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Biologic Response to Kind and Amount of Asbestos

Morris Kleinfeld, M.D.

Studies of the biologic response to different types of asbestos dusts indicate that their inhalation in adequate concentrations can produce pulmonary and pleural fibrosis and/or several types of malignancy, chiefly of the lung, pleura and peritoneum[1] Associations between asbestos dust exposure and malignancy of the gastrointestinal tract have been reported[2 16] However, a general consensus with regard to this association has not been evolved[3] Most of the evidence of association between asbestos exposure and human disease has been acquired from occupationally exposed groups

Effects of Exposure to Different Types of Inhaled Asbestos Dusts

1. Asbestotic Pneumoconiosis Of the different pathogenic effects associated with asbestos dust exposure, the first clearly demonstrated adverse effect of asbestos in man was pulmonary fibrosis or asbestotic pneumoconiosis There is general agreement that all forms of asbestos in commercial use can produce fibrotic effects in the lungs[4] Asbestotic pneumoconiosis is characterized roentgenographically by diffuse interstitial fibrosis of variable degree sometimes associated with pleural fibrosis and calcification Clinical signs include lung crepitations finger clubbing and dyspnea, physiological changes are consistent with a restrictive lung disorder manifested by decreased forced vital capacity diminished diffusion capacity and decreased pulmonary compliance.

Asbestotic pulmonary fibrosis has been produced experimentally in various animal species However, data on relative fibrogenicity of different asbestos dusts in animal work has not been consistent[5 6] Human data on relative fibrogenicity of different asbestos dusts is still inconclusive Murphy, Ferris and Burgess[7] studied pipe coverers exposed mainly to chrysotile and amosite dust Asbestosis was first observed after 13 years of exposure to the dust or about 60 million particles per cubic foot (mpcf) years The prevalence was 38% after 20 years of exposure In a recent unpublished study of talc workers exposed to a mixture of talc with tremolite and anthrophyllite as the predominant fibrous components, Kleinfeld, Messite and Langer[8] found only one case of pneumoconiosis among a group of 39 workers whose mean exposure was 16 2 years with a range of 11 to 22 years. The mean dust concentration to which the workers had been exposed over a 20 year period was 23 mppcf with an average minimum concentration of 6 and an average maximum of 68 mppcf. In both studies[7 8] consideration was given only to time-weighted average exposures Peak concentrations were not mentioned Lacking data on peak exposures and since the operations differed significantly one cannot truly compare the relative pathogenicity of the dusts referred to in the two studies

As in the case of bronchogenic carcinoma the factor of smoking must be considered in relation to asbestos exposure and development of pulmonary fibrosis In a study of 100 asbestos textile workers Weiss[9] found that the prevalence of pulmonary fibrosis was 40% in smokers and 24% in non-smokers. Age, sex and duration of exposure to asbestos did not account for this difference The prevalence of pulmonary fibrosis rose with increasing amount and duration of cigarette smoking and with increasing exposure to asbestos.

2. Bronchogenic Carcinoma Available data confirm a relationship between past occupational exposure to asbestos dusts and higher than expected incidence of bronchogenic carcinoma[10-12] Some studies have demonstrated differences in degree of risk among different occupationally exposed groups probably related to type and concentration asbestos fiber, nature of work performed, and other factors such as smoking cigarettes[13] and presence of metals in the asbestos dust[14] For example, in a study of mortality in relation to occupational exposure in the asbestos industry, Enterline, DeCoufle and Henderson[12] observed differences in respiratory cancer mortality between maintenance service workers and production workers Two possible explanations were offered for the differences in respiratory cancer mortality between these two groups, one that intermittent asbestos exposure of maintenance service workers probably at very high level, produced excess respiratory cancer but no great excess of asbestosis; another explanation was based on types of asbestos to which these two groups of workers were exposed Sixty-four percent of the maintenance service workers with high exposures had been exposed to crocidolite asbestos whereas 8% of the production workers with high exposures had been so exposed, indicating that crocidolite was more carcinogenic than [illegible] asbestos dusts namely, chrysotile

Director, Division of Industrial Hygiene, New York State Department of Labor, 80 Centre Street, New York, N.Y. 10013 and Clinical Professor of Environmental Medicine, New York University Medical Center

Reprint requests to 400 Orangeburg Road, Montebello, N.Y. 10901

amosite, to which these workers were exposed. Cigarette smoking is an additional factor of importance. In a study of insulation workers, Selikoff, Hammond and Churg[13] reported a mortality risk 92 times greater among insulators who smoked cigarettes compared to men who neither smoked cigarettes nor worked in the insulation industry. More recently, the role of trace metals has also been considered a major factor in carcinogenesis among asbestos insulators[14].

Wagner, Gilson, Berry et al[10] commented that the risk of bronchogenic carcinoma is clearly related to the intensity of past exposure and to the risk of asbestosis. When the environmental control is sufficient to eliminate asbestosis, the excess risk of bronchogenic cancer diminishes. Wagner and associates also indicated that it is not known whether the type of asbestos inhaled influences the risk of bronchial cancer in man. Experiments in animals suggested to them that it should because chrysotile produces less severe fibrosis than does amosite or crocidolite in equal doses.

The question of whether the carcinogenic role of asbestos is related to the specific kind of fiber is more difficult to answer than the question of dose-related response. For this purpose Wnght[4] indicated that populations with long-term exposure to only one variety of fiber are needed. Virtually all fabricating processes use more than one variety within the same premises at any one time or have used more than one variety at various times. Populations restricted to mining and milling operations in the production of asbestos fiber lend themselves best to a study of the effects of a single kind of asbestos fiber. It is these populations which can provide the answer to the influence of a single variety of asbestos fiber in terms of carcinogenesis. However, the role of different types of asbestos in raising the incidence of bronchogenic cancer appears to be dose-related and may depend upon the specific category of fiber especially in regard to degree of effect.

3 Mesothelial Tumors. Primary malignant tumors of the pleura and peritoneum, formerly regarded as exceedingly rare by most pathologists are being reported more frequently, particularly among workers exposed to asbestos dust. Since Wagner's[15] first reported 33 cases of mesothelial tumors in a part of South Africa important for crocidolite mining, investigators in other parts of the world[16,17] have examined the distribution of mesotheliomas in the general population and among occupationally exposed asbestos workers. The results indicate a fairly good relationship between exposure to different asbestos dusts, namely, crocidolite, chrysotile and amosite or mixtures thereof, and the occurrence of mesotheliomas. Wagner[18] pointed out that amphibole fibers, which are straight, are more likely to reach the periphery of the lung in contrast to chrysotile fibers, which resemble stretched coils and are readily intercepted by the bronchi, especially at bifurcations. The lesser risk of developing mesothelioma from exposure to chrysotile fibers may be due to their curly nature, which prevents most of them from reaching the pleura. Wagner has, therefore, emphasized that quantitative studies of the distribution of different types of fiber within the lung following inhalation need to be extended. However not all amphibole fibers show an increased prevalence for mesothelioma production. Despite a thorough search no mesotheliomas have been associated with anthophyllite asbestos production in Finland.

Timbrell, Griffiths and Pooley emphasized the importance of fiber diameter in addition to fiber shape in relation to development of mesothelioma. They provided a plausible explanation for differences in frequency of diffuse mesotheliomas in the Northwestern Cape of South Africa where only crocidolite is mined compared to the Transvaal region where both crocidolite and the closely related amosite are mined. The occurrence of mesothelioma in the Transvaal is rare. The mean fiber diameters of Transvaal crocidolite and amosite were three times those of Northwestern Cape crocidolite. Timbrell et al postulated that differences in diameter would influence the ability of fibers to penetrate to the periphery of the lung and pleura where the tumors develop. Because of their greater aerodynamic size, a higher proportion by mass of Transvaal fibers will be deposited in the larger airways by gravitational settling and hence will reach the periphery of the lungs with much less efficiency than the shorter and smaller diameter fibers of the North western Cape. The greater penetration to the deeper alveoli adjacent to the pleura by the smaller crocidolite fibers could account for differences in incidence of mesothelioma among workers in the two areas. In addition to the biologic importance of fiber diameter and shape, other factors such as metallic cations and enzymes present in asbestos dust remain to be evaluated, particularly in view of the fact that not all mesotheliomas are related to asbestos dust exposure.

There have been a variety of animal studies in which experimentally induced mesothelioma has been reported in different animals.[21,22] Of particular interest is the study of Roe, Carter, Walters et al[23] who produced pleural and peritoneal mesothelioma in mice subcutaneously injected with crocidolite, amosite and chrysotile and thus have shown evidence of migration of fibers, a finding which helps explain peritoneal mesothelioma in workers exposed to different asbestos dusts.

One noteworthy feature about the occurrence of asbestos mesotheliomas has been the long period, commonly over 30 years between first exposure to asbestos and appearance of mesothelioma[16,17,24,25]. Whitwell and Rawcliffe[24] observed that the interval from first exposure to asbestos and appearance of mesotheliomas ranged from 13 to 63 years with a mean of 42 years. They expressed the opinion that the incidence of mesothelioma will continue to rise with increasing use of asbestos until about 40 years after adequate protective measures have been taken. Another important feature about mesothelioma in contrast to bronchogenic carcinoma is that cigarette smoking does not appear to be an important factor related to its development.

4 Pleural Calcification. Calcified pleural plaques have been reported among workers exposed to anthophyllite, chrysotile, amosite and tremolite, or mixtures thereof[26–29]. Multiple or bilateral pleural plaques are regarded by some investigators as virtually diagnostic of asbestos related disease[30]; however, other causes of pleural calcification are well known. Robinson[31] found pleural plaques in 2.7% of 1,829 autopsies performed chiefly upon adult males. No relationship to typical asbestos bodies, degenerative or neoplastic disease or

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known infectious disease was discovered. Robinson indicated that pleural plaques should not be considered proof of asbestosis nor termed "benign fibrotic mesothelioma".

With regard to those occupationally exposed, pleural calcification rarely appears until 20 years after first exposure and does not necessarily correlate with pulmonary fibrosis. Pleural calcification also appears to differ in frequency in different occupationally exposed groups, but studies to date have not explained such differences. The finding of pleural calcification or pleural plaques has been reported as being common in large segments of populations not directly exposed occupationally to asbestos but living in or near regions where asbestos fibers are being produced and used[32 33]

There is no evidence that presence of pleural plaques bears any relation to the development of mesothelioma. In Finland and Eastern Quebec where a greater frequency of pleural plaques has been reported, there has been no increased frequency of mesothelioma[4] Furthermore, one cannot conclude that presence of pleural calcification is an indicator of previous asbestos exposure since other causes lead to this condition, nor can it be assumed that absence of plaques excludes a history of exposure to asbestos.

Effects Related to Quantity of Inhaled Asbestos Dusts

1. Correlation of Environmental Exposure and Biologic Response Balzer and Cooper[34] reported asbestosis among insulation workers exposed to levels not exceeding the time-weighted average of 5 mppcf Chrysotile and amosite were the principal types of asbestos minerals to which the group studied was exposed

Murphy, Ferris and Burgess et al[7] reported that asbestosis was first observed in the group they studied after 13 years of exposure, or about 60 mppcf-years The highest average concentration was 10 0 mppcf and lowest 0 8 mppcf with an overall average of 5 2 mppcf Amosite and chrysotile were used but no crocidolite was present No asbestosis was found in men exposed less than 60 mppcf-years Twenty percent of those exposed for 75 to 100 mppcf years were considered to have asbestosis No attempt was made to correlate workers who had asbestosis with the characteristics of different jobs in the workplace nor with time spent on the job. Peak concentrations were not given.

In a recent unpublished paper, Williams, Baier and Thomas[35] compiled data on exposure levels at various textile processing operations in two plants for 37 years and 20 years, respectively. Even though exposures were mainly below 5 mppcf and in many instances below 2 mppcf, 64 workers were reported to have asbestosis.

In an unpublished study, Kleinfeld, Messite and Langer[8] found only one case of pneumoconiosis in a group of 39 workers exposed to commercial talc containing tremolite and anthrophyllite as the major fibrous components, despite a mean exposure of 16 2 years with a range of 11 to 22 years and a time-weighted average of 23.0 mppcf The mean fiber count, obtained only in 1970, was 34 fibers/ml with a fiber length greater than 5 microns/ml The range varied from a low of 8 to a high of 160 fibers/ml In a comparative study of talc workers employed in two different plants and exposed to the same minerals, these authors[8] observed a significantly increased prevalence of pneumoconiosis based on chest roentgenograms and clinical findings in the workers who had four times the mean fiber count than the comparative group even though mean age and average duration of exposure and range were similar for both groups, indicating a dose-response relationship.

Enterline, DeCaufle and Henderson[36] recently demonstrated convincing evidence for an exposure-response relationship between chrysotile asbestos, measured in terms of million parts per cubic foot years (mppcf-years), and risk of malignant and non-malignant respiratory disease Specifically, the risk of respiratory cancer increased from 166 7 (Standardized Mortality Ratio) at minimal exposures to 555 6 at cumulative exposures in excess of 750 mppcf-years The percentage increase exceeded 300 With regard to non-malignant respiratory disease, the increased risk was not only to pneumoconiosis and pulmonary fibrosis but to other diseases of the respiratory system as well

McDonald Rossiter, Eyssen et al[37] reported on 129 primary thoracic neoplasms among 9 304 former employees in a chrysotile asbestos mine and mill. Five of the neoplasms were mesotheliomas. Although the authors concluded that even heavy asbestos exposure carried only a modest risk of contracting lung cancer and an even lesser risk of contracting mesothelioma, Selikoff[38] in commenting on McDonald's "heavily exposed" group stated that these workers demonstrated five times as much lung cancer as the group of "lightly exposed" workers.

Whereas bronchial cancer is more clearly related to intensity of exposure, data on mesothelioma are less certain with regard to the influence of quantity There are many examples where exposure has been short, though not necessarily slight[10]. As mentioned by Wagner, Gilson, Berry et al[10], mesothelial tumors apparently occur more frequently in the peritoneum than in the pleura when the exposure has been extensive, but the route of entry of dusts into the abdomen is not known Epidemiological studies show that there is much clearer evidence of risk of mesothelioma varying with type of asbestos than in the case of bronchial carcinoma The study of Kiviluoto and Meurman[39] provides evidence that exposure to anthophyllite very rarely causes mesothelioma The very long period that elapses between first exposure and development of mesothelioma has prevented an estimate of what proportion of an exposed group develops mesothelial tumors Wagner, Gilson, Berry et al[10] believe that the proportion is likely to be fairly small, much less than that following exposure to bladder carcinogens for example As true for pleural calcification, not all pleural mesotheliomas are relatable to exposure to asbestos, there are presumably other causative factors This makes interpretation of the relationship between asbestos exposure at a low level and mesothelioma difficult There is need for more prospective studies on the quantity as well as type of asbestos burden in the lung and occurrence of mesothelioma.

2. Mortality Experience From Lung Cancer, Asbestosis and Other Non-Malignant Respiratory Diseases Studies of the mortality of workers in different asbestos industries and trades and different asbestos dust exposures[3 16 17 19 36 40] indicate that past exposure to different asbestos minerals has contributed to an excess of mortality of cancer of the lung

ura and peritoneum and its com-
cations, and non-malignant
piratory disease over the general
pulation In several studies an excess
deaths from gastrointestinal
lignancy[2 16] has been reported.
Studies on mortality experience point
the importance of elapsed time from
ial exposure and duration and degree
exposure as factors which increase the
of malignant and non-malignant
piratory disease. In some instances
ere exposure was of short duration
degree was relatively high, there was
excess of observed deaths from can-
of the lung and pleura and cancer of
er sites compared to the number ex-
cted Knox, Holmes Doll et al[40]
nd, in a preliminary report, that after
st controls were introduced in a
tish asbestos textile plant during the
30's, the incidence of respiratory can-
fell from a tenfold excess to a rate
nilar to that in the general population
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With regard to type of asbestos Kle-
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excess of mortality from cancer of the
g and pleura among talc workers ex-
ed to a mixture of talc and tremolite
significant increase in incidence ap-
ared in the oldest age group, 60 to 79
ars rather than in the middle age
up 40 to 59 years This was at
riance with their findings among
bestos insulators exposed to chrysotile
d amosite whose duration of exposure
as similar to that of the talc workers
mong the asbestos insulators there was
increased incidence of lung and
eural cancers in both middle and
dest age groups There was no excess
carcinoma of the gastrointestinal tract
d peritoneum in talc workers whereas
asbestos workers gastrointestinal and
neal malignancy was significantly
eased compared to the general
pulation, as also observed by Selikoff,
mond and Churg [16]

Discussion and Conclusion

mal studies have been useful in
monstrating certain factors that explain
the action of asbestos however
a precise animal model from which to derive a dose-response relationship for extrapolating risk factors in producing disease is lacking. Unfortunately, the amount of asbestos dust required to produce pathologic effects in animals is unusually large in proportion to amounts to which man is exposed. Hence, animal data which have shown different responses to different types of asbestos[5 6] cannot be used as a basis for drawing firm conclusions as to the relative pathogenicity of different types of asbestos in man. One major impediment in evaluating the relative pathogenicity in man is the fact that in most instances industrial exposures are not solely to one type of asbestos mineral but rather to a mixture of several plus metals and oils and possibly other minerals

There are only a few studies which relate malignancy in exposed groups to a single type of asbestos[16–19] Most epidemiological studies that appear to indicate differences in pathogenicity among types of asbestos contain flaws in that they lack quantitative data on cumulative exposures, fiber characteristics and presence of cofactors Therefore it is difficult to grade different types of asbestos as to relative carcinogenicity with regard to either asbestosis or neoplasia

Studies to date indicate that both shape and size of asbestos fibers are significant factors in determining respirability deposition, retention and clearance from the pulmonary tract and thus are important determinants of the site and nature of tissue response The importance of fiber diameter and length in explaining the disparity in the prevalence of mesothelioma in the Northwestern Cape and that of the Transvaal region of South Africa has been strengthened by the study of Timbrell Griffiths and Pooley[20] The curly shape of the chrysotile fiber offers an explanation of its interception by the bronchi especially at bifurcations in contrast to amphibole fibers which are needle-like and may, therefore, reach more deeply into the lung parenchyma and pleura Since one of the amphiboles, namely anthophyllite has rarely been associated with mesothelioma production factors other than shape and size must be considered

Until recently, most work and speculation involved only fibers detected by the optical or light microscope There is no generally accepted basis that permits assignment of relative risk factors to fibers in the electron microscope range compared to fibers in the light microscope range. Suzuki and Churg[41] contend that submicroscopic fibers are responsible for most of the biologic changes produced by asbestos. Other investigators have also pointed out that the fine dust particles below 1 micron in length may be just as damaging as dust particles containing both large and small fibers[42] Gross[43] informed us that inhalation of the submicroscopic asbestos fibers experimentally produced only a phagocytic response; he does not believe that submicroscopic fibers are responsible for the more extensive biologic changes produced by asbestos. It is possible that the relative risks associated with fibers of different sizes are different for malignant and non-malignant changes Further studies bearing on this matter are necessary Kleinfeld Messite and Langer[8] found that the nature of the dust samples analyzed indicated that fiber counts of aerosols did not provide a true picture of exposure to asbestiform minerals because they included talc fibers but excluded many small asbestos fibers and "aggregate fibers" which contained substantial amounts of asbestiform minerals namely tremolite and anthophyllite

In light of recent observations, one cannot exclude the influence of cofactors on biologic effects as a major determinant of pathogenicity Dixon, Lowe, Richards et al[14] postulated that asbestos fibers probably serve as vectors in producing disease by carrying toxic or oncogenic substances to vulnerable sites Relevant studies included analysis of various types of asbestos to determine components present in each with special emphasis on metals and polycyclic hydrocarbons[44 45] The present consensus is that contaminants are present but that identification of a specific pathogenetic role for them requires further study If subsequent investigations verify that trace metals and other fractions of the various types of asbestos dust do in fact play a major role in producing asbestosis or neoplastic diseases customarily associated with exposure to asbestiform mineral dusts, then existing standards governing exposure to asbestiform minerals in the United States and Great Britain undoubtedly will be subject to revision

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ASBESTOSIS

BIOLOGIC RESPONSE TO KIND AND AMOUNT OF ASBESTOS

Moris Kleinfeld, M.D.

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