The Biomedical and Epidemiological Characteristics of Asbestos-Related Diseases: A Review

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The purpose of this paper is to provide the reader with an overview of the biomedical and epidemiological characteristics of asbestos-related disease based upon currently available information. Epidemiological and experimental data developed over the past 20 years have greatly added to our knowledge of the biological effects of asbestos, particularly in relation to clinical disease. This information has substantially strengthened the evidence linking asbestos to specific health effects.

Lung cancer and mesothelioma are clearly the most important asbestos-related causes of death among exposed individuals, although the accumulated data is suggestive of the existence of an excess risk of gastrointestinal and a variety of other neoplasms. Animal studies confirm the human epidemiological results and indicate that all commercially available fiber types are capable of producing lung cancer and mesothelioma. Experimental implantation and injection studies also show that the carcinogenicity of mineral fibers (including asbestos) is directly related to their dimensionality and not their chemical composition.

Although the asbestos-related medical and scientific literature is voluminous, many issues related to the biological activity of asbestos fibers are as yet unresolved. Due to experimental and analytical limitations, questions concerning risk at low-level exposure, dose-response relationships, and individual susceptibility remain problematic.

HISTORICAL BACKGROUND

Although the twentieth century has been the setting for much of the controversy and intrigue surrounding exposure to asbestos, fibrous asbestos minerals have long been used by man. Pottery, dating from the stone age, exhumed in the region ranging from southern Sudan to northern Kenya has been found to contain amphibole asbestos fibers. Archeological studies in Finland have also provided evidence that asbestos was incorporated into pottery by 2500 B.C. [1] Pausanias, the early Greek geographer, wrote of lamps made during the fifth century B.C. with incombustible wicks, while the Romans used asbestos cloths to contain the ashes of nobility during cremation [2]. An often-recounted story tells of an asbestos table cloth owned by the French emperor, Charlemagne. In order to impress guests and enemies alike, he would throw the table cloth into the fire to clean it and recover it unharmed.

From these rather humble and curious beginnings, a Middle Age oddity developed into a major industrial giant during the nineteenth and twentieth centuries. With the rediscovery and development of large deposits of asbestos in Canada and South Africa, commercial exploitation of this commodity became a reality. An initial stimulus to the genesis of the asbestos industry was provided by the industrial revolution of the late nineteenth century. The development of machines for the production and use of power

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brought with it the need for packing and insulation [3]. Although the post-industrial revolution period was the setting for the early manufacture of asbestos products, it was not until the advent of World War II that the creation of many new and innovative asbestos products occurred. Subsequent decades continued to spawn fresh ideas for practical applications, ranging from filters for the wine industry to plastics, paints, and asphalt. With markets for asbestos products rapidly expanding, U.S. production levels soared to well over one hundred thousand tons per year in the early 1930s, accounting for approximately 3.3 percent of the world figure [2].

Although exposure to natural sources of asbestos fibers in air and water is unavoidable, the greatest health risk to man is undoubtedly posed by the large-scale commercialization of this mineral. Nonetheless, the pathogenicity, or at least potential pathogenicity, of asbestos has been recognized and recorded for decades. In fact, the historical record extends back to Pliny the Younger (61–114 A.D.), who is said to have observed a correlation between sickness and asbestos exposure among slaves [3]. It appears, though, that neither this observation nor many others relating occupational hazards and disease were matters of concern until relatively recent times.

A number of “hallmark” observations concerning the potential pathologic nature of asbestos were made during the early part of this century. Anderson, in 1898, published a report indicating that asbestos fiber inhalation in occupational settings is injurious to the bronchial tubes and lungs [4]. Although neither mortality data nor clinical follow-up information were provided, this paper represents one of the initial reports of asbestos-related disease in the workplace. It also served to point out that clinical latency of the resulting pulmonary disease represented a major obstacle to establishing a stronger association between work with asbestos fibers and adverse health affects.

Murray, in 1907, reported a death due to pulmonary fibrosis in an asbestos textile worker without tuberculosis [4]. Autopsy showed fibrosis of the lungs and asbestos fibers in lung tissue. Almost two decades later, in 1924, Cooke [5] originated the term “asbestosis” in describing the clinical condition of female asbestos workers who had died from pulmonary fibrosis similar to that seen by Murray in 1907. In this report, Cooke also cited experimental pathology studies indicating that asbestos dust causes fibrosis in the lungs of guinea pigs [4]. Shortly thereafter, in 1927, the first major reviews of asbestosis were published by Cooke, McDonald, and Oliver [4]. These studies provided detailed clinical, radiological, and pathological descriptions as well as documentation of the high rate of asbestosis among textile workers spinning Canadian chrysotile asbestos.

The early 1930s produced a series of reports regarding the epidemiology and clinical characteristics of asbestosis. In 1930, Merewether, then Medical Inspector of Factories in England, 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” [6,3].

It was suggested by the author that the solution of this problem would be in dust suppression [3]. Merewether's report is also significant since the author hypothesized that different forms of fiber may have different biological activities. Subsequently, in 1933 and 1934, Merewether presented mortality data suggesting that asbestos workers had shortened life expectancies [4].

Over the next several decades it became apparent that asbestos fibers could be implicated in the etiology of a number of diseases, including lung cancer, mesothelioma, and gastrointestinal cancer. The possible association of asbestos exposure and the
development of lung cancer was first proposed in a group of studies published in the mid-thirties by Gloyne [7,8], Lynch [9], and Nordman [10]. Although cases of mesothelioma had been described as early as 1870, the first to mention a possible link to asbestos exposure appears to be an autopsy series published by Wedler in 1943 [11]. Not until 1953 was a large-scale cohort study conducted (among textile workers) indicating a strong association between occupational exposure and subsequent development of mesothelioma [12].

Many regard the 1960s as being the setting for the “awakening” of the scientific and medical communities to the dangers associated with asbestos exposure. Not only were studies published regarding disease occurrence in occupational cohorts, but reports also appeared concerning the possible dangers of environmental exposure [13]. The intense interest generated by the work of Selikoff and others during this time culminated in an international conference in New York in 1964 on the biological effects of asbestos, the proceedings of which were published in 1965 [14].

Since this time the relevant scientific literature has expanded considerably. Although questions remain, the existing data clearly indicate that asbestos fibers represent a serious hazard to human health. The challenge that remains is the accurate determination of the risk posed by such exposure and the institution of a rational and effective system for its management.

**PHYSICAL AND CHEMICAL CHARACTERISTICS OF ASBESTOS FIBERS**

“Asbestos” is a generic term for the fibrous form of a number of mineral silicates. These substances are found naturally in seams or veins in many igneous or metamorphic rocks and belong to one of two groups of rock-forming minerals, i.e., the serpentines and the amphiboles. The only member of the serpentine group is chrysotile (or white asbestos), which is by far the most common and commercially the most important type of asbestos. Ninety to ninety-five percent of all the asbestos used in the United States is chrysotile mined in Quebec, Canada. When in a vein of ore, chrysotile appears green and often occurs in the form of soft, flexible, long fibers which can be spun or woven. Chemically, it is a hydrated magnesium silicate which tends to lose its magnesium content under acid conditions, making it less desirable than the amphiboles for certain purposes. Chrysotile fibrils, when examined under electron microscopy, are shown to be hollow tubes of a variety of curved shapes, which may play a role in reducing their respirability.

The amphibole group contains crocidolite (blue asbestos), amosite (brown asbestos), actinolite, anthophyllite, and tremolite. Amosite is an acronym for Asbestos Mines of South Africa and is minerallogically known as cummingtonite-grunerite asbestos (a silicate containing magnesium and iron). It has been used to a larger degree than chrysotile for insulation under circumstances requiring greater chemical resistance. The amosite fibril is a solid rectilinear cylinder which is substantially thicker than that of chrysotile.

Crocidolite or “blue asbestos” is classified minerallogically as a riebeckite mineral, i.e., a silicate containing iron and sodium. The fibrils of crocidolite are solid rectilinear cylinders which are shorter, thicker, straighter, and less silky than chrysotile. These fibers possess a high degree of chemical stability and have found extensive use in areas requiring this quality, such as in the production of asbestos-cement pipes for transporting drinking water in cities [15].
Tremolite, a silicate containing calcium, magnesium, and iron, may occur as a contaminant in chrysotile and other minerals such as talc. Anthophyllite, although at one time produced in substantial quantities, is no longer of commercial importance.

Two structural properties of amphiboles which lead to fiber production are a preferred cleavage plane with resistance to cleavage in other planes and structural defect. Because of these properties, amphiboles may be more likely to split into thinner fibers of the same length during factory processing. This aspect of amphibole structure may have important biological consequences in regard to pathogenicity [16,17].

Several of the important properties which give asbestos its commercial value are its incombustibility and effectiveness and durability as a binding (or reinforcing) agent when combined with other materials such as cement or plastic. In general, the different types are resistant to high temperatures, electric current, and alkalis, and effectively absorb sound.

Due to the qualities cited above, few commodities have enjoyed the commercial success which has characterized asbestos over the past 100 years. In 1890 some 1,000 tons were produced, while today annual world production is of the order of six million tons [18]. The expansion of technologically based society has produced countless opportunities for new applications of this material. Unfortunately, the ubiquity of asbestos in modern society represents one of the most serious obstacles to its control.

THE BIOLOGICAL EFFECTS OF ASBESTOS

Asbestosis

Parenchymal Asbestosis: Pathology Asbestosis has been described by many authors as a diffuse interstitial fibrosis. Initially, the pathological characteristics of the disease have few features capable of distinguishing it from that seen in interstitial fibrosis of other etiology. One of the few, if not only, pathological findings that is specific is the presence of asbestos fibers in lung tissue, sputum, or bronchial lavage material, although if these are few in number their significance is minimized.

Much of the data concerning the initial pathological changes resulting from exposure to asbestos comes from animal experiments. In the laboratory setting a variety of animal species have been exposed to dust by inhalation or intratracheal injection. Unfortunately, an experimental animal which reacts to asbestos dust in quite the same manner as man does not exist, which limits the degree to which extrapolations can be made. Nonetheless, animal studies have provided clear evidence that asbestos is capable of inducing pulmonary fibrosis and a variety of neoplasms.

The initial effects of asbestos fibers are found in the respiratory bronchioles following the lodgement of fibers in this tissue. As a result, the bronchioles and their alveoli develop fibrous thickening of their walls [15]. This condition does not occur uniformly throughout the lung, and several years or decades must pass before a sufficient number of respiratory bronchioles and alveoli become affected to produce clinical evidence of asbestotic involvement.

The thickening of the walls of the airspaces is due, in large part, to cellular degeneration with subsequent formation of collagen fibers (scar tissue). The fibrous collagen is often found between the airspace and its associated capillary wall, which impairs the exchange of gases between lung and circulatory system. This localized impairment of gaseous exchange tends to become generalized as the involvement spreads. Ultimately, the scar tissue causes the walls of the air space to stiffen, thereby
reducing total lung capacity and decreasing compliance. Over extended periods of
time, the obliteration of capillaries may lead to a reduction in the total size/extent of
the pulmonary capillary bed, which, along with the resulting pulmonary hypertension,
may result in cor pulmonale.

Although pulmonary fibrosis may have various etiologies, the feature that clearly
differentiates asbestosis from other forms of lung fibrosis is the presence of asbestos
bodies. These structures are generally yellow-brown in color and measure about 80
micrometers or more in length and up to 25 micrometers in width. At the core of the
asbestos body is an asbestos fiber. The golden-brown appearance of the body is due to
the coat of iron containing mucoprotein surrounding the fiber. The iron component of
the coat is probably derived from hemoglobin. It is important to note that while their
presence in any quantity in lung tissue is strongly suggestive of asbestos being the cause
of any fibrosis present, a small number of such bodies may be found in individuals with
minimal exposure and no clinical or pathological signs of disease.

**Parenchymal Asbestosis: Physiological and Clinical Manifestations** Clinical
symptoms vary with stage of disease and rapidity of development. Although the most
common initial symptom is dyspnea upon exertion, often accompanied by dry cough, it
should be noted that cough appears to be most common among patients who are
cigarette smokers. In the less extensive cases, pain is often absent, although a feeling of
“tightness in the chest” may be present.

The dyspnea usually present progresses even when the patient is removed from
contact with asbestos, resulting eventually in the development of cor pulmonale and
death within 15 years of the onset of disease. In the later stages of diseases, cough,
sputum production, and loss of weight are frequently observed, and the patient is often
subject to recurrent respiratory infections.

On physical examination, the most distinctive sign of asbestosis is the presence of
rales. These findings are probably related to abnormal lung deflation and are
indistinguishable from those heard in other forms of pulmonary fibrosis [19].
Wheezing, commonly heard in cases of silicosis or coal workers’ pneumoconiosis, is not
heard in asbestosis, and indications of massive emphysema are rarely present.

As the disease progresses, other signs may be found, including finger clubbing and
cyanosis. While clubbing is seen fairly commonly in chronic respiratory disease, among
the pneumoconioses it is not commonly seen in cases of asbestosis [3]. Cyanosis is
indicative of interference with oxygen uptake in advanced pulmonary disease.

**Pleural Asbestosis** In addition to the lung parenchyma, inhalation of asbestos dust
is also associated with non-neoplastic changes of the pleura or pleural cavity known as
pleural asbestososis. Pleural asbestosis involves the pulmonary pleura, which is the serous
membrane covering the interior surface of the lung. The parietal pleura lines the inner
chest wall, diaphragm, and middle thorax structures. The changes associated with this
disease entity are pleural thickening, pleural effusion, hyaline plaques, and calcified
plaques.

In cases of marked parenchymal asbestosis, simple thickening of the visceral pleura
is a common finding. It consists of collagenization of the underlying connective tissue
layer (fibrosis), which is indistinguishable from that caused by other agents. As with
parenchymal asbestosis, changes in the visceral pleura are most commonly seen in the
lower two-thirds of the lung.

Pleural effusion has been reported in a number of studies regarding asbestos-related
disease [19, 20, 21]. This fluid is serofibrous or serohemorrhagic and may appear in the pleural cavity without producing clinical symptoms. Often, it contains a number of lymphocytes, erythrocytes, and possibly neutrophils but is sterile and usually rich in albumin. In most instances, pleural thickening is also present. Asbestos bodies are rarely found in the fluid, although they are generally present in the underlying parenchyma [22].

A pleural plaque is a localized fibrous thickening of a parietal pleural surface. They are often bilateral and symmetrical, occurring along the lower ribs or on the central tendon of the diaphragm.

The term plaque may refer to a substantial pleural thickening or to a hyaline or calcified plaque. Hyaline plaques are whitish raised areas of collagen fibers with sharply defined margins. They may appear on both visceral and parietal pleura but much more commonly on the latter. Calcified plaques have a more opaque white or ivory color and are mineralized thickenings found more commonly on the parietal than visceral pleura.

The presence of pleural plaques is usually associated with exposure to asbestos, talc, or mica, although the biological mechanisms responsible for their production are poorly understood. When pleural plaques are present, lung function may be reduced to some degree even though other symptoms of pathology may be absent. Controversy currently exists regarding the association of pleural plaques and various carcinomas as well as other diseases. Nonetheless, their presence is suggestive of exposure to asbestos fibers either by inhalation or ingestion [23].

Epidemiology of Asbestosis Morbidity studies using various occupational cohorts have provided the medical practitioner and epidemiologist with strong evidence of the ability of asbestos fibers to induce fibrotic lung disease in chronically exposed humans. One major drawback of these data is the limited information provided concerning the demographic, physiological, and exposure characteristics of the exposed population from which cases were drawn, i.e., the population at risk. From a public health standpoint, this information would be of value in estimating the expected prevalence of this disease among previously or currently exposed individuals. Without this information, it is not possible to assess the impact of asbestos exposure on overall mortality and morbidity due to fibrotic lung disease among the exposed population.

An additional limitation of the data currently available is the possible underestimation of the number of individuals actually exposed, i.e., at risk of developing asbestosis. In the past such groups as maintenance and clerical workers were not regarded as being at risk, while today evidence to the contrary exists. Nonetheless, the medical literature, despite its limitations, gives one at least a general impression of the prevalence of the asbestoses in a variety of occupational cohorts.

Data derived from occupational cohorts of asbestos miners and millers, although not extensive, consistently show a marked increase in pulmonary fibrosis with cumulative duration of exposure. In 1972, McDonald et al. [24] reported the results of a cross-sectional study involving chrysotile asbestos miners and mill workers in Quebec, Canada. Among the 1,015 study subjects, shortness of breath was observed to increase with estimated cumulative dust exposure. Two measures of lung function, FVC (forced vital capacity) and FEV1 (forced expiratory volume in one second) were found to decrease with estimated cumulative dust exposure in smokers and non-smokers.
McDonald et al., in a 1974 mortality study [25] of chrysotile miners and millers, observed increased mortality among individuals with parenchymal changes but not in those having only pleural changes. Among the study group of 5,083 employees, 32 deaths due to all respiratory diseases were recorded although only eight were expected, based on general population mortality data.

In a cohort of 485 miners and millers, Selikoff reported the prevalence of radiographic abnormalities to be 10 percent with pleural changes seen in 3 percent of all workers [4]. The prevalence of abnormalities among those employed less than five years was 5 percent.

Irwig et al. in 1979 published the results of a study of 1,801 crocidolite and amosite miners [26] showing that the prevalence of pleural changes increased from 2.5 percent for workers with less than one year of employment to 33.6 percent for workers employed 15 years or more. Parenchymal changes were found in 2.3 percent of workers employed less than one year and 25.7 percent of workers employed more than 15 years.

Textile workers constitute an additional occupational group from which a variety of epidemiological data have been derived. In 1968, using results of a study of 290 such workers, the British Occupational Hygiene Society estimated the risk of developing pulmonary disease for a working lifetime of 50 years to be 1 percent at an exposure level of two fibers per cubic centimeter [27].

In reviewing the prevalence of pulmonary fibrosis among 1,287 asbestos textile workers, Lewinsohn in 1972 reported zero prevalence for 0–9 years of exposure, increasing to 40.5 percent after 30–39 years of exposure. Pleural fibrosis prevalence was 1.6 percent in the 0–9 years' exposure group and 50 percent in the 40–49-year category [28].

Weiss in 1971 examined an occupational cohort of 100 textile workers [29]. The overall prevalence of fibrosis was 36 percent; 24 percent in non-smokers and 40 percent in smokers. None of the 11 non-smokers in this study with exposures less than 20 years had fibrosis.

In a cohort of 611 New Jersey asbestos factory employees, who in 1959 had passed 20 years or more since initial exposure, Nicholson reported 213 deaths from all causes over the period 1959–1973 [3]. Twenty-three, or 10.8 percent, were attributed to asbestosis, 14.1 percent to lung cancer, and 8.5 percent to mesothelioma.

A number of conclusions regarding asbestosis can be drawn from the data available in the medical literature. Ten to 20 years ago, dust levels in the industrial setting were generally much higher than today; therefore, a high incidence of asbestosis can be expected among those exposed for more than ten years during this time. This incidence rate may approach 50 percent for those exposed for more than 20 years. With the improvement in working conditions, it is expected that the number of new cases will decline and that a longer time will elapse before the disease becomes radiologically and clinically detectable. This situation may be particularly true for parenchymal fibrosis, since as exposure levels fall, pleural rather than parenchymal changes become more common.

**Lung Cancer**

*Background Information* Among the countries of Western Europe and North America, lung cancer is the leading form of cancer, with annual age-adjusted incidence rates among males exceeding 11 per 100,000 population in Great Britain and U.S.
blacks [30]. In the United States primary lung cancer accounts for 15 percent of all cancer cases and 25 percent of all cancer deaths. These statistics clearly demonstrate the high fatality rate experienced among lung cancer patients.

A variety of epidemiological, clinical, and laboratory studies have identified cigarette smoking as the predominant risk factor, with industrial exposure also playing an important role. Because of the feasibility of external manipulation of these factors, lung cancer is largely a preventable disease.

As with asbestosis, epidemiological evidence indicates that lung cancer risk is substantially raised among various asbestos industry employees, including miners and millers, textile and shipyard workers [31,32]. In fact, it is the major asbestos-related disease, accounting for a high proportion of all deaths in many exposed cohorts [33]. Although the medical literature of the 1930s and 1940s contains reports of an association between lung cancer and asbestos exposure [7,8,34,35], the first epidemiological investigation of this association was published by Doll in 1955 [12]. Two groups of subjects were examined. The first group was composed of 105 persons employed in an asbestos textile factory in northern England on whom autopsies were performed. Lung cancer was found in 18 instances, 15 times in association with asbestosis.

In addition, 113 men who had worked for at least 20 years in the same textile factory were followed up and their mortality experience compared with that which would have been expected on the basis of the mortality experience of the entire male population. There were 11 observed lung cancer deaths, compared to a calculated expected number of 0.8. This indicated that the risk of developing lung cancer in that factory during the time studied was 13.75 times that of the general population. All cases of lung cancer were confirmed histologically and were associated with asbestosis.

This same cohort was subsequently followed up by a number of investigators [36,37,38]. By 1957, dust levels in this factory were reduced by 50 percent to 80 percent of their 1955 value. The 1951 mean dust level was 10.8 fibers per cubic centimeter while the 1972 mean dust level was calculated to be 2.9 fibers per cubic centimeter. The lung cancer data presented indicated that the risk of developing lung cancer by the end of 1972 was 2.1 times that of the general population of England and Wales.

A 1980 study by Peto [38] once again compared the mortality experience of this occupational cohort. The 567 men entered in this analysis were subdivided into three groups. Group 1 was composed of 69 men with more than 20 years of asbestos exposure, more than ten of these years being before 1933 when dust reduction efforts became mandatory. Group 2 contained the data from 74 men with greater than 20 years’ exposure with less than ten years’ exposure before 1933, while Group 3 included 434 men having less than ten years of exposure between 1933 and 1950. The ratio of observed to expected number of deaths due to lung cancer in the three subgroups was 8.1, 2.0, and 1.6, respectively, indicating an association between death from lung cancer and increased exposure level.

Finkelstein [39], in 1983, published the results of a study conducted among 328 employees of an Ontario asbestos cement factory hired before 1960 and employed for a minimum of nine years. Both chrysotile and crocidolite asbestos were used in the manufacturing process. Twenty deaths due to lung cancer were observed, while the calculated expected number was 3.3, representing a sixfold increase in risk for lung cancer among the exposed population (death rates for the Province of Ontario were used to compute expected number of deaths).
Since the mid-1960s, a plethora of articles has appeared on the association of lung cancer with asbestos exposure, particularly in relation to occurrence of disease under various exposure conditions (i.e., dust concentration, various occupational settings, and so on). The appearance of these reports has led to the identification and exploration of a number of controversial areas: the effects of cigarette smoking, the association between type of fiber exposure and disease, peak vs. continuous exposure, dose-response relationship, and physical dimension of fibers as an indicator of carcinogenic potential [40,41,42,43,44]. The following will be a brief discussion of these topics based upon currently available data.

**Dose-Response Relationship for Asbestos and Lung Cancer** Although the existing data are consistent with the hypothesis that excess mortality from lung cancer following a fixed duration of exposure is proportional to airborne concentration of asbestos and that mortality increases with increasing duration of exposure, the poor quality of past exposure measurements severely limits quantification of this observation. Bearing this caveat in mind, three recent reports comparing lung cancer mortality to total exposure level of asbestos suggest the existence of a linear relationship between these quantities [45,46,47]. While all showed that respiratory cancer risk increased as exposure level increased, the numbers of cases in these reports are relatively small, making it difficult to specify accurately the shape of the exposure intensity-response curve after adjustment for duration of exposure.

**Differences in Mortality Between Fiber Types** The evidence for differences in the potential for inducing lung cancer among the various asbestos fiber types is mixed and inconclusive, although it is generally believed that crocidolite is biologically more active than chrysotile and that amosite occupies an intermediate position. Two studies provide support for this contention. The first [48] concerned 1,348 men from the asbestos industry who had retired during the years 1941 through 1967. The pertinent data comprised deaths that had occurred among these retirees through 1969. In addition to the observation of increased risk of death due to lung cancer in relation to asbestos exposure, individuals exposed to chrysotile alone experienced a death rate due to lung cancer that was 2.5 times greater than that observed among the general U.S. male population, while those exposed to both chrysotile and crocidolite had a mortality rate five times that of the general U.S. male population.

In the second study [49] a cohort of 5,645 white and black male workers was investigated. These men had been employed for at least one continuous month before January 1, 1970, in either one of two asbestos-cement building materials plants in New Orleans, Louisiana. All had their initial employment 20 years previously and had been followed through 1974. After stratifying subjects according to cumulative exposure, it was found that, among those in the most heavily exposed category, those exposed to dust containing both chrysotile and crocidolite had a higher level of excess mortality than those exposed to dust containing only chrysotile.

Clearly, several problems remain concerning the carcinogenic potential of different fiber types. One of the most important is the apparent scarcity for study of occupational cohorts exposed to a single fiber type over considerable time periods. Also, exposure data is often inaccurate or not available. Although animal experiments have supported the theory of differing carcinogenic potentials, extrapolations from animal systems to humans may not be appropriate due to differences in physiology,
routes of entry of fibers, and fiber exposure level. Data derived from this source must therefore be considered cautiously.

**Relation of Fiber Size to Cancer Development** The influence of fiber size on tissue response and the production of cancer has been decisively demonstrated experimentally by the failure of short fibers to cause disease [50,51]. Similarly, epidemiological studies have shown that the inhalation of short asbestos fibers has not caused an increased risk of death from non-malignant respiratory disease. With regard to lung cancer, the epidemiological evidence remains equivocal [15] to the extent that no firm conclusion can be drawn about this relationship based upon present information.

Even though long fibers are indisputably fibrogenic, a level cannot be specified below which fibrogenicity approaches zero. Adequate information is simply lacking regarding the movement and ultimate pathogenic action of those fibers observable only by electron microscopy [3].

**Effects of Cigarette Smoking** In the vast majority of studies of asbestos workers, information on smoking habits is absent. Selikoff, Hammond, and Churg, in 1968, were the first to publish a report on the effects of smoking on the incidence of asbestotic lung cancer [3]. It was found that asbestos workers who smoked had eight times the lung cancer risk of all other smokers and 92 times the risk of non-smokers who did work with asbestos. Based upon follow-up data from this study, it has been hypothesized that these carcinogens (asbestos and cigarette smoke) react synergistically to produce very high lung cancer rates among those exposed to both substances, while the risk among those exposed to either substance alone is significantly lower.

**Summary** Since the publication of Doll's 1955 study, evidence has accumulated clearly establishing that occupational exposure to asbestos substantially increases the risk of pulmonary carcinoma. As indicated earlier, cigarette smoking is perhaps the most important factor in the production of this increased risk. Although asbestos has relatively weak carcinogenic properties itself, this potential could be raised to effective levels if the dose is high, but with high doses pulmonary fibrosis becomes a likely cause of mortality, precluding the development of lung cancer. Nonetheless, it appears that asbestos can augment the effects of other potent carcinogens, such as cigarette smoke, producing a greatly increased risk of pulmonary cancer among those exposed to both substances [3].

With the institution of measures to reduce exposure levels in the workplace, pulmonary carcinoma is seen with increasing frequency, since early deaths due to asbestosis and other respiratory insufficiencies are less likely at lower dosages. In the early part of this century, asbestosis was an early killer and only those that avoided death due to this cause lived long enough to acquire lung cancer or mesothelioma. Today, bronchogenic carcinoma, followed by mesothelioma, is responsible for the early death of a large number of exposed individuals. Only the survivors from these diseases are open to later lethal effects of the now more slowly developing asbestosis. Over the next several decades, late deaths due to asbestosis may well decline due to dust control measures put in place in previous years. Unfortunately, it is unlikely that deaths due to asbestos-associated lung cancer will show a substantial reduction in the near future.

**Mesothelioma**

**Definition and Character** A number of issues have hindered the recognition of diffuse malignant mesothelioma by the medical community as a distinct pathological
entity. Among these are the rarity of the tumor in the early part of this century; the occurrence of what are apparently two forms of this tumor, i.e., the localized and benign versus the diffuse and malignant; and the possibility that an apparently primary tumor of the mesothelium may actually be a secondary growth from a primary tumor located in a different anatomical site [3]. Over the last 40 years two important developments have contributed to this tumor’s recognition and characterization: namely, its increased prevalence and implication of asbestos as an etiological factor [52]. By 1960, therefore, publication of detailed descriptions of the diagnostic details of malignant mesothelioma allowed for the standardization of diagnostic criteria and the acceptance of mesothelioma as a clinical entity [53].

Today, mesothelioma is characterized as a highly malignant cancer that originates in the lining of the chest or abdominal cavity. In almost all instances it is rapidly fatal, with median survival times averaging two to 18 months from diagnosis. More recently, selected patients treated initially with surgery, radiotherapy, and chemotherapy have achieved a longer median survival, with occasional patients disease-free at five years.

Until the publication of a report by Wagner et al. in 1960 [13], describing 33 cases of diffuse pleural mesothelioma in South Africa, this tumor was considered a rare clinical entity. Since then, the relevant medical literature has expanded substantially and currently includes case reports and epidemiological studies describing the increased occurrence of mesothelioma in specific occupational cohorts as well as in domestic and environmental settings.

Apart from its previous rarity, this cancer is also unusual histologically in that it is composed of cells capable of forming either adenocarcinoma or sarcoma or a mixture of the two [15]. In pleural mesothelioma, both the parietal and visceral pleura may be involved, with the parietal surface usually more extensively affected. Ultimately, the tumor spreads, covering the surface of the lung with dense, white, and often leathery tissue with little penetration of the lung parenchyma, although massive invasion occasionally occurs. Compression of the lung follows, with partial or total obliteration of the pleural cavity.

In the peritoneum, the tumor covers the intestines and tends to bind them together. Obliteration of the peritoneal cavity with incorporation of all viscera in the tumor mass may occur. Although mesotheliomas do metastasize, this condition is not common except for the involvement of regional lymph nodes. More distant metastases may appear in the liver, lung, and, to a lesser degree, in the spleen and bone [15].

Microscopically, malignant mesothelioma occurs in three forms; epithelial, mixed, or sarcomatoid in order of decreasing frequency [3]. Variability of histological structure, even within a single tumor, is characteristic of mesothelioma. In the purely epithelial form, the tumor forms glandular patterns and resembles an adenocarcinoma. The fibrous form of mesothelioma closely resembles a sarcoma, while the mixed type may show a variety of appearances and for that reason is very suggestive of mesothelioma.

Incidence and Epidemiological Characteristics As stated earlier, Wagner first drew attention to this tumor in 1960 in a report of 33 patients with mesothelioma in South Africa. Based upon occupational and residential histories, it was discovered that all but one had either worked in the crocidolite asbestos mines in the Cape Province, had handled asbestos in some capacity (e.g., transport of asbestos materials), or had lived near the mines. In this series both men and women were affected, with all patients dying of pleural tumors.
In 1964, Newhouse conducted a case-control study of patients dying of mesothelioma at the London Hospital [54]. All cases of mesothelioma occurring since 1969 were reviewed and the diagnosis was confirmed in 83 cases (41 men and 42 women). Occupational and residential exposure histories were obtained from surviving relatives and revealed that 52.6 percent had had a positive history of asbestos exposure. Of particular interest is the fact that 11 patients had neither a history of occupational nor household exposure, but had lived in the immediate vicinity of an asbestos factory. This study also provided evidence that domestic contact from dust brought home on clothes was important in the pathogenesis of mesothelioma.

A disturbing feature of many reports concerning cases of this tumor is that patients may give histories of short and apparently low-level exposures [55,56,57,58]. It must be remembered though that occupational and residential histories are often obtained decades after exposure may have occurred and that poor recall may play a role. Exposure may thus have been heavier than realized.

A summary of 22 countries indicated that a total of 4,539 malignant mesotheliomas were reported between 1959 and 1976 [15]. Since some of the mesothelioma deaths may not have been recognized, this total may represent an underestimate. A more recent study of the incidence of malignant mesothelioma in North America between 1960 and 1975 showed that there were 272 deaths from mesothelioma in the United States and 396 deaths from this tumor in Canada [59]. From this data, the annual incidence of mesothelioma in North America was estimated at 2.8 per million males and 0.7 per million females age 15 years and older.

The medical literature of the last ten years reflects the growing interest and heightened awareness surrounding malignant mesothelioma within the medical community. Many of these studies address the more controversial issues relating to this tumor, including the influence of dust concentration on the development of mesothelioma, the influence of duration of exposure on incidence, and the etiologic role of different fiber types. While the relationship between duration and level of exposure and the development of malignant mesothelioma remains unclear, epidemiological studies of occupational cohorts strongly suggest the existence of a gradient in potential potency to induce mesothelioma among different fiber types.

McDonald et al. in 1978 traced 199 persons exposed to crocidolite between 1939 and 1942 in three Canadian factories. Comparison of the mortality pattern within this group with that observed in the Quebec chrysotile mining and milling industry indicated that mesothelioma was some 60 times more frequent in the crocidolite- than in the chrysotile-exposed cohort [60]. There was also a major difference in the site of the mesothelial tumors; in the crocidolite cohort, six of the nine cases involved the peritoneum compared with only one of the 11 in the chrysotile cohort. The authors ascribe this difference in mortality to the fiber type. Similarly, Wignal and Fox in a 1981 report [44] observed a substantial excess risk of mesothelioma among a cohort of female gas mask assemblers exposed to relatively high levels of crocidolite. Thus, the epidemiological and experimental evidence suggest that there is a gradient from crocidolite to chrysotile asbestos in their potential potency to induce mesothelioma, with amosite occupying an intermediate position.

**Latency Period** Following the recognition of an association between asbestos exposure and the occurrence of mesothelioma, it became clear that the interval between initial exposure and the onset of disease is long, usually 35 years or more. Data from epidemiological studies indicate that at least 30 years from initial exposure
only 20 percent of the total mesothelioma deaths in an exposed cohort will have taken place [15]. The existence of this latency period does not mean that the malignancy is established early on and grows slowly but rather that the transformation of normal cells to cancerous ones requires many years.

Curiously, a careful review of the available literature will reveal the existence of reports directly contradicting the above information. Cases of mesothelioma have been reported (although rarely) to occur after very short periods since first exposure [42] as well as in children in whom occupational exposure does not play a role [61]. In the case of workers, incorrect/inadequate occupational histories might provide an explanation, but in children it is most likely that some pathogenic mechanism other than asbestos is operative. This mechanism may be identical to that responsible for the sporadic cases of mesothelioma reported before asbestos was a significant public health hazard.

**Conclusion** Studies from many areas of the world indicate that the incidence of mesothelioma is rising, with some of the highest rates occurring in the United States, Germany, the Netherlands, and England [3]. Undoubtedly, this rising incidence is due to the rapid expansion of the asbestos industry and the increased use of asbestos products throughout this century. Unfortunately, widespread substitution of other material for asbestos has not occurred, contributing to the persistence of this hazard.

Because of the long latent period between exposure and development of mesothelioma, those individuals exposed during the 1940s are only now beginning to develop clinical disease. Projections based upon information derived from epidemiological studies predict that the number of deaths due to mesothelioma will continue to rise among asbestos workers such as those who worked in shipyards and asbestos factories [62]. This increase is expected to continue throughout the 1980s.

**Gastrointestinal Cancer**

Information concerning the possible relationship between asbestos and cancers of the buccal cavity, esophagus, stomach, colon, and rectum is derived largely from studies of occupational cohorts, although the incidence of gastrointestinal cancer has also been examined in non-occupational settings with known asbestos contamination. The total amount of evidence available, however, is meager, making the elucidation of a possible causal relationship difficult. In addition, the number of animal experiments reported is small and the experimental designs have generally been poor. Therefore, controversy still exists regarding this disease-exposure relationship.

In 1979, Selikoff et al. [63] published the results of a study of U.S. and Canadian insulation workers experiencing the largest number of asbestos-related deaths among any group of asbestos workers examined. The mortality of 17,800 asbestos workers was studied prospectively from January 1, 1967, through December 31, 1976. Overall, 2,271 deaths occurred with 120 due to gastrointestinal cancers. Based upon white male age-specific U.S. death rates for this period, only 69.5 were expected; a significant, although small, increase in mortality.

Elmes and Simpson, in 1977 [64], reports the results of a follow-up study of 170 insulators and pipe covers in Belfast, Northern Ireland. Expected deaths were derived from death rates for Northern Ireland, giving a ratio of observed to expected deaths from gastrointestinal cancer of 5:9.

In a study of London asbestos factory workers who had been exposed to crocidolite, amosite, and chrysotile, (4,600 men, 972 women) no statistically significant excess in gastrointestinal (GI) cancer deaths was observed among those with low to moderate
exposure. Both men and women with "high"-level exposure showed a significant excess of cancer deaths due to GI malignancies [33]. Gross and Braun summarize the epidemiological data based on occupational exposures as follows;

There has been an increased incidence of gastrointestinal cancers among some asbestos workers and among miners exposed to elongated amphibole crystals. This increased incidence has not been large and has been largely limited to those most heavily exposed. It has also been more pronounced in cigarette smokers. There are also investigations which failed to find any association between asbestos dust exposure and gastrointestinal cancer. . . [15].

It is therefore clear that the association of gastrointestinal cancer with asbestos exposure in the occupational environment is weak. Further epidemiological studies are necessary to define the relative risk accurately and clearly establish the possible influence of other factors in the etiology of these tumors.

EXPERIMENTAL STUDIES

The useful aspect of the majority of animal studies conducted to examine the health effects of asbestos has been their confirmation of previously established human data. They have also served to elucidate more fully the pathological mechanisms of asbestos fibers on specific organ systems. The ability of animal studies to predict human disease is limited by the relative resistance of some animal models to the human disease of concern; the uncertainty inherent in procedures used to extrapolate from experimental systems to estimate the possibility of the occurrence of similar effects in humans; and by the fact that lung cancer, the principal carcinogenic risk from asbestos, "is the result of a multifactorial interaction of causal agents, i.e., cigarette smoking and asbestos exposure, and is difficult to elicit in a single exposure circumstance" [65]. Nonetheless, animal studies have provided important information not available from human studies, such as data on the deposition and clearance of fibers as well as cytotoxicity.

Among the major findings to emerge from the laboratory is the demonstration that mesothelioma and lung cancer can be produced by all the major commercial types of asbestos: i.e., chrysotile, amosite, crocidolite, and anthophyllite [66,67]. Studies examining the deposition and clearance of fibers from the respiratory system of test animals suggest that the majority (approximately 99 percent) of inhaled fibers are eventually cleared from the lung by ciliary or phagocytic action. Of all fiber types, chrysotile appears to be most readily removed.

Implantation and injection studies show that the carcinogenicity of mineral fibers is directly related to their dimensionality and not their chemical composition [65,51,50]. Particles with dimensional aspect ratios of 3:1 or greater, longer than 4 micrometers, and thinner than 1 micrometer are most carcinogenic; however, deposition clearance and migration of fibers are also size-dependent. Therefore, these factors may also play an important role in carcinogenicity. Unfortunately, the interplay of all these size-dependent effects is poorly understood.

UNRESOLVED ISSUES

One of the more perplexing and technologically difficult questions to address in relation to asbestos-associated disease is the risk posed by low-level exposure. This issue is important because of the huge amounts of asbestos materials incorporated into buildings worldwide. Often, these materials are friable and are capable of being
released into the indoor environment, posing a health risk to those coming in contact with these airborne fibers. In the industrial setting, engineering control measures are capable of limiting exposure to extremely low levels in certain operations, although this is not the case in all industrial processes.

Current knowledge of the risks associated with low-level exposure relies on downward extrapolation from findings associated with high-level exposure. The uncertainty inherent in this process is considerable, severely limiting estimates derived by this process. Unfortunately, more satisfactory mathematical models have not been developed, making accurate predictions concerning the occurrence of excess disease at low exposure levels unattainable. Also, with the current work force experiencing substantially lower exposures than their counterparts in the earlier part of the century, the “latent periods” of the asbestos-associated diseases may be increased. The severity of these clinical manifestations may also be reduced. Both of these factors may complicate epidemiological analyses.

An issue closely related to the “dose-response” question, and largely ignored in the medical literature, is that of individual susceptibility (given comparable exposure to risk factors). Although studies of the immunological status of patients with asbestos-related diseases have been conducted, they are few in number and therefore the available data are sparse. Because an understanding of the interplay of factors affecting individual susceptibility may provide the basis for disease prevention strategies and long-range projections of mortality and morbidity, new methods in study design and analysis should be developed to address this question.

As described throughout this paper, a number of etiologic issues remain unsolved: namely, the mechanisms responsible for production of disease in the pleura (both visceral and parietal) and lung parenchyma, the apparent existence of a gradient in biological effects among fiber types, and the ability of asbestos to induce airway dysfunction [68]. Solution of these problems will not only provide information regarding specific pathological processes but may also have practical implications in the reduction of mortality and morbidity due to asbestos-related diseases.

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