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EXPOSURE TO ASBESTOS AND HUMAN DISEASE

DURING the past two decades, ill health resulting from exposure to asbestos has been the subject of intensive observation and research[1] — probably more intensive than research on any other environmental agent.[2] In the most direct target organ, the lung, and in its pleural coverings, there is a wide spectrum of response after exposure; not only acute and chronic inflammatory diseases but also cancer of these organs may occur. Research has been stimulated by the belief that the more complete our understanding of the mechanisms of pathogenesis, the better will be our ability to control the continued use of this mineral in today's complex technologic world.[3]

The review by Craighead and Mossman of the pathogenesis of asbestos-related diseases in this issue of the *Journal*,[4] which covers recent work in cell biology, is set in the context of pathology but also discusses the use of these minerals and regulatory considerations; it complements other recent reviews of the epidemiology of these diseases,[5] their impact on public health,[6] and current clinical issues.[7] Also important is a recent report that provides criteria for grading the pathologic changes in the lungs associated with asbestos exposure.[8] Systematization of pathological assessments can only enhance the pooling of experience from different centers or countries by maximizing the comparability of studies. The international classification of radiographs of pneumoconiosis[9] by the International Labour Office is an example of such systematization, and the dividends associated with its use are generally recognized.

Perhaps the major contribution of the review by Craighead and Mossman (and this may surprise readers not familiar with the field) is the emphasis placed on the shortcomings of our present knowledge of the pathogenesis of asbestos-related disease. Considering first the fate of inhaled fibers in the lung, it is now evident that the dust burden of the lung is primarily in the form of uncoated asbestos particles,[4] whether or not these conform to the definition of a fiber (i.e., a particle with a length-to-width ratio of 3:1). This definition probably originated rather arbitrarily from a need to standardize what was considered a fiber for purposes of industrial hygiene[6]: it is now widely believed that a much higher ratio, perhaps 10:1, would have been a better choice. Both fiber length[10] and mineralogic type[11] are important determinants of whether a fiber becomes coated and so takes on the familiar appearance of the asbestos body. Most asbestos bodies found in human lungs contain an amphibole fiber as a core,[11] even though chrysotile accounts for the greatest use and presumably the most exposure.[7] What permits some particles to lie apparently dormant in the lungs for long periods before evoking an organ response is not known, and there is no good explanation for the fact that all the disease consequent to asbestos exposure (including fibrosis of the lungs and

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pleura as well as cancer of these organs) may appear long after exposure has ceased.

Fibrosis of the lung (asbestosis) was recognized by the first decade of this century and has been the subject of much research in animal models. Nevertheless, Craighead and Mossman conclude that the pathogenesis of asbestosis remains to be established,[4] as does the importance of exposure dose as compared with individual "susceptibility" in the initiation and the progression of the fibrotic reaction. The finding of an acute inflammatory response in some early human lesions[4] raises the issue of whether there is a reversible component to the acute response in human beings, as suggested by work in animals.[12] Long-term studies in sheep[13] may help to answer this question. As for whether asbestos acts as an initiator or as a promoter of lung cancer, the authors of the review[4] favor the latter view; perhaps particles act as physical carriers of other environmental carcinogens to the basal epithelial cells. It is also possible that more than one mechanism is involved.[7]

There is perhaps even more uncertainty about the pathogenesis of pleural reactions than there is about parenchymal lesions. For instance, it is not clear how often acute exudative reactions, such as effusions (presumably usually clinically silent), precede the more chronic diffuse or localized fibrotic reactions of visceral or parietal pleura. It is also unclear how fibers reach the parietal pleura and concentrate there in such a way as to evoke plaque production after a long delay while leaving the visceral pleura intact; an adequate hypothesis for the pathogenesis of pleural plaques is needed to explain all these features.[14] Perhaps even more puzzling is what determines whether the pleural reaction will be benign or malignant. Not all would agree with the view expressed in the article[4] that malignant mesotheliomas are pathognomonic of asbestos exposure: these tumors were described by European pathologists in the 19th century — long before major commercial exploration of the asbestos minerals[15] — and there is little evidence even today that asbestos is responsible for many cases in men or women outside industrial centers.[3,16] What are described in the present review as "casual" exposures (i.e., usually domestic or neighborhood) are exposures that are intermittent but have often turned out to be to very heavy dust clouds of fine particles.[3]

In spite of considerable current interest in the topic,[7] the issue of whether asbestos exposure is associated with airway abnormalities is not addressed by Craighead and Mossman. The involvement of small airways in the early stages of asbestos-related lung fibrosis has in all likelihood its clinical counterpart, although there is no evidence about whether these abnormalities are reversible or not. The association between asbestos exposure and other forms of airway response, such as bronchitis or emphysema in the absence of asbestosis, also remains to be clarified, as do the confounding effects of cigarette smoking.

Finally, there is the question of whether there are differences in the pathogenic potential of the various fibers in this mineral group. Of particular concern is whether chrysotile (which has accounted for over 90 per cent of commercial uses during the past several decades) differs from the two amphibole fibers, crocidolite and amosite, which were used extensively during World War II and in the postwar building boom. The issue has been bedeviled by problems of comparing like with like,[3] by the difficulty of sorting out the relative contributions of exposure (duration, level, and particle size) and fiber type, and by the differences between exposure in the mining and milling of fiber and the secondary application of fibers in manufacturing. Thus, although it is clear that the rates of mesothelioma are different in different exposed populations, it has usually not been possible to assess the extent to which these differences are due to fiber type or to other factors. Some clarification has come from the application of modern methods of lung-dust analysis to autopsy material. In two case-control studies of mesothelioma, an excess of amphiboles (amosite in North America and crocidolite in the United Kingdom) was found in the lungs of the cases, whereas chrysotile contents were similar in cases and controls.[3,18] In a study of chrysotile miners in Quebec, almost as much tremolite (an amphibole contaminating some of the mined rock deposits) was found in the lungs as chrysotile, although the latter was clearly the main environmental contaminant.[17] These results are consistent with what has long been believed on the basis of more tenuous evidence — that there is preferential clearance of chrysotile, as compared with amphibole fibers, from body tissues and that this may contribute to the differences in the pathogenic potential of the minerals.

Epidemiologic evidence for a fiber gradient in pathogenic potential is strongest for mesothelioma, with crocidolite more strongly implicated than chrysotile, and amosite probably in between. The evidence is also reasonably strong for lung cancer, with crocidolite again more strongly implicated than chrysotile. For pleural reactions (pleural plaques and fibrosis), there may also be a fiber gradient, although other factors are almost certainly involved; for parenchymal fibrosis the evidence for a fiber gradient is minimal. At present it is believed that the biologic activity of asbestos particles relates to the degree of penetration and the amount of deposition in the lower respiratory tract, both of which depend mainly on their physical characteristics, including their aerodynamic properties. Particle size (and particularly length and fineness) may also determine oncogenicity. However, biologic activity is likely to be modified by the length of time that particles survive in the lung without denaturing, which may be related to their chemical characteristics. The most plausible explanation for differences in the pathogenic potential of various fibers is that these differences result from differences in both the physical and chemical properties of the fibers.

What is the clinical importance of the issues raised by the review in the *Journal*? Perhaps the most impor-

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tant is that health risks in relation to exposure to asbestos vary according to environmental factors. Some of these factors (such as exposure dose, particle size, and fiber type) are known, but there are undoubtedly others not yet recognized. Host characteristics probably also influence the response to exposure. Thus, in considering the individual patient with a disease known to be related to asbestos exposure, the wise clinician should avoid regarding any particular exposure as too short, too remote, or at too low a level (even if environmental counts were in compliance with the present regulations) to have accounted for the disease. Assessment of the importance of particular environmental exposures is often outside the clinician's expertise; it should be referred to appropriate consultants in industrial hygiene, engineering, or physics. In lung cancer the statistical probability that a given case is attributable to asbestos exposure may be estimated from exposure-response data,[18] which for practical purposes can probably be assumed to be linear, provided that the data available are applicable to the industry in which the subject was employed. Finally, the unpredictable clinical course of these diseases demands vigilance by the clinician with respect to past exposures, and the most powerful indicator remains the careful, complete, and precise occupational history.[7]

Whether the dust concentrations permitted by current regulations will in fact eliminate the future risk of asbestosis, as Craighead and Mossman suggest,[4] remains to be established. Similar suggestions in the 1930s proved to be premature. Evaluation of the impact of present controls on health issues is an urgent matter for research. Furthermore, a total ban on use seems unlikely in technologic societies,[3] in which it may be considered preferable to retain these versatile minerals for certain uses. Until it is established that asbestos substitutes do not carry health risks,[19] research into the mechanisms by which asbestos particles produce ill health should be vigorously pursued.

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REFERENCES

1. Acheson ED, Gardner M. Exposure limits — the scientific criteria. In: McDonald JC, ed. Recent advances in occupational health. Edinburgh: Churchill Livingstone, 1981:257-69.
2. Peter GA, Peters BJ. Source book on asbestos disease. New York: Garland STPM press, 1980:A1-K18.
3. Gloag D. Asbestos — can it be used safely? Br Med J. 1981; 282:551-3.
4. Craighead JE, Mossman BT. The pathogenesis of asbestos-associated diseases. N Engl J Med. 1982; 306:1446-55.
5. McDonald JC. Asbestos-related disease: an epidemiological review. In: Wagner JC, ed. Biological effects of mineral fibres. Lyon: International Agency for Research on Cancer, 1980:587-601. (IARC scientific publication no. 30).
6. Liddell D. Asbestos and public health. Thorax. 1981; 36:241-4.
7. Becklake MR. Asbestos related diseases of the lung and pleura: current clinical issues. Am Rev Respir Dis. (in press).
8. Craighead JE, Abraham JL, Churg A, et al. The pathology of asbestos-associated diseases of the lungs and pleural cavities. Arch Pathol Lab Med. (in press).
9. International Labour Office. Guidelines for the use of the ILO International Classification of radiographs of pneumoconioses. Geneva: International Labour Office, 1980:1-48. (Occupational health and safety series no. 22).
10. Morgan A, Holmes A. Concentrations and dimensions of coated and uncoated asbestos fibres in the human lung. Br J Ind Med. 1980; 37:25-32.
11. Churg AM, Warnock ML. Asbestos and other ferruginous bodies: their formation and clinical significance. Am J Pathol. 1981; 102:447-56.
12. Hunt DM. Experimental asbestosis: an investigation of functional and pathological disturbances. I. Methods, control animals and exposure conditions. Br J Ind Med. 1978; 35:129-34.
13. Begin R, Pleszczynski M, Masse S, et al. Asbestos-induced lung injury in the sheep model: the initial alveolitis. Environ Res. (in press).
14. Hillerdal G. The pathogenesis of pleural plaques and pulmonary asbestosis: possibilities and impossibilities. Eur J Respir Dis. 1980; 61:129-38.
15. McDonald JC, McDonald AD. Epidemiology of mesothelioma from estimated incidence. Prev Med. 1977; 6:426-46.
16. McDonald AD, McDonald JC, Pooley FD. Mineral fibre content of the lung in mesothelial tumours in North America. Ann Occup Hyg. (in press).
17. Rowlands N, Gibbs GW, McDonald AD. Asbestos fibers in the lungs of chrysotile miners and millers — a preliminary report. Ann Occup Hyg. (in press).
18. Enterline PE. Attributability in the face of uncertainty. Chest. 1980; 78: Suppl (August):277-9.
19. Wagner JC, Elmes PC. The mineral fibre problem. In: McDonald JC, ed. Recent advances in occupational health. Edinburgh: Churchill Livingstone, 1981:1-13.

SOUNDING BOARDS

AFTER LAETRILE, WHAT?

LAETRILE was moribund before Moertel et al. laid it to rest with the recent report of their prospective clinical trial.[1,2] It had been replaced in popularity by an approach unusual in the annals of unorthodox cancer therapy — one that represents more of a challenge than did Laetrile or its predecessors. This is the "natural" approach to malignant disease, which emphasizes cure through purification and the body's capacity to heal itself. The currently popular alternative approach is rooted in homeopathic and naturopathic beliefs, Indian and Oriental philosophy, and 19th-century theories of intestinal putrefaction. Promoters often evoke the time-worn conspiracy dogma, which states that the medical system, the Food and Drug Administration, and the federal government withhold true cures from the public, thereby perpetuating therapeutically useless and biologically harmful cancer treatments in order to further the Establishment's economic interests.[3,4]

Alternative cancer therapies in vogue today differ importantly from Laetrile and from other unproved remedies of the past. Previous unorthodox treatments were "medicines" or at least "medicinal." Examples were Dr. Bye's Combination Oil Cure, Dr. Chamlee's remedy for removing cancer viruses from the blood, Dr. Leach's Cancerol, Dr. Koch's glyoxylide, and many others that attained great prominence in their day.[5] They came in ampules, vials, or syringes, mimicking standard medications, and they were sold and administered in the usual clinical fashion by people in white coats.

Today's alternative remedies explicitly reject association with standard treatments, environments, and paraphernalia. These are anti-medicines, emphasizing purification through dietary regimens, detoxification

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