account for around 1% of all deaths. In 2005 Hodgson et al.[67] stated there were 1848 mesothelioma deaths in Great Britain in 2001 and mesothelioma deaths were predicted to peak at around 1950 to 2450 per year between the years 2011 and 2015 (Fig. 43.1). The Health and Safety Executive Data[68] suggested the peak would occur earlier than originally predicted and the maximum would be approximately 2000 deaths in or around the year 2010. According to Treasure et al.,[69]

> one in every 100 men born in the 1940s will die of malignant pleural mesothelioma. . . . For a man first exposed as a teenager, who remained in a high-risk occupation such as insulation throughout his working life, the lifetime risk of mesothelioma can be as high as 1 in 5. . . . The disease is increasing in frequency. . . . We will see many more mesotheliomas in the next 25 years. In the developed world alone, 100,000 people alive will now die from it.

In Australia, mortality from MM was stated to have been increasing since 1975. Mesothelioma incidence rates are among the highest in the world, and the Australian Mesothelioma Registry received 6129 mesothelioma notifications between 1986 and 2000. Of the mesothelioma cases with past asbestos exposure, close to 89% were work-related, about 3% were not work-related, and about 8% could not be classified. Of the persons who developed work-related MM, one in three worked in the construction industry and one in five worked in the manufacturing industry.

In contrast, Roggli,[70] based on his experience, suggests that a mesothelioma epidemic was beginning to wane in the U.S. Lemen,[71] using Surveillance Epidemiology and End Results (SEER) data and International Classification of Diseases (ICD-10-TEM) coding that went into effect in 1999, stated the accuracy for reporting mesothelioma was about 80% effective, which would mean that in the U.S. there were over 6000 cases of mesothelioma per year.

Etiology

Asbestos

The association of asbestos exposure and the development of mesothelioma has been reviewed in detail.[72–74] The chronology of asbestos is shown in Box 43.1 (Figs. 43.2 and 43.3). Asbestos is the single most important causative agent of mesothelioma. Numerous

Box 43.1. The History of Asbestos

4000 BCE	Asbestos was used for wicks in lamps and candles. "Asbestos" means inextinguishable or unquenchable.
2000–3000 BCE	Embalmed bodies of Egyptian pharaohs were wrapped in asbestos cloths to offset the ravages of time.
2500 BCE	Used in Finland to strengthen clay pots.
800–900 AD	Anecdotal evidence of Charlemagne's tablecloth made from woven asbestos.
1000	Mediterranean people used chrysotile from Cyprus and tremolite from upper Italy for the fabrication of cremation clothes, mats, and wicks for temple lamps.
1300–1400	Marco Polo visited an asbestos mine in China in the latter half of the 13th century. He concluded that asbestos was a stone and lay to rest the myth that asbestos was the hair of a woolly lizard.
Early 1700s	Asbestos papers and boards were made in Italy.
1724	Benjamin Franklin brought a purse made of asbestos to England. The purse is now in the Natural History Museum.
1828	United States patent issued for asbestos insulating material used in steam engines.
1853	Asbestos helmet and jackets worn by Parisian Fire Brigade.
1866	Molded lagging material made from water, glass, and asbestos.
1896	First asbestos brake linings were made by Ferodo Ltd., in England.
1900	High pressure asbestos gaskets made by Klinger in Austria.
1913	First asbestos pipes developed in Italy.
1919	Standard corrugated sheet asbestos introduced in Australia by Hardies.
1939–1945	Wartime use included fireproof suits and parachute flares. In the film *The Wizard of Oz* in 1939, the Wicked Witch of the West appeared on a broom made of asbestos.
1945–1975	Postwar construction projects relied heavily on the use of asbestos, reaching an all-time high in 1973.
1990s	The solid fuel boosters of the space shuttle are insulated with asbestos, one of the few remaining current uses.

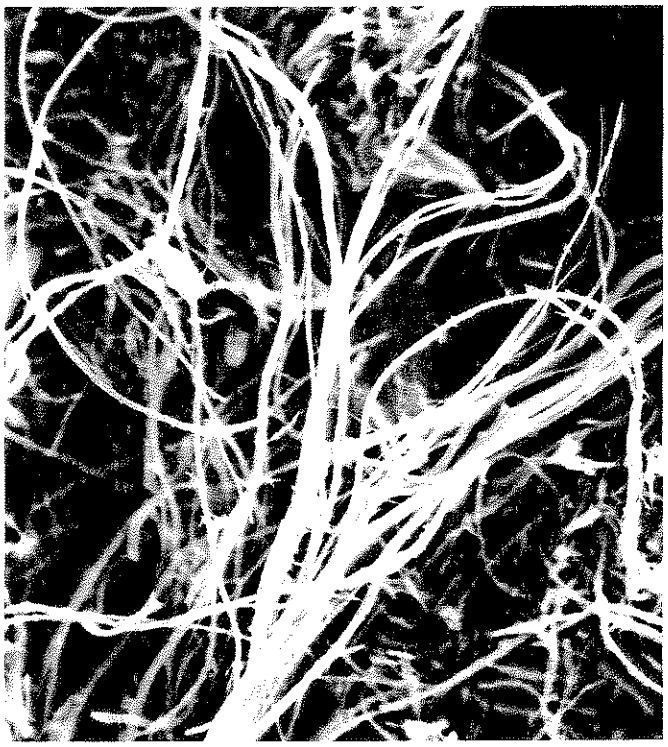

FIGURE 43.2. Canadian chrysotile fibers as visualized by scanning electron microscopy (SEM). The individual fibers are long and wavy (serpentine).

FIGURE 43.3. Scanning electron microscopy appearance of South African crocidolite fibers. In comparison to chrysotile fibers (Figure 43.2), these amphibole fibers are straight and show evidence of longitudinal splitting.

reports[31,59,75–86] have tabulated the percentage of mesothelioma cases associated with asbestos exposure (Table 43.3). The association between asbestos exposure and mesothelioma is stronger in men than in women and, in many series, very few women with mesothelioma have had a history of exposure to asbestos. The threshold amount of asbestos necessary to induce mesothelioma is unknown, although in most reports a dose–response relationship has been suggested[87,88]; that is, persons with a greater intensity and duration of exposure to asbestos have a higher incidence of mesothelioma. Small concentrations of asbestos may induce mesothelioma[89–97] (see

TABLE 43.3. Association of exposure to asbestos and incidence of mesothelioma

		Sex distribution			Cases associated with asbestos exposure		
Reference	Number of cases	Male	Unspecified	Female	Male	Unspecified	Female
Borow et al.[75]	72	64		8	55/55 (100%)		5/5 (100%)
Cochrane and Webster[76]	70		70[a]			60/70[a] (86%)	
Tagnon et al.[77]	61	61		0	45/56 (80%)		
Whitwell and Rawcliffe[78]	52	40		12	35/40 (87.5%)		8/12 (67%)
Hammar[79]	151	119		32	66/82 (80%)		10/22 (45%)
Taylor and Johnson[80]	30	23		7	17/23 (74%)		0/7 (0%)
Vogelzang et al.[81]	31	22		9	13/22 (59%)		2/9 (22%)
Newhouse and Thompson[31]	83	41		42	24/41 (59%)		17/42 (40%)
Peto et al.[82]	116	116		0	69/116 (59%)		
McDonald and McDonald[59]	557	395		162	188/344 (55%)		8/162 (5%)
Roggli et al.[83]	25	21		4	11/21 (52%)		0/4 (0%)
Oels et al.[84]	37	32		5	10/32 (31%)		0/5 (0%)
Brenner et al.[85]	123	84		39	16/84 (19%)		0/39 (0%)
Ratzer et al.[86]	31	21		10	4/31[a] (13%)		

[a]Gender not specified.

below). Malignant mesothelioma can occur via household exposure to asbestos.[98] Vianna and Polan[99] reported a relative risk of 10 for such situations compared to matched controls unexposed to asbestos. Kane et al.[100] reported 10 cases of MM in patients 40 years old or younger. In seven of the 10 cases, there was asbestos exposure—two occupational exposures and five household exposures. Cazzadori et al.[101] reported a case of pleural MM in a 37-year-old woman exposed to asbestos during childhood. From birth to age 10 she lived in a house next to an asbestos-processing factory. Asbestos exposure was confirmed by finding 0.3 asbestos bodies per milliliter in her bronchoalveolar lavage fluid. Huncharek[62] pointed out that exposure to asbestos was no longer confined to asbestos industry workers, and there were nonoccupational hazards such as household and building occupant exposures. Dodoli et al.[102] reviewed death certificates of 39,650 persons between 1975 and 1988 in Livorno, Italy and in 45,900 persons in La Spezia, Italy, between 1958 and 1988. A total of 262 cases of pleural mesothelioma were recorded, most of which occurred in persons occupationally exposed to asbestos in the shipbuilding industry. Thirteen cases of mesothelioma occurred in women who washed the asbestos-contaminated work clothes of their relatives, and six cases occurred in persons domestically exposed to asbestos, possibly from installing fireproof or nonconductive materials.

In 1997 Hammar et al.[103] reported on 103 women with mesothelioma of whom about 70 were exposed to asbestos, the most common source of asbestos exposure being domestic bystander exposure.

Proposed Nonasbestos Causes of Mesothelioma

Erionite

Theoretically, MM might develop at the site of pleural injury caused by almost any agent. Of particular interest has been a group of naturally occurring fibrous silicate minerals called zeolites. In 1975 and subsequent years, Baris and colleagues[104–108] reported that people living in Tuskoy and Karain (two small villages in central Turkey) had the highest incidence of mesothelioma in the world. In Karain, 21 of 50 deaths recorded in people over 20 years old during a 5-year period were caused by mesothelioma. People living in this region of Turkey were found to have very fine fibers of a zeolite called *erionite* in their sputum and lung tissue. These fibers were not found in similar specimens of people living in other areas of Turkey. A search for asbestos in soil, rock, and water samples was negative and it was hypothesized that airborne erionite fibers from building materials caused the mesotheliomas. Lillis[109] substantiated the findings of Baris et al. Sebastien and coworkers[110] demonstrated that 93% of ferruginous bodies from lung samples of two patients with MM from Tuskoy were formed on erionite cores. Wagner et al.[111] induced mesotheliomas in 38 of 40 rats inoculated with erionite. Rohl et al.,[112] however, were able to identify small amounts of tremolite and chrysotile in addition to erionite in environmental samples taken from Tuskoy and Karain (see Nonasbestos and Nonoccupational Mineral Fibers and Mesothelioma, below). They also reported that erionite was found in environmental samples taken from villages with no reported cases of mesothelioma. Recent studies have suggested a genetic susceptibility to mesothelioma in Turkey based on identification of mesothelioma in one village and not in another.[113,114]

Chronic Pleural Inflammation and Scarring

In 1985 Hillerdal and Berg[115] reported two patients who developed mesothelioma in regions of pleural scarring caused by tuberculosis that had been treated with pneumothorax. They reviewed the literature and found 20 additional cases of malignant tumors in pleural scars, 12 of which were found in areas of squamous carcinoma. They reported that squamous carcinoma was the most common tumor associated with scarring from chronic empyema and extrapleural pneumothorax. Malignant mesotheliomas have occurred years after chronic inflammatory lesions of the pleura; for example, chronic empyema or packing of the pleural cavity with leucite spheres as treatment for tuberculosis (so-called plombage therapy). Also, there are a few reports (about eight cases) of an association of peritoneal mesothelioma with familial Mediterranean fever (FMF), possibly related to recurrent FMF serositis.[116] Cases of this type are exceptional, and confounding factors for mesothelioma need to be addressed; for example, in relation to FMF, cases of mesothelioma have been reported in the Mediterranean littoral from white-washing of homes with tremolite-containing material, so that domestic and environmental tremolite exposure might represent a potential confounding factor for the association of FMF and mesothelioma.[117,118] In addition, most cases of postinflammatory mesothelioma with a short interval between inflammation and tumor are probably mesotheliomas that presented with a burst of inflammatory activity, perhaps related to production of cytokines or mediators of inflammation such as interleukin-8, before their final diagnosis as mesothelioma.[119,120]

Irradiation

The literature contains multiple reports of mesothelioma following exposure to ionizing radiation,[121–150] and excess rates of MM have also been reported among both Danish and German patients exposed to radio-active thorium dioxide (Thorotrast®) for radiologic procedures.[121,124,134,135]