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ASBESTOS - A SUMMING UP

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Notwithstanding the hazards of 'instant analysis', I shall attempt to highlight the issues raised in the past two days concerning the state of our knowledge on asbestos-related health effects. I will make particular reference to those matters which appear to require additional research in order to resolve scientific questions, the issues on which there appears to be some controversy among the participants of this symposium, and new knowledge which has recently been obtained.

During the first session on dust physics and chemistry of asbestos, it was apparent that there continues to be considerable interest in the role of physical dimensions in the pathogenesis of asbestos-related disease. Considerations included diameter, length, aspect and mass relationships. It was clear that further work was needed on the influence of fibre surface properties, and the possibility was again raised that surface properties of airborne asbestos fibres may be altered in the asbestos-cement industry.

There was unanimity of opinion that considerable progress has been made in the identification and quantitation of asbestos fibres in tissue - work which is in large part being performed in the laboratories of symposium participants, Doctors Pooley and Sebastien. Some concern, however, was expressed about variation in tissue mineral fibre counts between laboratories. Reassurance in this regard was provided by the investigators, who indicated that differences were not striking between the laboratories in Paris and Cardiff.

Questions remained concerning the effect of high temperatures on the physical integrity of asbestos fibres, a prominent example being the fate of asbestos in brake-linings during use. Is there consequent

altered crystalline structure with the production of unstable fibres?
No definitive answer seemed yet to be available.

The characteristics and fate of asbestos fibre in lung tissue continue to receive attention and may very well be dependent on fibre type. Apparently, in some laboratories, fibres shorter than 5 μ m in length represent a small proportion of total fibres in the lungs. Dr Gibbs raised the possibility that such short fibres are removed preferentially. It was further suggested that, while chrysotile seems to break down in tissue, curliness may not be important in peripheral lung deposition. Further support for this notion came from the observation that, in fact, only a small proportion of chrysotile fibres are 'curly'. In general, there seemed to be agreement among conference participants that carcinogenic potential of asbestos is closely related to fibre length.

Asbestos exposure in the asbestos-cement industry was considered by some at the conference to differ from other types of asbestos exposure, due perhaps in part to altered surface properties, or possibly because asbestos fibres may be coated with small calcium-containing particles. It was suggested that results of studies of 'pure' asbestos exposure should not automatically be applied to exposures in asbestos-cement manufacture.

In concluding the session on dust physics and chemistry of asbestos, participants were reminded of the technical problems in producing uniform-sized fibres for experimental use. This problem should be kept in mind when evaluating animal studies purporting to show the effects of uniformly small or large fibre exposures.

In the session on pathology and experimental pathology related to asbestos and other mineral fibres, a number of issues were raised by Dr Kannerstein. A possible excess of adenocarcinoma in asbestos-exposed workers has been suggested by a few investigators, but in general it is unlikely that there is cell-type specificity in asbestos-related cancers. While the observation that a certain type of cancer is present in unusual proportions may lead to detection of a previously unrecognized carcinogen, it seems that further investigation of lung cancer cell types associated with asbestos exposure is not likely to be rewarding.

There appeared to be little new information on the relationship of fibrogenesis and carcinogenesis with asbestos exposure; animal investigations seem not to have been helpful in resolving this important question. Some participants continue to ask whether an excess carcinogenic risk (lung cancer) is associated with asbestos exposure in the absence of pulmonary fibrosis (asbestosis). It was agreed that we will probably never be able to make this determination in individual cases; but preliminary epidemiological data suggest that the carcinogenic and fibrogenic doses in some aspects of the industry may be similar or

indeed that the fibrogenic dose may even be lower. On the relationships between asbestos exposure and smoking in determining the relative lung cancer risk, it should be pointed out that nonsmokers have been shown to be at greater risk than nonsmoking workers who have not been exposed to asbestos. Data from New York and Quebec suggest that asbestos exposure alone (without cigarette smoking) carries such an increased risk, although the number of excess cases is far smaller than for smoking asbestos workers.

I sensed disappointment (which I share) in the expression by some conference participants of continuing difficulty in diagnosing mesothelioma, in spite of the use of electron microscopic and histochemical techniques. There did not seem to be general agreement that all mesothelioma panels have uniformly helped to increase the precision with which the diagnosis of mesothelioma can be established. Some panels appeared to be more successful than others. It was suggested that perhaps pathologists should borrow some principles and approaches from the developers of the ILO U/C Radiographic Classification, with greater emphasis on standardization, quantitation of inter- and intra-observer variability and similar considerations. Discussants generally felt that data on dose-response relationships for mesothelioma were still inadequate; but the important contribution of Dr Whitwell was noted as a convincing demonstration of dose-relatedness for this tumour.

Other points in regard to experimental pathology included the suggestion attributed to Dr Pott that the carcinogenic properties of asbestos are enhanced by benzo[*a*]pyrene and *N*-nitrosamines but not by exposure to cigarette smoke. This finding appeared to the participants to be perplexing and required additional research. Also, while fibre length was generally recognized as an important determinant in carcinogenicity, there was little certainty concerning the possible influence of fibre diameter, this question also having relevance to man-made mineral fibre exposure. While the relationship between asbestosis and carcinoma of the lung generally receives more attention, the possibility was raised that the risk for developing mesothelioma may actually be reduced in the presence of asbestosis. Evidence on this point is obviously incomplete.

Unfortunately, little new data on the influence of host factors in asbestos-related disease emerged in the discussions. Questions raised included the possibility of lymphocyte/macrophage interaction and the observation that E rosettes correlated with small opacities in smokers. It was apparent that considerably more information concerning host characteristics and asbestos-related disease was greatly needed.

It has been hoped that *in vitro* methods may help to elucidate mechanisms in asbestos-related disease. Techniques include immunological, chemical and surface-active analyses. Does leaching of magnesium from chrysotile fibres influence their tumorigenic potential? Is chrysotile

more effectively cleared from the lungs than other fibre types? If the answer to the latter is 'yes', as suggested by Dr Pooley, this would reduce the 'survivor' fibre population in tissue and have important implications in relative fibre-type pathogenicity.

Dr Wagner suggested that a haemolysis system and measurement of macrophage toxicity may be of limited use in the study of asbestos-related carcinogenesis. Mammalian cell-line systems may be better; but this suggestion requires more work and confirmation.

When the discussion returned to analysis of tissue mineral fibre, the question was raised whether 'all' of the fibres in the lungs are recovered by extraction techniques. Both Drs Pooley and Sebastien responded affirmatively, indicating that the extraction methods can be checked by relating the known amount of added fibre and the results of the quantitative analyses. Dr Davies asked why there was less chrysotile in the lungs than one would expect from knowledge of exposure. One or more answers may include reduced lung deposition, alteration of fibre in the tissue, and an effect on chrysotile fibre of the extraction techniques. A discussant raised the question of how often we may miss chrysotile asbestos by optical microscopy with subsequent identification of this fibre type by electron microscopy. The Cardiff group suggest that this is very rarely the case. The question was nonetheless raised of whether electron microscopy should even be used for medicolegal purposes. Two general issues which were raised concerning mesothelioma include first, a valid diagnosis and second, proof of an asbestos relationship for medicolegal purposes. This discussant suggested that it might be desirable to employ strict criteria in the first instance and lenient ones in the second.

The conference then directed attention to clinical and radiological observations on asbestos-related pathology. Dr Bohlig supported the position that the chest X-ray film probably combines optimum sensitivity and specificity in worker surveillance for asbestosis. He emphasized that the ILO Classification and X-ray technique standardization still require attention in order to make this important method of measuring biological response optimally effective. It was pointed out that the 1979 revision of the ILO Classification represented an important improvement in this regard. The question was again raised, without apparent answers: can (or should) the classification be used for worker monitoring and compensation? Are we at this time agreed that crackles (rales) and other non-radiographic, non-invasive techniques have a very low order of specificity in determining the presence of asbestosis? It would appear so. Can there still be any doubt that the presence of asbestos (ferruginous) bodies indicates only fibre exposure and not disease? The discussion reflected some remnant of confusion concerning this point. Questions regarding ascertainment of asbestosis in an exposed individual lead ultimately to the need for determining when a worker should be removed from further asbestos exposure. No general agreement was detectable on this issue; but work

from our unit suggests that since pulmonary small irregular opacities detected radiographically progress in relation to cumulative or average dust exposure, and pleural abnormalities progress in relation to length of exposure or time since first exposure but not to dose, that radiographic evidence of asbestosis should lead to the prudent course of avoiding further exposure to asbestos dust. This course of action may not be necessary for workers who exhibit limited benign pleural abnormalities alone.

There seems good reason to ask whether in population studies we should consider a biological response in terms of a diagnostic constellation for 'asbestosis' or whether it is more useful to measure chest radiographic abnormalities (by the ILO Classification), lung function, or perhaps other indicators of disordered respiratory health and relate these to dose while accounting for other influencing factors (e.g., age, smoking) in the correlative analyses. The relative usefulness and validity of these differing approaches requires future attention. On another but related point, we still do not appear to be clear regarding the prognostic implications of pleural thickening, both diffuse and localized (plaques), although some information is available. Unfortunately, demonstrating an excess mortality risk in those with pleural abnormalities can only help to resolve this issue if dose can be eliminated as a cause for the differing mortality experience. Only long-term follow up of workers with known exposure can determine whether those developing pleural changes are at greater risk of developing malignant disease.

There is perhaps no more important scientific issue regarding asbestos health effects than that of the influence of fibre type on risk for asbestosis, lung cancer and mesothelioma. While uniformity of opinion has perhaps not yet been reached, most investigators have been convinced by both epidemiological evidence and tissue fibre analysis that risk is generally enhanced by exposure to amphiboles, particularly crocidolite. Nottingham gas-mask workers during the Second World War have had an alarming incidence of mesothelioma if they were exposed to crocidolite; but those whose exposure was limited to chrysotile seem to have had little risk for development of this tumour. Importantly, one should ask whether the chrysotile gas-mask workers (apparently making masks for civilians) have been adequately followed up in regard to mesothelioma risk. It has been pointed out that the increased pathogenicity of amphiboles may be related to the greater 'dustiness' of these types of fibres, perhaps in addition to differences in deposition and retention in tissue.

An interesting question was raised concerning the distribution of pleural and peritoneal mesotheliomas, which may change as time since first exposure lengthens. The Australian and South African cohorts are of interest in this regard. Further discussion on the malignant effects of asbestos exposure pointed to the perplexing inconstancy of

excess risk for gastrointestinal malignancy among the several mortality studies (e.g., such excess risk has not been found in the Rochdale and New Orleans investigations). A possible explanation for these findings would be that there is an added cofactor in some segments of the industry that produces the excess risk for tumours of the gastrointestinal tract.

Dr McDonald addressed the need for epidemiological data on the overall impact of asbestos-related disease in society and the effect of control measures on these diseases. Little evidence is available on these issues.

Several other points were made in the discussion of this session. Intriguing was the suggestion that exposure to coal or other nonfibrous dust may actually be protective in regard to development of lung cancer. Limited epidemiological data suggest this possibility but by no means confirm it. Additionally, questions remain concerning the distribution of fibres in the lungs and pleural lining of exposed workers. Anatomical reasons were pointed out (the very thin pleura) that may account for the difficulty in demonstrating pleural fibre burden. Whether the pulmonary/pleural distribution of asbestos is influenced by fibre type is of interest but largely unknown.

In the last session on asbestos, entitled 'Scientific Basis for Environmental Control of Fibres', the discussion centred primarily around dose-response relationships. In regard to carcinogenic effects, there appeared to be a consensus that the shape of the curve is linear and that no threshold exists. While in no way refuting these hypotheses, I would only raise the question as to whether we have come to this consensus by genuine agreement or by submission. There can be little doubt that cancer risks from low doses over a working lifetime have not to date been estimated by observations at these low levels of exposure but rather by extrapolation *via* the mechanism of statistical modelling. In the absence of observations, this is certainly the correct approach to risk assessment. However, the advantages of obtaining biological response data on long-term, low-level exposure with adequate follow up of exposed working populations are undeniable.

Additional but incomplete data have emerged in recent years to suggest the probability that dose-response curves differ for various phases of the industry; but how and whether this should influence public policy decisions is certainly not clear. Further, as regards the dose-relatedness of these diseases, one might ask if Mr Peto has surrendered on his 'no dose relationship' position. If he is right, what are the control implications? They seem both obvious and dismal. Happily, the great majority of the participants of this conference were convinced by the evidence that leads to the conclusion that the lower the dose of asbestos exposure, the lesser the risk of malignant and nonmalignant disease.

Finally, since the validity of dose-response relationships depends critically on measurement of exposure, it is appropriate to ask: are we now measuring airborne asbestos dust with adequate precision and sensitivity? Alternatives to the now widely applied optical microscopic counting of asbestos fibres are electron microscopic techniques and mass measurements. There seemed to be little discussion on this point by the participants of this symposium, which may suggest that these alternatives are not practical for wide use or that their biological validity or relevance has not been established.