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12th January, 1966.

Dr. A.E. Pufahl,
Assistant General Manager, Asbestos,
Union Carbide Corporation,
Mining & Metals Division,
270 Park Avenue,
New York,
N.Y. 10017, U.S.A.

Dear Dr. Pufahl,

You will recall that from time to time we have sent you extracts from publications which indicate concern felt in industry on the detrimental effect asbestos has on health.

We tried to obtain some information for Southalls Paper Mills, who wanted to use our asbestos in a sanitary tissue of the internal type. They were concerned about possible danger to health. We were unsuccessful then in obtaining answers to their specific questions, and could only deal with them in very general terms. However, I feel that we may now be able to be more specific when the occasion arises by using the information contained in the documents, British Industrial Biological Research Association and Report of Proceedings of an International Conference on the Biological Effect of Asbestos, copies of which we enclose with this letter.

We believe the documents are well worth having studied by the Medical Adviser to the Corporation, and it is our belief that we may well be able to take advantage of the fact that our material supposedly contains so little of the dangerous trace elements that are mentioned in these documents. If this is so, then we certainly have good copy for publicity use.

You will be interested to note that two American medical authorities attended the International Conference, namely Dr. H.E. Ayer, Public Health Service, Cincinnatti, and Dr. I.J. Selikoff, Mount Sinai Hospital, New York.

We would appreciate your comments and conclusions in due course.

Sincerely,

P.R. Cheston
Assistant Sales Manager

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c.c. Mr. H. Reichard, Mr. [illegible]

that the silicone fluid is devoid of silica granules.

[The intense fibrous tissue reaction and the presence of probably refractile crystals in the lesions described by Weiner et al. (_____.) have not been reported by other workers using pure liquid silicones. Two of the three silicone preparations, referred to by Weiner et al. (loc. cit.) contained mineral and vegetable fatty acids, both of which are capable of inducing in their own right the severe granulomatous reaction observed. It is quite probable that a significant or even a major role was played by the fatty acids in the induction of the reported severe fibrous lesions. If we are to believe the claim of the existence of silica granules in the silicone fluid preparation, then it is conceivable that the silica may have been a contributory factor in the production of the tissue reaction. However, a very reliable source of ours had no hesitation in refuting the claim that silicone fluid is contaminated with silica. Only under conditions of extremely high temperatures and high pressures and in the presence of oxygen is oxidation of silicone fluid to silica possible. For this reaction to proceed during shelf storage is not only highly improbable but well-nigh impossible.]

MESOTHELIOMA AND ASBESTOS

The development of tumours (mesothelioma) following exposure to asbestos dust tends to be insidious (BIBRA Bull. 1965, 4, 341). The initial obstacle to recognition of the hazard lay in correlating two episodes — exposure to asbestos dust, however light, and subsequent development of the tumour. Once this connexion had been established the problem assumed new and somewhat alarming dimensions since the time-lag between cause and effect may well extend to over half a century. Before 1930 the industrial and commercial importance of asbestos in this country was still relatively small. Thus it is only now that the incidence of diffuse pleural or peritoneal mesothelioma can be expected to show a steady upward trend. This pattern is becoming all too apparent.

Public interest in the problem should certainly have been aleated by a report in the Sunday Times (31 October 1965) on the work of Wagner & Thompson (Br. J. Ind. Med. 1965, 22, 261). Their important epidemiological study covered 83 patients (41 males and 42 females) with positively diagnosed diffuse pleural or peritoneal mesothelioma admitted to the London Hospital over the course of approximately 50 yr. Evidence of exposure to asbestos was obtained in 40 of the 76 cases whose background histories could be traced with relative accuracy. Of the remaining 36, 11 had lived within half a mile of an asbestos factory. In a control group of 76 in-patients, matched for sex and age, only 14 gave histories of previous direct or domiciliary exposure to asbestos.

The rise in reported cases of asbestos bodies in the lungs may reflect either an absolute increase in incidence or the results of more searching pathological examinations in the light of this new knowledge. Be that as it may, Cauna et al. (J. Am. med. Ass. 1965, 192, 371) report a 41% incidence of asbestos bodies seen in the course of 100 routine adult autopsies (47% in males; 34% in females), although none were found before the age of 24. No cases of mesothelioma or asbestosis could be identified and primary cancer of the lung was only present in two patients — one with asbestos bodies and one without. The authors draw attention to

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the problem of positive identification of the asbestos body and the differentiation between it and the similar structure encountered in talcosis. They believe that the problem is made more difficult because of the similarity between asbestosis arising from exposure to tremolite and talcosis. Histochemical differentiation is thought to be necessary, but the method used in the present study was electron-probe analysis. Nonetheless, the authors rejected findings which did not positively identify classical asbestos bodies and still produced an incidence much higher than previous studies had revealed at autopsy, notably 26.4% in Cape Town (Thomson et al. S. Afr. med. J. 1963, 37, 77) and 27.9% in Miami (Thomson, Conference on Biological Effects of Asbestos, New York, October 1964).

French workers have also drawn attention to the problem, and an analysis of histopathological findings has been published (Turiaf et al. Presse méd. 1965, 73, 2199). Although the asbestos industry in that country is not large, the incidence of mesothelioma is rising and concern is understandable.

Recording the incidence of asbestosis and mesothelioma and standardising diagnostic techniques formed part of the terms of reference of the Working Group convened, under the auspices of the Geographical Pathology Committee of the International Union against Cancer (I.U.C.C.), to look into the whole question of asbestos and cancer. The comprehensive report of the Group (Br. J. ind. Med. 1965, 22, 165) recommends three main lines of attack:

Epidemiological — more information is required concerning the results of exposure to particular types of asbestos fibre (amosite, crocidolite, anthophyllite, chrysotile or tremolite) by inter- and intranational studies in specified areas. It is recommended that studies be undertaken into the relation between dust dosage, the physical state of the dust and the incidence of asbestosis, carcinoma, mesothelioma and other tumours. It is also proposed to widen the field of enquiry to embrace ancillary occupations, such as transport, docks, building etc., which may involve less intensive exposure to asbestos. All cases of [illegible] mesothelioma should be rigorously screened to determine any possible exposure to asbestos dust.

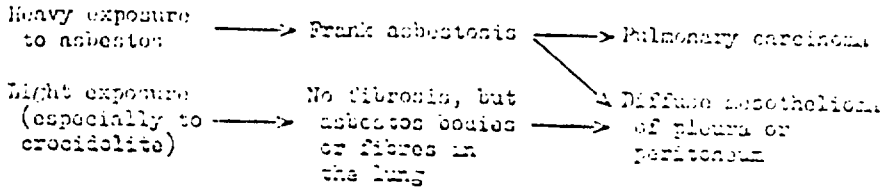
Pathological — it was felt necessary to standardise criteria for diagnosis under the careful supervision of a consultative panel of pathologists. An endeavour will be made to grade the degree of pulmonary fibrosis due to the presence of asbestos and routine examination of sputum, fresh lung or fixed tissues (where available) for asbestos bodies or fibres will be incorporated into all pathological examinations.

Physical and chemical — the possibility was discussed of establishing a centre to produce a set of analytical standards and to investigate the biological, physical and chemical characteristics of various types of asbestos fibre. Methods of identification of the different types of fibre in large samples of tissue and in lung sections were also discussed.

Investigations at the Pneumoconiosis Research Unit, Llandough Hospital, South Wales, were designed to resolve the suggested association between exposure to crocidolite dust and diffuse pleural mesothelioma occurring without intervening asbestosis, and between asbestosis and subsequent lung carcinoma (Wagner, Bull. Un. int. Cancer. 1965, 3 (2),

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2). The following mechanism could provide a possible explanation:



This pattern would go far to explain previous reports of low incidence of mesothelioma, especially where pathologists only considered the existence of this particular tumour in those cases showing frank asbestosis. The study of Newhouse & Thompson (loc.cit.) revealed that in 47 cases from the group showing positive mesothelioma, where tissue from biopsy or necropsy or sputum could be obtained for examination, 30 (62.5%) showed evidence of either asbestos bodies or asbestosis; but the majority of those showing frank asbestosis were workers actively employed in handling the raw material and therefore exposed to high concentrations of dust over long periods. It was also shown that the heavier and longer the exposure, the shorter was the interval before the onset of symptoms and the time of death. Obviously, therefore, the danger of incipient mesothelioma is present among those who are exposed through contact with a relative or who live in the vicinity of a factory and are thus subjected to only minimal exposure. Suspicion has been focussed on crocidolite as the causative agent in mesothelioma, but in most British factories a mixture of crocidolite, amosite and chrysotile is liable to be present in the atmosphere and mesothelioma may perhaps be caused by all or any of the various constituents of the dust. Studies on the organic components of asbestos are being carried out by Harington et al. (Rep. Br. Emp. Cancer Campn 1964, No.42, p.23). Two fractions of organic material can be determined: oils present naturally and oils arising from contamination during the manufacture or transport of asbestos. Extracted samples of a particular batch of amosite which had previously appeared to be non-carcinogenic, or only weakly so (Wagner, Nature, Lond. 1962, 196, 753), have been found to be associated with the development of mesothelioma in hamsters (Gelikoff, personal communication in 1964 to Harington et al. (loc.cit.)). A sample of the organic extract is now being given intraperitoneally to rats as part of a long-term test. Other work in progress includes investigation of the possible tumour-initiating activity of crocidolite and amosite oil in conjunction with the promoting agent croton oil (BIBRA Bull. 1962, 1 (2), 57). It has been shown that during a storage period of 6 months asbestos absorbs 70-85% of the jute oil present in jute sacks (Harington, Trans. N.Y. Acad. Sci. 1965; In press). One sample of extracted jute oil was shown to have tumour-promoting activity when a known carcinogenic polycyclic hydrocarbon was used as initiator. Wagner (loc.cit.) also reports on the relevance of the presence in asbestos of aromatic polycyclic hydrocarbons, including 3,4-benzopyrene. No hydrocarbons have been isolated from chrysotile (the most widely used type of asbestos), but crocidolite, which was mined in that area of South Africa with a high incidence of mesothelioma (Wagner et al. Br. J. ind. Med. 1960, 17, 260), contained 3,4-benzopyrene in relatively high amounts.

The suggestion has also been made that asbestos carcinogenicity may be related to the metals or metal complexes contained in asbestos fibres; chrysotile contains nickel (0.5%) and chromium (0.1%), while amosite has manganese (0.7%). Serum can elute small amounts of nickel, chromium, manganese and magnesium from chrysotile, and iron and manganese from

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crocidolite and amosite (Harington et al. loc.cit.).

Pleural mesotheliomas, similar to those found in human cases, can be established by intraperitoneal injection of asbestos into hamsters (Smith & Eleanor, Fedn Proc. Fedn Am. Socs exp. Biol. 1965, 24, 550).

There is a great sense of urgency in the search for a solution to the complex problem of the aetiology of mesothelioma. Cellular studies [illegible] may contribute to an understanding of the underlying [illegible]. Silica and asbestos are both fibrogenic, [illegible] to silicosis and asbestosis respectively, but silica is non-carcinogenic except when introduced into specific sites such as the pleural cavity of experimental animals. The effect of silica and asbestos on lysosomes and phagosomes (phagocytic vacuoles) in macrophages is being studied by Harington & Allison (Rep. Br. Emp. Cancer Campn 1964, No.42, p.24). When taken up by the phagocytes, inert materials have negligible effect on the [illegible] membrane, whereas silica (and presumably asbestos) causes [illegible] hydrolytic enzymes normally contained into the [illegible] to be released into the cytoplasm (Brit. Med. Bull. 1965, 21 (1), 5). Autolysis follows and, ultimately, cell death and fibrosis. This action can be neutralised by polyvinylpyridine-N-oxide which is taken up by phagosomes and lysosomes and apparently binds directly with the silica surface, preventing its toxic effect. Asbestos studies on similar lines are now in progress.

However, awareness of the problem and willingness to tackle it cannot completely mask the sobering thought implicit in this quotation from the report of the Working Group (loc.cit.): "..... further cases of these associated tumours are expected for many years to come, even if dust exposures are now greatly [illegible]". Dust exposures are in fact increasing, for the problem is not only confined to workers in the asbestos and contiguous industries. It concerns all of us who have asbestos boards in our ceilings and walls, asbestos mats on our ironing-boards or asbestos installations around the water pipes. Ultimately, some form of control over the manufacture, distribution and use of asbestos products is to be expected, but until such time, the prognosis of mesothelioma indicates the need for restraint and care in the handling and use of this potentially dangerous substance.
