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ASBESTOS AND HUMAN HEALTH WITH RECOMMENDATIONS FOR RESEARCH

W. Clark Cooper, M.D.

Accompanying the increasing use of asbestos minerals in the 20th Century, there has been an undercurrent of concern over their role as factors in human disease. When it was recognized 40 to 50 years ago that occupational exposures to asbestos could lead to a disabling pneumoconiosis, it was generally accepted that this could be prevented by vigorous dust control measures. While this is true, it is by no means certain that presently accepted standards are sufficiently rigorous. But more compelling in forcing a new appraisal have been recently observed associations between asbestos and malignancies of the lung, pleura and peritoneum. Then, when lung smears made during routine autopsies in several cities showed what were interpreted as asbestos bodies, it has become apparent that there are many gaps in the knowledge needed to interrelate these varied findings and to take appropriate action.

Much of the evidence bearing on the foregoing associations was included in contributions presented at a conference held in New York City in October of 1964, sponsored by the New York Academy of Sciences (1965). More recently, Gilson (1966) has provided a thoughtful summary. Following the New York meeting, a working group, convened under the auspices of the International Union Against Cancer (UICC), agreed on a very useful set of recommendations for studies and suggested standardization of terminology and procedures (1965). In December, 1966, the U.S. Public Health Service sponsored a meeting in Cincinnati, Ohio, at which American investigators in the field described work in progress and expressed themselves as to important areas of further investigations. These reviews and discussions have been drawn upon freely in the preparation of this report.

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When we speak of asbestos and human health, we are speaking on the environmental side of a wide variety of fibrous silicates, the most important in commerce being chrysotile, crocidolite, amosite, tremolite and anthophyllite. They vary chemically from deposit to deposit, even with the same type of asbestos. The fibers differ in many properties including rigidity, length, diameter and may occur with natural and accidental contaminants. On the biologic side, there are important species differences in response. Our knowledge of effects in man was first centered about manifestations ~~that were described~~ in heavily exposed groups, such as pulmonary fibrosis, pleural calcification and certain malignancies. These manifestations are still poorly understood in their pathogenesis, their interrelations and the relative importance of the different types of asbestos and co-factors. Data on dosage and response are meagre. Not until quite recently has the complexity of the problems associated with the inhalation of these fibrous minerals been fully appreciated.

This review will first summarize the background and present the state of knowledge relating to the major effects in man that have been attributed to asbestos minerals, drawing upon clinical, pathologic, radiographic, statistical, epidemiologic, physiologic and experimental evidence, cite major unanswered questions, and then attempt to summarize some of the urgent studies in man, lower animals and the environment that have been suggested.

ASBESTOSIS (ASBESTOS PNEUMOCONIOSIS)

The inhalation of asbestos fibers, of all types, can produce severe, potentially disabling or fatal, pneumoconiosis. From the first case description by H. Montague Murray in the Charing Cross Hospital Gazette in 1900 and more fully

reported in 1907 and similar cases by Auribault (1906), Marchand (1906), & Fahr (1914), a voluminous literature has grown on the subject.

Descriptions by Cooke (1924 and 1927) and others led to studies of incidence in the British asbestos textile industry, with Merewether (1930) and Merewether and Price (1930) concluding that 81% of those who had worked 30 years or more in asbestos textile plants had x-ray evidence of fibrosis. This led to regulations for environmental and medical controls in selected industries in the United Kingdom, which became effective in 1933. Soon afterward there was recognition of the disease in the United States (Lanza et al., 1935; and Egbert, 1935). Guides for acceptable dust levels were developed out of studies in a small number of textile plants by Dreessen et al. (1938). Concurrently, observations were being made in other asbestos-using or producing areas (Kruger et al., 1931; Alwen, 1935; Bohne, 1936; and Simson, 1931).

The gross and histologic appearance of the lungs in asbestosis has been described in a number of series, but criteria for diagnosis are not universally agreed upon. In addition to fine fibrosis around respiratory bronchioles and alveolar ducts, fibrosis of the pleura is common, often with calcified plaques. What appeared to be coated fibers were described in the first cases (Marchand 1906). These were called "curious bodies" by Cooke (1929)(who doubted their specificity); "asbestosis bodies" by Stewart and Haddow (1929) and Gloyne (1931). These were soon recognized as being regularly associated with asbestosis in man; but since they were found to occur also in asbestos workers without evidence of disease, they were not regarded as diagnostic of disease; the term "asbestos" body came to be regarded as more appropriate. In later discussions their formation and significance will be considered more fully.

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The radiographic changes in asbestosis have, because of their variety and lack of specificity in early stages, presented many difficulties in classification. The so-called "ground-glass haziness" of the lower portions of the lung fields, which has been recognized as an early change, proved difficult to describe and to standardize. With progression of disease, increase in linear shadows, most prominent in the lower lung fields, with thickening of the pleura, shagginess of the cardiac shadow, and densities corresponding to pleural calcifications dominate the picture. The need for a descriptive classification of films is well recognized. Several suggestions along this line were made at the New York meeting. The Public Health Service is appraising a classification developed by a panel (Jacobson, Felson, Pendergrass, and Bristol) and exchanges of views and films with those working similarly under the auspices of the UICC is contemplated. Ultimately, the development of representative films may be feasible. The following reports on radiographic changes should be consulted: Shull, 1936; Bristol, 1955; Jacob and Bohlig, 1955; Leathart, 1960; Williams and Hugh-Jones, 1960; Hurwitz, 1962; Caplan et al., 1965; Sluis-Cremer et al., 1965; Kleinfeld et al., 1966. Reports which emphasize pleural calcifications include those by Kiviluoto and Kjerp, 1932; Smith, 1932; Fehre, 1956; Frost et al., 1956; Muller, 1962; Kiviluoto, 1965; Selikoff, 1965; and Raunio (1966).

Clinically, dyspnea in asbestosis is often the first symptom and may correlate poorly with x-ray findings. Functional impairment is characterized by loss of pulmonary compliance, with diminished vital capacity and impaired diffusing capacity. The relative importance of thickened alveolocapillary membrane and of diminished pulmonary arterial circulation in reducing diffusing capacity has not been clearly determined. Pulmonary function in asbestos workers has been studied by Roemeld et al., 1940; Bastenier, 1955; Wright, 1955; Leathart, 1960 and 1963; Williams and Hugh-Jones,

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1960; Teirstein et al., 1960; Bader et al., 1961; Heard and Williams, 1961; Rubino et al., 1961; Thomson et al., 1961; Bjure et al., 1964; Bader et al., 1965; Hunt, 1965; Thomson et al., 1965; and Kleinfeld et al., 1966. Hunt's report is of particular interest in that a series of tests was used prior to employment and during exposure. There was evidence of declining vital capacity and gas transfer before the development of x-ray changes. Wright (1955) and Leathart (1960) have similarly noted functional impairment preceding x-ray changes. Thomson et al. (1961) found that inspiratory capacity, vital capacity, diffusing capacity for carbon monoxide, and compliance had the greatest power in discriminating between certified and uncertified asbestos workers in a study of 11 tests of function.

Incidence. Better figures on incidence are needed to clarify the magnitude of the problem, for comparisons between different groups at risk, and to evaluate the efficacy of dust control and other preventive measures. Because of differing diagnostic criteria and inadequate figures on populations at risk, valid comparisons between different groups are at present practically impossible. Thus, most of our data from the United Kingdom relates to new cases diagnosed each year under the Industrial Injuries Act. A recent summary (McVittie, 1965) shows an average of 45 new cases per year during the period 1959-63, suggesting an incidence of about 5 new cases per 1000 employed and at risk. A striking fact apparent in McVittie's data is that, while the textile industry at one time contributed most new cases, during the period 1955-63, 41% of new cases were in insulating workers. Also, many cases are being reported from those whose experiences began after the Asbestos Industry Regulations became effective in 1933; and some were from scheduled industries.

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Selikoff et al. (1965) examined 1,117 insulating workers in New York and reported abnormal chest films in 48.5%. Of 255 deaths from 1943 through 1962, workers with 20 or more years after joining the trade, 12 were attributed to asbestosis in individuals who had been insulating workers 32 to 59 years (average 48.5 years).

Cooper and Tabershaw (1966) in a preliminary review of chest films in 355 insulating workers in the San Francisco area, found 22% with definite abnormal films consistent with asbestosis. None was found in 102 men with under 10 years in the trade, whereas 32% of 127 with 20 or more years showed such changes.

Ferris (1966), reporting a followup study of insulating workers engaged in new ship construction and exposed to amosite, reported detectable pneumoconiosis after 10-12 years. After 20 years nearly all had abnormal chest x-rays. Inasmuch as the average dust counts were only slightly above 5 mpccf and it was assumed from a previous survey 20 years earlier (Fleischer et al., 1946) that conditions had not changed greatly over the 20 years, Ferris concluded that the estimate made by Wells (1965) of 50-60 mpccf-years as a minimum exposure required to produce pneumoconiosis was of the right order of magnitude. If this preliminary impression is borne out by more thorough analysis, then the present threshold limit is too high for a working lifetime.

Attempts to reproduce asbestosis in experimental animals were included in the experimental program of Gardner and his successors at the Saranac Laboratory during the period 1930 to 1950. Stewart (1930) had shown that guinea pigs which inhaled asbestos dust for 20 weeks developed asbestos bodies in 12 weeks, but he noted no fibrosis. Gardner (1943) exposing guinea pigs to chrysotile at heavier dosages and over longer periods, found both asbestos bodies and peribronchiolar fibrosis. He pointed

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out the remarkable differences in response between different species. (Gardner, 1942). Mice and dogs failed to develop either fibrosis or asbestos bodies. Vorwald et al. (1951) reporting in detail the 20 years of research at Saranac concluded that longer fibers of chrysotile (over 20 micra in length) caused peribronchiolar fibrosis that did not result when the same type of asbestos had been milled to produce fibers below 3 micra in length. Subsequently, Wagner (1957, 1961, and 1965), Holt et al. (1964 and 1965), and Davis have shown that short fibers will produce fibrosis in experimental animals. Knox and Beattie (1954b), however, have postulated that the mechanism which produces fibrosis in lower animals may not be the same as that producing the disease in man. As Nagelschmidt (1965) points out this question has still not been resolved. The interrelations between asbestos body production, asbestos body breakdown, and fibrogenesis developing years after exposure are still unclear.

Wagner and Skidmore (1965) have shown the rate of disappearance of chrysotile from the lungs of rats to be three times that of amosite or crocidolite. This correlates with somewhat less fibrogenicity. Gardner (1942) pointed out earlier that chrysotile disappeared after injection into extrapulmonary tissues and that in the dog, which produced no asbestos bodies and no fibrosis in the experimental situation, chrysotile introduced into the lung disappeared with one or two years. Knox and Beattie (1954a and 1954b) demonstrated that the mineral content of lungs in persons exposed to asbestos tended to decline after exposure had ceased. Nagelschmidt (1965) found that over half the lung specimens in a group of individuals who died with asbestosis (most of whom had been out of the industry for a number of years) showed no asbestos; he concluded that chrysotile was probably dissolved. Amphibole asbestos is far more insoluble; amosite was often the only asbestos mineral

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found in residues, even though exposures were mixed.

Asbestos minerals are modified by physical and chemical treatment, and this may modify biologic response. For example, chrysotile heated to 700°C for 2 hours no longer produces fibrosis or asbestos bodies in guinea pigs (Vorwald, 1951). It seems important that more experimental work be carried out to define more precisely the critical changes in asbestos mineral that inactivate it as a producer of fibrosis or asbestos bodies in lower animals.

Need for Research. It might be asked why studies directed toward asbestosis, or asbestos pneumoconiosis, should be an important part of a comprehensive attack on asbestos and health, in view of the relatively small numbers of workers involved and the likelihood that more vigorous dust control would make the problem one of the past. The answers are (1) the numbers of workers potentially heavily exposed is certainly between 50,000 and 100,000, with a undefined larger number who are peripherally exposed; (2) they are a highly skilled workforce with long tenure and potentially long exposures; (3) asbestos pneumoconiosis is at one end of a spectrum of effects and represents a definite indicator of relatively heavy exposure; (4) we do not know how dosage and response in pneumoconiosis relates to other asbestos-associated disease; (5) we have many individuals exposed to asbestos over the years for whom better medical and environmental management is necessary; and (6) there are indications that our present threshold limit value

is too high to prevent asbestosis over a working lifetime.

Studies in man are needed to determine the incidence of asbestosis in occupational groups with high, medium, and low exposures, both to single types and to mixed asbestos exposures. There should be serial studies in which clinical, radiographic, and physiologic changes are correlated, with the maximal use of pathologic material for ultimate comparisons. In such work the importance of emphysema and

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chronic bronchitis as a factor in prognosis needs consideration. The effect of cigarette smoking in enhancing functional impairment is important in guiding therapeutic management.

Studies such as those mentioned should be accompanied, whenever possible, by quantitative environmental data to be used in developing guides to safe exposure levels.

As a prerequisite to comparative studies, agreement on radiographic classification and pathologic criteria is urgent. It is not necessary to have complete standardization; but there is need for descriptive terminology and categories should be developed, with frequent interchanges of films between interested research groups.

Serial studies of pulmonary function, with emphasis on early evaluation of pulmonary vascular changes, are needed in populations with differing exposures.

Serial studies of sputum, using concentration techniques, are desirable for correlation on the one hand with environmental conditions and on the other with biologic effects. It is possible that we have been too complacent in assuming that an asbestos worker should be expected to inhale and expectorate asbestos in quantities sufficient to make asbestos bodies in the sputum a regular occurrence.

Studies in animals are needed to clarify the relative importance of long and short fibers of the various types of asbestos, with inclusion of fiber diameter as an important variable, in the production of fibrous changes in animals.

ASBESTOS BODIES

Characteristic bodies, recognized later as fibers coated with a material containing iron and protein, were described in the sputum and in lung tissue of individuals in whom the earliest diagnosis of asbestos pneumoconiosis were

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made (Marchand, 1906, and Fahr, 1914). Cooke and Hill (1927) provided the first detailed descriptions; but they at first questioned a specific relationship to asbestos and preferred the designation "curious body". Stewart and Haddow (1929) suggested the term "asbestosis body". Despite the more precise designation of "asbestos body" suggested by Gloyne in 1927, the term "asbestosis body", as Gloyne himself used it 2 years later, became generally accepted. Nevertheless, numerous observers stressed that the bodies should be regarded only as indicative of exposure to asbestos and not diagnostic of asbestosis.

As long as the coated fibers were found in individuals known to have been occupationally exposed to asbestos, their identity was not seriously questioned, although it was shown from time to time that similar objects were sometimes found in individuals with no known exposures to asbestos. Meurman (1966) summarizes 19 reports published between 1932 and 1962 in which asbestos-like bodies were associated with graphite, coal, hornblende, rutile, diatomaceous earth, carborundum, and talc (where possibly tremolite was involved). They were also found in individuals with no obvious dust exposures. These observations, and the demonstration that other fibers may produce such bodies in experimental animals, indicate that the asbestos body probably results from a non-specific reaction to any sparingly soluble fibrous foreign body as had been first suggested by Cooke (1929). Some have, therefore, suggested returning to Cooke's term of "curious body". Gloyne in 1951 recommended "pneumoconiosis body", eliminating etiologic but retaining diagnostic connotations. Gough (1965) recommended "mineral-fiber body" while Gross (1966) suggested "ferruginous body". The term "asbestos body", however, has now such wide currency in the literature that it will be used in this review despite its lack of precision.

Until about 5 years ago, the asbestos body was regarded as an interesting curiosity. Although it was not diagnostic, nor even necessarily indicative of

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asbestos, as Cooke had said in 1929, "there is no reason why any fine spicule of mineral should not have colloidal matter deposited around it and become moulded into a curious body. But as no other mineral dust is fibrous, this occurrence must be so rare as to be negligible from a diagnostic point of view." Consequently, the presence of these bodies in lung tissue sections of individuals with pulmonary fibrosis and an appropriate work history was an important morphologic feature to support a diagnosis of asbestosis. Their presence in sputum was regarded as being indicative of exposure but not diagnostic of disease. Simson and Strachan (1931) found asbestos bodies in 48 of 50 asbestos workers; many others reported their common occurrence in sputum and sometimes in the feces of such workers. Sleggs (1931) reported finding asbestos bodies in 115 individuals in Kimberley who had no occupational exposure to asbestos. Sluis-Cremer (1965) used sputum examinations as an epidemiologic tool in comparing exposed and non-exposed individuals in the N.W. Cape and Transvaal areas to indicate a higher apparent exposure in non-occupational groups in the former area. Evidence cannot be found however of any systematic study of sputum as an indicator of excessive exposure of new employees, or to give clues as to inadequate controls.

It was the detection of asbestos bodies in routine autopsy studies in recent years that has provided impetus to a further study of the bodies and their significance. Stewart (1928) had suggested that smears from the cut surface of the fresh lung at autopsy were useful for the detection of asbestos bodies, but the first reported application of this technique to a random population was that by Thomson et al. in 1963. They reported finding asbestos bodies in 26.4% of lungs examined in 500 consecutive autopsies in Cape Town. Similar reports from other areas have subsequently appeared as shown in Table I, with percentages reported positive ranging from 26.4% to 57.6%. Techniques have varied in the preparation

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of material, in portions of lungs studied, and the number of fields or areas scrutinized so that comparisons are impossible. All but one of the studies involved examination of lung smears or scrapes; Meurman studied thick (20-micron) sections of lung, a technique that should be applicable to the restudy of stored material. Several points emerge in reviewing these reports: (1) those who have seen the so-called asbestos bodies uniformly agree that they meet accepted morphological and staining criteria for asbestos bodies; (2) in most of the individual cases reported positive, the numbers were relatively scanty, but a certain proportion of each series had numerous numbers; (3) those with relatively numerous asbestos bodies were more often male than female and sometimes occupational backgrounds could be discovered; (4) routine or thin histologic sections have not shown more than about 10% of those positive by smear but thick (20-micron) sections gave a high yield; (5) when comparative studies were made, the bodies were found with comparable frequency in all lobes or segments of the lungs (Webster, 1965; Anjilvel, 1966; and Meurman, 1966); (6) no correlations were found between the presence of small numbers of asbestos bodies and diagnoses in two series in which this was attempted (Meurman, 1966 and Anjilvel, 1966); (7) in Finland (anthophyllite areas), there was a positive correlation between asbestos bodies and pleural calcification in autopsies.

Mavrogordato (1925), according to Simson(1928) had been able to produce asbestos bodies in guinea pigs with chrysotile. It has subsequently been shown that they can be produced with asbestos fibers in mice, cats, monkeys and hamsters and to some extent experimentally, but there is one report of a rat in an asbestos plant with them in rabbits. Rats and dogs do not respond with typical bodies. Davis (1965), studying developing asbestos bodies in guinea pigs by electron microscopy, has shown that fibrils of chrysotile below the resolving power of the light microscope may become coated. His conclusion was that the production of the chrysotile asbestos body is

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always intracellular, within alveolar macrophages, and that free asbestos bodies are found only after cell breakdown.

The prevailing view is that the coating is a protective device and that the coated fiber is not in itself fibrogenic. Vorwald (1951) showed that asbestos bodies introduced in large numbers in the guinea pig did not lead to fibrosis, although the bodies themselves could be detected in the lungs for long periods. It is possible in man, however, that breakdown of the coating occurs after many years and may be a factor in latency.

Gross has been able to produce pseudo-asbestos bodies by the intratracheal introduction of several fibrous minerals, as Vorwald (1951) had earlier produced them with brucite [$Mg(OH)_2O$] in the guinea pig. There is thus strong evidence, both from human experience and from work in animals, that fibers other than asbestos may sometimes produce bodies that mimic asbestos bodies. This does not diminish the need to determine whether or not the bodies actually seen in the general population are or are not predominantly coated asbestos. Positive identification becomes important, as well as the planning of studies to determine their significance if they prove actually to be asbestos minerals.

Berkeley et al. (1965) have recently summarized knowledge of the problem of identification. Removing the coating of the asbestos body is difficult; it is not removed by gastricjuice, by moderate trypsin digestion, nor by incineration at

. To remove the coating without altering the characteristic properties of the asbestos fiber is difficult. At present the combination of plasma torch incineration and electron probe incineration is the most promising approach.

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TABLE I

REPORTS OF ASBESTOS BODIES IN ROUTINE LUNG EXAMINATIONS

Place	Number examined	Per cent positive	Per cent** with many	Technique	Reference
Cape Town	500	26.4%	4.4%	Basal Smears	Thomson et al., 1963
Miami	500	27.2%	3.6%	Basal Smears	Thomson & Graves, 196!
Pittsburgh	100	41.0%	5.0%	Random Smears	Cauns et al., 1965
Johannesburg	120	39.2%	n.s.	UL & LL Smears	Webster, 1965
Finland	264	57.6%	6.4%	20 micra Sections	Meurman, 1966
Montreal	100	48.0%	4.0%	UL & LL Scrapes	Anjilvel, 1966
San Francisco	100	42.0%		Basal Smears	Cooper & Tabershaw, 1966

** Defined variously by different authors

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Current knowledge regarding asbestos bodies indicates need for the following types of investigation:

1. Validation of practical methods for positive identification of asbestos minerals--including type--in tissue and sputum, in and outside of so-called asbestos bodies.
2. Systematic application of such methods in sputum samples, autopsy specimens and biopsy specimens in
   a. Occupational groups with heavy exposures to asbestos
   b. Occupational groups with light or peripheral exposures
   c. Occupational groups exposed to other fibrous minerals (eg. fibrous glas
   d. Individuals living near asbestos mines, mills or plants
   e. Population samples, urban and rural, in technologically advanced and in underdeveloped areas.
3. Use of 20-micron section technique of Meurman to lung tissue from autopsy material of 10-20 and 30 years ago, to see if there has been upward trend.
4. Quantitation of asbestos bodies in groups such as the above.
5. Serial observations on sputum of new workers in asbestos trades and in those now in or leaving exposures to asbestos, to gain more information on the asbestos bodies as a biological indicator of exposure, using modern techniques for concentrating sputum.

The proof that a large proportion of those dying in any area actually harbor asbestos bodies will not clarify their significance in terms of human health. For this purpose, two approaches are suggested, which can well be combined with two and three above.

1. Greatly enlarging series of consecutive autopsies in several areas with standardizing quantitation and identification, for correlation with causes of death.
2. Obtaining quantitative data on the numbers of asbestos bodies in lungs of individuals dying in occupational groups with light or peripheral exposures to asbestos, concurrently with determination of relative

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risks in these groups to various causes of death. This might make possible extrapolation in terms of relative risk, to the general population with very scanty asbestos bodies.

MALIGNANCIES

Cancer of the Lung. The first suggestion that asbestos might be causally related to lung cancer was by Lynch and Smith (1935) who described squamous cell carcinoma in a South Carolina textile worker with asbestosis. Despite other isolated reports, the association was not firmly supported until Merewether (1947), as Chief Inspector of Factories, reported deaths from cancer of the lung in 31 of 235 cases of asbestosis that had been certified in the United Kingdom between 1924 and 1946. The rate of 13.2% compared with one of 1.32% in over 6000 cases of silicosis during the same period. Gloyne (1951) reported on autopsies of 1205 workers in the dusty trades. In 132 asbestos workers, 121 had pneumoconiosis and 14.1% had cancer of the lung, compared with 6.9% in 796 silicotics. These were not random cases, however, and were in a hospital where suspected tumors would have been referred. Doll (1955), after studying the causes of death among 105 men who had worked for more than 20 years in asbestos-exposed areas, concluded that their risk of lung cancer had been ten times that of the general population.

McCullough (1959), continuing the studies of deaths in asbestosis cases begun by Merewether, found that 65 of 365 deaths (17.8%) in diagnosed asbestosis cases were attributable to lung cancer. By 1965, Buchanan was able to carry this series through 1963 with the report that 121 of 392 or 30.9% of deaths of males with certified asbestosis were attributed to lung cancer. During the period 1961-63 over half (54.5%) of the deaths in the group were in this category.

In the United States, O'Donnell and Mann in 1957 reported 19 cases of lung

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cancer in 39 individuals with asbestosis working in a small plant in Pennsylvania. This led to a longitudinal cohort study utilizing BOASI records by Mancuso et al. (1963) in which all who had been employed in 1938 or 1939 were followed through mid-1960. Lung cancer accounted for 19 deaths, with 5.61 expected. There was also an excessive number of neoplasms of the digestive organs and peritoneum (18, with 8.1 expected). Twenty-eight of 195 deaths in the entire groups were listed as due to asbestosis, excluding the malignancies. Selikoff et al. (1964) reviewed deaths from lung cancer in 620 insulating workers in the New York and Northern New Jersey areas in whom over 20 years had elapsed since joining the trade; there were 45 compared to 6.6 expected. Recent updating of these figures shows 68 lung cancer deaths out of 325 total. Dunn (1965) found the number of lung cancer deaths in a group of California insulating workers 35-65 years of age and with 15 years in the trade, who were followed for 5 to 8 years, to be three times expected. It was the only occupational group he studied that had a significant excess, and it could not be explained by differences in smoking habits. Jacob and Anspach (1965) analyzed figures derived from a registry of asbestos workers set up in Dresden in 1952 and reported that lung cancer cases in males were twice expected, and those in females over 10 times expected. When individuals with diagnosed asbestosis were considered, the ratio of observed to expected was even higher. This study updated earlier Dresden reports which had showed no excess. All types of asbestos were involved in Dresden.

The study of Braun and Truan (1958) which did not indicate any excess of lung cancer in chrysotile miners in Quebec has been criticized by Heuper (1965), by Knox (1965) and Mancuso (1965) on the basis of the relatively small numbers who had had long work exposures as well as on the choice of a comparison group.

A high incidence of asbestos bodies and of pleural plaques in certain areas

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of Finland presumed to be related to anthophyllite asbestos has not so far been associated with an excess of malignancies (Meurman, 1966). Despite these negative reports, which ultimately may be found actually to reflect a relatively lower risk for the groups involved, the cumulative evidence provided by other studies leaves little doubt that there is a strong association between working with asbestos and lung cancer. Current pertinent questions relate to defining this relationship more precisely, in terms of the type of asbestos, the necessity for co-carcinogenic factors, and dose-response relationships.

Lung cancers associated with asbestos appear to affect the lower lobes more frequently than the upper lobes; e.g., in Dresden, the ratio of upper to lower was 1.0/2.2 compared with 2.5/1.0 in all Dresden lung cancers (Jacob and Anspach, 1965); all cell types are represented in most series, with adenocarcinomas somewhat higher than average (Heuper).

Evidences relating dosage to incidence of cancer are meagre; one such is the clue from work by Knox et al. (1965) indicating that men who entered work after 1933 when asbestos regulations went into effect were not showing any excess risk, although it is far too soon to draw conclusions. Dunn and Weir (1965) included plumbers and boiler makers who had given a history of exposure to asbestos in their analyses. They found that these former groups showed no excess as compared with a three-fold higher rate in insulators.

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Mesotheliomata. The first diffuse tumor of the pleura or peritoneum reported in association with asbestosis was that included in a thesis by Wyers in 1946 (reported by Gilson in 1966), in which he described an endothelial tumor of the pleura in a series of asbestosis cases he had reviewed. Leicher (1954) reported a peritoneal tumor in an asbestos worker in 1954, while Bonser (1955) reported 4 such tumors in 72 cases of asbestosis, two of whom were thought to have primary ovarian tumors. Keal (1960) reviewed 15 deaths in London Hospital in women with asbestosis and found that 9 had died with ovarian or peritoneal cancer. During the mid-fifties, Sleggs, working in Kimberley in South Africa, over a short period of time found 16 individuals with diffuse mesothelial tumors of the pleura. More complete histories, prompted by Wagner's finding of asbestos in one case, developed the information that many of them had lived near or worked in asbestos mines and mills in the North West Cape. Wagner, Sleggs, and Marchand (1960) reported 33 cases of diffuse mesotheliomas, all but one of whom had lived near or worked in crocidolite-producing areas. Their series was ultimately expanded to over 100. In rapid succession other reports appeared describing similar tumors in other areas. McCaughey, Wade, and Elmes (1962) found 15 diffuse pleural mesotheliomata in Belfast, in 12 of which asbestos bodies were found in lung sections; in 9 there were histories of shipyard work. By 1965, Elmes and Wade had expanded their series to 45 in Belfast, of whom 32 had had a history of light or heavy industrial exposure to asbestos. Of 24 lungs examined for asbestos bodies in sections, 88% were positive, compared with 25% in matched controls. Jacob and Anspach (1965), studying asbestos workers in Dresden, described 6 pleural tumors, with an average of 31.8 years from time of first exposure to diagnosis. Owen (1965) reviewed 30 diffuse pleural tumors in Liverpool, decided that 17 met criteria for diagnosis of pleural mesotheliomata. Of these 12 had been industrially exposed to asbestos; 7 of 10 with lung specimens

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available showed asbestos bodies in sections. Thomson (1963) reported asbestos in the tissue sections from lung bases of 15 individuals with pleural mesothelioma.

Lourihane (1964) reviewed 93 cases diagnosed as diffuse mesothelioma in the London Hospital during the years 1917-62; he accepted only 34 as mesothelioma on the basis of histologic characteristics and the elimination of a primary tumor elsewhere. Seventeen were pleural and 17 peritoneal. In 15 of 30 in which lung tissue was available, asbestos bodies were found in sections (not smears), compared with 4 in 127 control cases. Hourihane felt that an association between the tumors and asbestos bodies was confirmed, but this report should be consulted for additional data of interest.

Selikoff, Churg and Hammond (1965) reported a study of mesothelial tumors, in which three different approaches to the problem were used. In a review of 2,500 autopsies, 26 cases of asbestosis were found; and in these 4 pleural and 3 peritoneal mesothelioma were detected. In 6 of the 7, there were histories of prolonged exposure to asbestos; the seventh was a carpenter. No mesothelioma was found in absence of asbestos. The authors also reviewed files of the Armed Forces Institute of Pathology and found 45 cases in which mesothelioma had been diagnosed and lung tissue was available. In 5 of 19 pleural mesothelioma and 7 of 26 peritoneal mesothelioma, review of sections showed asbestos bodies, although in only 2 had there been seen on original examination. The third component of their study was an analysis of 307 deaths over the period 1943-1964 in insulating workers in whom 20 years or more had passed since they joined the trade. Ten mesotheliomata were reported, with a mean time since onset of work in the trade being 38.5 years. They found 3 pleural mesotheliomata reported in 31,652 deaths in the A.C.S. mortality study.

Newhouse and Thompson (1965 and 1966) studied 83 mesothelial tumors reported in

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London over a 50-year period. Of 76 that were traced, 51 had had some history of asbestos exposure--23 by having worked in a factory, 8 as insulating workers, 9 through relatives being employed in an asbestos industry or trade, and 11 by having lived near an asbestos plant. Matched controls from the same hospital had a significantly different pattern of occupations and residence.

Lieben (1966) reported 42 mesotheliomata located through inquiries in 162 Pennsylvania hospitals. Ten were in asbestos workers, 8 lived within 2 miles of asbestos plants, and 3 were family contacts of asbestos workers. He described an interesting occurrence of 4 diagnosed mesothelial tumors in 8 brothers employed in the same asbestos-products plant.

Several facts stand out when one reviews the current literature on mesotheliomata and asbestos.

1. The diagnosis can be a difficult one, requiring both careful autopsy procedures to rule out primary tumors and awareness of the range of histologic patterns that may occur (Hourihane, 1964; McCaughey, 1965; Churg and Rosen, 1965).
2. Finding hyaluronic acid in an effusion and certain acid mucopolysaccharides in a serosal tumor is a useful guide, but not an absolute criterion.
3. The many reports in recent years suggest an increasing incidence of mesothelial tumors, but no clear-cut evidence in which increasing awareness and interest in the tumor were ruled out.
4. All series in which mesotheliomata have been related occupationally to asbestos indicate that long periods between first exposure and diagnosis are common.
5. Many cases have occurred without diagnosable asbestosis.
6. In South Africa, there appears no excess in individuals living near or working with Transvaal blue crocidolite, or with amosite, whereas Cape blue crocidolite areas show many mesothelial tumors.
7. Most urban studies [illegible]

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Tumors of the Gastro-intestinal Tract. There is insufficient evidence available to evaluate the suggested association between occupational asbestos exposures and malignancies of the stomach and colon.

Selikoff et al. (1964), when they analyzed the mortality from 1943 through 1962 in insulating workers who had joined the insulating trade at least 20 years before followup began, found that there were 29 deaths from cancer of the stomach, colon, or rectum, compared with an expected 9.4; this gave a mortality ratio of 3 to 1. The observed/expected numbers for gastric cancer were 12/4.3, and for cancer of the colon or rectum 17/5.2. As of 1965, Hammond et al. (1965) reported that gastro-intestinal cancer deaths were 34 or 11.1% of all deaths. Mancuso and Coulter, in their series reported in 1963, also found a slight excess of cancer of the stomach, large intestine and rectum.

Similarly, Enterline (1965) found a slight excess in cancer of the digestive system in asbestos textile workers; but it was not statistically significant.

Because of the low incidence of gastro-intestinal malignancies, Hammond has suggested that there be pooling of data to obtain information more rapidly on this suggested association.

General Statements on Malignancies in Man.

It is apparent from the evidence in man suggesting associations between asbestos and malignancies that epidemiologic studies must take into account not only lung cancers but diffuse mesothelial tumors and other malignancies as well. Prospective studies will be needed that involve:

1. Populations with exposures to a single type of asbestos such as chrysotile, crocidolite, amosite miners and millers.
2. Populations with mixed exposures.
3. Populations with recognizable, but not massive exposures, such as construction trades other than insulators, garage mechanics, etc.

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4. Populations that have had high exposures in the past but which have been controlled, permitting determination of trends of time.
5. Populations with brief, but well-defined exposures in the past.
6. Populations who live in the neighborhood of asbestos plants.
7. Family contacts of asbestos workers.

Such studies could be important in testing hypotheses as to relative importance of different types of asbestos and co-factors as well as for developing a general dosage-response pattern. Hopefully, this could be extrapolated to estimate the probable significance in the general public of the slight exposures that might be more widely prevalent.

In such studies, it is important to agree upon criteria for diagnosis of mesothelial tumors; and a central registry, with consulting pathologists in various parts of the U.S. and other countries, should be developed promptly.

The relationship between pleural fibrosis, pleural calcification and mesothelial tumors needs elucidation.

Studies of Carcinogenesis in Lower Animals. Studies of the carcinogenic potential of asbestos minerals have rather clearly shown that tumors can be produced under certain circumstances. The Peacocks (1965) have produced tumors in the air sacs of White Leghorn fowls by introducing amosite and crocidolite into their air sacs. Rats and hamsters given chrysotile and amosite intrapleurally by Wagner (1964) and by Smith et al. (1965) have developed mesotheliomata. Therefore, although the inhalation of asbestos has not led to development of bronchiogenic carcinoma in experimental animals, the carcinogenic potential has been demonstrated.

This should be defined more sharply and the extent to which asbestos fibers or fibrils are inherently carcinogenic or act as carriers of carcinogens must be decided.

The occurrence of benzo[a]pyrene and other polycyclic hydrocarbons as con-

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taminants of crocisolite and amosite has been studied by Harington, as reviewed by Harington and Roe (1965). They suggest that in addition to oils naturally present in some forms of crocidolite, that storage in jute bags also adds oils. The role of trace amounts of certain metals, such as arsenic, chromium, iron, nickel, cobalt and beryllium needs also to be considered. Experimental studies on the role of asbestos mineral must, therefore, take into account not only the type, length, diameter, dosage, time of administration, but also the precise chemical characterization of the asbestos used and its contaminants. And, as Holt et al. (1965) have pointed out, prevention of cross contamination between exposure chambers is very difficult, as demonstrated by asbestos bodies appearing in untreated controls.

GRANULOMAS OF THE SKIN

A complete picture of potential health effects of asbestos should include mention of asbestos worts--a granulomatous reaction associated with spicules of asbestos lodged in the skin. The literature on this has not been reviewed, but no evidence of malignancy from this cause has come to our attention.

OTHER BIOLOGIC EFFECTS

Our knowledge of the migration of asbestos fibers in the body is meagre, in part due to the great difficulty in detecting them in histologic preparations unless there has been a reaction such as occurs when the asbestos body is formed. Studies with tagged asbestos bodies, either by fluorescent dyes (Berkley, 1965) or by induced radioactivity, should be carried out in animals who have ingested or inhaled asbestos.

Wyss (1953) described asbestos in urine, Stovin (1959) asbestos body in the

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thyroid and Bonser (1959) asbestos fiber in the spleen; Schepers (1965) stated that asbestos had been detected in the adrenal of a man with an adrenal tumor.

These various reports indicate that the potential of fine fibers to migrate within the body and to be carriers of trace metals or other chemical components and possibly provide persistent inplants in vulnerable sites might provide a valuable biologic tool.

ENVIRONMENTAL EVALUATION

Development of objective data on the working environment in asbestos producing or fabricating industries has been hampered by inadequate methods for the collection, identification and quantification of asbestos fibers and fibrils, which in turn have arisen not only from technologic limitations but also from uncertainty as to the parameters important in terms of health.

In the United States, studies by Dreessen et al. (1938) in which methods developed for use in controlling silicosis were applied, showed that relatively few fibers were collected by midget impingers. Nevertheless, it was recommended that dust counts by this method provided a good guide to dust contol; and although admittedly indirect this has proven useful as a basis for industrial hygiene.

Whether or not the recommended threshold limit of 5 mppcf is sufficiently low to prevent asbestos pneumoconiosis over a working lifetime is highly questionable. Wells(1965) has reported his observations in asbestos textile plants which indicate that pulmonary asbestosis began appearing when individuals had 50 to 60 million particles per cubic foot — years. Ferris' (1966) observations in a New England shipyard over the period 1945-65 support a similar conclusion. Marr's (1964) data on dust concentrations in West Coast shipyards where asbestosis was occurring indicated midget impinger counts averaged below the threshold limit value.

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necessary on the relative effect of control techniques in eliminating smaller particles as compared with larger.

If asbestos is indeed being collected in the lungs of a large segment of our population without occupational exposures, then it is necessary to determine its source. For this purpose, there is need for collections of large volumes of air in various locations: new asbestos and other fiber-producing plants, traffic arteries where braking is heavy, solid waste disposal areas, tailings of mines, etc. In this connection the reports by Laitmanen and others (1965) showing the detectable deposition of anthophyllite at distances of 1, 2, 5, 10 and even 20 kilometers from mines are of interest. Study on the simulated use of various asbestos products and their production of dust are needed

SUMMARY

The asbestos minerals, which have attained an annual world production of 3 1/2 million tons with hundreds of uses, have been associated with a number of health effects, the best known and most clearly established being asbestosis or asbestos pneumoconiosis, a disabling and sometimes fatal fibrosis of the lungs found in workers occupationally exposed for many years. Although dust controls have reduced the incidence and delayed the appearance of the disease in occupationally exposed workers, there is evidence that present published limits are not sufficiently low to prevent evidence of the disease from developing over a working lifetime. There are many unanswered questions as to pathogenesis, the importance of different types, diameters, and lengths of asbestos fibers, the earliest roentgenographic and physiologic changes, the dosage-response curves and many other aspects of this disease which has been known for about 60 years.

For about 30 years, evidence has been accumulating to indicate that there is

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increased incidence of lung cancer in workers exposed to asbestos minerals and there appears no doubt that this association is a real one. It is not as striking in those exposed only to chrysotile. More recently, associations have been demonstrated between asbestos and diffuse tumors of the pleura and peritoneum, formerly considered quite rare. The evidence for this association, at least with crocidolite, is now very strong. There are also recent suggestions of an increased risk of cancer of the stomach and colon in certain groups of asbestos workers, all with mixed exposures.

Studies in lower animals have confirmed the carcinogenic potential of asbestos fibers when introduced intrapleurally, but differentiation of effects of different types of asbestos is still not clear and the role of trace metals and organic co-factors has not been established.

During the past 4 years, studies of lung smears made from the lungs in routine autopsies in 7 urban centers (2 in South Africa; 1 in Canada; and 4 in the United States) have revealed what morphologically are asbestos bodies in varying numbers from very scanty to numerous, in from 27.6% to 57.6% of routine autopsies. Positive identification of the fibers responsible for producing these is urgent as well as evidence to use in evaluating their potential health implications.

In developing programs of research, it is recommended that, unless supervened by later knowledge or group agreements, terminology and techniques suggested by UICC (International Union Against Cancer) be considered as providing a good counting basis. A broad outline of suggested research areas follows.

In assigning research priorities, studies should be regarded as falling into two broad categories: first, those needed to insure prompt answers to urgent questions involving public policy and control efforts; and second, those needed

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to increase the base of information on the physical and chemical factors of fibrous materials involved in their interactions with animals and man, so that efforts to maintain safe working and living environments can be constantly revaluated and improved. In the first category comes programs aimed at clarifying the reports of asbestos bodies being present in the lungs of a third of our population. Are these truly responses to asbestos fibers or are other fibers involved? Where do these fibers come from, and what is their potential significance in terms of health? Is the number of individuals with such bodies increasing? Is there an increasing incidence of mesothelial tumors in our population and is this in any way related to asbestos mineral? Do fibrous minerals play a major or a minor role in the causation of lung cancer? Are certain forms of asbestos or other fibers more important in these relationships, and what co-factors are important?

Research is needed in man, in lower animals, and in the environment, with maximum communication at all levels.

Studies in man can be primarily clinical or epidemiological, the epidemiological being retrospective, cross-sectional, prospective, or combined, using industrial, community or hospital populations, with emphasis on detecting pneumoconiosis, impaired function, asbestos bodies, pleural changes, lung cancer, mesothelioma, gastro-intestinal tumors or other abnormalities. Techniques needed include histories, physical examination, x-rays, pulmonary function studies, sputum examinations, examination of biopsy and autopsy material, specialized serologic tests, mineralogic studies. Some suggested programs include:

A. Epidemiologic studies in selected populations

1. Occupational populations, to get incidence of various health effects, in groups with various types and levels of exposure.

a. Asbestos workers with exposure to one type of asbestos;e.g.

(1) Chrysotile miners (Quebec, California)

(2) Miners in selected foreign countries; e.g., Yugoslavia

b. Asbestos workers with relatively light exposures; e.g.

(1) Construction workers other than insulating workers

(2) Automobile brake repair employees

(3) Workers in controlled industries

(4) Operators spraying asbestos

2. Non-occupational populations, with medium to light exposures

a. Wives and children of asbestos workers

b. Individuals living in neighborhoods of asbestos plants

3. Occupational populations with asbestosis, to develop criteria for continued employment, utilizing symptoms, function tests, radiographic appearance, and sputum studies

B. Studies of special problems relative to susceptibility and co-factors

1. Blood typing

2. Latex fixation

3. Cigarette smoking

4. Virus infections

C. Studies of pathologic material; re: asbestos bodies.

1. Positive identification of asbestos bodies. **

2. Quantitative estimate of asbestos bodies in populations with high-medium-low occupational exposures and with no known occupational exposures. **

3, Correlations of asbestos bodies, pathologic changes and mineral content and identification. **

4. Studies of stored lung specimens for asbestos bodies to determine if there has been increasing proportion of positive. *

D. Agreements on classification

1. Radiographic classification of asbestosis, with representative films. **

2. Diagnosis of mesothelioma, with reference panels. **

3. Pathologic classification of asbestosis. *

4. Quantitation of asbestos bodies in tissues, methods. *

5. Quantitation of asbestos bodies in sputum, methods.

STUDIES IN LOWER ANIMALS

After preliminary testing of preparation and airborne dispersion of asbestos for creation of appropriate experimental environments, a systematic study may be made

** High priority * Relatively high priority

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of effects of a number of standardized samples of asbestos in a number of species of animals, by various routes of administration with strict attention to diameter, length, duration, dosage, trace metal and hydrocarbon content, looking for effects in terms not only of fibrosis, pleural changes, asbestos bodies, and malignancies but also migration, enzyme inhibition and any other effects. In such studies there should be use of various combinations with various co-factors, heated and unheated asbestos minerals, and actual products derived from brake linings, and other uses. Consideration should be given to use of tagged fibers in studying migration. Studies in tissue cultures might prove productive.

ENVIRONMENTAL STUDIES

There is need for more study of asbestos minerals as such in terms of their properties relative to health. Sampling the environment in various sites is desirable. High volume sampling for asbestos and other fibrous mineral should be done not only in proximity to industrial sites, but near highways where braking is heavy, and where airborne material is likely from dumps or tailings.

There should be a prompt reappraisal of existing evidence regarding the threshold limit, to determine whether or not the present level of 5 mpccf by midget impinger represents an adequately low time-weighted average.

GENERAL

Practical guidelines are needed for the management of those already exposed over a number of years to asbestos, in terms of periodic followup and recommendations for continued employment. This includes the role of sputum examination and functional tests.

Present compensation laws are a handicap in many states to the detection

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and management of asbestosis and other possible health effects in the asbestos worker. As part of a general problem involving chronic or delayed or nonspecific effects of occupational exposures, this should be placed on the agenda of those groups giving attention to necessary modifications.

There is need for an up-to-date annotated bibliography of asbestos and health effects.

Booklets to guide industrial hygiene practice in various asbestos using industries are needed.

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