資料３－１

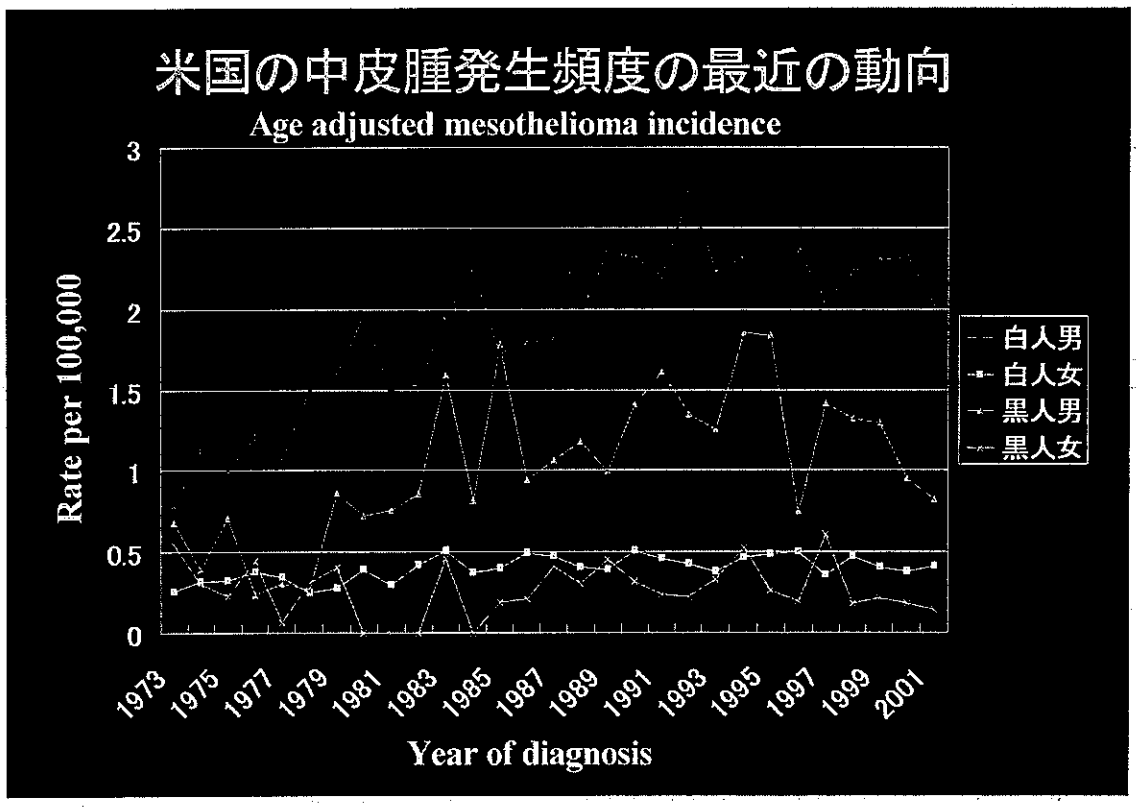
中皮腫等の医学的知見について

Ⅰ：一般環境経由のアスベストの曝露の可能性について

(1)80 年代にアスベストの職業性曝露が著明に減少した後、米国では environmental exposure に注意が向けられた。

(2)米国の都市の大気中アスベスト濃度は、1～100 ng/m3 で、最も多かったのは New York で、その繊維は非常に短い chrysotile fiber であった。しかし、都市の air pollution が中皮腫の risk を上げるという根拠は示されていない〔p.21 MESOTHELIOMA, BWS Robinson & AP Chahinian ed, MARTIN DUNITZ〕

(3)北米・西欧州の女性中皮腫の mortality は、この 20～30 年は変わっていない。



II ：石綿の飛散距離と中皮腫について

基本的事項：中皮腫と石綿曝露の因果関係

(1)中皮腫と石綿曝露との因果関係は明らかであり、否定する報告はない。

(2)データを解釈する前に、中皮腫とアスベストの因果関係を、アスベストを単一のものと考え解釈すると過大または過小評価につながる（下記確認）

a)代表的なアスベストには、crocidolite(青石綿)、amosite(茶石綿)、chrysotile(白石綿)がある。発ガン性は crocidolite≫amosite≫≫chrysotile である。

b)職業性曝露の場合、中皮腫になる危険性は

crocidolite：amosite：chrysotile =500：100：1 である。

〔Hodgson et al, Ann Occup Hyg, 2000;44:565-601〕

工場からの石綿の飛散距離と中皮腫

(A)石綿工場(アモサイト断熱材工場 Paterson, USA)と近隣住民(男子)の死亡状況の調査

〔Hammond et al. Ann N Y Acad Sci. 1979;330:417-22〕

"Mortality experience of residents in the neighborhood of an asbestos factory".

要旨：

1)アモサイト断熱材工場(1949 年～54 年操業)から 0.5 マイル(800m)内の居住区、他の地域との比較をコホートで検討。1962 年～76 年の死亡を調査

2)679 名中 5 名の中皮腫死亡あり（家族）

3)アスベストダストは操業を中止した 20 年後にでも従業員の家で見つかっている。

4)0.5 マイル内の居住区の mortality の増加を確認できなかった。

(B)石綿工場周囲 800m 以内に中皮腫 25 名中 11 名が在住していた事例

〔Newhouse & Thompson, Br J Ind Med. 1965;22:261-9〕

London でアスベスト曝露が明らかでない中皮腫患者 25 名の内 11 名が石綿工場周囲 800m 以内に居住

(C)Chrysotile 石綿工場(New Jersey, Somerville)周辺住民の中皮腫

1)1979-1990 年の 1358 人の New Jersey の中皮腫の調査で Chrysotile 石綿工場周囲が男性・女性とも多い

Ⅲ：今後の中皮腫の発生数の予測

(1)Finland の Tossavainen は本邦を除く 11 カ国のアスベスト消費量と中皮腫死亡数もとに解析；　170 トンのアスベストが中皮腫を 1 人発生させる。

〔Tossavainen A: Int J Occup Envion Health, 10:22-25, 2004〕

(2)この結果を参考に単純計算する

1960 年初頭の本邦のアスベスト輸入量は年間 10 万トンである。40 年の潜伏期間を経た 2000 年の中皮腫の予測死亡数は 588 人となる。実際には 1998 年は 570 人、1999 年 647 人、2000 年 710 人であり、潜伏期間を 38 年とすると符合する。本邦のアスベスト輸入量のピークは 1974 年の 35 万トンであり、2014 年には中皮腫死亡数は 2000 人/年を超えることも予想される。

Ⅳ：中皮腫の医学的知見について

A：中皮腫であれば、どの位の割合で石綿曝露が原因といえるのか？

(a)多くの論文があり、各々の報告でデータが多少異なる。それらを総括したものとして、

○　Fraser & Parē の Diagnosis of Diseases of the Chest (4th Ed) **(資料 2)**

(1)50%以上とするものが殆どで、多くが 80～90%である。

(2)女性より男性において暴露との因果関係が明確である。

＊crocidolite と amosite に接触のあった職種が中皮腫になるリスクが高い。chrysotile を扱った群の比率と異なって当然である。

B:中皮腫発症について石綿以外の原因、要因はどのくらいあるのか？

(a)アスベスト以外の繊維状鉱物

erionite(Zeolite 属の一種)が中皮腫と胸膜プラークを引き起こす。Erionite は Central Turkey と Western US の土壌に存在するゼオライトの一種である。

(b)放射線

1)放射線照射野に second malignant neoplasm として稀に発症。

照射後 19.5 年で中皮腫が発症する〔Cavazza et al, Cancer, 1996;77:1379-1385〕

2)広島と長崎における原爆被爆者における中皮腫の発生状況〔Mesothelioma in Japan, P.351-358. MESOTHELIOMA, BWS Robinson & AP Chahinian ed, MARTIN DUNITZ〕

長崎：中皮腫死亡１名あり。

1970～1994年に胸膜原発性腫瘍で40名、肺癌で1217名死亡

広島：英文報告例はなし。1959～85年中皮腫の増加ある(邦文論文)

(c)ウイルス感染等

Ⅴ：中皮腫のstagingと生存率について

（資料３）

Ⅵ：中皮腫の確定診断を行う方法や診断の正確性について。病理診断における中皮腫の診断方法について

（資料４）

Ⅶ:病理組織またはその他の検査によって中皮腫の原因を石綿と特定することはできるのか？（例　石綿小体、石綿繊維が無くても、石綿が原因である例もあるのか？）

資料②-1

CHAPTER 72

Pleural Neoplasms

MESOTHELIOMA

Diffuse mesothelioma is an uncommon, but increasingly recognized, malignant neoplasm derived from mesothelial cells of the pericardium, peritoneum, or pleura; rare cases apparently derived from mediastinal mesothelial cysts have also been reported.[1] Of all these sites, the pleura is by far the most common. The neoplasm is important not only because of its dismal prognosis but also because of the potential economic impact of litigation and workers' compensation.[2]

Epidemiology

Before 1960, mesothelioma was so rare that its very existence was questioned by some prominent pathologists.[3] Although it is now a well-established entity, the tumor is indeed very uncommon; for example, the overall incidence in the United States has been estimated to be only about 2 cases per million per year.[4,5] However, incidence figures vary considerably in different geographic regions, largely reflecting the likelihood of environmental or occupational asbestos exposure. For example, incidence rates in areas that have had heavy shipbuilding activity, such as Seattle and Rotterdam, have been found to be 20[6] and 60[7] per million, respectively. There is evidence that the incidence has been increasing in the recent past (at least in men and in some geographic regions) and may not cease until the early part of the next century.[8–11]

The incidence of mesothelioma also shows a striking sex predominance, a finding largely, if not entirely, related to the increased likelihood of occupational asbestos exposure in men: it has been estimated that only about 5% of women in North America have such exposure[12] and that 85% to 90% of all mesotheliomas occur in men.[13] In groups of women who have occupational asbestos exposure, incidence rates are equivalent to those of men.[15] It is thus unlikely that gender itself is a risk factor. The vast majority of cases of mesothelioma occur in adults, the mean age at diagnosis being 60 to 65 years.[13,16] It has been estimated that only 2% to 5% of tumors appear during adolescence or childhood.[17]

Etiology

There is good evidence that the majority of cases of mesothelioma are related to a carcinogenic effect of asbestos. However, there are some patients in whom the lung asbestos burden is relatively slight[18] or overlaps that of the general population.[19] In addition, the tumor was recognized at the turn of the century when little asbestos was being used[20] and sporadic cases occur in children too young to have had significant asbestos exposure within the usually accepted latent period.[21] Although these observations may reflect the existence of a very low threshold for asbestos-related neoplasia, other factors, including fibrous minerals such as erionite, radiation, and pleural fibrosis, have been clearly implicated in a small number of cases.[22] The possibility that hereditary, infectious, or dietary influences may be important has also been considered.

Asbestos

The close association between asbestos and mesothelioma was first reported by Wagner and colleagues in 1960.[23] Since that time, abundant evidence has been published confirming their observation,[24] and it is now clear that exposure to asbestos is by far the most important risk factor for the development of this neoplasm. (Despite this, it should be remembered that many more cases of pulmonary carcinoma have been associated with asbestos exposure than mesotheli-

oma.[25]) The evidence in favor of a pathogenic relationship between mesothelioma and asbestos is derived from several sources.

Epidemiologic Studies and Clinical Experience Showing a Strong Relationship between Asbestos Exposure and Mesothelioma. A history of exposure to asbestos varies considerably in different series of patients who have mesothelioma,[26] a feature related in part to the particular population under study; however, it has been greater than 50% in most studies[27–35] and as high as 80% to 90% in many.[36–41] In some reports in which the number of asbestos-related cases is relatively small, the lack of association may be the result of an inadequate occupational or environmental history: it is well known that the neoplasm can develop after minimal asbestos exposure[28, 42] and many years after the initial contact (*see* farther on);[19, 43] in addition, secondary contact from a family member may be easily missed if not carefully assessed.

As indicated previously, the association between asbestos exposure and mesothelioma has generally been found to be much stronger in men than in women;[4, 38] however, in one review of 105 female patients who had the tumor, 74 (80%) of the 93 for whom information was available had a history of contact with the mineral.[44]

Epidemiologic studies show a high incidence of the tumor in individuals involved both in the mining and production of asbestos and in the numerous secondary occupations associated with its use (Table 72–1).[16, 45–47] Workers at particular risk in the latter occupations include those in the construction, oil refining, and railroad industries, insulators, garage mechanics, shipbuilders, and plumbers. As indicated previously, some occupations have been associated with an especially high risk; for example, a number of investigators have shown a dramatic clustering of cases in the vicinity of shipyards,[6, 48–51] the incidence of the tumor in such regions being as high as 6.2 per 100,000.[7] As might be expected, spraying asbestos-based insulation material has also been associated with a significantly increased risk of the disease.[52] Occupational asbestos exposure can also occur in uncommon or apparently unlikely situations. For example, exposure (and

Table 72–1. OCCUPATIONS AT RISK FOR ASBESTOS EXPOSURE: MINING, MILLING, MANUFACTURING, AND SECONDARY USES

PROCESS	PRODUCTS MADE OR USED	JOBS POTENTIALLY AT RISK
Production		
Mining		Rock mining, loading, trucking
Milling		Crushing, milling
Handling		Transport workers, dockers, loaders, those who unpack jute sacks (recently replaced with sacks that do not permit fibers to escape)
Primary Uses		
Spray insulation	Spray of fiber mixed with oil	Spray insulators (construction, shipbuilding)
Filler and grouting		
Manufacturing of		
Textiles	Cloth, curtains, lagging, protective clothing, mailbags, padding, conveyor belts	Blending, carding, spinning, twisting, winding, braiding, weaving, slurry mixing, laminating, molding, drying
Cement products	Sheets, pipes, roofing shingles, gutters, ventilation shafts, flower pots	Blending, slurry preparation, rolling, pressing, pipe cutting
"Paper" products	Millboard, roofing felt, fine-quality electrical papers, flooring felt, fillers	
Friction materials	Automotive products: gaskets, clutch plates, brake linings	
Insulation products	Pipe and boiler insulation, bulkhead linings for ships	
Applications		
Construction		
New construction	Boards and tiles; putties, caulk, paints, joint fillers; cement products (tiles, pipes, siding, shingles)	Direct: carpenters, laggers, painters, tile layers, insulation workers, sheet metal and heating equipment workers, masons Indirect: all other workers on construction sites, such as plumbers, welders, electricians
Repair, demolition		Demolition workers for all of these
Shipbuilding		
Construction	Insulation materials (boards, mattresses, cloth) for engines, hull, decks, lagging of ventilation and water pipes, cables	Laggers, refitters, strippers, steam fitters, sailmakers, joiners, shipwrights, engine fitters, masons, painters, welders, caulkers
Repair, refits	Insulation materials, as described for "Construction"	Direct: all above jobs on refits, dry dock, and other repair operations Indirect: maintenance fitters and repairers, electricians, plumbers, welders, carpenters
Automotive industry		
Manufacture	Gaskets, brake linings, undercoating	Installation of brake linings, gaskets, and so on
Repair	Gaskets, brake linings, undercoating	Service people, brake repairers, body repairers, auto mechanics

Modified from Becklake MR: Asbestos-related diseases of the lung and other organs: Their epidemiology and implications for clinical practice. Am Rev Respir Dis 114:187, 1976.

mesothelioma) has been documented in workers involved in the manufacture of cigarette filters[53] or gas masks,[54] in the production of jewelry,[55] and after the preparation of an asbestos-based cement product in a home basement.[56]

There is good evidence that exposure to asbestos outside the workplace is also hazardous.[51] Such contact can be secondarily related to occupation; for example, mesothelioma has been reported in wives, children, and siblings of individuals who work in asbestos plants, cement factories, or shipbuilding sites, in some cases probably after asbestos exposure during laundering of the workers' clothes.[14, 51, 57, 58] Similarly, an increased incidence of tumors has been documented in individuals who reside near factories that process asbestos, presumably as a result of an increased level of asbestos in the atmosphere.[16, 59] It has also been speculated that significant contact with asbestos may occur in office buildings or schools in which asbestos has been used for insulation, fireproofing, or acoustic control;[46] however, although occasional case reports[60] and the results of epidemiologic studies[61] have shown that asbestos-related disease (including mesothelioma) does occur in these settings, the magnitude of the problem appears to be very small.[4] Some cases of nonoccupational environmental mesothelioma are also related to the presence of asbestos in the soil, as in some regions of Greece,[62, 63] Corsica,[64] Turkey,[65] and Cyprus,[66] where significant quantities of tremolite have been found in this source.

Studies of Asbestos Burden in the Lungs of Patients with Mesothelioma. Many investigators have documented an association between an increased number of asbestos bodies and/or fibers in lung tissue and the presence of mesothelioma.[67–71] For example, in one study of 50 workers seeking compensation in Quebec, 48 had an asbestos body or total fiber count greater than the 95% confidence interval of a control population.[72] Asbestos body and fiber counts are not always elevated in the same patient. For example, in one investigation of the lungs of 18 patients who had mesothelioma in which the asbestos body counts were within normal limits, 6 were found to have an asbestos fiber burden in the upper fifth percentile of normal levels.[73]

Despite the finding of an increased number of asbestos fibers in the lungs of many patients who have malignant mesothelioma, several groups of investigators have found this number to be intermediate between those found in the general population and in patients who have asbestosis.[18, 29, 74] In one study of patients in the latter group, an increased incidence of pulmonary carcinoma was found in those with moderate to severe asbestosis and of mesothelioma in those with minimal or slight disease.[75] It has been speculated that this finding may reflect a dose relationship between asbestos burden and the development of asbestosis and lung cancer that does not exist for mesothelioma;[76, 77] this, in turn, suggests that there may be no threshold of asbestos burden below which there is no risk for the development of mesothelioma. Although this hypothesis has not been proven conclusively, some experimental evidence supports it.[78]

Experimental Studies in Animals Showing the Development of Mesothelioma after Asbestos Exposure. Diffuse mesothelioma morphologically similar to that seen in humans has been shown to develop after instillation of asbestos fibers into the pleural space[79, 80] or trachea[81] of various animals.

Mesothelioma Risk and Asbestos Fiber Type. The risk of developing mesothelioma varies considerably with the type of asbestos to which an individual is exposed. The majority of evidence indicates that the greatest risk occurs with the amphiboles crocidolite and (to a lesser extent) amosite;[71, 82–85] the risk with anthophyllite appears to be very small.[86] The importance of chrysotile has been the subject of some debate;[11, 79, 87] although the results of most studies suggest that exposure to this substance is associated with an increased risk of mesothelioma, there is substantial evidence that the risk is much smaller than that of crocidolite and amosite and may, in fact, be related to the presence of contaminating tremolite.[88–91]

The variable pathogenicity of the different types of asbestos may be related to their different physicochemical characteristics. Long straight fibers, such as those of the amphiboles, tend to be transported to the periphery of the lung, whereas the irregular curly shape of the chrysotile fiber predisposes to its deposition in the more central airways.[79] Thus, amosite and crocidolite tend to accumulate in relatively large numbers in the peripheral portions of the lung close to the pleura. There is also evidence that chrysotile fibers fragment with time and are transported out of the lung via the mucociliary escalator or lymphatics.[79, 92] Amphiboles, on the other hand, are relatively stable and remain either constant in number in an individual who is no longer exposed or continue to accumulate over the lifetime of an individual who is continually exposed. For example, in one study of workers in a Norwegian cement plant, analysis of fiber types showed approximately 92% of the fibers to be chrysotile, 3% amosite, 4% crocidolite, and 1% anthophyllite.[93] However, electron microscopic and x-ray microanalysis of lung tissue samples from workers who had died of mesothelioma or pulmonary carcinoma showed a completely inverse proportion, the percentage of chrysotile asbestos fibers ranging from 0% to 9% and of amphiboles from 76% to 99%. There is also experimental evidence that chrysotile and crocidolite fibers interact differently with chromosomes of mesothelial cells,[94] possibly reflecting a different carcinogenic potential.

Other Fibrous Minerals

Because the risk of mesothelioma appears to be closely related to the size and shape of inhaled asbestos fibers, attention has been directed to the possibility that other minerals that have the same physical characteristics as asbestos also may be pathogenic. The most clearly implicated of these minerals is erionite, a member of the zeolite group that is found in the soil of central Turkey and the western United States (*see* page 2452). Several epidemiologic[95–97] and experimental[98] studies have provided evidence implicating this substance in the production of both pleural plaques and mesothelioma. A variety of man-made fibers, including fiberglass, can also induce cancer when introduced directly into the pleural space of animals;[79, 99] however, inhalation of these substances by humans does not appear to be associated with an increased risk of mesothelioma.[100] A possible association with silica fibers in inhaled sugar cane has also been reported.[101]

Radiation

Although the findings of several reports suggest that external radiation is responsible for occasional cases of meso-

thelioma,[102–105] this is clearly a very uncommon event. For example, in one retrospective review of 1,000 patients who had received thoracic radiation at the M. D. Anderson Cancer Center, only 3 were considered to have developed complicating mesothelioma.[106] In another series of 251,750 women who had breast carcinoma (of whom approximately 25% had received radiotherapy) and 13,743 patients who had Hodgkin's disease (about 50% having had radiotherapy), mesothelioma developed in only 6 patients (in 2 who had breast carcinoma and radiotherapy and in 4 who had carcinoma and no radiotherapy).[107] In one review of eight cases of radiation-associated mesothelioma, the mean age at the time of diagnosis was 45 years and the average interval between radiation and diagnosis of mesothelioma was 21 years (range, 11 to 29 years).[108] Experimental evidence suggests that the risk is significantly increased when radiation is combined with asbestos exposure.[108] An increased incidence of mesothelioma (predominantly peritoneal) has also been documented in patients who have a history of exposure to Thorotrast.[109]

Infection

Simian virus 40 (SV40) is a double-stranded DNA organism of the papovavirus group that normally infects the kidneys of rhesus monkeys.[110] The virus was inadvertently transmitted to many humans in contaminated polio vaccines in the late 1950s and early 1960s. Although potential adverse effects associated with such transmission were inapparent for a long time, concern was raised when it was found that the virus has a variety of oncogenic effects in tissue culture and can induce mesotheliomas in hamsters.[111] Moreover, a number of investigators have found DNA sequences identical to those of the virus in a substantial proportion of human mesotheliomas.[112–116] The oncoprotein of the virus (SV40 large cell antigen [Tag]) has been found to bind and inactivate retinoblastoma family proteins[114] and p53,[115] suggesting that the virus may mediate oncogenesis by inactivating tumor suppressor genes. These observations provide evidence of a possible role for SV40 in the pathogenesis of mesothelioma, either by itself or as a cofactor with asbestos. However, not all investigators have been able to demonstrate evidence of the virus[117] or of associated oncogene mutations[118] in mesothelioma, and further studies are necessary before it can be concluded that SV40 has a pathogenic role in the development of the tumor.

Rare cases of mesothelioma have been documented in patients who have the acquired immunodeficiency syndrome in the absence of asbestos exposure;[119] although their number is insufficient to be certain of a true relationship, it has been postulated that the tumor may be secondary to human immunodeficiency virus or cytomegalovirus infection. Based on the observation of two cases of mesothelioma in 458 patients who had *Yersinia enterocolitica* infection, one group of investigators speculated that immunologic reactions related to the latter organism might be involved in the pathogenesis of the tumor.[120] In one investigation of 50 mesotheliomas in which *in-situ* hybridization was utilized in an attempt to detect Epstein-Barr virus–encoded RNA-1, no evidence of infection was identified in any tumor.[121]

Genetic Factors

A familial occurrence of mesothelioma has been documented by several investigators.[122–126] Although many cases are likely the result of a common source of environmental or occupational asbestos exposure,[126a] it is also possible that there is a degree of genetic susceptibility. For example, in one investigation of the first-degree relatives of 196 patients who had pathologically confirmed mesothelioma, a twofold increase for the risk of the tumor was found in asbestos-exposed men who had two or more relatives with a history of cancer.[127] In another study of 39 patients who had mesothelioma, 28 (71%) reported a parental history of cancer (most often of the gastrointestinal tract) compared with 114 of 259 (44%) in an age-matched control group.[128]

Miscellaneous Factors

Malignant neoplasms occasionally arise in relation to a chronically scarred pleura after chronic empyema or therapeutic pneumothorax for tuberculosis; although most of these are squamous cell carcinomas,[129] occasional tumors morphologically similar to mesothelioma have been described.[130] The results of one epidemiologic investigation suggest that ingestion of some carotenoid fruits and vegetables may decrease the risk of developing mesothelioma.[131] There is no evidence of a pathogenetic association between the tumor and tobacco smoke.[132, 133]

Pathogenesis

The pathogenesis of asbestos-related mesothelioma is far from clear.[79, 134] As indicated earlier, the size and shape of asbestos fibers are important determinants of carcinogenicity, those that are relatively long and thin being the most harmful.[80, 82, 135] As an example of the significance of this feature, it is possible to prepare samples of chrysotile that are long and straight (in contrast to their natural state) and that are at least as carcinogenic as amosite, both in inhalation experiments and after introduction of the fiber into the pleural space.[80] Support for the importance of this feature is derived from a study of cultured human mesothelial cells in which the presence of longer asbestos fibers was associated with an increase in the potent mesothelial mitogen epidermal growth factor.[135a] It is possible that factors associated with particle deposition or clearance are also important in determining pathogenicity.[136] Although it is unclear exactly how they emigrate from the lung, fibers have been shown to be concentrated in "black spots" (focal aggregates of carbon-laden macrophages) in the parietal pleura;[137] because there is evidence that most, if not all, mesotheliomas originate in the parietal rather than in the visceral pleura,[138] such localization may be important pathogenetically.

Instillation of asbestos into the peritoneal space of experimental animals is rapidly followed by evidence of mesothelial injury and an inflammatory reaction;[139] mesothelial hyperplasia, sometimes atypical cytologically, ensues and can remain for months after the initial asbestos contact.[140] It is possible that oxygen radical production induced by asbestos fibers may be important in the inflammatory reaction and in causing cell damage.[141] A variety of such molecules can be seen in association with asbestos, derived either directly