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MESOTHELIOMAS AND CHRYSOTILE

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Abstract—see p. 415.

MALIGNANT mesotheliomas are, for practical purposes, incurable cancers which occur rarely except when there has been exposure to fine durable respirable fibres. It has not been possible to make a realistic estimate of the frequency of mesotheliomas which are not due to fibre exposure because, in Western countries, everyone is exposed to some fibres and these fibres will be found in the lung at autopsy whether they are the cause of the mesothelioma or not.

HUMAN EPIDEMIOLOGY: PROBLEMS IN INTERPRETATION

Because it is not possible to identify those cases not due to fibre exposure, the relative risk due to exposure to each fibre type can be estimated only by epidemiological comparisons between groups whose exposure is known. This knowledge must include not only the level and duration of exposure but the proportion of each fibre type making up the exposure. The comparisons should include groups with no known exposure. From such comparisons it is possible to construct, for each fibre type, a dose–response relationship with mesothelioma both for single fibre exposure and for mixed exposure. As we have already heard in relation to specific occupations we are a long way from achieving this situation. There are many reasons for this.

One of the problems which impede the setting up of reliable comparisons between groups is the long latent interval between exposure and the development of the mesothelioma. Measured from first exposure this is somewhere between 40 and 50 years (ELMES and SIMPSON, 1976; McDONALD *et al.*, this Workshop). There is some confusion in the literature about the latent interval because many of the reported groups apparently showing shorter intervals have not been followed up for 40 years, let alone for the 60 or 70 years from first exposure which would be necessary to get a reliable estimate of the human experience. For a comparison between two groups with exposure to fibres to be valid the latent interval and the level and duration of exposure need to be matched. It is a waste of time matching groups unless the latent interval is at least 30 years and preferably from 30 to 60 years.

Another important feature of published studies is that the tumours can occur in individuals with exposure but no clinical or radiological evidence of asbestosis. In these cases the only evidence of fibre exposure is a lung fibre content higher than that

normally expected in the general population. This group has been identified in prospective epidemiological and other studies as by-stander exposures, people with a brief full-time occupational exposure and unexpected cases such as the housewife who regularly washed the insulator's dusty overalls (ELMES, 1971; GIBBS *et al.*, 1989). These are all circumstances which would not be expected to give rise to a risk of lung cancer or asbestosis and indicate risk at a lower level of exposure. Therefore the prevention of mesothelioma may be more difficult than the prevention of asbestosis and the associated lung cancer.

It is difficult to achieve a reliable diagnosis of mesothelioma in an individual case and the reluctance of pathologists to submit tissue to expert panels means that the bulk of the individual case reports are unreliable in this respect. Furthermore the case reports and many of the survey series are unsupported by lung analysis for any fibre, let alone a fibre analysis with reliable differentiation between chrysotile and the various amphiboles. Even some large series which were originally reported as exposed to a single fibre type have since been shown to have had mixed exposure, so that many early and some recent reports have to be re-interpreted or discarded. The old official view in the United States and some other countries that all mineral fibres were 'asbestos' and had to be considered as a single entity from the health and safety point of view has delayed the acquisition of new knowledge on the relative risks of the different fibres. This has already been discussed this morning in relation to the different branches of the industry and need not be gone over again. It does mean that there are only a few studies which are relevant to the risk due to pure chrysotile exposure.

THE STARTING POINT—1964

The position at the time of the New York Academy meeting can be summarized as follows:

(1) the relationship between mesothelioma and 'asbestos' put forward by Wagner had been confirmed in the user industries in most Western countries;

(2) the evidence from the South African mines showed that the mesothelioma risk was confined to the North-west Cape, there were no cases from the mines (not even crocidolite mines) in the Transvaal or Swaziland. This evidence seemed to indicate that even with the (by our present standards) very high exposure in the mine mills in South Africa there was no risk of mesothelioma from amosite or chrysotile. This evidence was not widely accepted. The apparently low incidence of mesothelioma in the Canadian mines was also doubted and the possible influence of amphiboles due to the processing in Canada of crocidolite ore from South Africa during the war discounted.

At the end of the meeting a UICC working party recommended that priority should be given to studies of single-fibre-type exposures (UICC, 1965). These have proved more difficult to carry out than was expected at the time and it is this work, some of it very recent, which has to be assessed today.

EVIDENCE SINCE 1964

Amphibole and mixed exposure

Abundant evidence of the high risk of mesothelioma became available during the following 10 years from amphibole mines and mills and from industries and

occupations where amphibole fibre was one of the main constituents. In Europe the emphasis was on crocidolite, because this had been the fibre which was considered best for insulation where there was steam condensation. In the United States and Canada amosite was more widely used for this purpose and after some delay evidence began to appear (mainly from lung fibre content studies) that amosite was the main cause of the risk when there was a mixed exposure to chrysotile and an amphibole (McDONALD *et al.*, 1982).

Military gas-mask makers were a good example of a pure crocidolite with a very high risk of mesothelioma after short exposure (Jones *et al.*, 1980). There has been only one study that I know of, of pure chrysotile exposure in the making of civilian gas-masks (ACHESON *et al.*, 1982). There was probably no risk of mesothelioma. Unfortunately this study was not backed up by lung fibre analysis. Comparisons like that, where the same or similar processing is carried out with amphibole or a mixture in one chain of factories and using pure chrysotile in another chain, could have been carried out in several other industries (friction materials, asbestos cement, mill board, etc.). They have been slow to appear.

The amosite anomaly, by which I mean the persistant low risk of mesothelioma in the amosite mines and mine mills (Webster, personal communication 1993) contrasting with the relatively high risk of mesothelioma in the insulation use of amosite has not been resolved yet.

'Pure' chrysotile exposure

(a) *Southern Africa.* The chrysotile mines in the Transvaal, Swaziland and Zimbabwe appear to have exposed large numbers of workers to high levels of pure chrysotile (Rees *et al.*, 1992) and yet there have been very very few cases of lung cancer let alone of mesothelioma among the miners and mine mill workers (Webster, personal communication 1993; and Baloyi, this Workshop). Formal epidemiological studies have been attempted but social and political difficulties have meant that the results are incomplete. While it is claimed that there is no risk of mesothelioma in spite of a high chrysotile lung burden in men who have worked for many years in the mills this evidence has not gained wide acceptance. More extensive studies of lung fibre content are needed to confirm that there is little or no fibrous tremolite in these men. The fact that skilled workers and managers moved between the amphibole and the chrysotile mines and that limpet spray containing crocidolite was processed in a special department at Havelock complicates the situation but probably explains the very few cases of mesothelioma which have been reported from these chrysotile mines.

(b) *Australia.* Here the experience with crocidolite in Wittenoom seems to be similar to the North-west Cape of South Africa. But again we lack good epidemiological studies of the men who only worked in the chrysotile mines and we have no information on the tremolite content of this chrysotile or of the lungs of the men who milled it. The lung fibre content from Australian mesothelioma cases in general has been analysed by fibre type but the reports of this work have led to some confusion and it will be interesting to hear today what the Australian view of the role of chrysotile is in causing their mesotheliomas.

(c) *China and Russia.* Both China and Russia mine large quantities of chrysotile but we have little sound epidemiological evidence as to whether the mesotheliomas in these two large areas are confined to those exposed to imported amphibole. In China there are areas where the clay used commercially is contaminated with crocidolite, they mine tremolite and the big chrysotile deposit in the Gobi desert contains tremolite, so that a great deal of epidemiological work will be needed to clarify the situation. Unfortunately although information may be more readily available from the states of the former U.S.S.R. the present situation may delay the completion of epidemiological studies there.

(d) *Turkey.* Early reports from the south-east region seemed to implicate chrysotile as the cause of a high incidence of lung cancer and mesothelioma. Closer study revealed that the fibre here and in some other areas is tremolite (YAZICIOGLU *et al.*, 1978, 1980). The localized occurence of erionite fibres in the tuff rock in Cappadocia has been a lesson which it is to be hoped that we have all learnt (BARIS *et al.*, 1987). All durable fibres of the right size and shape are dangerous.

(e) *Eastern Europe and the Mediterranean basin.* There is a large area here where there is tremolite in the rock and this contaminates the soil. In most areas the only risk is pleural plaques in the agricultural workers but there are areas like Northern Greece where lung cancers and mesotheliomas occur (CONSTANTOPOULOS *et al.*, 1987, 1991). This contamination extends around the old chrysotile mines in Cyprus, Northern Italy and Corsica and has led to confusion as to the true cause of the mesotheliomas (and pleural plaques) found in these areas. The examination of sheep and goats' lungs seems to have clarified the situation a little and it is likely that the serious disease in these areas is due to tremolite and not chrysotile, but this is difficult to prove (MCCONNOCHIE *et al.*, 1987; PIOLATTO *et al.*, 1990; VIALLAT *et al.*, 1991).

(f) *Finland.* In the early days we were assured that anthophyllite caused lung cancer and asbestosis in the miners, and pleural plaques by environmental contamination of the air around the mine. It was supposed not to cause mesothelioma but, like all dogmatic statements in medicine, time (and some recent reports) is proving this wrong (TUOMI *et al.*, 1989).

(g) *Mines in Canada and the United States.* Until the evidence from Libby, Montana, proved the importance of fibrous tremolite in a mine (AMANDUS *et al.*, 1983), the situation in the mines in Eastern Canada and the United States has been difficult to resolve. While the very detailed studies by Corbett McDonald and his group (some of which have already been described at this meeting) have banished the idea of a high hidden mesothelioma risk in this area, they have confirmed a low level of risk. It is of a different order from that in the crocidolite mines in South Africa and Australia, but, significantly enough, seems to vary from mine to mine. It is for us to decide in discussion whether this low level of mesothelioma risk is due to chrysotile alone, to tremolite alone, to crocidolite alone or to any combination of the three. I don't know whether any more studies of the miners and millers are needed (they must be nearly as well studied as the coal miners in South Wales). I have not yet seen a proper study of the

British Columbian mines with a measurement of the tremolite content of the ore, the commercial product or the lungs of the workers.

(h) *User industries in Europe, the United States and Japan.* Not enough effort has been made to select and study workers from factories where the type of fibre used over the years has been well documented and correlated with the lung fibre content at autopsy. The well-known Lancashire factory cohort followed by Doll and his colleagues [DOLL, 1955] was put forward as a 'pure' chrysotile exposure because the crocidolite usage in the late 1940s and early 1950s was considered insignificant. At first it seemed unimportant because, as a result of the controls introduced in the 1930s, the risk of asbestosis and lung cancer was falling. At this stage of the study there were no mesotheliomas which fitted well with the South African experience of chrysotile. But the mesotheliomas started to appear in the late 1960s and were attributed at first to chrysotile. It was not until the late 1970s that lung fibre analysis became available and showed levels of crocidolite consistant with the view that this was the cause of the mesotheliomas and possibly of the asbestosis and lung cancers as well.

The relatively late appearance of mesotheliomas in various sectors of the asbestos cement industry in Europe and the United States (which had previously been thought to be free of this risk) is associated with the introduction of crocidolite to aid in the manufacturing process, which started in the late 1940s and continued until relatively recently. Various studies have been done, some of which were described this morning, to determine the exact relationship between this crocidolite use and the malignancies to see whether chrysotile contibutes to the risk. There are but a few in both the friction (Berry, this Workshop) and asbestos-cement (THOMAS *et al.*, 1982) industries where only chrysotile has been used and where the risk of mesothelioma and lung cancer is not raised.

The Asbestos textile industry in the U.K. has been bedevilled by the use of crocidolite during the period relevant to our present mesothelioma experience. Some textile plants in the United States used only chrysotile but the increased risk of lung cancer in one factory has already been discussed today in relation to the presence of tremolite fibres in the lungs of the workers. It is not clear whether any mesotheliomas can be attributed to this exposure (they would be expected if the tremolite exposure was sufficient to cause lung cancer).

(i) *Animal studies.* These are due to be discussed in detail tomorrow but for the purposes of the present discussion it is necessary to remember:

(1) the early inhalation and injection studies in rodents showed that all types of asbestos, at extremely high levels of exposure, could cause lung cancer and mesothelioma, chrysotile being the most dangerous. This confirmed the view of those epidemiologists who believed that all types of fibre should be treated as equally dangerous; and

(2) elaborate studies since then have shown that chrysotile behaves differently from the amphiboles in that it changes and is cleared from the lung tissue whereas the amphiboles remain unchanged and are cleared slowly if at all. Those epidemiologists who believe there are at least two orders of magnitude difference between the risk created by the amphiboles and that created by chrysotile have used these differences to explain the anomaly.

VIEW FOR DISCUSSION

Our present view as to whether humans develop mesothelioma as a result of exposure to chrysotile must be based on human experience rather than on animal experimentation. We have been hearing the evidence about this human experience and as I warned at the beginning of this paper the evidence is not yet conclusive.

We can assume that there is a dose–response relationship but not necessarily that it is linear. Because the exposure in the mines and mine mills was very high at the relevant time and because the risk was low in mines which gave rise to detectable tremolite burden, and because there is no detected risk at mines where tremolite has not been confirmed, it is possible to reach two conclusions.

(1) that the risk would be negligible if the mines and mine mills were kept within present day safety limits; and

(2) that it may be possible to mine chrysotile ore containing less than a certain amount of fibrous tremolite without any risk of mesothelioma. This may already be happening. Such 'clean' chrysotile should carry no risk to the user or the general public provided current safety procedures are enforced.

[For the discussion of the issues raised in this and the other allied papers see pp. 416–417.]

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