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Editorial

Asbestosis and Neoplasia

In at least one fourth of the adults who die in urban areas in the United States and other industrialized countries asbestos bodies are found in the lungs [1–6]. This observation has led to the recognition of asbesto-related disease as a potential serious modern urban hazard [7–9].

Indeed, Thomson [4] has predicted that asbestos-induced neoplasms will rival cigarette-induced lung cancer in the next several decades. This prediction is based upon five observations and one assumption. The known data may be summarized as follows: (1) Asbestos inhaled under industrial conditions will produce a serious pneumoconiosis (pulmonary asbestosis) [10] even with relatively light exposure [11]. (2) Under similar conditions of heavy [12] or light [13] industrial exposure, workmen die of neoplasms more frequently than expected. (3) Widespread contamination of the environment [14,15] may occur both from industrial sources (such as asbestos-containing dusts from construction sites) and from disintegration or use of asbestos products (such as asbestos-containing floor tiles and brake linings [16]. (4) Such environmental contamination may result in widespread inhalation and retention of small numbers of the mineral fibers [1–6]. (5) Under certain conditions (for example, residence within a half-mile of an asbestos factory or in the household of an asbestos worker) environmental exposure has been shown to produce serious disease [17–20]. The prediction that widespread asbestos contamination of city air will be associated with widespread neoplasia, however, is still an assumption, an extrapolation from the observed data since we do not know at this time whether or not the small amounts inhaled as the result of asbestos air pollution have an effect comparable to the much larger amounts inhaled in industrial or intimate environmental circumstances. The question will not be resolved for some time because of the long latent period between initial contact and the appearance of clinical disease. Although there are variations based upon individual idiosyncrasy, intimacy, duration and continuity of exposure, and perhaps also upon such factors as the variety of asbestos used (chrysotile, amosite, crocidolite, anthophylite, tremolite) and the presence of other concomitant dusts, by and large it may be said that disease caused by asbestos is rarely manifested in less than ten to twenty years from onset of exposure.

PULMONARY ASBESTOSIS

The case report which gave the disease its name [21] was of a woman asbestos textile operator who had begun this work twenty years before. Alerted by this and similar cases, a survey of British factories was undertaken; evidence of asbestosis was found to be common, but only in those whose occupational exposure to asbestos had begun many years before [10]. Similar experiences were soon recorded in the United States [22]. The counterpart of acute silicosis was almost never observed, except perhaps under the most unusual circumstances [23].

This situation still obtains. In a recent study

TABLE 1*

ROENTGENOGRAPHIC CHANGES IN ASBESTOS INSULATION WORKERS

Onset of Exposure (yr.)	No.	Per cent Normal	Per cent Abnormal	Asbestosis (grade)		
				1	2	3
40+	121	5.8	94.2	35	51	23
30–39	194	12.9	87.1	102	49	18
20–29	77	27.2	72.8	55	17	4
10–19	379	55.9	44.1	158	9	0
0–9	346	87.6	10.4	36	0	0
	1,117	51.5	48.5	366	126	50

* Selikoff et al. [11].

of over 1,100 asbestos insulation workers, chest roentgenograms disclosed abnormalities in only 10 per cent of those whose exposure to asbestos began less than ten years before and in only 44 per cent of those who had been first exposed to asbestos from ten to nineteen years before. Moreover, these abnormalities (roentgenologically evident parenchymal fibrosis and/or pleural fibrosis and calcification) tended to be minimal in extent. On the other hand, in those with onset of exposure to asbestos from twenty to twenty-nine years before, chest roentgenograms showed abnormalities in 72 per cent of the older workmen and in over 90 per cent of those with more than thirty years from onset of exposure (Table 1) [11].

The explanation is twofold. First, asbestos rarely provokes an acute inflammatory reaction in the lung. Rather, the fibrosis which results is *slowly progressive*. The asbestos fibers remain *in situ* where inhaled but the tissue response to them is indolent, albeit progressive and apparently irreversible. This course of events is seen both in human and experimental asbestosis [34–37]. Second, asbestotic fibrosis is of the diffuse interstitial variety, which may not be readily apparent on roentgenograms in its earlier stages [28] and sometimes not even when extensive [29]. There is a tendency, therefore, to underestimate the presence and extent of clinical disease.

Pulmonary asbestosis has been aptly characterized as a monosymptomatic disease, with dyspnea its cardinal clinical finding. Yet this feature, and the physiologic and morphologic changes responsible for it, are not early findings. In the asbestosis found among insulation workers in the United States, dyspnea was present in only 1 per cent of those with less than ten years of work experience, and was minimal in each case [11]. Even in those with ten to nineteen years from onset of exposure, complaints of dyspnea were recorded only in twenty-eight of 379 men examined and these were minimal in all but one instance. In contrast, of 121 men with more than forty years from onset of exposure almost half had dyspnea, more often than not moderate or severe in degree. Finger clubbing, cyanosis and extensive fine basal rales all tend to develop only after a long time from the onset of industrial asbestos exposure.

The pulmonary physiological defect in asbestosis is associated with the pattern characteristic of the alveolar-capillary block syndrome [30], with reduced vital capacity, fairly well preserved maximum breathing capacity, hyperventilation at rest and particularly on exercise, decreased diffusing capacity of the lung, impaired oxygenation of the arterial blood and reduced pulmonary compliance. None of the parameters shows significant change early in the course of the disease, not even vital capacity which has been demonstrated to be perhaps the most sensitive index of progression of the disease [31,32].

In most instances, therefore, the term "early asbestosis" is of uncertain meaning. If it is intended to designate clinical asbestosis of minimal or limited extent and severity, considerable time will have elapsed, perhaps one or two decades before manifestations have become evident. In a lesser period from onset of exposure it is likely that few or no changes indicative of clinical disease will be present even though histologic changes will be quite underway [33].

LUNG CANCER

In 1935 Lynch [34] reported a case of lung cancer in a man with asbestosis. The associati

deaths from 1958 to 1964 only eleven were due to pulmonary insufficiency. Death from pulmonary asbestosis occurred at an average of 25.7 years from onset of exposure whereas the latent period between onset of exposure and death from lung cancer was 30.7 years. With improvement in industrial conditions, and less exposure to asbestos, Dresden asbestos workers survived long enough to reach the period in which lung cancer occurred!

MESOTHELIOMA

Scattered reports of neoplasms of the mesothelial surfaces of the pleural and peritoneal cavities in association with asbestosis have been available for over thirty years. Weiss [42] suggested an etiologic relationship in 1953 but such proposals faced the difficulty of infrequency of reported cases and the absence of population and epidemiologic studies. The possibility of a causal relationship was greatly strengthened by the report of Wagner and associates in 1960 [43] of thirty-three cases of diffuse pleural mesothelioma in South Africa, thirty-two of the thirty-three patients having had at least suggestive evidence of potential exposure to asbestos. Other large collections of cases of mesothelioma of the pleura or peritoneum associated with exposure to asbestos have appeared, including those of McCaughey, Wade and Elmes [44], Owen [45], Hourihane [46], Churg, Rosen and Moolten [47], Webster [48], Enticknap and Smither [49]. This tumor now follows lung cancer as an important cause of death among asbestos workers. In fifty-six consecutive autopsies of workers in one asbestos factory, nineteen cases of peritoneal mesothelioma were found [49]. In a series of 325 consecutive deaths (1943 to 1966) among asbestos insulation workers, seventeen were due to mesothelioma of the pleura or peritoneum [50], an extraordinarily high incidence (approximately 5 per cent) for a tumor otherwise so rare; the prevalence in the general population at this time has been calculated to be approximately 1 in 10,000 deaths [38]. The association of mesothelioma with exposure to asbestos is so striking as to suggest that a history of exposure to asbestos be sought whenever the histologic diagnosis of mesothelioma is made.

Once again, there is a striking latency. As with lung cancer, it is unusual to find mesothelioma associated with asbestos in less than twenty years from onset of exposure; generally, the latent period is over thirty years. Also as with lung cancer, there is no regular correlation between the severity of asbestosis and the occurrence of mesothelioma, and many instances occur in subjects in whom there is little or no roentgenologic evidence of asbestosis. The Dresden experience may be recalled in this connection, too. During the period when early death from cor pulmonale was common no mesotheliomas were seen, but in the later period, when severe asbestosis was no longer as common, 19.4 per cent of all thoracic tumors were primary in the pleura. The latent period from onset of exposure in these cases averaged 31.8 years.

OTHER NEOPLASMS

The neoplastic potential of asbestos may not be limited to the lung and mesothelial surfaces. Other tumors may be related to asbestos exposure, although the evidence for this is not as well defined at this time [38,51]. Cancers of the stomach and colon seem to be significantly increased among asbestos workers. In two studies in which the initial exposure to asbestos could be dated, the cancers of the stomach and colon occurred after the same long latent period characteristic of lung cancer and mesothelioma [51,52].

PLEURAL CALCIFICATION

Scattered instances of calcification of the pleura, chiefly of the parietal pleura, were reported in the 1930's but their frequency and importance as a roentgenologic sign of asbestos exposure were not appreciated until the report by Jacob and Bohlig [53] in 1955 who found such calcification in approximately 5 per cent of 343 Dresden asbestos workers. The significance of this characteristic x-ray finding was emphasized by Kiviluoto's report in 1960 [11].

Recent studies have not only confirmed the frequency of pleural calcification among workmen exposed to asbestos but have also demonstrated that this finding too is strongly dependent upon a long latent period from onset of exposure. As can be seen in Table II, roentgenologically apparent pleural calcification is rare within twenty years from onset of exposure, only five instances having been found among 725 asbestos insulation workers in this category. Once the twenty year point is passed, however, visible pleural calcification becomes much more common and is found in more than half the men in whom more than forty years have

TABLE II*

PLEURAL CALCIFICATION AMONG ASBESTOS INSULATION WORKERS

Onset of Exposure (yr.)	No.	Per cent Normal	Per cent Calcification	Extent of Calcification (grade)		
				1	2	3
40+	121	42.1	57.9	37	20	13
30–39	194	65.4	34.5	46	15	6
20–29	77	89.6	10.4	8	0	0
10–19	379	98.9	1.1	5	0	0
0–9	346	100.0	0.0	0	0	0
	1,117			96	35	19

* Selikoff, I. J. [54].

elapsed since the onset of exposure [54]. These data should be interpreted in the light of knowledge that pleural calcification of limited extent and radiodensity is usually not visible in the x-ray film [5]. It is likely that parietal pleural changes with hyaline and sometimes calcified plaques will occur in all asbestos workers, if they live long enough.

PROGRESSION OF ASBESTOS DISEASE WITHOUT CONTINUED EXPOSURE

Knowledge concerning the latent period of asbestos-related disease has been derived primarily from observations of industrially exposed population groups, although epidemiologic studies of random instances of such disease, especially mesotheliomas, have given similar results [20,43]. These and other epidemiologic studies have demonstrated that asbestos-related disease may occur without continued exposure from industrial sources. The explanation for this presumably is as follows: The asbestos fibers inhaled initially largely remain in place, although some may be removed in the bronchial secretions for many decades after cessation of exposure and others may gradually be dissolved in body fluids [55]; this last possibility has not been definitively established. As a result, tissue reaction to the retained fibers goes on, even in the absence of inhalation of additional amounts. Thus a workman who has been continually exposed to asbestos for, let us say, twenty-five years carries within him a composite biological effect. The initial burden of inhaled fibers is associated with a twenty-five year effect, those inhaled twenty years before are experiencing a twenty-year effect and so on, the fibers but recently inhaled adding the effect associated with newly deposited material. The clinical resultant is the summation of all these effects.

This analysis explains the reluctance of many physicians to advise asbestos workers with many years of experience but in good health to leave their employment, since their ultimate fate may be determined *not* by their current exposure but by their exposure many years before. The same situation holds in many cases of minimal silicosis or respiratory disease associated with coal mining.

EXPERIMENTAL STUDIES

Reference has already been made to the slowly progressive fibrosis in experimental asbestosis, counterpart of the latency in the human disease. Similar findings are observed in experimental studies of neoplasia associated with asbestos. Wagner [56] produced mesotheliomas in rats by a single intrapleural injection of several varieties of asbestos but these tumors did not appear for fifteen to twenty-three months, a considerable portion of the life span of the animal. Smith produced pleural mesotheliomas with asbestos in the hamster but, again, these did not appear until 244 days after injection [57]. Pleural disease has also been found in hamsters following the intratracheal instillation of asbestos but the same requirement of a long latent period has been observed [58].

DIAGNOSIS OF ASBESTOS DISEASE

It is clear that a painstaking occupational history is essential in those clinical circumstances in which the possibility of asbestos-related disease is being considered in differential diagnosis. This is particularly true in instances of (1) interstitial pulmonary fibrosis of undetermined origin, (2) pleural calcification (either unilateral or bilateral), (3) pleural or peritoneal mesothelioma, (4) alveolar-capillary block syndrome (even in the absence of radiologically evident

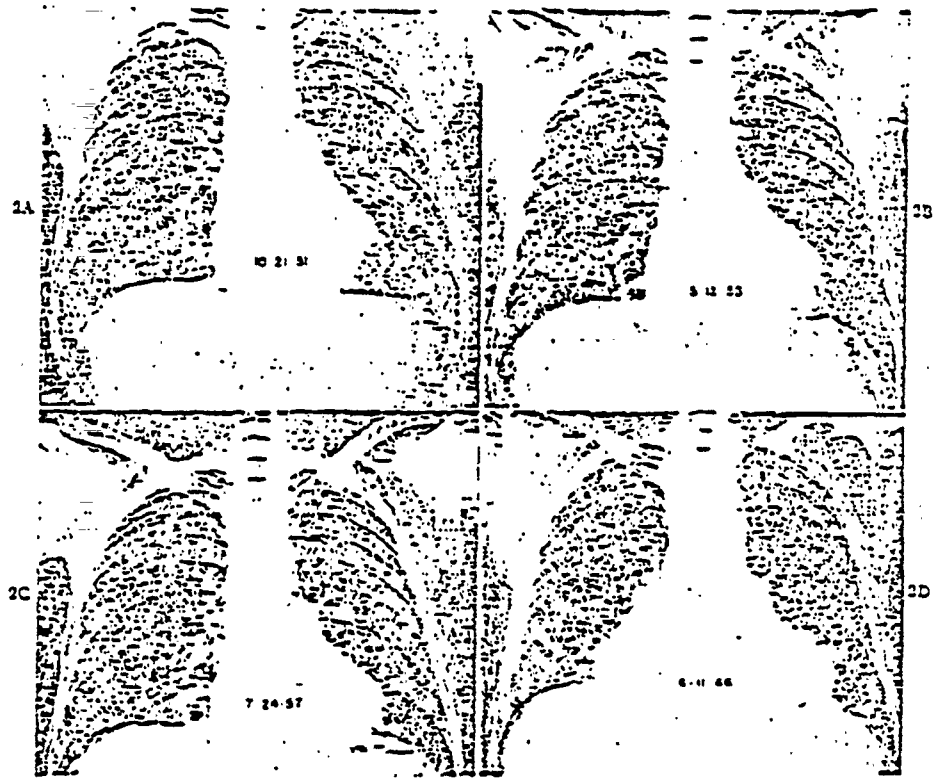

FIG. 2. Patient R. K. Serial roentgenograms of the chest taken between 1931 and 1946. Progressive fibrosis is evident, most prominently at the bases. Pleural calcifications are present (D). This man worked as an asbestos weaver in a brake lining factory for only four months in 1935, with no subsequent exposure to asbestos. Note that the fibrosis first became evident on roentgenograms in 1953.

interstitial fibrosis), (5) lung cancer and (6) fibrotic pleural plaques (unilateral or bilateral). In such cases the recent occupational history is of less interest than the work the patient did twenty, thirty or more years before (Fig. 2). The exposure may have been brief—a matter of a few months or less—and the occupation not necessarily one ordinarily thought of as related to asbestos. Of the individuals industrially exposed only a minority are asbestos textile and asbestos products workers. There are, for example, more asbestos insulation workers than asbestos weavers. Over 3,000 uses for asbestos are currently known [59], ranging from filters used in the manufacture of beer to repair cements for home furnaces, from re-entry nose cones for our space vehicles to certain valve packings and welding electrodes. The construction industry uses a great many materials containing asbestos; for example, a carpenter may repeatedly saw asbestos building board, a plumber and steamfitter frequently uses asbestos rovings for joints, an electrician is no stranger to asbestos-covered wire and cable. In the shipbuilding industry, asbestos finds many uses and, because of tight quarters and close working conditions, indirect occupational exposure (for example, a welder inhaling the asbestos dust derived from an insulator close by) may be usefully explored in the occupational history.

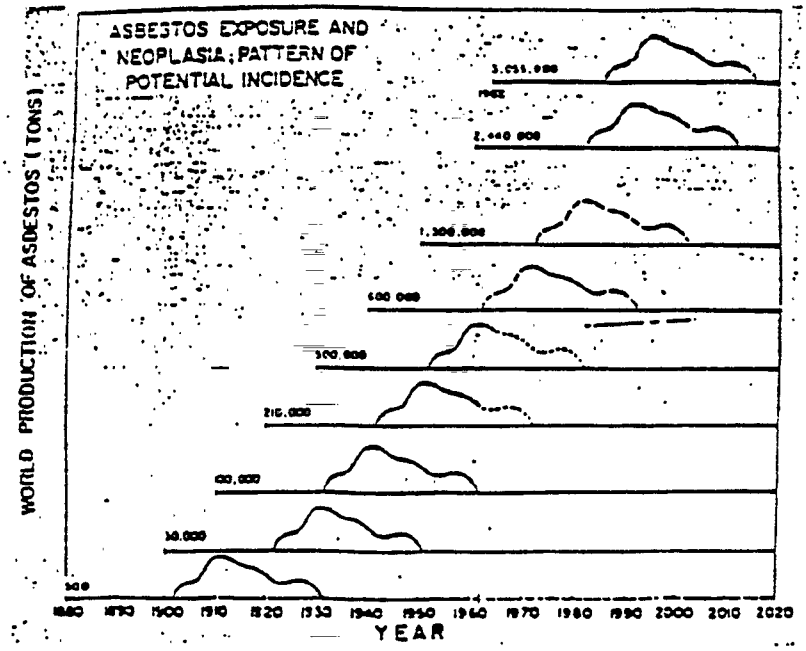

FIG. 3. A projection of the potential incidence of neoplasia due to asbestos. The curve shown in Figure 1 has been superimposed on levels of world production of asbestos shown in the ordinate. The neoplasia associated with greater utilization of asbestos will not be in evidence until the 1990's. The shaded areas indicate the cases which have become manifest, the unshaded areas represent potential cases.

Indirect occupational exposure may also be important in the building trades and in many other as yet incompletely investigated occupations. A complete list of potential direct and indirect occupational exposures to asbestos is manifestly impossible here, but perhaps enough has been said to indicate that a bit of detective work during the occupational history, especially with respect to work two, three or four decades before, may be diagnostically rewarding.

Although many instances have been recorded, data are not available to characterize completely the effect of cessation of exposure from external sources, since large groups of asbestos workers whose exposure has been discontinued have not been observed and compared with others with the same exposure who have continued at their work. Such data as are available [*54*] would suggest that both elapsed time since first exposure and total years of exposure are of importance. There are no epidemiologic data, such as are available for cigarette smoking [*60*], which indicate that cessation of exposure is associated with a subsequent decreased risk of lung cancer. Smoking data, moreover, should not necessarily be transposed to asbestos exposure, in view of the retention of inhaled asbestos fibers which has no clear counterpart in the cigarette problem.

Definitive diagnosis of asbestos disease depends upon the finding of asbestos, either in the form of asbestos fibers or asbestos bodies in effected tissues. However, their discovery in routine postmortem studies is simply evidence that *at some time* asbestos fibers have been inhaled, without indicating when such inhalation occurred. The connotation would be different in each case since, as we have seen, disease could be anticipated only as a result of inhalation that had occurred a considerable time before. Therefore, we should perhaps take little comfort from the circumstance that, in most

instances, neither pulmonary fibrosis nor neoplasia is associated with the asbestos currently being found postmortem.

It is likely that most asbestos now being discovered postmortem in persons who have not been industrially exposed has been of recent deposition. The basis for this assertion lies in the economic data concerning asbestos. Until 1870 asbestos was an exotic rarity. The unusual qualities of these mineral fibers—fireproof, waterproof, wear- and chemical-resistant—were soon found to have important uses in our rapidly expanding industrial civilization, and almost each year saw a rapid increase in the world production of this mineral. From 50 tons per year ninety years ago, world production has now reached almost 4,000,000 tons per year. As Gilson has pointed out [61], asbestos can truly be called the twentieth century mineral, since its output has increased over a thousand-fold in sixty years compared with a mere fifty-fold for oil, an industry often regarded as the symbol of industrial growth. The asbestos brought to the surface of the earth increases year by year, and the total is a cumulative one. As has been aptly said [1] the fiber has "a half life of infinity" so that each year's production adds to the cumulative total of all that has been produced before.

The frequency, nature and extent of disease due to asbestos is a matter for future observation. A graphic picture of this potential problem is given in Figure 3 in which the curve of the latent period of cancer of the lung and pleura is superimposed upon the production records of asbestos. The neoplasms now encountered associated both with industry and environment are consequent upon inhalation of asbestos associated with the limited asbestos production of some thirty years ago. The neoplasms associated with current utilization and exposure to asbestos will not be evident until the 1990's.

Yet to be resolved are such important questions as whether different kinds of fibers exert the same biological effects, the nature of the dose-disease relationship, sources and extent of environmental contamination, the range of industrial exposure (inadequately documented at this time), the range of neoplastic effects of asbestos exposure, standardization of roentgenologic and physiologic studies, and even whether asbestos bodies may not sometimes be the result of inhalation of mineral fibers other than asbestos [62]. In our own laboratory, data are accumulating to suggest an important co-carcinogenic effect of cigarette smoking in asbestos workers [63] possibly due to adsorption of carcinogenic substances onto the asbestos fiber, but possibly also due to histologic or other changes induced in the affected lung.

CONCLUDING REMARKS

Asbestos is a most valuable material, essential in our industrial society. We recognize and study its dangers so that we may devise means of minimizing or avoiding them. Diligent, ingenious and often expensive improvements in industrial hygiene practice [64] may help to eliminate heavy or unnecessary exposure. Awareness of the potential risks of environmental contamination is also necessary at this time, at least until the future tells us whether Thomson's assumption is right or wrong.

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