Reprinted from
THE CANADIAN MEDICAL ASSOCIATION JOURNAL
92, 1020-1025, May 8, 1965

PLAINTIFF'S EXHIBIT

ASA-673

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Asbestos and Cancer

The Report and Recommendations of a Working Group Convened Under the Auspices of the Geographical Pathology Committee of the International Union Against Cancer

EDITOR'S NOTE—In October 1964, the New York Academy of Sciences sponsored an international meeting on the biological effects of asbestos. Following this meeting, some 40 delegates from Australia, Canada, Finland, France, Germany, Great Britain and Ireland, Italy, South Africa and the United States were invited to study the vast amount of information which had been presented with a view to the organization of an international study of asbestos and cancer. The terms of reference of this Working Group covered three major aspects of the problem: epidemiology, pathology and experimental pathology, and physics and chemistry.

The findings of the Working Group and their recommendations arising from these studies are recorded, in slightly abridged form, in the following report.

THE ASSOCIATION OF EXPOSURE TO ASBESTOS DUST AND CANCER

THE main types of asbestos of commercial interest are amosite, anthophyllite, chrysotile, crocidolite and tremolite. There is evidence of an association between exposure to asbestos and malignant neoplasia. This has been established mainly on information from Germany, Italy, South Africa, the United Kingdom and the United States of America.

The types of tumours which have been shown to be associated with exposure to asbestos dust are:

1. Carcinoma of the lung.
2. Diffuse mesothelioma of the pleura and peritoneum.

There is some suggestion of an association also with gastrointestinal carcinoma, and possibly with ovarian tumours.

The latent period between first exposure to the dust and detection of the related tumours is many years, usually 20 or more. Instances up to 60 years have been reported. For this reason, further cases of these associated tumours will be expected to occur for many years to come, even if dust exposures are now greatly reduced.

Present evidence indicates that the associated carcinomas of the lung are not limited to exposure to any one type of asbestos fibre. However, further investigations are urgently needed to establish whether the degree of risk is importantly related to the type of fibre inhaled.

In the case of mesotheliomas evidence from several countries suggests that exposure to crocidolite (blue fibre) may be of particular importance, but it cannot be concluded that only this type of fibre is concerned with these tumours, and further investigation of this problem is needed.

Certain types of asbestos fibres in the virgin state have been found to contain oils, waxes and other organic matter. In addition, asbestos fibres readily absorb hydrocarbons subsequent to mining. Small or trace amounts of various elements such as nickel and chromium are also found associated with some types of fibre. The possible role of such associated materials in the development of tumours, following exposure to asbestos dust, is not yet clear.

These findings, when considered in relation to the great increase in the use of asbestos for many purposes in all countries, suggest that a more serious and widespread hazard from exposure to asbestos dust may exist than is widely appreciated.

RECOMMENDATIONS ON PROBLEMS REQUIRING EPIDEMIOLOGICAL STUDY

1. *That the relationship of fibre type to the risk of developing asbestosis, carcinoma of the lung, and mesothelial and other tumours be investigated.*

International and intranational comparative studies of mining and other populations exposed to only one type of fibre are recommended.

Studies of the effect of exposure to different types of asbestos fibre within a country are likely to be of special value, but studies of groups exposed to apparently similar fibres in different parts of the same country are also likely to be informative.

2. *That the relationship of dust dosage (including concentration and duration of exposure), and the composition and physical state of the dust to the incidence of asbestosis, carcinoma of the lung, mesotheliomas, and other cancers be studied.*

Comparative studies in factory populations in the asbestos textile and other manufacturing processes using asbestos are likely to be useful, especially when there are records of past dust measurements. In any prospective studies of new entrants, the measurement of dust by a standardized method should be regarded as an essential part of the investigation.

3. *That the effects of removal from further exposure to asbestos dust be investigated.*

It is important to establish the subsequent morbidity and mortality from asbestosis, and the mortality from cancers associated with exposure to asbestos in population groups no longer exposed to the dust.

4. *That further investigations be made of past and all future cases of diffuse mesothelial tumours of the pleura and peritoneum to establish any association with asbestos and other factors.*

These tumours should be diagnosed on the criteria suggested by the Panel on Pathology (see below) and the diagnoses should be reviewed by a panel of pathologists with experience of these rare tumours. The tumour and lungs should be investigated for the presence of asbestos by physical and chemical methods (see below).

5. *That studies of morbidity and mortality be extended to asbestos-exposed populations that have not so far been widely investigated.*

(a) It is recommended that special attention be directed to surveys in the insulating, asbestos cement and asbestos products industries and other plants in which asbestos is regularly used.

(b) It is also recommended that, since incidental exposure to asbestos dust may occur in certain trades and occupations, attention be directed to the handling and transporting of asbestos, pipe fitting, and the building and ship-building industries.

(c) It is recommended that surveys be made to study environmental and community exposures, including populations near mines and factories and elsewhere.

(d) It is recommended that general population surveys be made nationally and internationally to establish by standardized methods, in areas of presumed high and low exposure to asbestos dust, the prevalence of asbestos bodies and fibres.

(e) It is recommended that surveys of asbestosis in domestic and wild animals be extended to areas of high and low exposure.

6. *Epidemiological Methods*

(a) *General*

In addition to the usual information about the individual collected in such surveys, special attention should be directed to a detailed, social (including smoking habits), occupational, environmental, and medical history from early childhood to elucidate any possible exposure to or association with any type of asbestos or other dusts. A study of the family unit or household may be of interest in view of the occasional reports of significant neighbourhood and household exposures.

In view of the association between exposure to asbestos dust and pulmonary fibrosis and its complications, it is important to obtain as much information as possible about morbidity and mortality from *all* causes, with particular attention to: asbestosis, chronic bronchitis and emphysema, bronchiectasis, diffuse interstitial fibrosis, pneumonia, tuberculosis, cor pulmonale, carcinoma of the lung, diffuse mesothelial tumours of the pleura and peritoneum, gastrointestinal tumours, and ovarian tumours.

(b) *Clinical Criteria*

Symptoms

It was agreed that in all surveys the presence or absence of cough, sputum, dyspnea, and chest pain should be recorded as a minimum. This should be recorded using a standardized questionnaire.

Signs

It was agreed that when physical examination was possible the minimal observations should include the presence or absence of *clubbing of fingers, cyanosis, and basal rales in the chest.*

It was agreed that the measurement of sputum volume (first hour on rising) and degree of purulence recorded in a standard way[1] was useful in association with the questionnaires for assessing

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the prevalence of bronchitis, and this may be relevant to the disability caused by asbestosis.

The epidemiological usefulness of examinations of sputum for asbestos bodies and fibres is at present uncertain but needs investigation.

(c) *Classification of Chest Radiographs of Asbestos-exposed Individuals*

There is no international or national standardized classification of the radiological appearances of asbestosis. It is recommended that a scheme based if possible on an extension of the I.L.O. Classification (1958)[2] be developed. The aim should be to specify separately and record semiquantitatively the principal radiological features seen in asbestos-exposed groups, but exposure to mixed types of dust is not uncommon and the appearances may, therefore, include those caused in part by other pneumoconioses.

It is recommended that a working group be set up to develop and test a new international classification.

(d) *Lung Function Assessment*

The preferred lists of lung functions to be used will vary according to the type of survey and the facilities available. A list of minimal and additional tests likely to be of use is as follows:

Minimal

Forced vital capacity (F.V.C.)
Forced expiratory volume over 1 sec. ($F.E.V._{1.0}$)

Additional

Transfer factor (diffusing capacity) of lung for carbon monoxide—single breath method
Lung compliance
Standard exercise test
Peak expiratory flow
Airways resistance

RECOMMENDATIONS ON PATHOLOGY AND EXPERIMENTAL PATHOLOGY

1. *Diagnosis of Asbestosis*

(a) *Macroscopic Examination*

At necropsy the parietal pleura should be stripped if possible with the thoracic contents. It is desirable that at least one lung be inflated with fixative and whole lung sections be prepared.

It is recommended that special note be made of the following:

Pleura: for thickening and plaques (defined as localized areas of stiff hornlike material[3]). The site and size of all pleural lesions should be recorded.

Lungs: The presence of interstitial fibrosis, bronchiectasis, cystic change, tuberculosis, pneumonic consolidation and tumours. The site of any tumour should be recorded as precisely as possible.

Mediastinal tissues should be examined for evidence of neoplastic infiltration and for tuberculosis.

Peritoneum: Parietal and visceral fibrosis in the peritoneum, such as parietal plaques and "sugar-icing" of the spleen, should be recorded.

(b) *Microscopic Examination*

It is recommended that at least six sections be examined from the lungs before the degree of asbestosis is decided and these blocks should be taken from specific sites and identified in the following standard manner:

1. Apex of right upper lobe, pleural surface.
2. Right middle lobe, lateral pleural surface.
3. Right lower lobe, middle of basal surface.
4. Left upper lobe, central section.
5. Lingula, central section.
6. Left lower lobe, central basal section.

In addition, sections should be taken from the bronchi and peritracheal and peribronchial lymph glands, and from any suspicious or abnormal tissue.

(c) *Assessment of the Severity of Asbestosis*

It is recommended that this assessment should be based on the severity of interstitial fibrosis and the amount of tissue involved. The proposed scheme is as follows:

EXTENT OF LUNG INVOLVEMENT	DEGREE OF ASBESTOSIS	DEGREE OF INTERSTITIAL FIBROSIS
Slight →	Slight ←	Slight
Moderate →	Moderate ←	Moderate
Marked →	Marked ←	Marked

A category of "minimal" asbestosis is also proposed to describe slight focal fibrosis in the region of the respiratory bronchioles associated with the presence of asbestos bodies; such changes are commonly confined to sections taken from the bases of the lower lobes.

This scheme puts more emphasis on the extent of the lesions than the degree of fibrosis (which should be averaged for the six sections). Thus, a lung with moderately extensive disease but only slight severity of fibrosis is graded as "moderate asbestosis". The use of an average assessment of the six sections makes it impossible to have a grading of slight involvement and moderate or marked degree of fibrosis.

(d) *The Detection and Significance of Asbestos Bodies and Fibres*

Sputum

The presence of asbestos bodies and fibres is an indication of the exposure to asbestos dust and not evidence of asbestosis. It is therefore suggested that

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the bodies should be referred to as "asbestos bodies" and not by the previously used term, "asbestosis bodies". Because of their sporadic appearance and, in the case of fibres, their relation to recent dust exposure, quantitative assessment of bodies and fibres in sputum is not, in the light of present knowledge, a very useful procedure but might become more useful when further investigated.

In sputum detection by direct examination under a coverglass and the use of phase contrast, oblique illumination or narrowed condenser diaphragms is proposed. If sputum concentration is used antiformin or "Eusol" treatment is recommended.

Lungs

From fresh lungs, the greatest number of positive results are obtained from smears from the base of a lower lobe (of the thickness of a thick blood smear as for malarial parasites), air-dried and mounted in balsam. A rough quantitative examination by low-power magnification is easy and practicable. For fixed lungs the smear technique is of limited value, and unstained sections 30 microns thick are recommended.

Fibres

For investigation of asbestos fibres in lung sections, microincineration, acid treatment, and examination by phase-contrast are suggested. Morphologically the fibres appear as straight rods of varying lengths and thickness, but with longitudinal shredding, and in the thicker fibres smaller fibrils may be recognized. While there are other structures described as pseudo-asbestos bodies, or curious bodies, little difficulty is found in distinguishing the genuine from the others. These other types usually have a carbon-black centre and a shape which is other than linear, but the body that can mimic an asbestos body completely is the small one found in talcosis, which may be tremolite, a form of asbestos.

Chemical Analysis of Lung Tissue

Where possible, blocks of tissue from the six areas chosen for histological study should be taken and the amount of collagen relative to total proteins estimated by the standard hydroxyproline methods. The results of collagen estimations should be expressed in absolute amounts and as percentages of defatted dried lung tissue.[4]

2. *Diagnosis of Diffuse Mesothelial Tumours*

(a) *Macroscopic*

The salient characteristic of the diffuse mesothelioma is its predilection to spread along the serosal membrane in which it occurs. In the pleural cavity, the entire surface may become replaced by a continuous layer of tumour, owing to symphysis of the pleural surfaces. This is uncommon in the peritoneum where the surfaces often remain separate but covered by isolated plaques and nodules or diffuse infiltration. Only those mesothelial tumours in which serosal spread is unequivocal should be termed "diffuse". A few benign diffuse mesotheliomas have been described. Almost all diffuse mesothelial tumours show evidence of malignancy by direct infiltration of adjacent tissues and organs and metastases to regional lymph nodes.

The differentiation from metastatic tumour is the main problem in diagnosis and can only be made with complete certainty by the exclusion of all other sources of tumour at necropsy. Because of the tendency of the tumour to surround and infiltrate subserosal organs, these organs most commonly come under suspicion as points of origin. The possibility that the primary growth may have been surgically removed must be borne in mind.

(b) *Microscopic*

Diagnosis is possible because the growth commonly shows histologic patterns which occur infrequently in other tumours and especially those which might metastasize to serosal membranes. Particularly helpful is the presence in some diffuse mesotheliomas of a mixed structure of malignant elements of both epithelial and mesenchymal character, or other diverse combinations. Growths in which only one type of cytoarchitecture is present may also have a highly distinctive pattern; for example, (1) a tubular or tubulo-papillary pattern in which the tumour cells show marked uniformity and are cubical or flattened; (2) masses of collagen in which there are either (a) cleft-like spaces lined or occupied by tumour cells, or (b) fine hyaline strands which form complex meshworks and laminated bundles. Other examples of these tumours may have an entirely non-specific structure presenting the appearance of a spindle cell sarcoma or of an anaplastic tumour.

Because of the difficulty in clearly distinguishing on histologic grounds alone some of these growths from metastatic tumours, cases diagnosed from biopsy material should be called "probable mesotheliomas". In epidemiological studies precise details of the pathological evidence on which the diagnosis was based should be stated.

(c) *Histochemistry*

Most of the mucoid material within mesotheliomas, although often intimately associated with the surfaces of the tumour cells, is extracellular. Intracellular or intratubular mucin of an adenocarcinoma will usually take mucicarmine or PAS stains. The absence of these reactions in a tumour which contains mucoid material can, when taken with the other features, be useful additional evidence of a mesothelial tumour.

Hyaluronic acid is often present in mesothelial tumours. The demonstration of its removal from the tissue sections by specific hyaluronidase prepa-

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rations is a useful histochemical test, but since the acid is soluble in water, the test requires that the tissues be fixed in a special precipitating fixative, such as formol alcohol acetic acid.[5] It also appears likely that the quantitative measurement of hyaluronic acid in effusions, where this polysaccharide has been isolated and chemically characterized, may well become a reliable method for assisting in the diagnosis of mesothelioma, but it is emphasized that positive results for both the histochemical and chemical tests for hyaluronic acid are found in only a proportion of cases of mesothelioma and they should not be used as sole diagnostic criteria.

(d) *Exfoliative Cytology*

The contribution to the diagnosis of diffuse malignant mesothelioma by exfoliative cytology of serous fluids requires: (1) that the exfoliated neoplastic mesothelial cells sufficiently resemble exfoliated non-neoplastic mesothelial cells to allow them to be recognized as having a mesothelial origin, and (2) that they also possess the generally accepted features of malignancy. The latter are not often present, so a definite diagnosis of mesothelioma is then difficult.

Usually mesothelioma cells, while atypical, do not appear malignant but still show evidence of mesothelial origin. From cytology of the serous fluid it is possible to be strongly suspicious and in a few cases confident of the diagnosis of mesothelioma, but usually its presence can only be reported as possible.

The diagnosis of malignant mesothelioma by exfoliative cytology requires a familiarity with the non-neoplastic mesothelial cell. Mesothelial hyperplasia and hypertrophy can easily be mistaken for malignant mesothelioma and *vice versa*. It may be imprudent to do more than suggest malignant mesothelioma if there is not good supporting clinical, radiological or biochemical evidence. The exfoliated malignant mesothelioma cell must also be distinguished from the adenocarcinoma cell, by far the commonest malignant cell recovered from serous fluids. This cell is well described in standard texts of exfoliative cytology.

(e) *The Use of Tissue Culture in the Diagnosis*

The various manifestations of mesotheliomas in some cases cause difficulty in distinguishing such tumours from bronchogenic carcinoma, metastatic ovarian carcinoma, fibrosarcoma, etc. It is therefore recommended that where possible biopsy specimens of pleural and peritoneal neoplasms be studied after short-term passage, (a) *in vivo*, and (b) *in vitro*, to determine whether the rate of growth and/or morphology after transplantation can provide useful criteria for a differential diagnosis of mesotheliomas. To achieve this it is recommended that clinical pathologists seeing these tumours co-operate with workers in experimental carcinogenesis who are using tissue-culture methods.

3. *The Contribution of Experimental Pathology*

It was agreed that various types of asbestos induce in many species of animals lesions similar to those seen in human cases of asbestosis, mesothelioma, and carcinoma of the lung, but the need for more precisely planned experiments was emphasized.

The desirability of using healthy animals of known response to asbestos under quantitative conditions of exposure by inhalation, feeding, and parenteral injection at several sites was accepted. Experiments in great variety are being undertaken in many parts of the world, particularly in Canada, Great Britain, South Africa and the U.S.A. The prospect of providing standardized samples of chrysotile, amosite, crocidolite, tremolite and anthophyllite asbestos for experimental work was welcomed.

It was agreed that there was a need for improving methods of identifying the type of asbestos in submicroscopic fibres in tissues. Further studies of the rate of formation and resistance to destruction of asbestos bodies in different species of animals may be useful.

It is recommended that there be closer collaboration between clinical and experimental pathologists and other scientists in the field of experimental pathology, biochemistry, and biophysics, as applied to the problems of the biological action of asbestos.

4. *Proposal for Pathology Reference Panels*

It is recommended that central consultation and reference panels be set up on regional, national and international levels. These panels will:

(a) Assist in establishing standards for pathological classification of asbestosis.

(b) Serve as consultation centres for diagnosis of mesotheliomas and other tumours associated with exposure to asbestos.

(c) Provide for general exchange of pathological material related to asbestosis and its associated tumours.

It is further suggested that a comprehensive atlas on the pathology of mesotheliomas should be prepared.

RECOMMENDATIONS RELATING TO PHYSICS AND CHEMISTRY

1. *Reference Samples of Asbestos for Experimental Work*

It is anticipated that there will be an expansion of demand for asbestos of various types for biological and other studies. It is at present impossible to predict the biological effects of differences in mineral composition, size distribution, associated organic matter and trace metals in different samples of asbestos. Also, fibres from a particular mine may vary in composition and in the amount of absorbed material.

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It is therefore recommended that:

(a) Standard reference samples, of respirable size, of amosite, chrysotile, crocidolite, tremolite and anthophyllite be prepared from as pure parent material as possible and held at the Pneumoconiosis Research Unit (P.R.U.) in Johannesburg for distribution to centres requiring them. (These standards should also serve as references for comparison with larger amounts of material—such as may be required for inhalation or chemical extraction.) It is proposed that samples of chrysotile from different countries—for example, from Arizona, Havelock (Swaziland), Quebec and Shabani (Southern Rhodesia)—be included in the reference collection.

(b) The standard samples be analyzed and characterized quantitatively by:

Chemical and spectrographic analysis.

Optical and electron microscopy, for determination of shape, size distribution, and optical properties such as refractive indices, extinction angle, etc.

X-ray diffraction analysis by the powder technique.

Specific surface measurement by low temperature gas adsorption.

Determination of amount and type of organic matter present.

(c) Oils and waxes isolated from asbestos be prepared and also distributed through the P.R.U., Johannesburg.

(d) When the standards have been collected and prepared, the P.R.U., Johannesburg, will notify workers of their existence through the U.I.C.C. Bulletin and any other appropriate channels.

1. *Identification and Quantitative Assessment of Asbestos in Tissues*

In tissue sections it may be only possible to identify the type of asbestos present. For quantitative studies of the amount present in any organ such as the lung, it is necessary to analyze representative samples of the organs.

It is recommended that:

Tissue sections should be treated to remove organic material, for instance, by ashing or treatment with active oxygen; but this will not remove the asbestos bodies completely, and chemical treatment may be necessary to free the fibres. The best method for this is not known, but treatment with acetic acid may be useful. Identification of the type of fibre can only be made on free asbestos fibres and not on fibres inside asbestos bodies. It is recommended that methods of distinguishing asbestos from other fibres which may be present be further investigated. This can probably best be done by phase contrast or polarized light microscopy. It is also recommended that the treated sections be examined by electron microscopy for recognition of submicroscopic fibres.

For large samples of tissue, acetic acid, hydrogen peroxide and formamide methods be tried as they appear to be superior to ashing, but the best method of extraction of mineral matter from tissue is not yet known and needs further study. However, the quantitative determination of asbestos in the residue obtained in this way is difficult but could be based on chemical analysis, x-ray diffraction, or fibre counts. It is recommended that methods for concentrating such asbestos and separating different types of asbestos from each other be further investigated.

Reprints may be obtained from the National Cancer Institute, 790 Bay St., Toronto, Ont.

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