were three deaths per 100,000, with a highest arguable estimate of 20 and lowest that was "insignificant"; at this level of exposure, the risk for chrysotile was "probably insignificant," with a highest arguable estimate of 1 death per 100,000.

One point also worth emphasizing is that the estimated RRs, ORs, SIRs, or proportional mortality ratios (PMRs) for cohort and case-control studies on mesothelioma represent cases in excess of any background risk from background exposures; in all cohort and case-control studies, the control group represents a comparable group of individuals with background (or greater[303]) levels of asbestos in their lungs, so that the risks delineated by such studies represent risks in excess of no exposure and background exposure.[44]

In line with these considerations, the Industrial Injuries Advisory Council (IIAC) in the U.K. set forth in 2005 a comment concerning causation of mesothelioma,[304] similar to and reaffirming the criteria for causation originally set out in 1996:

> Mesothelioma is a rare disease in the general population almost always caused by asbestos, so that attribution to occupation is far more straightforward [than lung cancer] and does not require epidemiological evidence. . . . The last IIAC review of asbestos-related diseases in 1996 . . . recommended that benefit for mesothelioma be awarded for claimants in any occupation involving asbestos exposure at a level above that commonly found in the environment at large. . . . The Council recommends that the prescription for [mesothelioma] should remain unchanged.

Commercial Chrysotile and Mesothelioma: Can Chrysotile-Only Exposure Induce Mesothelioma?

Chrysotile represented about 95% of past production and usage of asbestos, and it is still mined in particular in Russia (the world's largest producer), Canada (the world's largest exporter), Brazil, China, and Zimbabwe; small chrysotile mines also operated at some times in other nations, such as the U.S. and Australia.

There appears to be general but not universal agreement that commercial chrysotile as exemplified by the chrysotile mined and milled in Quebec has the capacity to induce mesothelioma, not only in experimental animals but also in humans. Nonetheless, Canadian chrysotile contains trace amounts of tremolite, including fibrous tremolite (a noncommercial amphibole), as a contaminant. The amount of tremolite appears to vary from one sample to another, but is generally <1%. Some authorities claim that the occurrence of mesotheliomas among the Quebec chrysotile miners and millers is a consequence not of the chrysotile per se but rather of the coexistent trace quantities of tremolite. The amphibole hypothesis,[305,306] which argues that chrysotile itself has little or no mesotheliomagenicity and that mesotheliomas following chrysotile exposure are a consequence of the admixed commercial or trace contaminant noncommercial amphibole fibers, remains the subject of dispute.[306–312]

Analysis of the asbestos fiber content of lung tissue from the cohort of Quebec chrysotile miners/millers has consistently demonstrated disproportionately high concentrations of tremolite in comparison to chrysotile (Table 43.10).[313] This appears to represent a bioaccumulation phenomenon whereby chrysotile is cleared from lung tissue more rapidly than the tremolite, so that the tremolite not only persists but increases in proportional concentration. In this respect, the tremolite content of the lung tissue can be used as an index of past chrysotile-only exposures, and some claim that the incidence of mesotheliomas in the same cohort can be related directly to the tremolite content.[313,314]

Mesotheliomas related to the use of tremolite in whitewash or stucco have been reported in Turkey,[315,316] Greece,[118] Cyprus, Corsica,[317] and New Caledonia[318,319] (see also Schneider and Woitowitz[117]). Tremolite has also been implicated in lung cancer and mesothelioma induction among vermiculite miners in Montana,[320,321] who were exposed only to tremolite-actinolite fibers.

TABLE 43.10. Asbestos fiber concentrations in lungs at autopsy from 21 mesothelioma cases among Quebec chrysotile miners and millers (fibers per microgram [μg]; geometric means)

Place of employment	No. of cases	Chrysotile	Tremolite	Crocidolite	Amosite
Mines and mills					
Thetford Mines	14	12.8	104.1	0	0
Asbestos	5	4.3	7.5	1.7	0.3
Factory					
Asbestos	2	2.1	0.5	6.4	0.3

Source: Modified from McDonald et al.,[313] Table 2 in the original reference; see also Table 1 in the original. In calculating geometric means, a zero count has been replaced by half the detectable limit. For crocidolite and amosite, all counts were zero; i.e., below the detection limit. For fiber counts/g lung tissue, multiply the raw figures by 10^6.

Case[322] 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/10^6/yr for men in British Colombia and the U.S. in 1982 and 1973–1984, respectively, and well above the often-cited MM "background" rate of 1 to 2 cases/10^6/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]

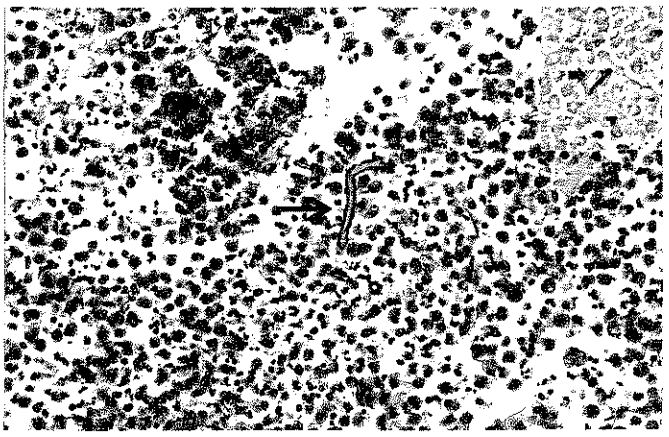

FIGURE 15.17. Eosinophilic pneumonia within a patient with allergic bronchopulmonary aspergillosis. A degenerated hyphal fragment of *Aspergillus* with associated Splendore-Hoeppli phenomenon is present (arrow). The presence of septate hyphae consistent with aspergillus is confirmed on Gomori's methenamine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

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

replacement of bronchi or bronchioles by necrotizing granulomatous inflammation[210–212] (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 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

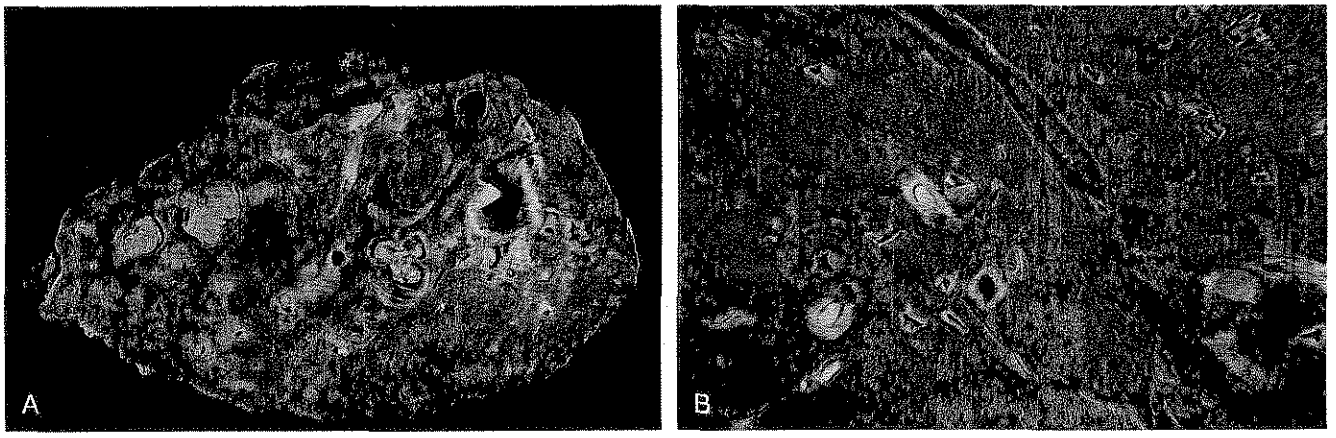

FIGURE 15.18. **A**. Bronchocentric granulomatosis. Bronchial walls are dilated and thickened. Lumina of bronchi are filled with cheesy material (straight arrows). A mucoid plug partially extrudes from a large bronchiectatic airway (curved arrow). (Courtesy of the A.A. Liebow Pulmonary Pathology Collection 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.)

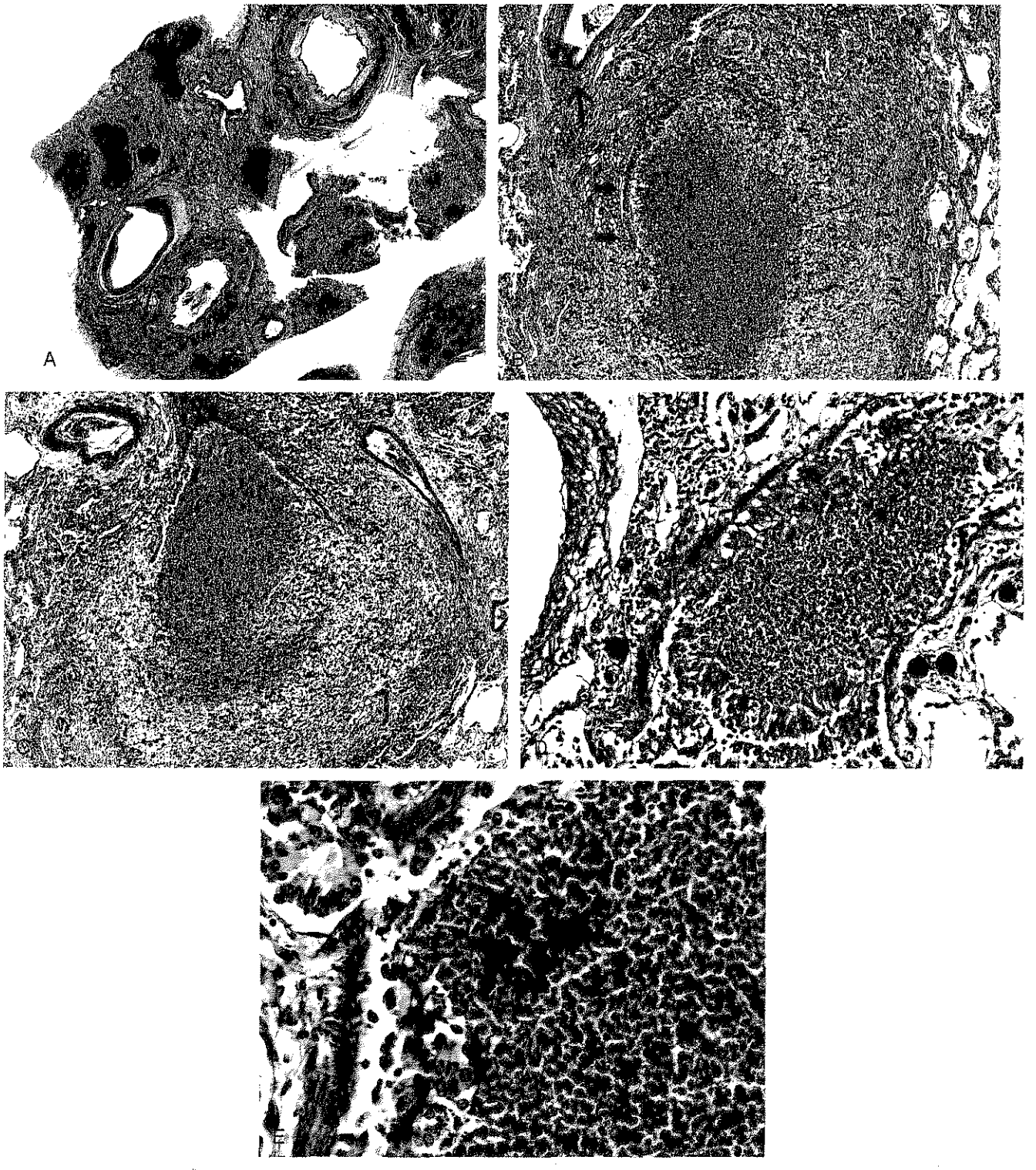

FIGURE 15.19. **A.** Bronchocentric granulomatosis. Multifocal areas of necrosis are present replacing bronchi. Note adjacent arteries are relatively uninvolved. **B.** Bronchocentric granulomatosis in a patient with cystic fibrosis. The bronchial mucosa and wall are replaced by granulomatous inflammation (short thick arrows). The bronchocentric nature of the granuloma can be discerned by its location adjacent to a relatively normal pulmonary artery (upper left hand corner, long thin arrow). A portion of the bronchial mucosa is also intact. The necrotic center of the granuloma overlies the bronchial lumen. **C.** Bronchocentric granulomatosis. Elastic trichrome stain highlights the bronchocentric location of the granuloma and shows partial destruction of the bronchial elastic lamina (same case as Figure 15.20B). **D.** Exudative bronchiolitis. Foci of exudative bronchiolitis were present in other areas of the lungs consisting of necrotic debris, disintegrating neutrophils, and eosinophils (same case as Figure 15.20B). **E.** Exudative bronchiolitis. Periodic acid-Schiff (PAS) stain. Rare septate fungal hyphae are present within the center of this focus of exudative bronchiolitis confirming allergic bronchopulmonary aspergillosis (same case as Figure 15.20B).

the WHO/IPCS monograph stated that during "early" years when poor or no control measures were used, there was "high total dust exposure," especially during grinding of brakes and the use of compressed air to blow off dust, but lower levels "were measured when engineering controls were introduced."

The same WHO/IPCS monograph set forth the mean airborne asbestos fiber concentrations measured during maintenance and replacement of brakes. Studies carried out in 1976 revealed mean concentrations of 3.8 fibers/mL for grinding truck brakes and 15.9 fibers/mL for blowing out brakes. Different studies carried out in the same year also found a mean airborne fiber concentration of 3.8 fibers/mL for grinding brake blocks, 16 fibers/mL for blowing out the brakes, and 2.5 fibers/mL for "dry brushing." Subsequent studies have generally found lower airborne fiber concentrations, but one investigation carried out in 1985 found that blowing off and grinding brakes produced a mean airborne fiber concentration of 6.25 fibers/mL. Other investigations also recorded elevated airborne fiber concentrations from such maintenance and replacement work on brakes,[344,345,352] whereas later studies recorded lower[353,354] or no significant[351] elevations of airborne fiber concentrations.[343] Furthermore, in Germany, Rödelsperger et al.[355] recorded the presence of long fibers 5 μm or more in length in the airborne dust.

A study by Butnor et al.[356] on lung tissue fiber analysis for 10 cases of MM among brake mechanics found that the individuals with elevated fiber counts had "excess" commercial amphibole fibers in their lung parenchyma and that elevated levels of noncommercial amphibole fibers—such as tremolite as a marker for chrysotile, or anthophyllite or actinolite—were found only in those who also had elevated levels of commercial amphibole fibers, leading to the conclusion that those subjects had "unrecognized" exposures other than the brake dust exposure. However, this study concerned only a small number of MM cases associated with exposure to brake dust, with no analysis of MM risk relative to parenchymal asbestos fiber concentrations.

In addition, one of these cases was evaluated by Dodson et al.[357] by ATEM, which found high concentrations of chrysotile in parenchymal lung tissue and two chrysotile asbestos-cored asbestos bodies.

Several reviews have argued that there is no increased risk among automotive mechanics,[343,358–360] These publications have been funded by the automotive industry, related to litigation in the U.S.[343,361] Those same reviews have also been criticized by Egilman and Billings[361] on a number of grounds and, in generic sense, by Egilman and Bohme[362] and Gennaro and Tomatis.[363] These latter three reviews can be regarded as adversarial or polemical, but they do raise substantive issues of risk assessment such as stratifying cumulative exposures within the group being studied in order to avoid underestimating the risk for those exposed or, conversely, overestimating the risk for those not, or only minimally, exposed.[364]

In addition, to evaluate any risk cogently, a distinction should be made between work on worn (heat-altered) versus work with new brake linings and, perhaps, between those who worked with brake materials for passenger cars as opposed to those who worked with brake materials for heavy vehicles (trucks).

It is well known that death certificates are a poor measure of disease outcome because of their inherent limitations, and studies that rely on death certificate diagnoses are subject to error as was pointed out by Paustenbach et al.[343] relative to the Connecticut friction products study. Death certificates simply may not list the disease under investigation (e.g., mesothelioma). It is also essential that all cases of the disease in question are captured by the study: this is a major problem when the duration of the study is short and cannot allow for the long latencies that underpin MM induction by asbestos. Another issue that must be taken into account is ensuring that the control reference population is truly unexposed in order not to underestimate the risk of disease in the exposed group.[303] A further question is whether the individual studies reviewed had the statistical power to detect small increments in risk if they did exist.[38,365]

Data in Australia point to an increased risk of mesothelioma among brake mechanics. The Australian Mesothelioma Register (AMR) Report for 2002 lists 59 cases of mesothelioma for the exposure category *brake linings–made/repaired* (single exposure only) and a further 19 cases for the same class of exposure but with multiple patterns of exposure, giving a total of 78 cases.[36,43,193,366] Taking into account census data for automotive mechanics in Australia, it has been estimated that brake mechanics have a MM rate of at least 20 cases per million person-years, as discussed in the Dispute Settlement Report for the WTO[42] (i.e., a risk that is up to about 20-fold greater than the background risk of mesothelioma). In addition, it has been noted that the increase in the number of cases of mesothelioma apparently related to work on brake linings roughly parallels the increase in the number of cases of mesothelioma related to other occupations that involved asbestos exposure.[367]

As of 2007, the AMR data constitute the strongest evidence for an increased risk of mesothelioma among brake mechanics who ground and chamfered new brake pads/linings/blocks, but those figures have been criticized as inferior in probative value to formal epidemiologic studies (an issue debated at some length in the WTO report on chrysotile[42]). In terms of science, the question of whether automotive mechanics—and especially dedicated brake mechanics with protracted exposures to dust derived from the grinding/chamfering of new brake

blocks/linings—have an increased risk of MM remains unresolved and contentious.

Summary

- The association between asbestos inhalation and the development of MM fulfills all of the Bradford Hill criteria[368] for the establishment of causality, in terms of the strength, consistency and specificity of the association, biologic gradient (dose-response), relationship in time, experimental evidence, reasoning by analogy, biologic plausibility, and coherence of the evidence (and its apparent resistance to falsification[369,370]).
- All forms of asbestos have the capacity to induce MM, but the commercial amphiboles crocidolite and amosite are substantially more potent on a fiber-for-fiber basis than chrysotile (white asbestos). The exact ratio of potencies for crocidolite, amosite, and chrysotile remain somewhat uncertain, with different ratios being cited in the literature.
- No lower (minimum) threshold level of exposure to asbestos has been delineated below which there is no increase in the risk of MM, and most authorities approach causation of mesothelioma by asbestos from the perspective of a no-threshold model.
- From the Peto model and its modifications, the risk of MM can be related to cumulative asbestos exposure (assessed from the intensity, frequency, and duration of exposure) multiplied by time in years raised to about the cubic or 4th power), so that other factors being equal, the time elapsed following commencement of exposure is a major probability factor for risk; that is, early exposures are more significant for MM risk than later exposures, other factors remaining constant.
- Epidemiologic studies indicate that there is no increase in the risk of MM for at least 10 years following the commencement of exposure, and the Helsinki criteria,[220] for example, adopt a minimal 10-year latency interval in order to assign causation of MM to asbestos; other authorities require a minimum latency interval of 15 years.
- One factor that emerges from the Peto model and its modifications is that when there are multiple asbestos exposures, each contributes to cumulative exposure and hence to the risk and causation of MM, within an appropriate latency interval.
- Asbestos alone appears capable of acting as a *complete* carcinogen for the mesothelium. As such, asbestos and the secondary reactions associated with its inhalation are apparently sufficient over time to elicit malignant transformation of the mesothelium.
- Only a minority of those exposed even heavily to asbestos develops MM, even after heavy exposures to amphibole asbestos. This has given rise to the notion that there may be a possible genetic predisposition to MM.

The Molecular Pathogenesis and Pathology of Malignant Mesothelioma

The mechanisms whereby asbestos fibers induce malignant transformation of mesothelial cells have long remained elusive, despite extensive investigation.[371–374] Nonetheless, there have been substantial advances in uncovering some of the mechanisms for the induction of MM, and these appear comparable to the multiple steps implicated in the development of other cancers. It is now recognized that asbestos fibers themselves are carcinogenic,[37] mainly by indirect mechanisms, and that malignant transformation is a multistage process, correlating with the known long latency interval between the first exposure to airborne asbestos fibers and the subsequent diagnosis of the MM (see later discussion). However, no single molecular event or series of events can explain all MMs, and most studies have investigated only single steps in what appears to be a highly complex sequence of cellular and molecular events (Fig. 43.9).

Malignant mesotheliomas do not commonly show mutations in oncogenes, but rather multiple alterations in

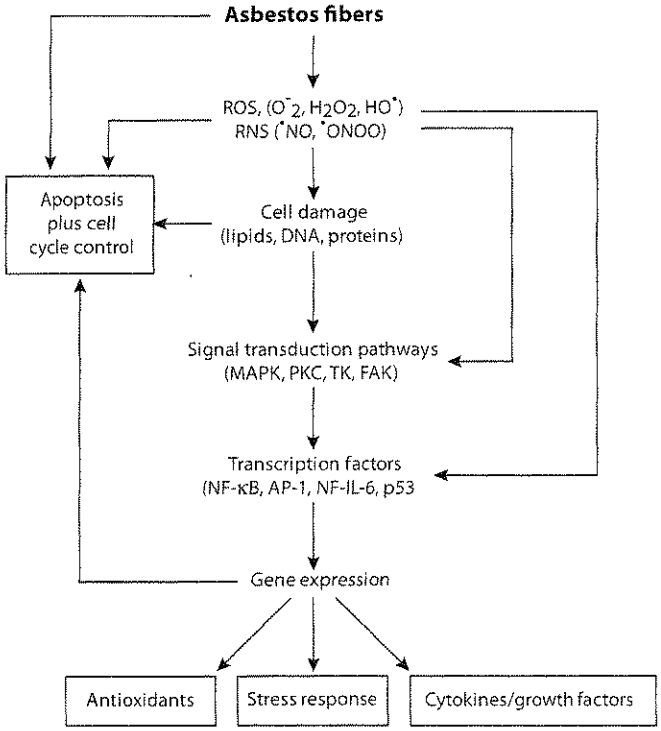

FIGURE 43.9. Mechanisms of asbestos-induced pleuropulmonary toxicity. Schematic illustration of the likely pathways involved in asbestos-induced damage. ROS, reactive oxygen species; RNS, reactive nitrogen species; MAPK, mitogen-activated protein kinase; PKC, protein kinase C; TK, tyrosine kinase; FAK, focal adhesion kinase; NF, nuclear factor; IL, interleukin. See text. (Modified from Kamp and Weitzman.[371])