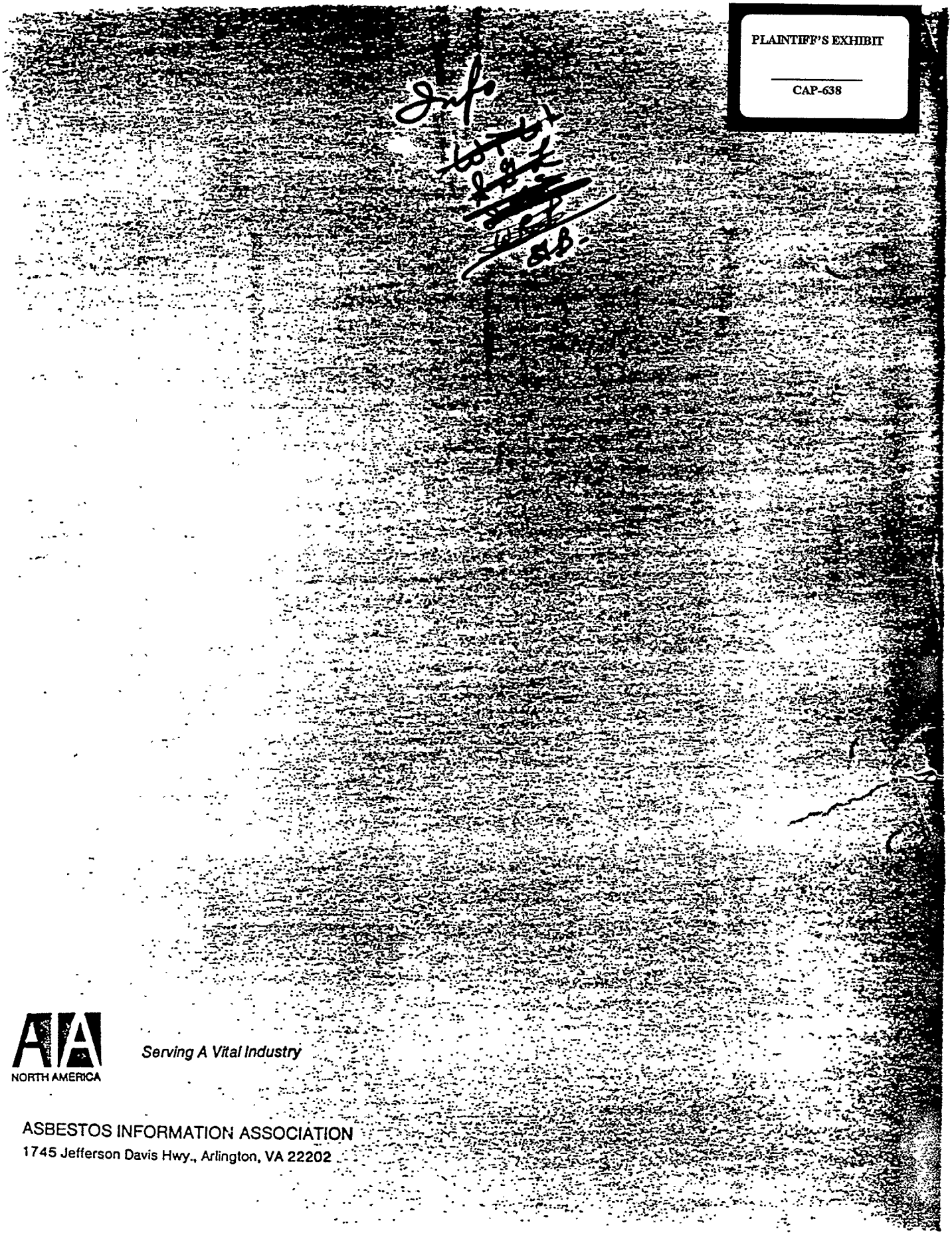
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BIOLOGICAL EFFECTS OF MINERAL FIBERS

LYON, SEPTEMBER 25-27, 1979

REPORT BY DR. HILTON C. LEWINSOHN

This three day meeting was attended by approximately 240 people and severely strained the facilities of the IARC where it was held.

In his opening remarks John Higginson, Director of IARC, made reference to Gershon Fishbein's article in his "Occupational Health and Safety Letter" of September 8, 1979 and indicated that the IARC was contemplating legal action because of Fishbein's allegations.

The first two sessions dealt with experimental pathology, both in vivo and in vitro. The importance of physical and chemical characteristics of fibers in disease mechanisms was one of the main themes of these two sessions. Such characteristics as crystalline structure, fibrous structure, length and diameter, chemical formulation and chemical impurities were all investigated.

The toxic influence of mineral fibers is dependent on fiber morphology, surface area and surface conditons and modifications undergone in the human body.

Gibbs pointed out that fibers found in lungs at post mortem represent the results of exposure a long time previously whereas air sampling measures immediate conditions. The UICC samples which are used in animal experiments or in vitro experiments are also representative of "immediate" conditions. According to Gibbs, amosite fibers have a greater median length than other fibers, e.g.:

median L/D	crocidolite > amosite > chrysotile	in mining & milling
median Mass	crocidolite > amosite > chrysotile	
median D	amosite > crocidolite > chrysotile	
median L	amosite > crocidolite > chrysotile	

The work of Timbrell and Gale relating to the alignment of asbestos fibers in a magnetic field is of practical value in the development of automatic counting devices.

Techniques now available for examining the mineral content of human tissues have demonstrated mineral fibers in lungs, besides those of the common varieties of asbestos. Among those found in tissue examined in Cardiff and in Paris were mullite, muscovite/illite, talc, iron, titanium and other fibers. In all, 31 different fibers have been found in human lungs.

In another study, a correlation between fiber counts and pathologic changes in the lungs could not be made. In some cases of asbestosis following exposure to chrysotile, this mineral cannot be identified and may be attributable to chrysotile solubility in the lung.

Timbrell found that in examining anthophyllite fibers in human lungs the length of fiber found in a child's lung was greater than in adult lungs and speculated as to whether long fibers penetrate children's lungs more readily than adult lungs. Fibers of 100 microns in length will be retained in adults whereas fibers as long as 300 microns will be retained in a child's lung.

According to Pooley, the majority of fibers found in the human lung are greater than 6 microns in length.

The question of length and diameter of asbestos and other fibers was discussed. It is obvious that international standardization of definitions, terminology and measurement techniques is needed. Professor Elmes pointed out that information from animal experiements should not be extrapolated directly to human safety. John Davis of Edinburgh stated that long amosite fibers have a greater median diameter, but are by far the most fragile fiber and break down very rapidly into shorter fibers. Other varieties of asbestos are more stable. This raises the point with regard to the sort of fibers needed for animal studies and for reference samples. Can satisfactory samples be produced for use in experiments to explore the question of long versus short fibers?

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Mr. Kannerstein discussed the papers presented for the second session. He noted that it was now obvious that analysis of lung tissue for fibers had to be thorough and indicate all fibers present. Mullite and attapulgite were two fibers he mentioned. Attapulgite is a clay mineral and is used in many commercial applications. Bignon and his coworkers have demonstrated the presence of attapulgite in pleural fluid and urine in exposed persons.

In asbestos exposed populations, lung cancer was apparently more common in the lower lobes and peripheral tumors were more common than central ones. He quoted Whitwell's finding that 34% were adenocarcinomas, 22% squamous, 14% carcinoma simplex, 26% oat-cell and 4% other cellular varieties. It would appear that since 1974 adenocarcinoma has become the predominant type of lung cancer to be seen and thus suggests that industrial factors, according to Vincent et al (1977), (particularly heavy metals) may be responsible. Vincent et al do not mention asbestos.

Dr. Kannerstein posed the question as to whether, in the absence of pulmonary fibrosis, there is an excess of lung cancer. He pointed out that this is influenced by the definition of asbestosis (fibrosis) and whether it is clinical, radiological or anatomical (pathological). No definite studies have been made to discover what the nature of the relationship is, but Seal feels that lesser forms of pulmonary fibrosis are present and it is important to identify it.

He quoted the recent "JAMA" editorial by Selikoff which showed that there was a five-fold increase in death-rate in non-smoking asbestos workers compared with non-exposed non-smokers.

He discussed the diagnostic problems in mesothelioma and pointed out that these were often difficult cases and could have complex or deviant or rare subgroups. Special techniques could be used to aid in diagnosis such as histochemistry (hyaluronic acid, PAS stains), transmission and scanning electronmicroscopy (identify microvilli in carcinoma and mesothelioma), chemistry (staining methods) and immunofluorescence techniques.

Mesothelioma diagnostic panels could help control observer variation, allow for consensus opinions to be reached, could grade the certainty of diagnosis, attempt to overcome inadequacies of information on tissue, and resolve disagreement through meetings and discussions. McCaughey et al had shown that in Canadian Tumour Registries 51% of cases had inadequate material available for study. Peritoneal tumors of uncertain histogenesis were more common in females than in males.

The presentation concluded with remarks on the demonstration of asbestos fibers in lung tissue. The disappearance of chrysotile from lung tissue as opposed to amphiboles was noted, as well as the finding by Sebastian and his colleagues of small chrysotile fibers in the periphery of the lung and pleura.

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Dr. Pott's paper, read by Kannerstein, dealt with whole animal experimental data. It pointed out the differences in susceptibility of different animals. The rat is the most commonly used animal, but it has a longer latent period for response, the tumor yield is less and it has a lesser ability to form asbestos bodies than other animals. Mice, golden hamsters, rabbits and primates have all been used experimentally.

Fibers less than 5 microns in length are cleared more efficiently from the lung. The half-time of clearance of chrysotile is 60 to 90 days, according to Morgan. Fibers which do not reach the pleura or peritoneum cannot produce mesothelioma. The magnesium:silicon ratio after three months exposure is altered in the lungs.

Intra-tracheal instillation in European hamsters has shown that fibers less than 4 microns in diameter could be found subsequently in other body organs.

Fibers in the gastrointestinal tract can penetrate, (although it was not stated how) and be found in other organs. Attapulgite has been found in urine and Smith has shown that UICC fibers in the drinking water of hamsters penetrates the gut. The work of Gibel was mentioned, but criticized on the grounds of experimental method and design.

Carcinogenicity of fibers has not been adequately explained. Smoking increases the incidence of lung cancer, but not mesothelioma. This may be due to the presence of benzo-a-pyrenes on fibers in the lung affecting parenchymal tissue and not having the same effect on the pleural mesothelial tissue.

There is a considerable amount of experimental evidence to suggest that there are different biological effects for different types of fiber. Non-coated glass wool fibers appear to be more reactive biologically than coated fibers. The work of Smith only produced pleural tumors after intrapleural injection of fibers longer than 20 microns. Stanton's work indicated that fibers less than 0.25 microns in diameter and greater than 8.00 microns in length had the greatest effect.

Leeching of ions from fibrous minerals or the effects of heat could affect biological reactions. Wagner had shown that the UICC fibers had their highest carcinogenicity when inhaled and their lowest carcinogenic effect when injected.

Long, thin fibers are the most carcinogenic. It is not proven that fibers less than 5 microns in length do not produce fibrosis or tumors. The carcinogenic potential of short fibers may be weak but this may be related to dose (numbers). A lot of short fibers may be as dangerous as a few long fibers.

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The discussion of the papers on human pathology dealt mainly with the diagnosis of lung cancer and asbestosis. It was pointed out that in many instancer a medico-legal situation arose which forced the issue of diagnosis. Three areas were discussed, namely, (1) whether the presence of asbestosis is necessary for lung cancer to be attributed to asbestos exposure, (2) whether there were differences in histological tumor varieties related to asbestos and (3) the differential diagnosis of mesothelioma.

Dr. Seal felt that the first question was very difficult to answer. Whitwelll had concluded that considerable fibrosis had to occur before cancer developed. Seal stated that parietal pleural plaques were found more commonly in persons with carcinoma of the lung than any control group. He feels that "asbestosis" occurs in amounts missed by the average pathologists. However, even if "asbestosis" is recognized, in the presence of a few asbestos bodies, one still cannot conclude that a lung cancer is asbestos-induced. According to Seal, an overt case with confirmatory clinical data available such as chest X-rays and pulmonary function tests, will not be missed by the pathologist. When a patient presents with lung cancer, where minimal X-ray changes have gone unnoticed, the pathologist is equally liable to miss the lesion. Other types of exposure may also produce similar effects, e.g., bird fanciers with hyaline pleural plaques and pulmonary fibrosis.

Asbestosis should only be used to refer to asbestos induced parenchymal fibrosis as pleural plaques are very common and most follow minimal exposure. Minor degrees of plaque formation should alert the pathologist to the possible role of asbestos in lung cancer patients and lead to a careful macroscopic and microscopic scrutiny of the lung. Classical asbestosis leading to respiratory disability is likely to be obvious on macroscopic examination, severe in microscopic extent and with asbestos bodies seen with ease and associated with an Ashcroft count of over one million forms/Gm dry weight. Lesser degrees of asbestos induced fibroses exist which are probably important aetiologically when carcinoma of the lung supervenes. Further work needs to be carried out to establish whether even lesser grades of asbestosis than the above are important in the aetiology of lung cancer and whether in such cases EM quantitative and qualitative techniques are mandatory.

According to Seal, minor degrees of interstitial fibrosis are very common in the lungs of urban middle-aged males, with very low EM fiber counts. It is probable that viral infection, bacterial infection after antibiotic therapy and minor degrees of non-mineral dust immunologically induced fibrosis occurs, and it will be important to establish the extent of this, otherwise all pulmonary fibrosis with a trivial fiber content may wrongly be regarded as industrial in origin.

There is a need to identify other inorganic materials in fibrotic lungs in order to establish a possible causative role, either primary or secondary, in interstitial lung disease.

Dr. Davis described results of animal experiments with chrysotile and amosite. UICC Chrysotile caused more lung damage in rats than other UICC fibers. Chrysotile contains more long fibers. Samples of chrysotile and amosite from factories were

compared. Factory chrysotile contains fewer long fibers and they are thicker than fibers in the UICC sample. Animals breathing this dust developed slightly less fibrosis and fewer tumors. Factory amosite contained more long fibers than UICC amosite and produced more fibrosis. Neither UICC amosite or factory amosite produced any tumors.

Several suitable techniques are available for extracting asbestos fibers from tissues, including (1) Sodium hypochlorite digestion technique,
(2) Low temperature ashing,
(3) Combinations of digestion and ashing.

Sebastian felt there was a need to standardize techniques, but on the whole in France, U. K. and the Netherlands agreement was quite good and present-day methods are virtually standardized.

Leineweber stated that aggressive separation techniques help to destroy man-made mineral fibers in tissues. This influences the meaning of data comparing the lung burden of people who acquired their dose-level in industry but are not studied until after exposure ceased. What is the burden at the time disease is developing? He stressed the importance, in experimental work, of characterizing fibers as fully as possible. He cited the following examples:

(1) acid leached chrysotile may not be 90% leached.
(2) brake-linings and brake-lining dust can exist in two different forms; i.e., dust in fabrication and dust generated by wear of the product present when it is removed or replaced.

Timbrell pointed out that it may be necessary when examining tissue to use electron microscopy as fibers get smaller and there is then no indication of length or true diameters. Alignment in a magnetic field greatly reduces the number of times a fiber will cross a field or grid boundary and greatly reduce counting errors. Dr. Jones felt that light microscopy missed most small fibers of chrysotile and most amosite fibers less than 3 microns in diameter.

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(The following is a summary of the session on clinical and radiological observations on asbestos-related pathology which I prepared in the course of my duty as rapporteur at the meeting in Lyon, September 25-27.)

Eleven papers were selected for discussion in this session and reviewed by the principal speaker (Dr. Bohlig).

In opening the discussion the Chairperson pointed out that these papers were mainly of an epidemiological, rather than a purely clinical or radiological, nature.

Discussion took place on Radiology as a diagnostic tool, its precise use in the diagnosis of pleural abnormalities, its value in the recognition of the progression of observed changes and the value of non-radiological indicators.

The effect of different fiber types and their influence on clinical and radiological response was briefly mentioned.

The diagnostic criteria applied are dependent, to some extent, on the purpose for which the diagnosis is being made. If the main purpose is individual patient care, rather than epidemiological studies of groups of workers, then the manner in which films are interpreted assumes a different level of importance. A paper which illustrated the problems involved in measuring radiological change in a large group of workers, and the difficulties encountered in the analysis of X-ray reading results originated from the national survey of asbestos workers in the United Kingdom and drew attention to the negative aspects rather than the positive strength of the chest radiograph as an epidemiologic tool. In this study, problems encountered related to inter- and intra-observer variabilities in X-ray reading, geographic dispersion of readers and the timeframe of the study. These factors are thought to have accounted for the negative radiological progression observed, and this has led to the need for revision of the study methodology.

In contrast to the disappointing results thus far obtained in the evaluation of the X-ray readings in the U. K. study, it was pointed out that in another study in Canada, given all the weaknesses inherent in reading films, the presence of abnormal findings was a reasonable predictor of mortality. Even changes of 0/1 profusion of irregular small opacities carry the risk of increased mortality. It was pointed out that this only applied to studies of large numbers of X-rays and required the use of three trained readers. It was not directly applicable in the daily physician practice as a prognostic tool.

In the mines and mills where non-fibrous mineral dust is present, X-ray changes may include a significant number of evenly-distributed, small, rounded opacities which apparently have no sinister significance.

Discussion then ensued with regard to the value of clinical, radiological and physiological techniques as tools for the medical surveillance of asbestos-exposed populations. Issues relating to the prognostic value of the medical surveillance tools were discussed. Some felt that individuals exhibiting radiological change could continue employment under modern conditions in industry with much lower levels of exposure than those which existed in the past, even though the prognosis was already poor and the cancer risk increased. The reason given was that the cancer risk probably related to the higher levels experienced under poor conditions in the past, and that small increments would not have a further effect. This point of view was vigorously challenged on the grounds that, because mortality and morbidity are both dose-related, small increments of dose were bound to increase the

risk, taking into account any additional lag period. Additional dose should therefore be equated with additional risk.

Because it is not known whether there is a link between malignant mesothelioma of the pleura and radiological pleural abnormalities and whether such abnormalities are of prognostic significance, more precise tools are needed for the radiological definition of pleural changes. A valuable technique appears to be the use of computer-tomography in the differential diagnosis of asbestos-induced pleural thickening. The value of diaphragmatic straightness as an indicator of unsuspected diaphragmatic pleural thickening or pleural plaques was discussed. It was pointed out that straightness of the diaphragm may be seen not only in cases of pulmonary fibrosis, but also, for example, in persons with obstructive airways disease, and that in theory it also could be due to the "stiffness" in the lung rather than "stiffness" in the pleura. For these reasons, and on the basis of the evidence presented, there was reluctance to accept this as a reliable sign in the diagnosis of asbestos-related pleural disease without further study in asbestos exposed populations.

There was readiness to accept the conclusion implicit in prospective data reported that whereas parenchymal changes on X-ray were related to dust concentration, pleural changes were related to length of exposure irrespective of dose. Thus pleural abnormalities continue to progress with age, irrespective of further exposure, while parenchymal abnormalities progress as a function of increments to lifetime exposure. It was suggested that pleural changes probably represent an important radiological sign in the constellation of changes observed in low-grade exposure groups when parenchymal changes were less likely to be observed. To illustrate this point, findings in amosite plant workers, household contacts of asbestos workers and chemical plant maintenance workers, all of whom exhibited pleural changes, were presented and discussed. It was, however, felt that these results should be interpreted with caution in view of the lack of quantitative environmental exposure data and the reliance on assumptions of exposure derived from job descriptions or interview information. However, it was recognized that in groups indirectly exposed, for example, shipyard populations surveyed in various countries, pleural abnormalities are a consistent finding.

An earlier study by Edge suggesting that pleural plaques observed in shipyard workers were associated with an increased incidence of cancer was discussed and it was concluded that the findings had resulted from a study based upon a biased population sample (patients attending a chest clinic for treatment) for whom a retrospective study of the X-ray appearances was carried out.

Pathologists also hold the view that where asbestos exposure is low pleural plaques are fairly commonly seen. Furthermore, as radiological techniques for their detection improve, it is likely that pleural plaques will be seen with greater frequency and approach the number which pathologists have been accustomed to see for some time. To the pathologist, the main value of pleural plaques is that their demonstration calls for careful examination of the lung. Parenchymal disease of any degree is also rarely found in these cases as opposed to its common occurrence in association with malignant disease.

Discussion also brought out the important point that plaques and diffuse pleural thickening were of different epidemiological significance, yet the present ILO U/C classification of radiographs for pneumoconiosis does not enable differentiation between them. This should change when the new 1979 ILO U/C classification comes into general use.

Non-radiological indicators consistent with what are believed to be the early (and possibly reversible) pathologic changes were discussed and their value as adjuvants to radiology in the diagnosis of asbestosis was debated. The justification put forward for paying closer attention to such findings as asbestos bodies and siderocytes in the sputum, basal rales, restrictive ventilatory insufficiency and impairment of alveolar-capillary diffusion was that the process may be detected before it is radiologically evident, at which point it is believed to be progressive and irreversible. It was emphasized that sole reliance could not be placed on any one indicator alone and only a combination of findings might perhaps permit earlier diagnosis of asbestos-related pulmonary disease.

Discussion on the significance of asbestos bodies confirmed the accepted viewpoint that they should be regarded as an index of exposure and not of disease. In the presence of other non-radiological indicators, however, they may well constitute confirmatory evidence for the diagnosis of asbestosis. Emphasis was also given to another well accepted fact, namely that not all "asbestos bodies"contain asbestos fiber cores and in certain circumstances it may be necessary to confirm the presence of asbestos in the core in view of the increasing use of other fibers in industry. The view was also expressed that asbestos bodies are largely an indication of exposure to amphibole fibers and it appears that chrysotile fibers produce few bodies.

Certain areas invite further research. Thus further information is required on the prognostic significance of pleural disease and more precise radiological definition is needed. It was emphasized that studies of large populations relying upon radiological interpretation should be carefully controlled by means of standardized techniques, and training of readers in a clearly defined time frame, to minimize the effects of inter- and intra- observer variability. Studies are also required to determine more precisely the effects of removal of affected workers from further exposure, and to determine the prognostic significance of radiological changes in those persons who continue to be exposed to low levels in modern industry.

Clinical and radiological observations have two main objectives, namely (1) use in research leading to improved medical surveillance and prevention of disease, and (2) use in making medico-legal decisions in matters of compensation of disabled workers. The question of compensation for asbestos-related disease was briefly discussed. Even if there were precise international guidelines, it is likely that some deserving cases will not be accepted for compensation while others without disablement or significant disease may benefit. An opinion was expressed that illness should be compensated for the "risque social" and not merely the "risque professionnel".

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The epidemiology of asbestos related diseases was reviewed by Dr. J. C. McDonald. Among the priorities which needed attention was the study of industry differences, an item which did not appear in the 1972 Conference report to the director of the IARC.

According to McDonald, the main issues are:

(1) Are differences in asbestos exposure in different sectors of the industry an important factor?
(2) Are all fiber types equally responsible for disease?
(3) What are the other factors working with or against asbestos?
(4) The need to clarify exposure-response relationships.

Lung cancer is probably caused by all asbestos fiber types. The risk is not only confined to smokers. The relative risk in non-smokers is as high as in smokers. The relevance of fiber types is less clear and the problem is to compare like with like, e.g., in a given situation with another type. Only major differences in risk are meaningful. In his work attention has been focused on miners and millers where he believes a clear dose-response relationship exists. Little data on amosite and crocidolite experience would be available from this meeting but reports from South Africa and Australia were welcomed. The South African study, however, was a cross-sectional one and not longitudinal. The Australian study was quite different in scope and design from the study of Quebec miners.

Quebec miners and millers were exposed to chrysotile, the Western Australians had been exposed to crocidolite. The Quebec miners and millers had more than 20 years since exposure and had been employed for more than one year, the Australians had been employed for fifteen years or more. This meant that there was more than 15 to 20 years of follow-up. The Standardized Mortality Ratios for Quebec miners was 1.28 and for the Australians it was 2.47.

Pure crocidolite does carry a risk of lung cancer as evidenced by the Nottingham and Canadian "gas-mask cohorts". Workers exposed for short periods had twice the expected lung cancer rates. Under conditions of mixed exposure, workers exposed to amphiboles appear to have a higher risk than those exposed to chrysotile only.

Criticizing the Rochdale study, McDonald said that these textile workers' overall SMR was twice the number expected, the risk appears to have been substantially higher than in mining, there were considerable uncertainties about the fiber levels and data on smoking were not available. The role of smoking in asbestos related disease has been demonstrated by Sarraci and by Selikoff. The combined effect of smoking and asbestos exposure is closer to the additive than the multiplicative model in the Quebec chrysotile miners. Although the relative risk for non-smokers is as great as for smokers, from the public health point of view, the absolute risk of smoking was the most important.

The geographical distribution of malignant mesothelioma indicated it to be concentrated around dockyards and asbestos plant towns. Most data suggest that there is a stronger risk with crocidolite than chrysotile. The role of amosite is still uncertain. Amosite factory workers in New Jersey have a high risk, but it is not as great as that in insulation workers and no mining risk data of value is available. American insulation workers were probably exposed to amosite rather than crocidolite.

For the study of the cohort of Western Australian crocidolite miners 3.3% of the deaths thus far have been due to mesothelioma with a peculiar absence of peritoneal and a deficiency of all abdominal tumors. In the cross-sectional study of black South African crocidolite mine workers, 2% of 236 men had developed mesothelioma 20 years after first exposure.

Prevalence of mesothelioma

African crocidolite mine-workers (1974)	2%	236 men
Canadian gas-mask workers (1965-77)	1-2%	approx.
Quebec chrysotile miners & millers (1965-77)	0.5%	approx.

20 years from first employment

In the Jones study of the British gas-mask workers, of 166 deaths, 17 (10%) were due to mesothlioma and in the 56 Canadian gas-mask workers, 9 (15%) deaths were due to mesothelioma.

In their naval dockyard study, Rossiter and Coles had analyzed more than 1,000 deaths and found no excess mortality. 13 deaths resulted from asbestos-related disease other than mesothelioma and 28 deaths were from mesothelioma. It would appear that a low level exposure associated with a high mesothelioma rate is indicative of crocidolite as the major etiologic fiber.

Dr. McDonald discussed differences found in fiber content of lungs in cases and controls and the fact that higher counts of amphiboles are found in cases than in controls, whereas this is not the case for chrysotile. If chrysotile disappears from the lungs, it disappears equally from cases and controls. Further studies are needed to determine more precisely what is in the lungs of cases and controls.

No papers on gastro-intestinal malignancies were contributed to the symposium. Insulation workers seem to show an excess of those tumors whereas others do not. Is there another factor present and if so, what is it?

Laryngeal cancer shows a small excess in Selikoff's studies and in Newhouse and Berry's study, whereas in Quebec there is no excess and a definite smoking relationship is found. Newhouse in her study of hospital admissions found only 15 neoplastic conditions among 206 women and only 2 had asbestos exposure. Among the males, the neoplastic group was significantly older than the other groups and cigarette smoking was significantly more common. Alcohol consumption, considered independently of cigarette smoking, did not appear to be related nor was past asbestos exposure found to be associated with neoplastic conditions of the larynx in this group of patients.

During the discussion, Dr. Jones of Nottingham in the U. K. gave details of his study of gas mask workers. Workers manufacturing gas masks for civilian use were exposed to chrysotile only whereas those making military gas masks were exposed to crocidolite. In the Nottingham factory, civilian masks were only manufactured for five months and the rest of the war military masks were made. There have been no mesothelioma cases in workers who only made civilian gas masks whereas 33 cases have occurred in all those employed for the rest of the war. Another factory in the North of England where only civilian masks were made is now being studied. The majority of cases of mesothelioma have been found in people with more than 1,000 fibers per milligram of lung. The fiber has been identified as crocidolite. There are no chrysotile fiber counts in excess of 1,000 fibers/mg in mesothelioma cases. The crocidolite used came from the Western Australian mines.

Dr. Alison McDonald described the results of a survey of malignant mesothelial tumors in North America when 274 fatal cases in 1972 were ascertained. Controls were selected for each case from hospital patients with metastatic pulmonary cancers from a primary tumor outside the lung. Specimens of lung tissue were obtained from 172 autopsy cases and their matched controls. Pieces of lung tissue were obtained from 100 case-control pairs. Thus far, 37 case-control tissue specimens (pairs) have been analyzed by Dr. F. D. Pooley. Chrysotile fibers were far more prevalent than any of the amphiboles. There was a clear excess of amosite fibers in male cases compared with controls. For crocidolite and tremolite there was a marginal excess in cases, but the numbers are too small to interpret; for anthophyllite there was no difference. Amosite levels were high in insulation workers and shipyard workers, and lower levels werre found in factory workers, heating trades employees and plumbers. Crocidolite was hardly ever found. Dr. McDonald's data supports the view that crocidolite has not been widely used in the U.S.A., although it has been widely recognized as an important cause of mesothelioma in Europe and other countries outside the U.S.A. The epidemiological evidence which suggests that the risk of mesothelioma after chrysotile exposure is low is also borne out by this study.

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Introducing the session on the scientific basis for environmental control of fibers, the Chairman, Dr. Westerholm, pointed out that science provides the material upon which preventive action is based. Scientific material is used by politicians, regulators and administrators. Drs. Acheson and Gardner jointly reviewed the subject matter for this session and outlined the present situation with regard to health standards in various countries. (See the attached tabulation which was prepared by the Asbestos International Association in May, 1978 for the Task Force on Occupational Respiratory Disease established by the Canadian Thoracic Society and the Health Standards Division, Department of National Health and Welfare.)

In discussing dose-response relationships, it was pointed out that a true determination of dose meant knowledge of the amount of fiber reaching the target organ and the period of time required to produce an effect. In man, to date, the only data comes from the measurement of workplace concentrations. Other factors to be taken into account in estimating dose include reproducibility of response in groups of people or in animals, appropriateness of the measurements, comparability of data, determination as to what measures of cumulative dosage are appropriate and the convertibility of measurements made by differing methods.

The problem of the long latent period from first exposure to detection of an effect means that data regarding illness which is diagnosed at the present time relates to past exposures many years ago. It is therefore important to insure that dust measurement techniques are standardized throughout the time period involved. The effect of improvements and refinements in measuring techniques in relation to the lapsed interval and cumulative dose must be considered when using industrial hygiene data for the purposes of framing standards. It was generally believed that the conversion from mppcf to f/ml could not be satisfactorily achieved.

Estimation of cumulative exposure is too rigid and medical data may be insufficient because measurement of sickness and mortality may be subject to observer and other error.

It is fundamental when relating illness to exposure (dose) to state precisely how disease is defined and what data have been used to reach a diagnosis. Completeness of data and adequate follow-up are essential before drawing final conclusions. An example of a confused situation is that which arises when cancer of the pancreas is diagnosed in error for peritoneal mesothelioma.

The essential answer to be derived from studies of dose-response relationships is whether a safe threshold level exists below which no disease can occur. With regard to lung cancer, this cannot as yet be finally resolved as there are few data relating to exposure at low levels.

Taking the broadest view of the problem, there would appear to be no evidence of safe thresholds with the present range of industrial experience and the conclusion, therefore, based upon such evidence as there is, is that there is a linearity of the dose-response curve and no known safe threshold for all the asbestos associated diseases.

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TABLE 3

ASBESTOS STANDARDS*

	Regulations	Standard Concentration	Prohibitions or Exceptions
AUSTRALIA	Regulations determined by each State are based on model asbestos regulations prepared and recommended by the National Health and Medical Research Council of Australia which generally follow the U.K. and U.S. practice.	4 f/ml - all types	Use of crocidolite is restricted in many States. Special approval for its use is required. In other States its use is banned. Spray in most States now requires special permission.
AUSTRIA		3 f/ml - all types	None.
BELGIUM	In draft	2 f/ml - all types	Spray.
CANADA	Special regulations for mining	Different standards in each Province varying from 2 f/ml to 5 f/ml.	
DENMARK	1972 under consideration	2 f/ml - all types 1 f/ml	Spray, thermal noise or moisture insulation. Additional limitations include use of crocidolite, subject to exception.
EAST GERMANY		100 ppcc	
FINLAND	July 1977	2 f/ml - all types	Spray use of crocidolite (subject to exemption of Labour Protection Board).
FRANCE	August 1977	2 f/ml - all types	Spray.
HOLLAND	April 1977	2 f/ml - chrysotile, amosite, crocidolite no standard set	Spray, thermal insulation, acoustic, decorative or preserving. All forms of use of crocidolite. All subject to exception for economic or technical feasibility.
IRELAND	1972 1975	2 f/ml - chrysotile, amosite 0.2 f/ml - crocidolite. Amendment to provide for application to all situations in addition to manufacture.	No prohibition. Special requirements are specified when crocidolite is involved, i.e., marking of containers, notification of Inspectors.
ITALY	None	Instituto Medicine di Lavoro have recommended 2 f/ml for chrysolite, amosite, crocidolite, "non detectable dust" is advised.	Some trade unions have agreements with employers to follow U.S. standards.
NORWAY	1973 Amended April 1977	5 f/ml - all types 2 f/ml - all except crocidolite	Spray; electrical, acoustic, condensation insulation, crocidolite (subject to exception).
SOUTH AFRICA	Similar to Australia, but for mining operations regulations are in draft form which aim to the establishment of 2 f/ml standard by stages.		
SWEDEN	1975 (1/7/76)	2 f/ml - all except crocidolite 1 f/ml - " " "	Crocidolite (1975) use of A/C products except for pipes (1976), flooring and wall covering, glue, filler and joint filler (1977).
SWITZERLAND		1 mg/m^3 - all types	None.
UNITED KINGDOM	1969	2 f/ml - chrysolite, amosite 0.2 f/ml - crocidolite (Advisory Committee on Asbestos is currently considering whether there is need for additional regulations, including the adoption of a tighter standard for asbestos dust concentrations).	No prohibition. Special requirements are specified when crocidolite is involved, i.e., marking of containers, notification to Inspectors.
USSR	The standard expressed in mg/m^3 varies with the percentage of asbestos present in dust. 1 mg/m^3 >30% asbestos 2 mg/m^3 10 - 30% asbestos 6 -1 mg/m^3 <10% asbestos		
U.S.A.	O.S.H.A. 1972 5 f/ml - all types July 1976 2 f/ml - all types (O.S.H.A. is currently conducting hearings, including technical and feasibility studies on possibility of 0.5 f/ml standard. Conclusions not expected before late 1978.)		Spray is prohibited in certain States. A distinction is made in respect to "bound in" asbestos products to which the O.S.H.A. regulations are modified.
WEST GERMANY	June 1976	2 f/ml - chrysotile, amosite no standard set for crocidolite (fine dust - 0.1 mg/m^3 - all types.	None.

*Compiled for the Task Force by the Asbestos International Association, May 1978.

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The general discussion on asbestos was introduced by Dr. Hans Weill. Dr. Weill proposed that there were three main subjects to discuss, namely research issues, controversial issues and agreed issues. In the light of these issues, he reviewed the following topics:

(a) Physical dimensions of fibers in disease,
(b) Cell type and pathology,
(c) In vitro experimental pathology,
(d) Clinical epidemiological studies.

(a) Physical dimensions of fibers in disease.

Additional attention needs to be focused on the surface properties of asbestos fibers. Problems exist in the identification and quantification of the mineral fiber burden of tissue and reasons have to be found for the variation in counts between different laboratories. The effect of high temperature on fibers, for example, as in brake-linings, and the disordering of the crystalline structure which occurs, needs to be studied.

Short fibers may be preferentially removed from the lungs, but there is not always general agreement on this. Is the curliness of chrysotile important in determining its deposition in the lung? Does chrysotile break down in tissue and disappear from the body? There is as yet no general agreement on this either. The carcinogenic potential of fibers is related to their length, but it is not yet clear how diameter influences this potential.

In the asbestos cement industry, there is a need to explore the proposition that fibers coated with cement, calcium coated particles and fibers otherwise locked in are different biologically.

(b) Cell type and pathology.

There is no clear cut evidence that the cell-type of lung cancers can determine whether a tumor is asbestos-associated or not.

The fibrogenic dose may be different from the carcinogenic dose and very little is known about these effects. Are there data from exposed populations which will help resolve this? The carcinogenic risk in smokers has been confirmed and the rleative risk is now considered to be equal in smokers and non-smokers.

Pathologists continue to have diagnostic difficulties in the recognition and diagnosis of mesothelioma and Dr. Weill wonders whether the mesothelioma panels have really helped in this regard. He believes that there is a need to standardize their diagnostic methods and approach. Whitwell's important paper on dose-response relationships should receive the attention it deserves.

Benzo-a-pyrenes enhance carcinogenesis in experimental animals, but smoking in humans does not influence the mesothelioma incidence. We still know very little about host factors and obviously need to know a lot more. The work of Dr. Margaret Wagner is interesting and should be continued.

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(c) In vitro studies.

Which of the in vitro studies help to understand carcinogenesis and what is the role of these studies? More work needs to be done in this area.

It is important to determine whether leaching of magnesium from chrysotile affects carcinogenesis as has been suggested. Is chrysotile more readily cleared from the lungs?

Differences need to be explained between animal pathology and human epidemiological studies and this will need research at the cellular level.

The work of Pooley and Sebastian in counting fibers in tissue needs to be closely examined and the question answered as to why there is less chrysotile found in lungs than one would expect from the amount of exposure. It is imporant to know how often chrysotile fibers cannot be seen in the lungs by optical microscopy when it can be found using electron microscopy. This is an imporant issue to resolve if work in some centers is to continue on the basis of one or another method.

(d) Clinical and Epidemiological Studies.

Dr. Bohlig had pointed out that chest X-rays optimize sensitivity and specificity for recognizing asbestosis early in medical surveillance. Standardization of techniques, reader training, etc., enables use of this tool for assessing dose-response relationships. The standardized technique is useful for independent reading of films of various population groups from different centers and could help resolve difficulties of interpretation of dust effects. The order of specificity of non-radiological techniques in relation to radiology needs to be determined more precisely.

In determining the biological response to asbestos, Dr. Weill questioned whether we should be talking about response in terms of a diagnostic constellation, or whether we should use X-rays, lung function tests, etc., age, sex, race, smoking habits, etc. The purpose for which surveillance is undertaken affects the outcome.

The prognostic implications of pleural abnormalities have not been resolved and long-term studies of exposed populations are needed.

There is strong and ever strengthening evidence concerning differences in pathogenic potential of different fiber varieties and Weill questions the need for additional information on this. More information is needed on the reason for the difference in gastro-intestinal risk in various populations studied and the search for a cofactor should continue.

The chrysotile exposed gas-mask makers described by Jones needs to be adequately followed.

Whether the pathogenicity of crocidolite relates to an enhanced dustiness of this material or not does not change the caution about this fiber variety.

More data is needed about the size, shape and other characteristics of fibers which reach the pleura and better information is needed on fiber distribution within the lungs and pleura.

There seems to be general agreement about the linearity of the dose-response curve and the absence of a known threshold, but Weill wonders whether this is genuine agreement! There do appear to be differences in dose-response curves in different industries, but a lot of necessary confirmatory data is lacking. It is incorrect and incomplete to base a standard on the results of a study of one particular plant in the United Kingdom and it may be wrong to do so on the basis of the Quebec miners as well. If Peto's postulate that dose doesn't matter is accepted then the implications are profound. Are we using appropriate measurements for airborne dust? Fiber counts are only useful if they allow us to control disease, and if mass estimation gives more information upon which to base dose-response relationships, then it should be used. There is a need to continually review the way we measure exposure. He concluded by remarking that the cancer risk was becoming detectable at about the same exposure point as radiological and physiological effects become noticeable and this suggests that cancer risk and the other effects may be occurring at about the same dose and perhaps the risk of fibrosis may even be occurring at a lower dose.

In the discussion which followed, Timbrell stated that methods will shortly be available to enable us to measure the length and diameter of fibers in dust clouds instantly. We now need to develop lung retention curves so that it will be possible to compare the distribution of fibers in lungs with the conditions in industry which led to their inhalation many years ago. The amphiboles are ideal for development of lung retention curves and this statement is also applicable to the newer fibers being used. This will allow manufacturers to predict risk and allow modification of their products.

Langer pointed out that chrysotile fiber in brake linings does survive braking and degraded or partially degraded fiber may also be found. The degradation of chrysotile in its use or through action on it of body metabolism must be taken into account in carcinogenesis. Fiber seen in tissue is a relic of the past and amphibole survives whereas chrysotile does not. This might mean that only a small amount of chrysotile is needed for tumor production.

Dr. Gluckman amplified Weill's comments on the value of mesothelioma panels by emphasizing that panels must meet regularly, use microscopes and discuss problems. In his opinion, postal panels do not work adequately. He does not believe that mesothelioma will be underdiagnosed. Electron microscopy is useful where the presence of ferruguious bodies is the only index to exposure, where degradation of chrysotile fibers has occurred and may have a significant adjuvant effect in the diagnoses of mesothelioma.

Dr. Victor Alexander of the U. S. OSHA expressed the opinion that tumor cell-type distribution can serve as a finger-print indentification pattern in occupational lung cancer and felt that relevant conditions included bis-chloromethyl ether, asbestos and smoking, and that his was a subject with relevance to medico-legal questions and regulatory standard setting. Dr. Alexander did not offer any evidence in support of his proposals.

Returning to the question of mesothelioma diagnosis by pathologists and panels, Hunter stated that the European mesothelioma panel started work four years ago and there has been a steady development of pathological agreement on diagnosis whereas death certificates record more cases than are ultimately agreed on by the panel. There is a small number of cases where there is disagreement and these are the ones which are useful to discuss in a panel. Much clearer diagnostic criteria should become available as a result of this process.

Dr. Seal said that pathologists cannot accept that there is a linear dose-response curve without a threshold. Pathologists see many lungs in a community with a slight degree of pulmonary fibrosis and therefore need to shift the emphasis to definitely acceptable fibrosis. If they do this, then he believes there is a threshold.

The discussion then veered away from pathology to clinical diagnosis, epidemiology and dose-response relationships. George Wright discussed the objective assessment of rales by recording techniques and stated that this was an active field of on-going research. Elmes agreed that recording rales was another method of getting an early indication of changes in the lung, but warned that it would not help in diagnosing asbestosis and that we do not know what the findings mean in terms of prognostic significance.

The frequency with which chest X-rays should be taken was discussed. It was agreed that annual radiology was not helpful and probably should be discouraged. Other tests should be substituted which increase the sensitivity of the system and the worker should probably only be seen and X-rayed every 5 years. This enables the physician to give a reasonable opinion. Elmes was of the opinion that unless something very unusual was seen in the X-ray, the persons should not be advised to change jobs or give up work. This advice should only be given where rapid progression was noted as this correlated with bad dust control in the plant. Annual X-rays are not a valuable early diagnostic tool for intra-thoracic malignancy. Bob Jones of Tulane disagreed with Elmes and felt that a person should not be allowed to continue exposure if there were low-grade, radiological changes as it is hard to justify any increment in dust exposure because of progression which occurs with cumulative exposure. Liddell pointed out that in Quebec where most of the population studied consisted of heavily exposed millers rather than lesser exposed miners, in a study of deaths up to 1977 in just under 1,000 men who had X-rays available in 1966, the best predictor of death was the X-ray and not symptoms or lung function tests.

With regard to the linear dose-response curve with no known threshold, Dr. Becklake felt that no other theory was acceptable from the point of view of human health. This, however, was a scientific point of view and in practical everyday terms there are thresholds. We extrapolate from high exposure levels to obtain low-level effect estimates. Evidence will come from testing the hypothesis implicit in standard setting that there is a no-effect level. This will mean prospective longitudinal studies. The non-radiological indicators need to be studied more to determine their value in early detection of effects. There is no reason to do the tests unless they affect the outcome of surveillance and provide valuable data. A statement regarding areas for planned research is needed and she hopes it will include prospective planned research into the effects of low-level exposure and their prevention.

Robock felt that until dust measurement techniques are standardized and the effects of fiber shape are defined, we cannot begin to draw linear dose-response curves. Dr. Smither pointed out that it is in the area of low-level exposure that people are now working. Individual susceptibility needs to be investigated and in order to prevent disease in low-levels of exposure we must learn to recognize the hypersusceptible individuals, prevent them from being exposed or remove them from exposure. Peto suggested that the best available data had to be used for standard-setting, and speculated as to whether we should choose standards to regulate by industry, e.g., a standard for miners or a standard for factories. Gibbs pointed out the difficulties in retrospective use of epidemiological materials. Only four groups have been able to construct dose-response curves. Do standards protect health? Are we surveying populations adequately? We need to use epidemiology to answer these questions and have to set up a standard method of recording environmental factors as well as standardization of response variables.

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The following is an abstract from Dr. Smither's report on the symposium which adequately summarizes the sessions on mineral fibers other than asbestos.

"Studies on Other Mineral Fibres.

On the late morning session of the third day the meeting turned its attention to other mineral fibres. Bolinder pointed out that so far no adverse effects had been reliably demonstrated in man. Sarracci reported no significant excess in standard mortality from 5 fiberglass manufacturing plants in the U. S. A. Enterline confirmed this, and added that many of these plants had used asbestos in the past.

Leineweber emphasized that only the morphological characteristics of what he preferred to call "vitreous" fibres were of importance in comparing them with asbestos, since their chemical characteristics were so variable that at most only a secondary effect could be attributed to their chemistry.

In general, environmental measurements showed that airborne concentrations of MMMF were much lower than asbestos fibre concentrations. In the manufacturing industry counts were always lower than 1 f/ml and usually very much lower. Enterline confirmed this assessment in reporting that he had found levels of only 0.3 f/ml. Hodgson also reported fibre counts well below 2 f/ml and low mass concentrations, under 10 mgm/cu.m.

While Haider was able to demonstrate an increased mortality for what he described as "dust workers" there were very many different types of dust involved in his study, and they were not adequately defined.

The outstanding paper on fibres other than asbestos was that presented by Baris on the incidence of pleural mesothelioma in two villages in Turkey, due to zeolite. Although this study has been well reported elsewhere, the Symposium had no hesitation in congratulating him on a brilliant piece of epidemiological detective work.

Conclusion

There was little new reported at the Symposium, but that was probably not the object of the exercise. The AIRC at Lyon is sufficiently prestigious to have its report of the Symposium taken very seriously, with an undoubted effect on future research and possible legislation."

(from Symposium on the Biological Effects of Mineral Fibres. Lyon, 25-27 September, 1979 Report by W. J. Smither, 8 October, 1979

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