

MEDICAL TOXICOLOGY CONSULTATION:

Male, deceased	Claim No.:
File No: 8895	Genex File:
Date: 7/15/97	SSN:
	DOI: Unknown

Medical toxicology consultation is requested by GPW of Insurance Carrier, concerning the above-captioned patient.

Provided on July 8, 1997 are the following medical records:

M.D., Cancer Therapy & Research Center.

M.D., University of Texas at Tyler.

M.D., Institute for Drug Development, Cancer Therapy and Research Center.

M.D., Medical Oncology, University of Texas Health Science Center at San Antonio.

Southwest Texas Methodist Hospital, San Antonio, and M.D.

San Antonio Metropolitan Health Department, Division of Occupational Health.

M.D., Texas Occupational Medicine Institute.

In-patient consultation by M.D., Infectious Disease.

Baptist Memorial Hospital, San Antonio.

Copy of death certificate.

The medical records cover an episode of ENT surgery, an episode of hernia repair, and finally the diagnosis of metastatic adenocarcinoma of undetermined origin around May of 1995. At that time, a large tumor mass was noted to be present in the abdomen with metastatic lesions to the brain and a mass in the ileopsoas muscle, described as containing areas of calcification.

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I have reviewed the consultations rendered by a number of physicians, several of whom support a relationship between bronchogenic carcinoma and the patient's employment as a firefighter. All opine the presence of an increased risk of lung cancer in firefighters and an absence of an identifiable alternate risk in this particular patient of a relatively young age, that a causal relationship between employment as a firefighter and occurrence of lung cancer is established to a degree of reasonable medical probability.

On the other hand, the problems brought out by MD of the Texas Occupational Medical Institute are the absence of support in the medical literature for a statistically significant increase in lung cancer among firefighters, the question of origin of the tumor being somewhat complicated because of the calcification present in the ileopsoas metastasis, if it were a metastasis; the absence of established definitive carcinogens in the firefighters' environment; and unknowns with regard to intensity, duration and nature of potential exposure (for example, to what extent was respiratory protection being use in the vicinity of a fire).

Review of the medical records reveals the tumor to have been metastatic and present in numerous organs at the time of its first identification in May, 1995, so it had been in its growth phase for a variable but prolonged period of time prior to the diagnosis. There is some mention of potential for asbestos exposure in the course of the patient's employment as a firefighter and, in my opinion, asbestos plays no possible role in this patient's tumor primarily because of relatively low intensity of exposure. Although exposure certainly may have occurred, it would have been far less than that sustained by career insulators with whom I am familiar, and in which population latency is closer to 20 or more years. Furthermore, the carcinogenic potential of asbestos in the absence of smoking cigarettes is far less than the carcinogenic potency of cigarettes in the absence of asbestos. None of these factors, in my opinion, establish asbestos as a contributing factor to this patient's neoplastic process.

If this was, in fact, a lung primary, the occurrence of a metastatic lesion in the ileopsoas muscle that contains calcification is really inconsistent. Also, a tumor which calcifies is extremely slow growing and so would have an exceptionally long latency.

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One of the more recent papers concerning risks among firefighters for cancer is "Occupational Mortality Among Firefighters: Assessing the Association," by Guidotti, where the conclusion finally is drawn with regard to cancer of the lung that there may be certain cases with unusual characteristics where causation might be considered and they describe the situation typical of this patient, i.e., relatively young firefighter without other obvious risk factors. This, however, does not establish a causation within reasonable medical probability. Even if a statistically significant increase in incidence of lung cancer among firefighters were to be established at, say, an increased risk in the order of 20 to 25%, still with regard to any individual case, this does not reach the strength of reasonable medical probability. The risk factor would have to be increased to over 2, at which point the probability of a case such as this patient being the result of his employment as a firefighter, other things taken into consideration, might well reach reasonable medical probability. Cancer at other sites is discussed but none of the other sites have any stronger association than that rather questionable association alleged to relate to cancer of the lung. A copy of this paper is attached as being a general review representative of the State of the Art which, in my opinion, fails to meet the reasonable medical probability standard with regard to causation of cancer in the current patient.

While there is no doubt that potential for exposure to substances known to be associated with induction of cancer occurs in the course of the occupational environment of firemen, nonetheless this risk has been ameliorated considerably in the last 20 years by more frequent and consistent use of respiratory protection when involved in a highly contaminated area.

While adenocarcinoma, either primary or metastatic to the lung, from an alternate primary source is a relatively rare event in a patient of this age, on the other hand it is an event which does occur in the general population absent exposure to any risk factors including firefighting. In reasonable medical probability, the strength of association of the adenocarcinoma manifest in this patient and his workplace fails to meet a test of reasonable medical probability.

Eric G. Comstock, M.D.

EGC/cw

cc:

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Attachment:

Guidotti TL. Occupational Mortality Among Firefighters:
Assessing the Association. J Occ Environ Med, Dec. 1995;
37(12):1348-1356.

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In response to the affidavits offered by Dr. Guidotti attributing, in reasonable medical probability, the lung cancer in the patient to his employment as a fireman, the following discussion demonstrates the relationship to be biologically implausible and fails to meet the certainty needed to reach reasonable medical probability.

The biology of cancer growth characteristics was set out clearly by Collins in his 1956 publication, "Observations on Growth Rates of Human Tumors." Tumors grow by doubling, starting with a single cell, and do not become clinically manifest until growth is sufficient to interfere with essential body functions or to be recognized by x-ray, body scans or palpation. The rate of growth of a cancer is determined by its doubling time. Doubling time is a function of the tumor type. Adenocarcinoma of the lung has a relatively long doubling time compared to most cancers. The doubling time of a tumor is determined by measurement of size over a period of time and has been determined for a spectrum of cancer types. Collins demonstrated that cancer cells must double 30 to 35 times to form a tumor mass of one to four centimeters in diameter. Once the doubling time of a tumor type is determined, it may be multiplied by 30 to 35 generations to determine the length of time that the tumor has been growing prior to clinical diagnosis. The mechanics of a protracted pre-clinical growth interval are illustrated in Figures 1 and 2 (see Collins, attached). Observations of metastases of various tumor types to the lung where growth is readily measured by serial x-rays are presented in Table 1. It is seen that doubling time varies from 11 days to 164 days. Thirty doubling times require 330 days for the fastest growing tumors to 13.4 years for the more slowly growing tumors. These data underestimate the growth of a primary lung tumor because spread of cancer through the blood to lodge in the lung is usually a clump of cells representing a number of generations occurring prior to lodging in the lungs. Adenocarcinomas arising as a primary tumor in the lung would have a latency longer than that demonstrated by Collins.

When seeking the causation of cancer, exposure must have occurred prior to the onset of malignant doubling. Consequently, any exposure to any substance, however potent its carcinogenic

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potential, is irrelevant if it occurs following the onset of the tumor growth phase.

Rothman and Poole, in "Causation and Causal Inference," Chapter 1 of Cancer Epidemiology and Prevention, 1996 (attached), explain the concept of latency as being the sum of two events -one, induction and two, growth. Consequently, to the growth time must be added an additional time required for interaction of the causative agent (chemical) to induce the transition from a cell which is under the control of natural restraints to a cell which has escaped control and initiated a phase of growth without restraint. It is the induction plus growth which accounts for a latency of 15 to 25 or more years for most chemical carcinogens. The carcinogens in cigarette smoke account for the dramatic increase in lung cancer incidence among smokers 50 to 69 years of age. Since most smokers started smoking in their teenage years, the latency exceeds 30 years.

Another fundamental axiom in toxicology is the dose response relationship. This property must be manifest to establish causation. When the alleged dose is not a single event as with this case, then it is approximated by intensity times duration of exposure. Response is measured in the case of cancer as the proportion of exposed persons who develop the response over a period of observation. Because of latency as discussed above, the longer the observation period, the higher the proportion of the population which develops a response when controlled for duration and intensity of exposure. This relationship is exemplified by the generally accepted formula defining risk of lung cancer from cigarette smoking by the product of average intensity of smoking in packs per day times the number of years, expressing the dose as pack/years. The risk of cancer of the lung among smokers has repeatedly been demonstrated to be a function of pack/years smoking experience.

When diagnosed with adenocarcinoma at the age of forty-one, the patient had been a fireman for 12 years. A minimum growth phase for adenocarcinoma of the lung is about eight years with an average of 12 to 14 years. Adding additional years for an induction period supports a conclusion that any external influence which might have caused his cancer occurred prior to his employment as a fireman.

Long latency is emphasized by Guidotti, 1993, page 936, stating that "a significant excess (lung cancer) was observed among firefighters in Edmonton, with over 35 weighted years of fire-fighting, suggesting that an excess due to occupational exposure may be confined to the highest exposure groups."

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It is noted that the data are confounded for lack of adjustment for smoking. The overall standardized mortality rate for lung cancer was 142 (95% CI 91-211) insignificant. With dose determined by years of exposure, the current patient clearly does not qualify as a member of the groups with 35 years exposure.

In his affidavit, Dr. Guidotti notes that the patient is unique because he is a non-smoker and the SMR for a population not corrected for smoking requires adjusting the expected risk downward, thereby uniquely raising the odds ratio applicable to this patient achieving a ratio in excess of two. This correction and adjustment is strongly biased toward increasing the apparent odds ratio for this patient since it does not take into consideration the patient's age.

Data attached on the age-adjusted incidence of lung cancer shows this patient had not yet reached the age range where the major effect of smoking on lung cancer incidence is expressed. Consistently, studies show the vast majority of excess lung due to smoking occurs after the age of fifty.

Peto, 1986, an expert on lung cancer recognized internationally, observed that "a three fold increase in daily dose-rate may produce only about a three fold increase in effect (cancer), while a three fold increase in duration might produce about a hundred fold increase in effect. Hence, a few decades after cigarette smoking becomes widespread, national lung cancer rates may remain misleadingly low even though they will eventually become extremely high."

Data recently published in "Smoking and Tobacco Control Monograph 8" from the National Institutes of Health (attached) show the death rate among currently smoking men by age, noting that the increase in risk of lung cancer death at age 40 to 44 is trivial compared to the rapid increase above 50 years to a rate of 500 to 800. The date of risk of lung cancer universally supports very minor contribution below age 50, consequently the correction arbitrarily made by Dr. Guidotti for the purpose of inflating the odds ratio is inappropriate since the risk of lung cancer in smokers and nonsmokers does not differ significantly in men in their early 40's. Even in populations with a very high incidence of nonsmokers, the significant increase occurs after age 44 (Enstrom, 1978, Table 2, "Age Adjusted Lung Cancer Among California Mormons"). Accordingly, this patient's age does not place him in a relatively high risk even among nonsmokers.

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The second error committed by Dr. Guidotti which serves to artifactually increase the association of lung cancer with fire-fighting arises from the admission in his affidavit that the patient has been exposed to second hand smoke since birth yet indicates that there are no risk factors other than employment as a firefighter. Surely Dr. Guidotti, who has devoted a major segment of his professional career to issues of smoking and cancer, is aware of the risk of lung cancer from second hand smoke as shown by the EPA position that environmental tobacco smoke (ETS) is a human carcinogen. The association of ETS with lung cancer is similar to the association of lung cancer attributed to a career firefighter. Because of confounders which are prevalent in both populations, the data is not dissimilar, with an odds ratio exceeding 1.0 but less than 2.0 in both instances. (References attached.)

Dr. Guidotti's research failed to show a relationship between duration of employment as a fireman and lung cancer incidence with "the highest among those employed less than one year and a generally declining risk thereafter until 40+ weighted years." Correction of the data using an exposure opportunity index "demonstrated that the risk was greatest in less heavily exposed firefighters and in workers with no firefighting experience until 35+ weighted years." The patient was not a member of either of the highest risk groups. The overall SMR of 142 was reported as not significant.

An inconsistency in his research which reduces its strength when projected to other firemen in other cities is the failure to find increased risk of lung cancer in one city while increased risk of lung cancer was confined to the other (Edmonton).

First, Dr. Guidotti publishes his own research which fails to demonstrate a dose response relationship between employment as a firefighter and lung cancer. Then he publishes an analysis of the world literature and concludes that there is evidence of an association but not of sufficient magnitude for a general presumption of risk defined in reasonable medical probability. Then he builds a series of assumptions placing the present patient in a population for which there is no control group and concludes the a reasonable medical probability relationship exists in this particular case while not discussing alternative causation from second hand smoke.

Neither exposure to chemicals nor smoking is necessary for cancer of the lung to occur. Active Mormons have been studied by numerous investigators as a population with one-third less chance of occupational chemical exposure (West, 1980) and a low incidence

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of smoking. With removal or at least substantial reduction of these known risk factors, cancer of the lung still occurs (Enstrom, 1989).

In conclusion, if the patient's adenocarcinoma of the lung was the result of chemical exposure, then the exposure occurred prior to his employment as a fireman. Second hand cigarette smoke with a latency of 41 years is a more biologically plausible cause of lung cancer than exposure to smoke as a fireman but neither reaches a certainty sufficient to meet the test of reasonable medical probability.

Eric G. Comstock, M.D.

EGC/cw

Attachments