

Further evidence of nonasbestos-related mesothelioma

A review of the literature

by Premysl V Pelnar, MD¹

PELNAR PV. Further evidence of nonasbestos-related mesothelioma: A review of the literature. *Scand J Work Environ Health* 14 (1988) 141–144. Asbestos is not the only cause of malignant mesothelioma. An updated review of the literature is presented with reports on mesothelioma with unknown causes (spontaneous cases) in animals and humans and on mesothelioma in man in association with exposure to erionite-zeolite, exposure to ionizing radiation, and chronic inflammation and in animals in association with biological (viral), chemical, physicochemical, and physical agents.

Key terms: biogenic silica, chronic inflammation, erionite-zeolite, ionizing radiation, viruses.

For the last 25 years malignant mesothelioma, a tumor of the pleura, peritoneum, pericardium, or rarely of other sites, has been strongly linked with exposure to asbestos, mainly to its amphibole varieties. However, asbestos is not the only cause of mesothelioma, as noted in an earlier review (27).

Mesothelioma has been known to pathologists for 100 years as a spontaneously occurring (ie, cause unknown), though rare disease. A number of important epidemiologic studies of mesothelioma in which a significant proportion of cases had had no exposure to asbestos has been identified (27). Further such studies have since been published (7, 11, 13, 14, 18, 25, 29, 32).

Several reported rare cases of mesothelioma of the tunica vaginalis testis have been discussed (27). A more recent study (35) reports that mesothelioma of the tunica vaginalis testis in an 86-year-old man had also infiltrated extensive areas of the skin. The patient was a cabinetmaker who had never been exposed to asbestos.

Less rare are cases of malignant mesothelioma of the pericardium. Over 100 cases of the disease have been reported elsewhere (27). Although exposure to asbestos could not be excluded in some of them, most of the cases appeared to be spontaneous. Other cases are as follows: a single case in Sweden (5), two in Germany (10), and one in Japan (24). In one of the patients, asbestos was found in the lungs at autopsy. But in the other, a 77-year-old woman, no asbestos exposure was known, and no asbestos was found in the lungs. Another study (12) presented the case of a 60-year-old woman who died of pericardial mesothe-

lioma three years before the first report of an asbestos-mesothelioma link (37).

A case of malignant mesothelioma of the anterior mediastinum was recently published (34). The patient's husband was intermittently associated with asbestos, working as an oil-burner repairman. He worked in areas that were heavily insulated with asbestos, but he changed from his workclothes into street clothes before returning home. The patient did not wash the workclothes. She had worked in a school which was inspected, and no loose ceilings or asbestos deposits were revealed. Thus, an asbestos origin for this tumor seemed unlikely.

Another two cases published recently (20, 30) are interesting from a clinical point of view. In yet another case (38) the myocardium was also invaded by the tumor. No asbestos exposure was mentioned for any of the three cases.

It is generally accepted and documented that mesothelioma linked with exposure to asbestos has a long, or excessively long, latency period between first exposure to asbestos and clinical manifestation. This long latency period, by itself, seems to exclude asbestos as an etiologic factor for mesothelioma in children. Other evidence against the asbestos link to mesothelioma among children has been discussed elsewhere (27), to which have now been added six cases from Israel (17, 39). In the Israel study the possibility of placental exposure to asbestos by the fetus was suggested, but the other studies did not speculate on the cause of what appears to be a spontaneous disease.

A review (28) published in 1984 added further evidence for causes other than asbestos, mainly in the form of mesotheliomas induced in animal models by chemicals or viruses. Although the relevancy of such studies to man is still unclear, it was argued that animal tests should continue to be used, because the occurrence of a large number of apparently nonasbestos-related malignant mesotheliomas in humans strongly

¹ McGill University, School of Occupational Health, Montréal, Canada.

Reprint requests to: Dr PV Pelnar, McGill University, School of Occupational Health, 1130 Pine Avenue West, Montréal, Québec, Canada H3A 1A3.

Table 1. Mesothelioma carcinogens other than asbestos.

Mesothelioma carcinogen	Reference
<i>In animals</i>	
Unknown (spontaneous cases)	
Guinea pigs	Arnold et al (3), Mehnert et al (21)
Trout	Herman (15)
Biological	
C-type virus	Mehnert et al (21)
MC29 avian leukosis virus	Pelmar (27), Peterson et al (28)
SV40 virus	Peterson et al (28)
<i>In animal experiments</i>	
Chemical	
Ethylene oxide	Pelmar (27)
Ethylene dibromide	Pelmar (27)
Polymethane	Pelmar (27)
Diatomaceous earth	Pelmar (27)
Sinapaldehyde	Pelmar (27), Peterson et al (28)
l-Nitroso-5,6-dihydro-uracil	Pelmar (27)
Methyl(acetoxymethyl)-nitrosamine	Pelmar (27), Peterson et al (28)
N-methyl-N-nitrosourea	Peterson et al (28)
N-methyl-N-nitrosourea ethane	Peterson et al (28)
Polysilicone plastics	Peterson et al (28)
Diethylstilbestrol	Peterson et al (28)
Nickel powder	Peterson et al (28)
Beryllium (?)	Pelmar (27), Peterson et al (28)
Heavy metals (?)	Pelmar (27)
Physicochemical	
Glass fibers	Pelmar (27)
Aluminum oxide	Pelmar (27)
Tremolite	Pelmar (27)
Attapulgite	Pelmar (27)
Dawsonite	Pelmar (27)
Silicone carbide	Pelmar (27)
Potassium titanate	Pelmar (27)
Erionite-zeolite	Peterson et al (28), Wagner (36)
Physical	
Ionizing radiation	Peterson et al (28)
<i>In man</i>	
Unknown (spontaneous cases)	
	Chiappino et al (7), Fincham (11), Haider (13), Hasan et al (14), Law et al (18), Otto (25), Pelmar (27), Pillgram-Larsen et al (29), Spriggs & Grunze (32)
Physiochemical	
Erionite-zeolite	Pelmar (27), Peterson et al (28), Wagner (36)
Physical	
Ionizing radiation (?)	Anderson et al (1), Antman et al (2), Beier et al (4), Pelmar (27), Peterson et al (28)
Long-term chronic inflammation (?)	Chahinian et al (6), Hillerdal & Berg (16), Pelmar (27)

suggests the possible importance of agents other than asbestos in the induction of this neoplasm.

In animals, 139 cases of spontaneous peritoneal mesothelioma were found among 6 596 autopsied golden hamsters (3, 21), and a case was reported in rainbow trout (15). In one of the hamster studies, transplantable mesothelioma-line C-type virus particles were found with electron microscopy and a virus origin was suggested for the mesothelioma. This possibility is consistent with the previously discussed induction of

mesothelioma by MC29 avian leukosis virus (27, 28) and SV40 virus (28). The relevance of these findings with respect to human mesothelioma is not known, but the tumors induced by the avian leukosis virus were described as remarkably similar to those occurring in mammals, particularly man.

Many chemical carcinogens have been shown to induce mesothelioma in animals. Previously discussed (27) have been two warnings from the National Institute for Occupational Safety and Health in the United States on ethylene oxide and ethylene dibromide, as well as reports on mesothelioma caused by polymethane, diatomaceous earth, sinapaldehyde (a wood lignine constituent), l-nitroso-5, 6-dihydrouracil, sterigmatocystin, methyl-(acetoxymethyl) nitrosamine, and herbicides. There are also reports (28) on polysilicone plastics, N-methyl-N-nitrosourea, N-methyl-N-nitrosoureaethane, and diethylstilbestrol.

The production of mesothelioma in animals by metallic nickel powder (28) and a possible link with heavy metals and beryllium exposure and the occurrence of mesothelioma among humans have also been previously discussed (27).

Well-known, and previously reported (27, 28), is evidence of physical carcinogenesis as demonstrated in animal experiments. Mesotheliomas were induced by the intrapleural introduction of asbestos and a number of other materials not necessarily considered carcinogenic, ie, glass fibers, aluminum oxide, tremolite, attapulgite, dawsonite, silicon carbide, and potassium titanate.

Also previously discussed (27, 28) was an accumulation of cases of mesothelioma in Turkish area inhabitants in which the tumors were believed to be caused by erionite-zeolite, as well as the carcinogenic effect of erionite and zeolite in animal experiments (26, 36).

Exposure to ionizing radiation seems now accepted as a cause of some cases of mesothelioma. In addition to reports already discussed (27, 28), new evidence has been presented (2). In a study of four cases of mesothelioma, two pleural and two peritoneal, in persons with no known asbestos exposure, the disease developed in three cases following therapeutic radiation for another tumor. The fourth patient had cosmetic radiation to a scar after thyroidectomy. In all these cases the mesothelioma developed within the field of radiation. Elsewhere a patient developed peritoneal mesothelioma nine years after radiation therapy for carcinoma of the cervix of the uterus (4). No contact with asbestos was known, and radiation was considered the cause. Gynecologists should be alerted to this cause of peritoneal mesothelioma, for which the evidence is mounting. Another unusual case report (1) presented mesothelioma in a boy aged 16 years. He had resided all his life on a farm near a small rural community and had no known contact with asbestos. At the age of two years he received pulmonary irradiation for a metastatic Wilm's tumor. The authors did not doubt that radiation was the cause of his disease.

Chronic inflammation appears to be of importance as a cause of mesothelioma. Previously discussed (27) have been instances of tuberculosis infection and long-term treatment of tuberculosis by pneumothorax and pneumoperitoneum as linked with mesothelioma. Other such cases have been reported since (16). An evaluation (6) of 69 patients with diffuse malignant mesothelioma seen from 1974 to 1980 documents several cases not supposed to be caused by asbestos. Among them is a Turkish patient with a long history of familial Mediterranean fever with recurrent peritonitis who developed peritoneal mesothelioma. The possibility of exposure to zeolite comes to mind, but the paper does not say whether the patient lived in Turkey, or in New York, from which the paper originates.

An interesting question to be investigated is the link between mesothelioma and sugarcane. In a 1976 report (9) five cases of mesothelioma came from one agricultural community in India where the common feature was that all the patients had been engaged in farming and manipulating sugarcane. No other cause of malignancy was revealed or suspected.

Table 1 lists nonasbestos causes of mesothelioma reported in the literature.

This report was followed by an epidemiologic study (31) from the state of Louisiana in the United States showing an excess mortality from lung cancer associated with sugarcane farming in southern Louisiana parishes. High lung cancer mortality was also noted in two of three sugarcane farming counties in the state of Florida. No excess incidence was reported from Texas, however, where sugarcane farming was introduced only recently. The authors did not mention mesothelioma, but, as far as lung cancer is concerned, they speculated that the burning of excess leafage, which produces airborne irritating fibrous particles, might be a causal link. Another study (22, 23) supports this opinion. An excess risk of mesothelioma (four cases) was also reported (19) from Swedish sugar beet sugar refineries; however some exposure to asbestos could not be excluded (33). Moreover, it was noted (8) that sugar beet would by no means produce similar residues as sugarcane and could not be linked with similar cases of carcinogenesis.

Experimental evidence of a number of agents capable of inducing mesothelioma in animals, clinical evidence of human mesothelioma caused by erionite-zeolite (and probably or possibly by some other irritating effects), and a certain proportion of nonasbestos-related cases in all epidemiologic studies of mesothelioma leave little doubt that asbestos is not the only cause of this malignancy. As scientific research of cancer continues, it can be safely predicted that a cause will be found for the nonasbestos-related unexplained, spontaneous cases of malignant mesothelioma.

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