

Case³²² has extensively reviewed the biohazards of tremolite, including epidemiologic investigations in humans and experimental data on animal models. He also favored the expression chrysotile/tremolite for Quebec chrysotile, but is of the opinion that it is the tremolite component that causes mesothelioma.

The Quebec Chrysotile Cohort

In an analysis of mesotheliomas among the Quebec chrysotile miners and millers, up to 1997, McDonald et al.^{313,314} reported 38 mesotheliomas, most of which occurred after prolonged and heavy exposure, especially at the mine where the greatest concentrations of trace tremolite occurred (Thetford). In comparison to the Thetford main complex, relatively few mesotheliomas occurred among workers at the Asbestos mine and mill (23 versus eight), despite nearly equivalent person-years of observation. In addition, asbestos fiber analysis on lung tissue demonstrated crocidolite and amosite in five of the eight cases from the mine and mill at Asbestos and in two out of the five mesotheliomas from the Asbestos factory (Table 43.11).³¹³

The clear implication of this study is that the risk of MM was related strongly to years of service in the central area at Thetford where geologic factors "would probably result in tremolite, some in fibrous form, being mined with the ore."³¹³ In addition, the MM rate for miners and millers was >2.5 times higher at Thetford mines (excluding the smallest mines) than at Asbestos, and this difference was also attributed to differences in the amount of fibrous tremolite in the ores. Despite these differences within the cohort for the distribution of MM related to chrysotile and tremolite (and also to crocidolite and amosite at the Asbestos factory and the Asbestos mine and mill), the results clearly indicate that Quebec chrysotile has the capacity for mesothelioma induction. The abstract describes 25 MMs from the Thetford mines,³¹³ representing a mesothelioma rate of 337 per million person-years, substantially (almost 20-fold) higher than the incidence rate of about 17 cases/10⁶/yr for men in British Columbia and the U.S. in 1982 and 1973–1984,

respectively, and well above the often-cited MM "background" rate of 1 to 2 cases/10⁶/yr.

In the final two paragraphs of the paper, McDonald et al.³¹³ commented, "The tremolite hypothesis, if correct, has several important implications. First, it supports the widely but not universally held view that most, if not all, asbestos-related mesotheliomas are caused by amphibole fibers. This in turn points to fiber durability and biopersistence as critical factors in aetiology."

A report from the *Institut National de Santé du Québec* pointed out that the average annual rate of increase in the incidence of MM in Quebec during the period 1982–1996 was 5% for men, and that work in the (chrysotile) mines was associated with 35% of a total of 691 cases of asbestos-related diseases (MM, asbestosis, and lung cancer).³²³ An earlier report from the same institute found that average adjusted incidence rates for pleural MM were 32% and 92% higher for men and women, respectively, in Quebec "than those of Canadian men and women in all other provinces combined."³²⁴ The second (2005) institute report also commented that multiple criteria for causation "show that chrysotile is carcinogenic" and that "safe use of asbestos is difficult, perhaps impossible, in industries such as construction, renovation, and asbestos processing."³²³

Mesotheliomas have also been produced in experimental animals by implantation and inhalation of chrysotile (presumably also containing trace amounts of tremolite). Mesotheliomas can also be induced in rats by intraperitoneal injection of chrysotile, with evidence of a dose-response effect.²²⁷

Other Chrysotile-Exposed Cohorts and Studies

In addition to the Quebec chrysotile miners and millers, mesotheliomas have also been reported among other workforces apparently exposed to chrysotile only, with much smaller amounts of contaminant tremolite.

Even so, it is doubtful whether chrysotile exists in the complete absence of contaminant amphiboles. For example, Yano et al.³²⁵ reported a 25-year longitudinal cohort study on male asbestos workers exposed to

TABLE 43.11. Mesotheliomas among Quebec chrysotile miners and millers, 1997

	Number of mesothelioma deaths	Person-years (thousands)	Mesothelioma rate (per million person-years)
Thetford Mines:			
Main complex and the oldest of the smaller mines	23	65.14	353
The five smallest mines	1	6.01	266
Asbestos:			
Mine and mill	8	60.64	132
Factory	5	10.84	462

Source: Modified from McDonald et al.³¹³

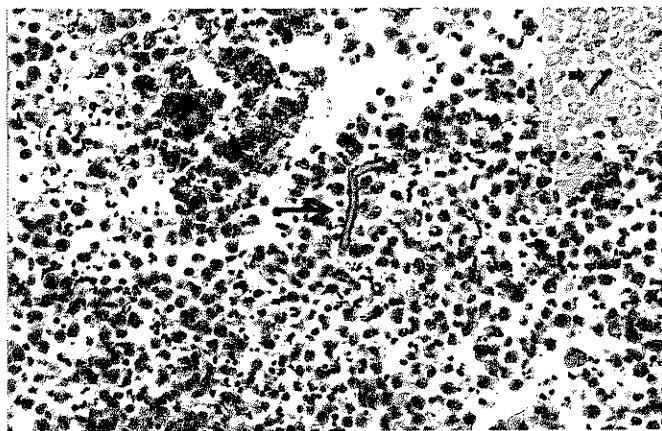


FIGURE 15.17. Eosinophilic pneumonia within a patient with allergic bronchopulmonary aspergillosis. A degenerated hyphal fragment of *Aspergillus* with associated Splendore-Hoeppli phenomenon is present (arrow). The presence of septate hyphae consistent with aspergillus is confirmed on Gomori's methenamine silver (GMS) special stain (inset, short arrow).

replacement of bronchi or bronchioles by necrotizing granulomatous inflammation²¹⁰⁻²¹² (Table 15.5). Grossly, lungs from affected patients show dilated bronchi and bronchioles with thickened walls filled with cheesy mucopurulent material. Adjacent arteries appear grossly uninvolved (Fig. 15.18). Histologically, airway walls are replaced by epithelioid histiocytes, which often show a palisaded arrangement oriented radially with respect to the bronchiolar lumen. In some cases, the abrupt transition from bronchial mucosa and wall to granulomatous

TABLE 15.5. Histopathology of bronchocentric granulomatosis

Major features

- Bronchi/bronchioles replaced by necrotizing granulomatous inflammation
- Degenerated noninvasive fragments of fungal hyphae may be identified within centers of the granulomas
- Parenchymal granulomas typical of invasive fungal hyphae or mycobacterial infection are not identified
- Other organisms (e.g., mycobacteria) are not identified

Minor features

- Exudative bronchiolitis
- Chronic bronchiolitis

inflammation facilitates recognition of this pattern. In other cases, bronchial and bronchiolar walls are completely replaced by granulomatous inflammation. In these cases, the interpretation of bronchocentric granulomatous inflammation can be inferred by noting the preferential location of the granulomatous inflammation adjacent to pulmonary arteries (Fig. 15.19A,B; Table 15.5). An elastic tissue stain can be helpful in confirming this interpretation. In addition to highlighting pulmonary arteries, it may show remnants of elastic lamina from the bronchial wall (Fig. 15.19C). Surrounding the granulomas there is a dense chronic inflammatory infiltrate within the immediate peribronchial tissue consisting of lymphocytes, plasma cells, and eosinophils. Pulmonary arteries adjacent to granulomatous lesions are sometimes involved, but the involvement appears secondary to the bronchial wall inflammation and not the primary pathologic feature. Foci of obstructive pneumonia may be

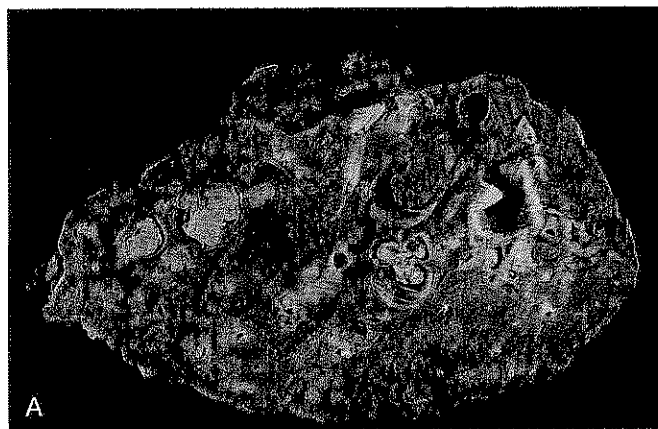


FIGURE 15.18. **A.** Bronchocentric granulomatosis. Bronchial walls are dilated and thickened. Lumina of bronchi are filled with cheesy material (straight arrows). A mucoid plug partially extrudes from a large bronchiectatic airway (curved arrow). (Courtesy of the A.A. Liebow Pulmonary Pathology Collection and Dr. David Dail.) **B.** Close-up view of another case showing

dilatation and thickening of walls of small bronchi that are distended by cheesy material (straight arrows). A focal area of mucoid impaction is also present (curved arrow). (Courtesy of the A.A. Liebow Pulmonary Pathology Collection and Dr. David Dail.)