

defect found was not related to the appearance of bronchitic symptoms. Prospective studies are needed, however, to confirm the situation regarding these lung-function studies.

Immunological action of TDI

The major problem in any study of the effects of human exposure to TDI is the separation of its irritant from its potentially sensitizing properties. Some indication of an immunological response has been obtained in animals (*Cited in F.C.T.* 1965, 3, 545) but attempts to demonstrate such a response in apparently sensitized workers have failed, although complexes of TDI with human serum albumin stimulated the lymphocytes in these sensitized individuals (*ibid* 1970, 8, 235). Further attempts to demonstrate circulating antibodies in human serum have been made in 55 workers all with symptoms suggesting TDI sensitivity (Taylor, *Proc. R. Soc. Med.* 1970, 63, 379). In this study, a complement fixation method, a red cell-linked antiglobulin technique and a modified passive cutaneous anaphylaxis test in monkey skin were used. Although 23 of the patients reacted positively in at least one test, correlation of results between the tests was poor, indicating that they detected antibodies either of slightly different specificity or of different immunoglobulin class. Until suitable laboratory diagnostic tests for TDI sensitization are devised, the aetiological relationship between circulating antibody and symptoms of clinical sensitization will remain obscure.

Immunological studies in monkeys and guinea-pigs failed to show whether the effects of TDI on respiration in man are likely to involve an immune mechanism (Stevens & Palmer, *ibid* 1970, 63, 380). Although exposure of the respiratory system to TDI rendered it more susceptible to subsequent exposure to low levels of the compound, the inadequacy of current immunological techniques prevented the drawing of any conclusion as to whether this greater sensitivity involved an allergic mechanism.

Conclusions

More information is clearly needed on the aetiological mechanisms of man to TDI and possibly also to other isocyanates. The present study has shown the inadequacy of the TLV, reduced in 1961 to 0.02 ppm, and the need for a more accurate value of 0.02 ppm. Future lung-function and other studies will be needed to establish a technique for monitoring TDI in the atmosphere and the development of suitable markers (*ibid* 1970, 63, 368) are of interest.

ASBESTOS: QUESTIONS STILL UNANSWERED

Introduction

Occupational exposure to asbestos may lead to the formation of asbestos bodies in the lungs and to the development of asbestosis and tumours (mesotheliomas) of the pleura and peritoneum (*Cited in F.C.T.* 1970, 8, 207). The aetiological relationships between asbestos bodies, asbestosis and lung tumours are poorly understood and the presence of asbestos bodies in the lungs of the general population complicates the issue still further. Moreover, epidemiological studies are still in their infancy and the importance of the nature, severity and length of asbestos exposure in tumour development needs to be more clearly defined. Improvements in the working environment introduced relatively recently should reduce the occupational health hazard significantly, although the full benefits to be gained may be masked for a time by the experience of past exposure.

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Experimental and epidemiological studies

Although epidemiological studies have attached special significance to crocidolite in the induction of mesothelioma tumours, other forms (amosite and chrysotile) have produced tumours in experimental animals, and chrysotile has been claimed to produce tumours in man (*ibid* 1968, 6, 657; *ibid* 1970, 8, 208). All three forms produced mesotheliomas when administered intrapleurally to SPF or Standard rats in the form of a suspension containing 20 mg dust (Wagner & Berry, *Br. J. Cancer* 1969, 23, 567). The percentage incidence of mesotheliomas was 64% for chrysotile, 59% for crocidolite, 59% for crocidolite from which oils had been removed by extraction and 40% for amosite in SPF rats and 69, 68, 64 and 31% in the corresponding groups of Standard rats. In general tumour incidence was inversely related to survival times, but the group differences were more marked in SPF than in Standard rats. Deaths from mesothelioma occurred earliest in the chrysotile group (353 days in Standard rats), followed by the groups treated with extracted crocidolite (376 days), crocidolite (417 days) and amosite (557 days) but after this time lag there was a rapid onset of mesotheliomas. It was necessary to distinguish between mortality from mesotheliomas and from natural causes and this was achieved using life table methods, but a mathematical model has been tested and found suitable for analysis of experiments involving smaller groups of animals (Berry & Wagner, *ibid* 1969, 23, 582). The study described above was initiated in 1962 and work is now in progress on several additional projects, including an attempt to establish a dose-response relationship in rats by injecting crocidolite and chrysotile in a range of doses and a study using the inhalation route, which is more relevant to human experience.

Epidemiological studies are gradually helping to ascertain which forms of asbestos are carcinogenic. In Australia, 15 cases of pleural mesothelioma have been reported in workers exposed to asbestos for 6 months-30 yr (Milne, *Med. J. Aust.* 1969, 2, 669). Some workers had a history of exposure to crocidolite. In an informative review, Wright (*Am. Rev. resp. Dis.* 1969, 100, 467) cites unpublished data presented at a symposium on pneumoconiosis held in South Africa in 1969. Reference is made to the inability of anthophyllite and chrysotile to produce mesotheliomas in Finnish and Canadian workers respectively. The Finnish workers exhibited asbestosis and a three- to fivefold increase in the incidence of bronchial cancer, but Canadian workers showed no evidence of an increase in bronchial cancer. Mesotheliomas have been found in workers in some but not all of the crocidolite mines in South Africa so far examined, the striking exceptions being the crocidolite mines in the Transvaal. Less surprisingly, no cases were associated with the chrysotile mines in this area, but a few mesotheliomas among the Transvaal amosite mines have been recorded. Vigliani *et al.* (*Medna Lar.* 1968, 107, 481) could find no evidence of increased cancer of the lungs or pleura in Italian workers exposed to chrysotile. Wright (*loc. cit.*) also refers to a report indicating that chrysotile penetrates to the deep lung structures less readily and is cleared from the lung faster than either amosite or crocidolite. Summing up these epidemiological findings, it would appear that crocidolite and, to a much lesser degree, amosite produce mesotheliomas, while anthophyllite and chrysotile do not. In considering some of the apparently anomalous findings, Wright (*loc. cit.*) suggests that asbestos acts as a cocarcinogen rather than a true carcinogen, but the justification for reaching this conclusion on the supporting evidence must be questioned. The possible existence of a dose-response relationship between severity of exposure and bronchial cancer is also discussed and seems a more tenable proposition.

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Examination of the causes of death among 4500 workers in an asbestos factory during 1933-1964 (Newhouse *Br. J. Ind. Med.* 1969, **26**, 294) found that the mortality rate started to exceed the norm after 10 yr from the first exposure to mixtures of amosite, crocidolite and chrysotile. A significant excess of deaths from cancer of the lung and pleura even among workers with less than a 2-yr period of service and from respiratory disease in workers with more prolonged service was confined to the heavily-exposed groups. A retrospective examination of death certificates, autopsy reports and histological specimens pertaining to 301 workers from an asbestos factory revealed an underestimate of mesotheliomas in the certified causes of death, 15 additional cases being discovered in 84 histological re-examinations, but the incidence of bronchial cancer had not been greatly underestimated (Newhouse & Wagner, *ibid* 1969, **26**, 302). Moderate to severe asbestosis was found in all confirmed cases of lung carcinoma.

Asbestos-body formation

The mechanism of formation and the aetiological significance of asbestos bodies have been discussed earlier (*Cited in F.C.T.* 1970, **8**, 209). More light has been thrown on the development of an asbestos body from an asbestos fibre by electronmicroscopic studies involving either intratracheal instillation of soft or harsh chrysotile or amosite into hamsters (Suzuki & Churg, *Envir. Res.* 1969, **3**, 107) or intrapleural injection of chrysotile into guinea-pigs (Davis, *Exptl. mol. Path.* 1970, **12**, 133). These and earlier studies (*Cited in F.C.T.* 1968, **6**, 659) suggest that the process entails the coating of the asbestos fibre with acid mucopolysaccharide before its phagocytosis by the alveolar macrophages, and the subsequent transfer into the phagosome of haemosiderin granules which have accumulated in the surrounding cytoplasm. The fibre thus becomes coated with a layer, or sometimes several layers, of dense granules to form an immature and subsequently a mature asbestos body. The bodies, which are produced largely in giant cells, are first seen about 2 wk after asbestos administration and their numbers increase to a maximum at about 6 wk. Asbestos bodies are formed from fibres longer than 5 μ and the process may involve no more than 0.1% of all the fibres present. Davis (*loc. cit.*) also provides evidence suggesting that in guinea-pigs the surface of the acid mucopolysaccharide coat serves as a depository for the laying down of calcium (in the form of apatite crystals) in the development of the fibrous lesions, which eventually calcify to produce plaques similar to those seen in human asbestosis.

The significance of asbestos bodies in the development of asbestosis and malignancy remains to be defined. Dicke & Naylor (*Dis. Chest* 1969, **56**, 122) identified asbestos bodies in scrapings of the lungs and lymph nodes from 19 out of 100 autopsies of members of the general population in Michigan, although the presence of asbestos fibres in the bodies was not confirmed. In only four of these cases were asbestos bodies found in the sections of lung tissue. Morphological evidence of asbestos bodies in the lungs of asbestos workers with mesothelioma was obtained at each of nine autopsies but asbestos bodies were not found in lung tissue removed from similar workers at thoracotomy (Milne, *loc. cit.*). In seven of the nine autopsy cases, the asbestos bodies were found in routinely stained sections of lung tissue. Otto & von Fragstein (*Arch. Gewerbepath. Gewerbehyg.* 1969, **25**, 193) observed sporadic needle-shaped particles in normal and silicotic lungs and an abundance of these particles in the lungs of men with a history of asbestos exposure. Histological similarities between asbestos bodies and these needles became evident when the needles exceeded 20 μ in length. Differences in the prevalence of these needle-shaped particles in the lungs are claimed to be of diagnostic significance.

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Asbestos haemolysis

Chrysotile (but not crocidolite, amosite or anthophyllite) haemolyses human erythrocytes *in vitro* (Cited in F.C.T. 1970, 8, 210). In a study of the mechanism of this phenomenon, Schnitzer & Pundsack (*Environ. Res.* 1970, 3, 1) inhibited chrysotile-induced haemolysis of sheep erythrocytes *in vitro* with ethylenediamine, succinic acid, carboxymethylcellulose and certain polystyrene sulphonate polymers, but polyvinylpyridine-*N*-oxide proved less effective. This pattern of inhibition is the opposite of that obtained with silica-induced haemolysis. Chrysotile is considered to owe its haemolytic activity to the surface area or degree of opening of the fibres. The exposed surface of chrysotile is essentially magnesium hydroxide, while the surface of the other forms is more like that of silica. Further work showed that chrysotile heated to 1000°C still retained haemolytic activity although the pattern of its inhibition was more like that of silica haemolysis than of haemolysis by unheated chrysotile. The significance of this haemolytic action to the *in vivo* situation in man is, like several other aspects of the asbestos problem, still questionable.

A COLUMN OF MERCURY: PART II

In our last issue we considered various ways in which man and domestic animals may be exposed to inorganic or organic mercury (Hg). It now remains for us to look further into the fate of this element within the animal organism and to try to relate this to its known effects.

Brain levels of Hg

While contamination of food has been shown to be a formidable hazard under certain conditions (Cited in F.C.T. 1971, 9, 140) inhalation is probably still the route which offers the greatest likelihood of intoxication. The preferential uptake of Hg by the brain following parenteral administration especially via the lungs is well known (*ibid* 1967, 5, 101), but further demonstrations of this effect have recently been reported. Cassano *et al.* (*J. Neuropath. exp. Neurol.* 1969, 28, 308) have studied the distribution of Hg in the brain tissues of mice and rats exposed to ^{203}Hg -labelled vapour at a concentration of about 8 mg/m³ for 6 hr daily for 10 days. Whole-body autoradiography of mice was carried out at the end of the experiment and at intervals up to 60 days afterwards. Micro-autoradiography of mouse and rat tissues was carried out immediately, and at intervals up to 50 days after the last exposure, brain extracts being measured for ^{203}Hg activity for up to 120 days. The highest Hg concentrations were found in kidney, brain and myocardium. In brain tissues, the highest concentrations were seen in certain neurons of the cerebellum (particularly in the nucleus dentatus neurons and Purkinje cells) and in the spinal cord, medulla, pons and midbrain. The general indication was that after penetrating to the brain, inhaled Hg was preferentially retained in nerve cells in two forms, probably as free Hg and bound to proteins. These two fractions appeared to be in equilibrium, since the decay of radioactivity in them showed parallel courses with time.

Nordberg & Serenius (*Acta pharmac. tox.* 1969, 27, 269) have reported that the Hg concentration in the brains of guinea-pigs exposed for 5 hr to radioactive Hg vapour at a concentration of 7 mg/m³ was 3.9 times higher than that resulting from 0.4 mg Hg/kg given intravenously as labelled mercuric nitrate, a finding in close agreement with the results of an earlier study in mice (Cited in F.C.T. 1967, 5, 101) and of another by the same