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KNOWLEDGE OF THE ASSOCIATION BETWEEN ASBESTOS AND DISEASE:

This note covers two matters:

- (a) the chronology of medical knowledge associating asbestos exposure and asbestosis, lung cancer, and mesothelioma
- (b) a review of specific literature in the CSR Limited technical library up to the mid 1950's.

(a) Chronology

I can do no better than refer to the brief chronology provided by Dr. McCullagh, and the more extensive and authoritative chronology given by Selikoff and Lee in "Asbestos and Disease" (Academic Press N.Y. 1978). A copy of pages 20 to 32 of the latter is attached.

(b) Literature in CSR Technical Library

Mr. I.P. Willington of my department has surveyed all periodicals which may possibly have been of relevance, and to which CSR subscribed in the years 1946-54. There were some references to asbestos mining, but very few on health effects.

The main articles found were as follows.

1. The Australasian Engineer, April 8, 1947.
Article on asbestos mining in Eastern Canada (Thetford Mines, Quebec). Description of mine and mill, no reference to dust control or health effects. Photographs of mining and processing show no respirators, and e.g. piles of fibre on floor at bagging station.
2. Chemical Engineering and Mining Review, April 10, 1951. Short paragraph on Asbestosis, as below.

"Asbestosis Studied Experimentally"

Inhalation experiments with asbestos dust and animals suggest that the action of asbestos dust on the lung is very different from the action of silica dust. Some conclusions from the experiments are:-

C 3753

- * Long asbestos fibres (20 to 50 Microns) are essential in the production of the peribronchiolar fibrosis: short fibres are incapable

- * The mode of action of the long asbestos fibre in the production of asbestosis is primarily mechanical rather than chemical in nature.
- * Duration of exposure required to develop asbestosis varies inversely as the concentration of long fibres in the atmosphere.
- * Established experimental fibrosis ceases to progress on discontinuance of dust exposure.
- * Aluminium hydroxide failed to neutralise the fibrosing action of the long fibre asbestos.
- * Inhalation of asbestos dust did not alter significantly the final outcome of tuberculosis.
- A.J. Vorwald, T.M. Durkan and P.C. Pratt in A.M.A. Archives of Industrial Hygiene and Occupational Medicine (Vol. 3, p. 1.)".

3. Rock Products, July 1954.

Article "More Efficient Mining and Modern Plant Double Asbestos Production" by Marion L. Briggs. Describes new Ruberoid Co., Newmont Asbestos Division plant in Lowell, Vermont USA.

Bag filters used to remove "all harmful dust and offensive odor".

4. Chemical Abstracts

The following references were found:

<u>Year</u>	<u>Vol</u>	<u>Abst. No.</u>	<u>Topic</u>
1946	40	4451-8	Health survey of pipe covering operations in constructing naval vessels.
1948	42	3875g	Asbestosis. Asbestos bodies and pulmonary asbestosis related to work in a factory processing waste asbestos, and raw Canadian asbestos.
1950	44	5037h	Panel on epidemiology, including environmental and occupational cancer. Refers to Proceedings of U.S. National Cancer Conference 1949. Lung cancer from asbestos mentioned as being discovered

1951	45	9772e	Diseases of the lung resulting from occupational dusts other than silica. Review in Thorax by K.M.A. Perry (1947). Asbestos one of many materials discussed.
1952	46	6291h	Carcinoma and asbestosis of the lung: report of a case. (T.K. Owen, Brit. J. Cancer. 5, 382, 1951)
1953	47	4471C	Lung carcinoma caused by asbestos inhalation. German article by F. Boemke.
1954	48	13043e	Experimental studies in metal cancerogenesis. Tissue reactions in rats and rabbits after parenteral introduction of suspensions of arsenic, beryllium or asbestos in lanolin. (Negative results with asbestos).
1954	48	3572i	The nature of lesions caused by asbestos and mica in experimental pneumoconiosis in guinea pigs. Indian article.
1954	48	14045e	Mineral content of the lungs after exposure to asbestos dust.
1955	49	9195h	Mortality from lung cancer in asbestos workers. Abstract of Doll article (Brit. J. Ind. Med. 12, 81 (1955)).

5. Journal "Asbestos".

May 1941: Safety Problems of The Insulation Contractor. Most important hazard is burns from hot pipes. (!)

Oct 1941: Blue Asbestos in Australia (extract of Report No. 49 issued by the Aerial Geological and Geophysical Survey of Northern Australia).

Sept 1945: Milling Asbestos by J.C. Kelleher. No mention of dust hazard. "Asbestos milling is like no other type of mineral recovery and therefore requires special machinery and mill design."

Oct 1945: Milling Asbestos Part II J.C. Kelleher. "The many millions of cubic feet of air being handled hourly by the air collecting system are heavily laden with fines. This must be deposited without being ejected to the atmosphere, to the detriment of the surrounding community. This objective is

"The finest particles are prevented from passing out to the atmosphere by such methods as electric precipitation or passage through canvas filtering bags."

- Nov 1945 Milling Asbestos Part III J.C. Kelleher General.
- April 1946: p. 14 Australia. Information on asbestos in Australia published by U.S. Bureau of Mines.
- Sept 1946: p. 10 Asbestos Mill at Wittenoom, Australia. Descriptive.
- June 1949: p. 4-16 Recent Trends in Asbestos Mining and Milling Practice by Michael J. Messel. p. 14 "Dust Collecting".

"In asbestos milling, which is a dry process, considerable dust is created in the various operations, together with a large amount contained in the air from the fan exhausts, as the fibre collector is really only a partially efficient separator. Some shorter fibres escape into the fan, and these, if recovered, have commercial value.

In the past, this air has usually been sent through ducts to a large settling chamber, where the heavier material is dropped because of reduced velocity and returned to a special circuit or department in the mill flow. At the end of the dust building there is a chimney for the exhaust dust. In one instance where this dust has been objectionable one company has installed a Cotrell system.

However, a recent successful development has been the application of bag type collectors with automatic shaking devices, which usually can be made to fit very nicely into the top of the conventional mill building. These units not only recover the valuable fibre, but also the dust, so there is a very small amount of exhaust dust in the atmosphere. Some companies are experimenting with the possibilities of recirculating this air. About 98% efficiency by weight is claimed for these units, and at present, there are many installations under way. The cost is approximately 20 cents per cubic foot of air, and about 1 sq ft of filter cloth is necessary for filtering 2 cu ft of air."

- June 1950: p. 18 "Milling 'Amosite' and 'Blue' Asbestos" e.g. "The milling processes for amosite and blue asbestos are quite a bit different from that employed in the preparation of Chrysotile." Reprint of article published by Department of Mines, Union of South Africa, in its quarterly report for July, August, September 1949. Hardness of host rock emphasised.
- July 1951: p. 32 Asbestos bagging machine described.
- Aug 1952: p. 12 Asbestos Deposits of Western Australia described.
- Dec 1954: p. 8 Reference to Department of Mines, Salisbury Southern Rhodesia bulletin on "The Problems of Dust in Asbestos Preparation."

6. Annual Reports of H.M. Chief Inspector of Factories (U.K.).

<u>Report for Year</u>	<u>Published</u>	
1946	1948	No reference to asbestos.
1947	1949	Key article. Statistics of co-occurrence of lung cancer and asbestosis. pp. 66, 78, 79, 80. (But see Buchanan, Annals N.Y. Acad. Sciences, Vol.132 Art.1, p. 510 - "an attitude of caution was adopted and no formal claims of any association were made".)
1948	1949	Asbestosis cases in table of pneumoconiosis.
1949	1951	p. 139 Pneumoconiosis table p. 144-146. Discussion of Asbestos Regulations 1931 and progress achieved. Critical of asbestos spraying; and use of unlined hessian bags for raw asbestos.
1950	1952	p. 152 Reference to Third International Conference of Experts on Pneumoconiosis called by I.L.O. in Sydney 1950.
1951	1953	Tables only.
1952	1954	p. 127 Note on progress in asbestos dust suppression in cording operations. p. 172 Table

1954	1955	p. 153 Loom dust control. p. 190 Update of 1949 cancer statistics.
1955	1956	p. 206 Further update of cancer/asbestosis statistics.
1956	1958	p. 141-145 Discussion of Asbestos Industry Regulations, 1931.

7. CSR Newsletter

Wittenoom operations are mentioned in various issues of the CSR Newsletter. None refer to dust or dust collection.

Examples are:

August 1948 (p. 83):	"Community Life at Wittenoom". Account by Mrs. A.R. Johnston.
Feb 1949 (p. 107):	"Wittenoom Gorge". Anonymous account of a visit.
March 1954:	Photographic competition. Two photos of mill by W.A. Dibdin.
Sept 1954 (p. 13):	The future of blue asbestos. Refers to Tariff Board enquiry.
Aug 1956 cover: p. 10-11	(old?) photo of mill Good prospects for Australian blue asbestos. - U.S. industrialists visit Wittenoom (Johns-Manville). - Mill output increases. - Increased employment and overseas credit. - Government recognition.
Mar 1957: p 12:	Mining of Blue Asbestos. Description of mining and building at Wittenoom. Photographs.
Sep 1958: p. 12	Wittenoom - a town has risen out of wasteland. Descriptive with photographs.

Note: See also South Pacific Enterprise pp 213-229 (1956).

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ASBESTOS AND DISEASE

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ACADEMIC PRESS N.Y. 1978

TABLE 1-4

United States Asbestos Consumption-1972 (40)^{a,c}

End uses	BM I ^b	BM II ^b	BM III ^b	Total
Construction	—	214,800	100,600	323,400
Floor tile	—	4,700	80,000	84,700
Friction materials	5,400	24,000	47,600	77,000
Paper	—	2,300	67,200	69,300
Asphalt felts	—	17,000	29,200	46,200
Packing and gaskets	2,000	18,000	10,800	30,800
Insulation	2,600	2,300	10,500	15,400
Textiles	7,600	—	100	7,700
Other	1,000	80,800	33,700	115,500
	16,600	363,700	387,700	770,000

^a Chrysotile, short tons.

^b BM I, Spinning.

^c BM II, Shingle and paper.

^d BM III, Shirts

^e Reproduced with kind permission of the publisher of Asbestos.

RECOGNITION OF PATHOGENICITY

Early Warnings

Pliny the Younger (61-114 A.D.), being of somewhat more sensitive conscience than was usual at the time, is said to have commented on the sickness of slaves who worked with asbestos (17,256). But there is no indication that his words were heeded. Occupational disease was not a matter of concern until 1472, when Ellenberg in Austria wrote the first account, and even this was not published until 1523-1524 (597). Agricola in 1556 and Paracelsus in 1567 emphasized the diseases of miners, but of course made no mention of asbestos. Zenker coined the term "pneumonokoniosis" in 1867 to cover anthracosis in coal miners as well as siderosis in iron miners (504), but since the number of asbestos workers in any one locality was small, there was little to draw attention to any hazard from its dust until the large workings were opened up in Canada and South Africa.

In 1906 H. Montagu-Murray reported to a Departmental Committee on Industrial Diseases in England concerning a case of pulmonary fibrosis in an asbestos worker on which he had done an autopsy in 1900, but an account of the case seems not to have been published (158), in spite of the fact that Adelaide Anderson, Lady Inspector of Factories,

had been moved in 1902 to include asbestos in the dusts long known as being injurious to man (17). In 1906 Aubault reported numerous deaths in a French asbestos spinning mill and weaving factory over the period 1890-1895 (55). Death in these cases was attributed to the effect of lime dust, but the workers thought it was due to lead. In 1908 Scarpa reviewed the fate of 30 asbestos workers who came to the Turin General Polyclinic over the period 1894-1906 with serious pulmonary disease, diagnosed as being tuberculosis, which was rapidly progressive (649). The association of tuberculosis with asbestos seems to have been in the forefront of physicians' minds, probably because of the disease's prevalence in the community at large at that time (717). To the extent that asbestos dust was considered, it was presumed to act like silica in aggravating response to the tubercle bacillus, as demonstrated by Collis in his Milroy Lectures for 1915 (151). [A]

Anderson's warning of 1902 was corroborated in 1914 when Fahr reported on a woman who had worked in an asbestos factory in Germany and had died of an acute illness with signs of pleuropneumonia (240). At autopsy there was chronic indurative pneumonia "with a large number of crystals of a peculiar nature, which were previously described by Marchand and Riesal in 1906." [Marchand made no mention of asbestos in connection with his "pigmentkristalle" (482).] Vague warnings of disease associated with asbestos were sounded in continental Europe as well as in England prior to World War I, but the real significance was not appreciated. A survey was made by the British Factory Department in 1910, following a death certified as "acute pulmonary phthisis in an asbestos worker" (probably Murray's case), but no health hazard was seen. In 1917 the Department again found no evidence of disease, but a suspicion seems to have been created, since improved ventilation in the asbestos factories was ordered and vigilance seems to have been increased.

In 1912 a Canadian health inspector examining conditions in an asbestos factory, as well as in mines and mills, noted the remarks of one of the oldest practitioners in Bedford, that the large amounts of asbestos dust floating in the air of the clogging room had a weakening effect on the lungs; but generalities of this nature are not uncommon and, as usual, were discounted (22). In 1918, Hoffman, a statistician and vice president of the Prudential Insurance Company in New York, called attention to the probable harmfulness of asbestos dust. He admitted the lack of data in the United States, but based his comments on the little known report by Murray in England. The extent of Hoffman's concern is indicated by his intimation that the Company would not issue life policies on asbestos workers (338). In 1918 as well, Pancoast, Miller, and

Landis noted radiological evidence of pneumoconiosis in the lungs of asbestos workers (566). The report, however, did not attract attention at that time.

Asbestosis Recognized

Historically speaking, the turning point came in 1924, although six years were to elapse before official recognition was granted. The effects of the intensive wartime production of all kinds of new materials had heightened awareness of industrial disease, and it was against this background that Cooke's report of a second known death from pulmonary fibrosis in an asbestos worker was seen (156). In a short note in the *British Medical Journal* he described the case of a 33 year old woman who had worked in asbestos factories for 20 years, 15 of them regularly. Cooke, McDonald, and Oliver reported further on this case in papers published in 1927 (157). The necropsy was done by Mackichan, who suggested that the lungs be sent for further examination. An X-ray had shown extensive fibrosis, more marked in the right lung. Macroscopically, the lungs showed thickened pleura over the entire surface of the lung, with dense adhesions to both the chest wall and the pericardium. Microscopically, there was extensive fibrosis with particles of mineral matter of various shapes but with sharp angles. Tuberculous lesions were also present. The lymph glands showed periaadenitis and fibrosis. There was extensive peribronchial fibrosis. Further studies and comments on asbestos disease, together with a description of the "curious bodies," later to be called "asbestos bodies," were given in another paper in 1929 (158). The word "asbestosis" appeared for the first time in the title of the second 1927 paper (157).

Acceptance was not immediate, however. Pancoast and Peppergrass, reviewing radiological appearances of the pneumoconioses, believed that the fibrosis of asbestos workers was due to admixed silica (567). Hadham, however, writing in 1927, considered that "silicatoses" was more damaging than "silicosis," but he was dealing with hard rock miners, not asbestos workers (61). In 1928 Simson reported four cases with autopsy findings from South Africa, and remarked that it had been known for some time that workers processing asbestos suffer from pulmonary disability (685).

In 1929 Haddow reported his experience to a BMA meeting (300). His partner, Grieve, had drawn his attention in 1926 to the fact that several patients with chest trouble were asbestos workers. Some 15 workers were examined and most were radiographed. In 1927, Haddow, Grieve, and Taylor had found remarkable fibrosis in the lungs which "Professor

Stewart recognized as similar to a case described by Cooke." Sir Thomas Oliver had described the clinical findings before the BMA in 1927 (560). The two patients thus reported soon died. The certification of a third death as due to "bronchopneumonia, secondary to chronic asbestos poisoning, causing pulmonary fibrosis" is credited by Haddow with inspiring official recognition of the disease. He went on to say "No death had ever been traced to asbestos dust in Leeds until the present series. . . I know that many workers had drifted away from the asbestos factory because they believed it was unhealthy. . . ."

In 1928, Seiler published what was claimed to be the first case in which other causes such as tuberculosis were definitely excluded (660). (Murray's case had not been formally published.) A good clinical description was given and, whatever the merits of the claim, this paper apparently engaged official attention (507). Bridge reviewed the situation in 1929 (112), and in 1930, Merewether, then Medical Inspector of Factories, and his colleague, Price, presented a report to Parliament, establishing "the fact that the inhalation of asbestos dust over a period of years results in the development of a serious type of fibrosis of the lungs," and indicating that the remedy would be in dust suppression (508,510).

In 1930 Wood and Gloyne were able to review 37 cases (798). Asbestosis had now definitely arrived! Indeed, reports given at an international conference in Johannesburg the same year gave the impression that at least some physicians had known about it all along, but just did not publish anything (23). Haslam's "Recent Advances in Preventive Medicine," published in 1930, included a subsection on pulmonary asbestosis (324).

Two almost simultaneous papers in 1930 made the first reports on cases in the United States, and each included postmortem findings. That by Mills was published in a journal with limited circulation (519) and largely escaped notice; that by Lynch and Smith benefited from its appearance in a national periodical (468). Donnelly (196) and Ellman (214), both writing in 1933, extended the record of cases in the United States and enlarged the clinical descriptions. The fears of Hoffman and the Prudential Insurance Company had proved well founded! In 1929, the Metropolitan Life Insurance Company initiated what may well have been the first systematic epidemiological investigation of asbestos workers. Over the period 1933-1935 Dreessen and his colleagues reported pneumoconiosis in tale workers (198,199), but the connection with asbestos was not clear. Fulton *et al.* published a preliminary account of a survey of asbestos textile plants in October, 1934, and a more detailed report in October 1935 (250). Lanza and his colleagues

issued a preliminary report in January, 1935, of the findings in an investigation made for asbestos companies in asbestos mines and mills in Canada and in fabricating plants along the Atlantic seaboard (441). Dust counts were taken and radiographs were made on 126 persons selected more or less at random from among those having more than 3 years of employment in the industry. The clinical symptoms were inconclusive, but 67% of the films were classified as positive. No unusual amount of tuberculosis was seen. In 1936 Shull reported on 71 workers who had been dismissed from asbestos plants in North Carolina, and found 16 to have slightly advanced, 35 moderately advanced, and 20 markedly advanced asbestosis; 4 of the 71 cases had had only 1½ years of exposure (679). In the same year McPheeters also reported on textile workers in North Carolina (503), and Lanza published his text on "Silicosis and Asbestosis" (440). Dreesen *et al.* reported in 1938 on a larger study of 511 employees in North Carolina textile asbestos plants, including many relatively new employees. But because of circumstances, unfortunately, they omitted many of those who had left for disability or for other reasons, and thus unavoidably weighted the evidence against the prevalence of disease (200).

In 1930, the International Labor Office in Geneva called attention to the urgency of studying conditions in the asbestos industry. The reports made by Fulton *et al.* on Pennsylvania plants in 1934-1935 were in direct response to this appeal (259). Merewether's Annual Report for 1933-1934 had included talc with asbestos as a pathogenic dust (506). Epidemiological studies were now well under way although they still lacked some sophistication of design.

On the European continent recognition was proceeding more slowly. In 1897, Netolljzky had expressed concern about the probably adverse health effects of the high dust concentrations in asbestos carding and weaving plants of the time (543). But after Fahr's paper of 1914, no attention seems to have been paid to the situation until a French paper by Dhers in 1930 (187), and four others from Germany in 1931 (21)—that by Düttner-Wobst and Trillitzsch described 8 cases from the neighborhood of Dresden; Kruger *et al.* found definite changes in the lungs of 30 asbestos workers out of 52 examined near Dresden; Beiniker recorded two cases with postmortem findings from a factory which made asbestos textile and insulation materials, and in the following year Gerbis and Icko recorded the examination of 33 asbestos workers near Berlin. Timmermans described asbestos bodies. By 1943, 20 autopsy cases had been assembled, but the reviewer, Wedler, estimated that the total probably amounted to 500 cases (783). In Italy, little was published after Scarpa's 1908 account until the Johannesburg conference, when

C 3761

Lovisetto and Mussa described well developed situations (23). In other European countries the first publications on locally occurring asbestosis appeared later, possibly because intensive manufacturing started later.

APPEARANCE OF OTHER PATHOLOGICAL CONSEQUENCES

Although it presented some differences, the pulmonary fibrosis developing in response to the inhalation of asbestos seemed at first to be understandable in the light of other dust diseases; asbestosis could be regarded as another variant of Zenker's general pneumoconiosis. In some respects, indeed, it appeared simpler, because the progressive massive fibrosis (PMF) that not infrequently develops as a complication of silicosis and of coal workers' pneumoconiosis rarely occurs in asbestosis. But other pathological events began to appear that were not so easily fitted into conventional patterns. These were finally to force reconsideration of etiological ground rules.

Pleural Asbestosis

A certain degree of involvement of the visceral pleura is only to be expected in extensive pulmonary fibrosis but the pleural changes following exposure to asbestos can go much further, or even proceed independently. In 1884, according to Noro (554), Curschman described pleural plaques as "Zuckerguss," and in the 1930s there were scattered references to calcareous markings in chest radiographs (661). Gloyne described "hornlike" changes in the pleura in 1933 (278). But it was not until 1935 that Lynch and Smith reported a case in which "the pleura of the right lung is thickened as a whole and is of cartilaginous and even partly calcareous quality over the base. That of the left lung is likewise thickened, but over the free portion it is rough, congested, and 'furred' with small nodules in the surface" (468). Lanza extended the descriptions in his text of 1938 (440). The characteristic "ground glass" appearance often seen in chest radiographs of those exposed to asbestos was accepted as due to pleural involvement. But in spite of this there was little mention of plural calcification in the earlier accounts of asbestosis (661). In 1943, Siegal and his colleagues reported the finding of numerous instances in examinations of talc miners and millers (682). In 1955 Jacob and Bohlig found pleural calcification in some 5% of 343 asbestos workers examined in Dresden (373). Since that time the presence of pleural plaques has been reported with increasing frequency, to the point that their demonstration in the absence of any other cause has

been accepted as fairly conclusive proof of exposure to asbestos. An explanation, given for the lack of early reports is that the formation of plaques, and even more so their subsequent calcification, is a slow process that seldom has time to develop in those who are responding with extensive parenchymal asbestosis and marked for a relatively early death (661).

Associated Bronchogenic Carcinoma

In May, 1935 Lynch and Smith, in the third of their United States papers on pulmonary asbestosis, published the first report of carcinoma of the lung in "asbestos-silicosis" (469). This was in a 57-year-old white man who had worked for 21 years as an asbestos mill weaver in an extremely dusty atmosphere. For five years he had noticed some shortness of breath, and his complaint on admission was pain in the right side of the "stomach." He was autopsied on March 17, 1934. An epidermoid carcinoma of the right lung was found, and extensive fibrosis and asbestosis were also seen. The authors did no more than draw attention to the simultaneous presence of the two diseases.

In October of the same year Gloyne published two cases from Britain, both in women (279). One had eight years of exposure as a spinner nine years before, the other only 19 months in the mattress and opening departments, 15 years before. Both had asbestosis; both had small carcinomas. The cause of death was not given; Lynch and Smith's case was mentioned. The author refrained from "any attempt to make out a case for an etiological association of these two diseases."

In July, 1936 Egbert and Geiger reported a case of a 41-year-old man who had worked since the age of 23 as a weaver in an asbestos factory in the United States. Both pleural cavities were completely obliterated by firm fibrous adhesions, there was extensive fibrosis, and a large tumor was found in the left lower lobe with extensive metastases (210). In December of 1936, Gloyne published a report of a third case in Britain (280).

In 1938 Nordmann published an account of two cases in Germany, again with a long period between cessation of exposure and the appearance of the carcinoma (552). In conjunction with other published cases they convinced him that this was an occupational disease. In anticipating objections to the assumption of a causative relationship between the two diseases, Nordmann noted that there were relatively few workers and that asbestosis itself was not sufficiently understood for many reports to have been made.

Thus, from three countries intimately concerned with the develop-

ment of the asbestos industry, there were now reports of bronchogenic carcinoma associated with asbestosis. The grim tale was to continue with more reports from the United States and Germany, and then in 1941 from France. By 1943 Homburger was able to list 19 cases by the addition of 3 of his own (347); he still was cautious in saying that the association of the two conditions is remarkably high but that there was no reliable answer to the question whether pulmonary asbestosis was to be considered an etiological factor in pulmonary carcinoma.

Wedler, in 1943, found a prevalence of 16% of pulmonary carcinoma in 92 postmortem reports on asbestotic patients collected from various parts of the world (783). Merewether reviewed the accumulated data for 1923-1946 in his 1947 Report of the Chief Inspector Factories (England) and found a prevalence of 13.2% in 235 necropsies in patients known to have died with asbestosis, as against 1.32% in 6,884 cases of silicosis (509). Wyers, in 1949, reported a prevalence of 14.8% among 115 deaths from asbestosis (805). Gloyne, in 1951, reviewed 1,247 lung specimens sent to him over the period 1929-1949 for microscopical examination for pneumoconiosis (281). His comments were as follows: "Whether [workers with a dust hazard] have a risk over and above [that of the general population] as a result of their occupation cannot yet be clearly shown, but the mortality of the asbestos workers is disturbing. In the present series, 14% of the patients with asbestosis also had primary cancer of the lung. This is all the more striking because so many of them (41.2%) were females."

Hueper, writing in the same year, took a stronger stand: "Although Warren rather recently maintained that the connection between asbestosis and lung cancer is of a coincidental nature, the actual existence of a causal relationship appears very likely (359)." (However, Holling and Jacob, writing in 1958, and basing their position on cases derived from the industries of Saxony and Thuringia, came to the conclusion that there did not seem to be increased incidence of pulmonary carcinoma in asbestos workers, although it did seem to be increased in women and it did seem to affect the lower parts of the lung more than usual (96). However, Doll had reported in 1955 on all of the coroner's necropsies since 1935 performed on persons known to have been employed at a large asbestos works. He concluded from the data that lung cancer was a specific industrial hazard of certain asbestos workers, and in a second part of the study found that the average risk among men employed 20 or more years had been 10 times that experienced by the general population (192). Braun and Truan, on the other hand, also writing in 1958, opposed any significant association, basing their opinion on a survey undertaken for the Quebec Asbestos Mining Association and reviewing

a cohort of some 6,000 Canadian miners who had a total exposure of 5 or more years, and who were on the employment rolls in 1950 (110). It should be pointed out, however, that the evidence for an association had been gathered, not from miners, many of whom had worked under open pit conditions, but from workers in enclosed manufacturing plants. Braun and Truan's survey also omitted data on 133 individuals who were lost from the cohort and who might well have been affected and, too, many of the mines and millers had but recently started work.

In the last twenty years many more data have been accumulated and more detailed information is now available about both the workers and the working conditions. The hesitation by the earlier investigators in accepting exposure to asbestos as a cause of pulmonary cancer will gain added interest when the data now available are examined in Chapter 12. In this connection the epidemiological studies of Mancuso and Coulter published in 1963 (475) and of the Mount Sinai group in 1964 (667) are of particular interest.

Emergence of Mesothelioma

The separation of bronchogenic carcinoma, in which asbestos is the causative factor, from that due to other causes has been, and still is, difficult. Mesothelioma had previously been a rare type of tumor, the sudden rise in incidence in the last forty years strongly suggests the operation of a new agent and, on the generality of the evidence, asbestos qualifies for the doubtful distinction. A number of cases had to be seen, however, and the association with exposure to asbestos had to be well substantiated before the etiological connection could be established. The etiological problems will be discussed later in Chapter 10. In the meantime, it is instructive to look at the early reports.

In 1931 Klemperer and Rabin published an account of five primary neoplasms of the pleura (410), providing a clear analysis of the pathological and histological findings; these have remained valid to the present. They drew attention to the first description of primary neoplasms of the pleura by E. Wagner in 1870, which was before asbestos was used in any quantity. They suggested that the term mesothelioma "be accepted to designate all the diffuse neoplasms of the pleura that arise from the mesothelium, whether they appear to be composed of epithelium, connective tissue, or both." In 1943 Saccone and Coblentz, in reporting 2 cases of endothelioma of the pleura, stated that some 200 authors had discussed the nature of the tumor and that they found 188 cases in the literature; still no mention of asbestos exposure was made (639).

In the case records of the Massachusetts General Hospital for 1917, Mallory *et al.* reported a case of mesothelioma of the pleura and pericardium (474). The victim had worked with asbestos, cutting insulation board, but the occupational exposure was not discussed as an etiological factor. In 1953 Weiss reported that in the 31 cases of asbestosis autopsied in Germany and described by Wedler in 1947, six had cancer of the lung as described in the preceding subsection, "but, in addition two [had] malignant tumors of the pleura (786)." To these Weiss added a third case of a man who had done insulation work in a dockyard from 1920 to 1935.

Two cases of mesothelioma were included in the eight of lung cancer in 4,000 asbestos workers in Quebec reported by Cartier in 1952 (133). Leichner, in 1954, described the findings in an autopsy done two years earlier on a 53-year-old man who had worked in an asbestos factory, principally as a spinner, from 1929 to 1951 (451). The patient had asbestosis as well as tuberculosis, and death was due to dissemination of the latter. At autopsy, however, in addition to the expected findings there was a grayish-white thickening of the serosa over the mesentery and the abdominal organs. Histologically, the peritoneum showed exuberant proliferation and intense swelling of the mesothelial cells, and other cytological findings were consistent with what we now recognize as mesothelioma. Leichner reported finding evidence of asbestos fibers in the tumor.

Bonsner, Faulds, and Stewart reported four primary peritoneal tumors associated with asbestosis in 1955 (101). In 1958, Van der Schoot reported on three insulation workers who had died of neoplasms, two of them apparently mesotheliomas of the pleura; Schornagel mentioned a case in the discussion that he had seen of peritoneal mesothelioma (756). In the same year, McCaughey described 11 diffuse (as well as two localized) tumors of the pleura that he had seen in Belfast, but, as is only too common, no mention was made of occupational or other exposure (490). Keal, searching the records of the London Hospital since 1948, was able to report in 1960 that of 23 women who had been inpatients with asbestosis, one had an ovarian carcinoma, four had peritoneal growths possibly of ovarian origin, and four had carcinomatosis of the peritoneum without a primary lesion being found (395).

By 1960 Wagner and colleagues were able to announce that in the previous four years they had seen 33 histologically proven cases of mesothelioma of the pleura, that 28 of these had some association with the Cape crocidolite asbestos field, and that 4 of the cases had been exposed to asbestos in industry (772). By contrast, the tumor was rarely

encountered elsewhere in South Africa, and apart from this series no neoplasm of this nature had been diagnosed among 10,000 lungs consecutively examined at the Pneumoconiosis Bureau or the South African Institute for Medical Research over the same period of time. Furthermore, no case had been found in a survey of malignant tumors in the black and cape coloured population of Johannesburg and the northeastern Transvaal. In the following year they were able to supplement the record with 8 more cases (692). The doubt cast upon the existence of such an esoteric tumor by no less an authority than Willis (793) seemed now to be exorcised.

Wagner went on to demonstrate the experimental development of pleural mesothelial tumors by the intrapleural injection of both chrysotile and crocidolite (764). At the International Congress on Occupational Health in 1963 he was able to report on more than 120 cases seen since 1956 (765). More than half of the cases never worked in the asbestos industry but had lived in the vicinity of the mines and mills, so that the importance of environmental (neighborhood) exposure was now established. Another important point was made in the course of this presentation, namely that there was no degree of correlation between the severity of asbestosis and the presence of the tumor. This opened the way to a later speculation that, perhaps, it is just those whose dosage has been low that escape advance asbestosis and live to acquire mesothelioma. Hourihane, following on from Keal's work, and reporting further peritoneal tumors, was moved to remark in 1964 that although many of the cases gave no history of industrial exposure, the association of the tumors with asbestos bodies in lung tissue makes it possible that brief or relatively trivial exposure may have occurred (353).

In 1965 the first case of pleural mesothelioma with asbestosis was reported in France (749). Anspach *et al.*, writing in 1965, indicated that pleural mesotheliomas had probably occurred in the neighborhood of Dresden, a center of the European asbestos industry, as far back as 1933, but that confirmatory evidence was lacking. Since 1950 there had been 35 cases of diffuse malignant pleural mesothelioma in Dresden. Of these, 9 had definite occupational exposure to asbestos, 9 involved a neighborhood risk, 2 had silicosis, 7 had no known exposure to dust, and 8 had no available history (47). The occurrence of mesotheliomas in Holland over the period 1950-1965 was reported by Stumphius, but no details were given to judge the possible relationship to asbestos exposure (723).

Thus was the stage set for the current views on the incidence of

mesothelioma and its relationship to asbestos exposure that will be reviewed in Chapter 10.

STATE OF MEDICAL KNOWLEDGE IN THE EARLY 1960's

"What's past is prologue!" The early 1960's is a convenient time at which to terminate a historical review of asbestos disease and proceed to elaborate present concepts. With the admirable hindsight of fifteen years we can see that the essential evidence had already been reported, but not yet in a fashion to be universally convincing. With a few important exceptions (192,441,765), the evidence at that time rested on scattered reports of small numbers of cases, and the cases themselves were sometimes selected or simply those that happened to come to the attention of the writer. The population base from which these cases came was seldom mentioned or could not be ascertained. The significance of pleural changes and the occurrence of mesothelioma in persons without a history of exposure to asbestos posed problems of credibility. The idea that asbestos could be a factor in the production of bronchogenic and other carcinomas was contested. That parenchymal asbestosis was very likely to occur in those who had been exposed to heavy dosage in the early years of the industry was clear enough, but what effect environmental controls proposed in the 1930's would have upon its future incidence was not known. The possibility that quite low dosages might have grave consequences thirty years after initial exposure was still tenuous.

Many things were needed to confirm the suggestions that were emerging from the studies then available; most importantly, systematic epidemiological investigation of large cohorts drawn from various types of industries, and comparison with adequate control populations. Some of these were already organized, but it was too early for the results to be adequately interpreted. We now know that much of the apparently negative evidence that was being adduced stemmed in some studies from coming to conclusions too soon, before the slow processes of carcinogenesis had a chance to make themselves apparent. We also know now that reduction of the heavy exposures that had led to early death from pulmonary fibrosis and cardiac failure would reveal those slower processes with increasing clarity. More sophisticated and sensitive ways of recognizing the disease processes at an early stage were badly needed, together with an ability to assess disability in those exposed before extensive radiographic changes heralded a shortened

life span. A series of international conferences, some already in the planning stage, were to accelerate these developments greatly.

So we will now pass to a survey of things as they are today, first describing the physical aspects of asbestos and its processing, then reviewing the various disease processes and their causation, and finally considering what can be done in the way of prevention and control of exposure and resulting disease.

Asbestos Minerals: Nature, Occurrence, and Properties

As indicated in Chapter 1 (Historical Background), the term asbestos was given to naturally occurring fibrous materials, later found to be minerals, which showed the properties of relative indestructibility and resistance to fire. That pragmatic definition could be applied to a number of minerals. Today we would limit it to naturally occurring, commercial, fibrous minerals of the serpentine or amphibole series. Fibrous forms of other minerals, such as wollastonite, fibrous brucite, or fibrous forms of calcite or gypsum would not be included (108). Even so, a certain heterogeneity is seen in the minerals encompassed, and some difficulty is experienced in fitting the commercial names for various varieties of asbestos to chemical or mineralogical classifications.

Asbestiform minerals fall into two major subdivisions: chrysotile, which belongs to the serpentines, and the amphiboles, including crocidolite, actinolite-tremolite, amosite, and anthophyllite (686). A large number of trade and mining terms have been applied to the asbestos minerals. For example, names that have been used for crocidolite vary greatly with the variety and location: potential crocidolite, asbestiated crocidolite, amorphous riebeckite rock, asbestiated mass-fiber riebeckite, acicular crocidolite, griqualandite, and tiger-eye, not to mention the well known blue asbestos; the scientific mineralogical names are now the rule (686). [A]

The crystalline structure of chrysotile is that of a layer of magnesium oxide hydroxide octahedra bonded to a layer of silicon dioxide tetrahedra in somewhat mismatched fashion that produces a curvature in