases of an unusual disease among co-workers in a small faciltiy coupled with the then active investigations going on in the area of environmental causes of this disease, I made contact with the new corporate medical director of the Olin Corporation to offer my assistance in the further investigation of this problem. Subsequently Dr. Robert Gilligan, Corporate Medical Director and I met on several occasions to exchange available information and to discuss some of the potential opportunities for further investigation of the problem. Later in the year I had the pleasure of meeting with Dr. Mark Hammill of Maryland, a consultant to the Olin Corporation to review with him plans for a broad-based retrospective cohort study of organic chemists in the research facility.

Since the end of 1981 my involvement with this matter has been limited to continuing contact with scientists working with the Olin Corporation to investigate this apparent epidemic. I remain unaware of any detailed data which has been generated from this work as yet nor of its conclusion. Since you have specifically requested of me an opinion regarding the likelihood that the causes of your clients were related to their work as organic chemists at the Olin Corporation, I will reiterate for you what I have said in many contexts including comments I made for the benefit of Mr. Ozlins' and Mr. Ardis' families upon their request, to Dr. Gilligan upon his, to Dr. Hammill and to yourself. Specifically, without the benefit of completion of the present study and without the benefit of the advances in our understanding of glioblastoma which I anticipate will be forthcoming within the next decade I must confess that on the face of it it appears very likely that a causal relationship exists between exposures to organic chemicals and subsequent development of glioblastoma as has occurred among these three research scientists at Olin. The basis for this opinion which I readily confess will require modification as more evidence comes forward is first, the known potential in the animal model for a wide variety of organic chemicals to induce this particular tumor type; second, the several studies alluded to earlier suggesting from an epidemiologic point view the clustering of glioblastoma among individuals exposed to a variety of organic chemicals including oil refinery workers, petro-chemical workers, vinyl chloride workers and organic chemists; and third, because with the benefit of both a biological and epidemiologically reasonable prior hypothesis the coincidence of 3 cases occurring in co-workers in a relatively small facility seems most unlikely on the face of it to have occurred by chance alone. Consistent with the state of the art, of course, I cannot name the specific individual chemical exposure which I believe is causal in these cases nor would it be fair to say that an association between work with organic chemicals and glioblastoma is an unequivocally established and proven scienfitic fact in 1983. Nonetheless I do believe that the weight of the presently available evidence favors a causal relationship in the cases in question and I have made this opinion known to all of the participating parties.

I do wish to reiterate that although I do understand the need for the legal proceedings to go on even in the face of incomplete information that my principal concern and role in this matter remains that of the scientist. It was to my own office that the clustering of cases in question was first reported. It was our office that, working with the family members and some of their former colleagues as well as scientists around the country assembled the exposure lists which you

have returned, and hopefully it will be our office which will be able to assist Olin scientists in furthering the state of our present understanding. Although your own immediate attentions are necessarily otherwise I hope you can appreciate the seriousness of my own role.

Sincerely yours,

Mark R. Cullen, M.D.
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MRC:mm

CC: Dr. Robert Gilligan

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February 3, 1983

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Dear Mr. Carter:

I have reviewed the medical records that you have sent me on Mr. Ozolins and Dr. Ard is. I also reviewed the very brief summary on Mr. Karabinos. There is no doubt that all three had malignant gliomas. Dr. Ard is and Mr. Ozolins both died of their gliomas. We do not have follow-up information on Mr. Karabinos. Your letter states that all three worked at the Olin Chemical Company, Mr. Ozolins and Dr. Ardeis in the 1950's, 1960's and 1970's at Olin in New Haven, and Mr. Karabinos in the 1950's and 1960's at Olin in New Haven. In another letter you wrote to Dr. Cullen, a copy of which you sent me, you state that Dr. Ardeis was in charge of a vinyl chloride plant in Massachusetts. I assume this was for the Olin Chemical Company.

Mr. Ozolins was diagnosed as having his malignant glioma on September 18, 1980, and he died on April 7, 1981. Mr. Karabinos had his malignant glioma diagnosed on January 26, 1977. Dr. Ard is, who died on December 8, 1980, had his malignant glioma diagnosed on March 17, 1980. Thus we see that all three patients developed malignant glioma approximately 25 to 30 years after their first exposure to chemicals at the Olin Company. You also gave me a list of chemicals that Mr. Ozolins and Dr. Ard is were exposed to. Dr. Ard is was exposed to vinyl chloride which is highly suspect as a cause of malignant gliomas in humans, and also he was exposed to acrylonitrile which has produced malignant gliomas in animals. Mr. Ozolins was exposed to bis chloromethyl ether and acrylonitrile, both known to produce malignant gliomas in animals. They were also exposed to many other chemicals.

The question as to whether the chemical exposures of these three men were the cause of their malignant gliomas is one that I will try to answer in the rest of this letter. I am not a biostatistician so I cannot give you numerical evidence to show that this cluster is significant statistically. I understand that Dr. James Robins will do the statistical work to test the hypothesis further.

The origin of malignant gliomas is from the normal glial cells of the brain. These cells serve as supporting cells for the neural elements of the brain. The major glial cells of the brain are the astrocytes which comprise the vast majority of the intraparenchymal cells of the brain. They function as supporting tissue for the neurons. There are also oligodendrocytes and ependymal cells which line the fluid-filled cavities of the central nervous system. In adults most glial tumors arise from the astrocytes and occur in the cerebral hemispheres.

Cell cultures of astrocytes from rats have been studied by a

number of investigators. In these c ll cultures, normal glial cells are grown. Malignant transformation of these cells in culture has been produced by adding carcinogens to these cultures. In addition, injection of carcinogens into the veins of mice and rats, as well as inhalation and oral ingestion of carcinogens in these animals have produced brain tumors. The latent period between giving these carcinogens and the appearance of the brain tumors has been about 200 days, a relatively long period in the life span of these animals. These latency periods of 200 days correspond to the proposed latency period of 20 to 40 years for human brain tumors. In other words, investigators who have found an association between chemical exposure and the later development of brain tumors in humans postulate a 20 to 40 year latent period before these tumors develop.

A number of chemical compounds have produced brain tumors in rats when given by the oral, nasal or intravenous route. Also brain tumors have appeared in the offspring of pregnant rats given these agents during pregnancy. These experimental methods have been used to determine what compounds are carcinogenic in rats. The brain tumors which occur in experimental animals, particularly the rat, resemble the brain tumors that are found in humans. Dr. Harry Zimmerman, over the last 30 years, has implanted carcinogens in various parts of the brain and has produced malignant gliomas resembling those of humans. In his experiments, the type of malignant glioma or glioma produced depended to a great extent on the area where the pellet was placed. The conclusion drawn from these experiments are that carcinogens can produce tumors in the brain in experimental animals, that these tumors arise from the normal glial cells, and that these tumors are produced in the same way that human tumors are produced by malignant transformation of glial cells.

It is now well known that carcinogens or cancer-producing chemicals can produce tumors in experimental animals. What evidence do we have that these chemicals can produce malignant tumors in the brains of humans? The first suggestion that exposure to chemicals could lead to brain tumors in humans was in 1949 when Dr. Thomas F. Mancuso suggested an association of malignant neoplasms of the brain and central nervous system with the rubber industry. In April 1982, a symposium was held at the New York Academy of Sciences, and a number of investigators presented their data concerning the relationship of the various chemical exposures to the development of brain tumors. Dr. Mancuso presented figures from rubber workers in Summit County, Ohio, and found an approximately double incidence of brain tumors in those working in the rubber industry. Reeve presented data from union employees at the Texas City, Texas refinery in which the incidence of brain cancers was increased. In Dow Chemical workers in Texas, Reeve found a 2½ times expected number of brain tumors. Alexander presented data from petrochemical plant in Texas City, Texas, in which there were about twice as many deaths as expected, and Thomas studied unionized employees in oil refineries in petrochemical plants in Texas and again found a slightly greater than twice the expected number of brain cancers. There were several studies performed by industry investigators that did not find increase in expected incidence of brain tumors in chemical and petroleum refinery workers. These papers were criticized in the conference for including workers in the industry who were not exposed to chemicals, possibly diluting out the chemically induced brain tumors. In the same meeting, Nicholson studied chemical and petrochemical engineers in Texas and

Louisiana. They found ten brain tumors in operating engineers in chemical plants as opposed to 3.12 expected. Englund, in Sweden, found rubber industry workers to have a slight but definite increase of brain tumors, while Olin, studying chemists in Sweden, found five brain tumors vs 1.2 expected.

Other studies have been published which indicate that rubber industry workers have an increased incidence of brain tumors and also agricultural workers exposed to chemicals have an increased incidence of brain tumors. In addition, Waxweiler studied employees exposed to vinyl chloride in four plants of the United States, and found three brain tumors vs 0.9 expected. The concensus of the conference was that the number of studies correlating exposure to chemicals in the chemical, petrochemical, oil refinery and rubber industries indicated that there was a real association between exposure to these chemicals and the development of brain tumors, particularly glioblastoma multiforme or malignant astrocytoma. These latter two terms are synonymous. Malignant astrocytomas are the same as glioblastoma multiforme.

Reviewing all the data on association between exposure to chemicals in humans and the animal data with carcinogen production of brain tumors in rats, it is my opinion that there is a strong probability that the brain tumors which developed in Mr. Ozolins, Dr. Ard is and Mr. Karobinos were related to the many chemicals that they were exposed to in their work for the Olin Chemical Company.

I hope that this information is sufficient for your purposes. If it is necessary, I could further amplify on the data obtained in the numerous studies published in the literature on the relationship between brain tumors and industrial exposure in the United States and Sweden. I could also go into greater details of the production and means of production of brain tumors in rats.

Sincerely yours,

Edward S. Greenwald, M.D.

ESG/mlk