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Original Articles

FIFTEEN CASES OF PLEURAL MESOTHELIOMA ASSOCIATED WITH OCCUPATIONAL EXPOSURE TO ASBESTOS IN VICTORIA

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Fifteen cases of pleural mesothelioma occurring in Victoria are described. Occupational histories and the finding of asbestos bodies in lung tissue indicate a relationship between occupational exposure to asbestos and induction of pleural mesothelioma many years later. The exposure in some cases was relatively short but intense. Crocidolite or blue asbestos would seem to be particularly potent in the induction of these tumours.

PLEURAL MESOTHELIOMA, once regarded as an extremely rare tumour, has been diagnosed during recent years with increasing frequency the world over.

Following the work of Wagner *et alii* (1960) in South Africa, who related asbestos exposure to the causation of this tumour, many investigators have confirmed their results (Elmes *et alii*, 1965; Selikoff *et alii*, 1964). In Australia, the only sizeable asbestos mine was operated until recently at Wittenoom in Western Australia, and inhalationel exposures to asbestos fibres were very high. Only one case of mesothelioma has been reported as emaneting from asbestos exposure at Wittenoom (McNulty, 1962), but this is not surprising, since the average time taken after exposure for the development of mesothelioma is of the order of 25 to 30 years, and that period has yet to elapse amongst the majority of Western Australian asbestos miners.

Mortimer and Campbell (1968) have recently described two cases of pleural mesothelioma associated with asbestos exposure in Queensland, and predicted that "it is likely that the association will be encountered with greater frequency in the future".

In Victoria, there has been considerable occupational industrial exposure to asbestos fibre inhalation in the course of asbestos processing and, although there is no Victorian asbestos mine, industrial conditions of 25 to 30 years (and more) ago were such as to cause exposures in some circumstances of a similarly high order. Hence it is with interest that we have noted, in the smaller, more highly industrialized State, a recent increased incidence of pleural mesotheliomata. The series involves 15 patients with pleural mesothelioma whose occupational histories have been investigated. In those cases in which a patient has died, a search has been made, whenever possible, of stained lung-tissue sections for asbestos bodies.

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MATERIALS

Twelve patients presented at the Austin Hospital Thoracic Unit in the period from 1962 to 1968. When the first three cases were noted (Riddell, 1966) between 1962 and 1965, the writer's interest was aroused in regard to the possibility of their relationship to asbestos exposure, and a search of lung tissue sections showed asbestos bodies. Investigation began of past occupational exposure, and received an impetus with the appearance of a further nine cases in the succeeding three years.

A surgeon at the unit kindly permitted investigation of a private case.

Inquiry was then made of the pathologists of all major public hospitals in Melbourne; two further cases came to light, making a total of 15 in all. So far as I am aware, these represent the total of all cases of pleural mesothelioma diagnosed over the period 1962 to 1968 in Melbourne public hospitals.

RESULTS

The series consists of 15 patients, five of whom are still alive. There were nine males and six females. Autopsies were performed on nine of the 10 patients who died, and the diagnosis was made in the remaining six cases by examination of tissue removed at thoracotomy (Table 1).

The original diagnosis was not made in all cases by the same pathologist, but two pathologists have since examined all the tissue sections and are agreed that the diagnosis in each case is pleural mesothelioma.

Asbestos Bodies

Of the nine cases in this series which have come to autopsy, asbestos bodies have been seen in routine stained lung-tissue sections in seven, and digestion-concentration-extraction of lung tissue revealed asbestos bodies in the other two. In the remaining six cases, search was made of diagnostic lung and pleural biopsy sections and no asbestos bodies were seen.

History of Occupational Exposure

Occupational histories are detailed in so far as the availability of facts allowed, and in 13 cases there was evidence of asbestos exposure.

TABLE 1

Case Number	Patient's Sex	Occupational Exposure	Asbestos Bodies[1]	Intensity of Exposure	Duration (Approximate)
1	M	Truck driver for firm handling asbestos	+	Mild	1940 to 1965
2	F	Winding asbestos string on to welding rod; buffing	++++	Heavy	1942 to 1945
3	F	Munitions factory, Australia	++	Unknown	1941 to 1945
4	F	Denied by relatives	++ (by digestion-concentration)	Unknown	Unknown
5	M	Munitions factory, India	No sections available	Unknown	? 1910
6	F	Winding asbestos string on to welding rod; buffing	No sections available	Heavy	1942 to 1947
7	F	Father worked in asbestos cement factory	No sections available	Very mild	? 1930
8	F	Winding asbestos string on to welding rod; buffing	Not available	Heavy	1937 to 1939
9	M	Naval dockyard worker in Scotland and Australia	Not available	Heavy	1939 to 1968
10	M	Denied by patient	+ (by digestion-concentration)	Unknown	Unknown
11	M	Winding asbestos string on welding rod; maintaining and setting winding machine	++++	Heavy	1935 to 1950
12	M	Naval dockyard worker	++++	Heavy	1942 to 1968
13	M	Naval dockyard, Malta	++	Heavy	1930 to 1942
14	M	Lagger	++++	Heavy	1920 to 1950
15	M	Carding asbestos fibres	Not available	Heavy	1942 (6 months)

[1] Asbestos bodies classified as follows:
1 to 3 per slide: +
4 to 10 per slide: ++
11 to 20 per slide: +++
20 per slide: ++++.

One fact worthy of note is that four of those with unequivocal evidence of asbestos exposure had been employed at the same firm during World War II or soon after. They were each unaware that any co-worker had suffered from a similar condition. Their exposure had been extreme, and the type of asbestos was Cape blue (crocidolite). This group will be considered in more detail in the discussion.

Living

Four of the five patients still alive at the time of writing had been first exposed to high concentrations of asbestos fibre about 25 years before. The remaining patient denied exposure, but stated that as a young woman she had cared for her father who worked for a firm manufacturing asbestos-cement sheeting.

Dead

For the 10 patients who had died, occupational histories were obtained by interviewing relatives, friends and acquaintances from work. Five had had severe exposure to asbestos (all showed many asbestos bodies in stained lung-tissue sections). Of the remaining five patients, one was interviewed before death and denied ever being exposed to asbestos. His wife subsequently agreed with this. Two patients were said by relatives to have worked in munitions factories, thereby probably being exposed to asbestos. One patient had worked as a truck driver for the same firm previously mentioned as a source of four cases in which heavy exposure had been experienced inside the factory. He had thus probably been exposed himself, though not to the same extent. One patient had worked only in the clothing trade as a machinist and there was no history of using asbestos.

Hence the total series of 15 consists of nine cases in which there was definite and heavy occupational exposure to asbestos, four cases in which exposure was probable, and two in which no evidence of asbestos exposure was forthcoming.

Occupations

The occupations as stated by those interviewed are tabulated. There are two patients listed as "munitions worker"; the quantitative relationship to asbestos exposure is not clear, but description of the working conditions by an experienced chemist leaves no doubt but that there was ample opportunity for exposure to asbestos.

Ship building and labouring in a naval dockyard are well known to be occupational sources of asbestos exposure. Ashcroft (1968) and Harries (1968) described mesotheliomata occurring in labourers at the Royal Dockyards, as well as in boilermakers, fitters, shipwrights and welders.

Lagging, asbestos carding and asbestos string winding all involved heavy asbestos exposure about 25 years ago, and the truck driver is known to have worked for the asbestos winding firm, though he was generally employed at a different branch.

There is one patient, listed as "domestic", whose father worked for an asbestos-cement firm. It is conjectural as to whether she was thereby exposed to asbestos. She denies ever handling very dusty clothes. If she was in fact exposed, a domestic occupation was the only source, because she has never been employed anywhere else but at home, and has never lived near any firm processing asbestos.

In reference to occupational histories it is pertinent to stress the difficulty of obtaining an accurate history, especially from friends and relatives. Some patients may

volunteer a precise history in detail. For example, the asbestos carder, who is a highly qualified scientist, was employed in a small, poorly ventilated room during wartime, carding asbestos fibres for use as respirator filters, working in a cloud of asbestos dust for six months. However, for other patients, the appropriate information often requires very careful elucidation, as the following histories may demonstrate.

CASE 6.—The patient, a female aged 46 years, was said to be a "ledger operator". She left school at the age of 13 years and worked as a domestic for about seven years. She then worked, for about five years, for a firm manufacturing welding electrodes, leaving this to be employed for five years examining hosiery. She then went to night school, learned typing, and graduated through a series of office jobs to her present position as ledger operator.

She denied any exposure to asbestos at first, but when asked to describe what she did at various firms, she recalled that the welding electrode was required to have asbestos string wound round the metal core as a binder for the flux with which it was later impregnated. There had been lots of asbestos dust in the air from the winding spools, and she, in common with three others in our series, had worked in this atmosphere subject to heavy exposure for a period of about five years, starting about 25 years ago.

Investigation confirmed her description, but the whole process has since been completely changed: little or no asbestos is now used depending on the type of electrode, and an efficient exhaust system is installed.

CASE 14.—The patient was a male, aged 75 years at death, whose occupation was listed as "barman". This patient was thought clinically to have a bronchogenic carcinoma. After autopsy, the pathologist diagnosed a pleural mesothelioma, and the large, radiologically visible pleural plaques were recalled. Asbestos exposure was considered and a retrospective search through the lung sections revealed asbestos bodies.

No next of kin was known, but contact was eventually made after some months with a friend at the club where the patient had worked as a barman for the previous 15 years.

The friend, on questioning, recalled that the patient had been a lagger for 30 years before this, and had proudly exhibited a gold presentation watch as evidence of his long service. Search of the relevant firm's records and discussion with the medical officer confirmed these facts.

Asbestosis

No patient was regarded clinically or radiologically as suffering from asbestosis, but pleural plaques were radiologically visible in one case, that of the lagger mentioned above, in which the duration of exposure and time-lapse since its inception were by far the longest of the series. These plaques are strongly suggestive of asbestosis (Oosthuizen *et alii*, 1964), or at the least, of severe occupational exposure to asbestos.

Duration of Exposure

All those known or presumed to have been exposed to asbestos began their exposure either during or before 1942. The longest exposure was 33 years, but it is noteworthy that five patients had been exposed for five years or less, one of them for only six months.

DISCUSSION

The association of asbestosis and asbestos exposure with bronchial carcinoma is generally accepted. Whilst acknowledging the general critical comments of Willis (1963), it is suggested that the tumours in this series have a pattern quite distinct from pulmonary carcinoma in many ways, namely, macroscopic appearance, histopathological characteristics, clinical picture and symptomatology, and, finally, in postoperative course, so that they represent a different type of asbestos-induced malignant disease from the more common bronchogenic carcinoma. Histologically, the picture is consistent with pleural mesothelioma (R. J. Riddell, personal communication), and despite careful search no autopsy revealed evidence of other primary tumours or of metastatic spread from other tumours either into the thorax or out to the pleura. The acceptance of mesothelioma as an occupational hazard of asbestos is now becoming widespread (*Leading Article*, 1968).

It is important to note the work of Gross *et alii* (1968), who have shown that the term "asbestos body" is a generic one describing a microscopic body whose longitudinal nucleus is a single fibre, very commonly but not always asbestos, on which a yellow-brown coating has been deposited in bead-like form. The resultant club-shaped or beaded body they prefer to call a "ferruginous body" and they have shown that an assiduous search of lung tissue (that is, by lung digestion and concentration followed by microscopic examination of the liquid concentrate as a smear) reveals these "ferruginous bodies" almost invariably in every autopsy. However, the lungs of those patients previously exposed in life to asbestos produce large numbers of ferruginous bodies, whereas it may require diligent searching of the concentrate to find a single body in others previously unexposed to asbestos.

The searching of a lung section obtained as a routine at autopsy and stained with haematoxylin and eosin is obviously far less efficient than the digestion and concentration method of Gross *et alii*, and may be expected to give point to the quantitative difference between the unexposed and exposed. Thus in our series there was no difficulty in finding, by means of a simple search of stained tissue, asbestos bodies in those known to have been exposed (Figure 1). Nevertheless, before the taking of full and careful occupational histories, in some cases, the presence of asbestos bodies had not been remarked on, even though retrospective search revealed them, sometimes in abundance (Figure 2). There are at least two reasons for this. Histopathological diagnosis is generally made on low-power examination and rarely does the pathologist find the need to search carefully a whole section under high power, which he usually must do to find those asbestos bodies that are discrete and not clumped. Also, the asbestos body, as Beattie (1961) has shown in experiments using animals, is not an unchanging thing, but varies in form from a fine filament with a greenish-yellow coating to a comparatively short, thick, dark-brown, segmented, sometimes clubbed body which can very easily be missed.

What is the significance of finding asbestos bodies at autopsy in seven out of nine cases of mesothelioma, by simple search of routinely stained sections?

The first factor to bear in mind is the apparently trite but important statement that the method of making the slide has a great influence on the number of cases in which these bodies can be identified. The figures vary from 99% (Gross *et alii*, 1968) to 6% (Hourihane, 1964), but no comparison is possible because of the different techniques employed. Obviously, the larger the amount of

lung digested or volume of lung searched, the greater will be the yield; with regard to smear techniques, the number obtained from a basal smear could prima facie be expected to be greater than that from, say, lateral or apical smears because, firstly, "asbestosis is most frequently found in the lower parts of the lungs, but may involve the

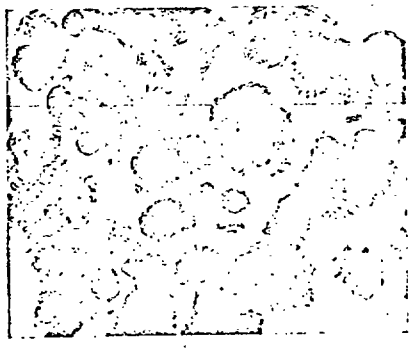

FIGURE 1: Asbestos bodies in lung tissue of former asbestos winder (Case 2). Some are fragmenting into granules. (Oil immersion.)

midzones and the upper lobes" (Gough, 1965) and secondly, radiological evidence shows that asbestosis occurs primarily at the lung bases. Random lung sections could be expected to yield the least number of all, so that our finding of seven cases out of nine appears very significant.

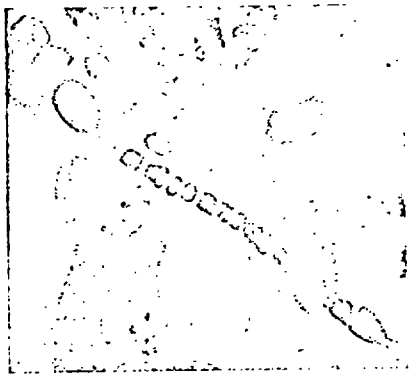

FIGURE 2: Asbestos body in lung tissue of former asbestos winder whose occupation was said to have been "invalid pensioner for years" (Case 2). Note dark, discrete beading over whole length of fibre. (Oil immersion.)

The second factor to consider is that the patience and experience of the viewer in relation to asbestos bodies must have a bearing on the findings. Some experience in viewing sputum smears of asbestos workers was found to be advantageous in identifying asbestos bodies.

The series of Ashcroft (1968) provides the only work with which some comparison with our results may be made, inasmuch as he also assessed the presence of asbestos bodies in a series of cases of mesothelioma in which "lung tissue was available for histological examination". He found asbestos bodies in 21 cases out of 23 (91%). A majority (15 out of 21) showed only "scanty asbestos bodies in lung sections". In our series, seven out of nine (77%) showed asbestos bodies, but only one could be described as scanty, and the majority (five out of seven) were comparatively plentiful. Ashcroft compared his mesothelioma series with a concurrent series of asbestos body counts taken by smear as a routine at autopsy, and found the difference to be highly significant. We have as yet no series for comparison but our figures, being of the same order as those of Ashcroft, suggest a similar interpretation. Taken in conjunction with the fact that all seven patients had definite or presumptive evidence of asbestos exposure, the relationship of asbestos inhalation to mesothelioma seems clear in this group.

The type of asbestos may be important. It is generally agreed that of the three common types of asbestos, namely, amosite, chrysotile and crocidolite, the last named, often called "blue asbestos", is the most potent in mesothelioma production (Wagner, 1965). Other sorts of asbestos may possibly be incapable of inducing mesotheliomatous growths. Cape blue asbestos, the South African form of crocidolite, which Wagner found to be the causal factor in his original series, was the only type of asbestos used by the small firm of welding-rod manufacturers previously mentioned.

Apart from the series as a whole, the discovery of the small subgroup of four patients who, having been diagnosed as suffering from mesotheliomata, were later found to have worked together, about 25 years before, at the same firm for a relatively short period under conditions of heavy exposure to inhaled crocidolite dust, reinforces the findings of overseas workers that these conditions are casually related to the development of pleural mesothelioma.

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REFERENCES

ASHCROFT, T. (1968), "Asbestos Bodies in Routine Necropsies on Tyneside: A Pathological and Social Study", *Brit. med. J.*, 1: 614.

BEATTIE, J. (1961), "Inhaled Particles and Vapours", edited by C. N. Davies, Pergamon, New York: 434.

ELMES, P. C., MCCAUGHEY, W. T. E., and WADE, O. L. (1965), "Diffuse Mesothelioma of the Pleura and Asbestos", *Brit. med. J.*, 1: 350.

GOUGH, J. (1965), "Biological Effects of Asbestos", *Ann. N.Y. Acad. Sci.*, 132: 368.

GROSS, P., UTIDJIAN, M., and DE TREVILLE, R. (1968), "Ferruginous Bodies in Human Lungs", *Arch. environm. Hlth*, 17: 327.

HAMERS, P. G. (1968), "Asbestos Hazards in Naval Dockyards", *Ann. occup. Hyg.*, 11: 135.

HOCHHAUSE, D. (1964), "The Pathology of Mesotheliomata and an Analysis of their Association with Asbestos Exposure", *Thorax*, 19: 268.

LEADING ARTICLE (1966), "Health Hazards of Asbestos", *Lancet*, 1: 930.

McNULTY, J. C. (1962), "Malignant Pleural Mesothelioma in an Asbestos Worker", *Med. J. Aust.*, 2: 953.

MORTIMER, R. H., and CAMPBELL, C. B. (1963), "Asbestos Exposure and Pleural Mesotheliomas", *Med. J. Aust.*, 2: 720.

OOSTHUIZEN, S. F., THERON, C. P., and SLOTS-CREMER, G. K. (1946), "Calcified Pleural Plaques in Asbestosis", *S. Afr. Mediese Bydrae.*, 10: 436.

RIDDELL, R. J. (1966), "Three Cases of Mesothelioma", *Med. J. Aust.*, 2: 554.

SELIKOFF, I. J., CHURG, J., and HAMMOND, E. C. (1964), "Asbestos Exposure and Neoplasia", *J. Amer. med. Ass.*, 188: 142.

WAGNER, J. C. (1965), "Epidemiology of Diffuse Mesothelial Tumours", *Ann. N.Y. Acad. Sci.*, 132: 575.

WAGNER, J. C., SLEGGS, C. A., and MARCHAND, P. (1960), "Diffuse Pleural Mesothelioma and Asbestos Exposure in the North Western Cape Province", *Brit. J. industr. Med.*, 17: 260.

WILLIS, R. A. (1953), "Pathology of Tumours", fourth edition. Butterworth, London: 131.

ANAEMIA IN PREGNANCY IN WESTERN AUSTRALIA

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Children and pregnant women in any community are the first to show signs of poor nutrition, and the picture presented by the public patients attending the antenatal clinic in Perth, Western Australia, gives no cause for complacency. Nutritional anæmia is common, shows a distinct seasonal incidence which can be related to a time of comparative food shortage with high prices, and is prevalent amongst racial minorities, especially the Italian-born.

Seven per cent of all patients attending the antenatal clinic are iron deficient and 2% are folate deficient to a degree that causes the hæmoglobin level to fall below 10·0 gm/100 ml, but the actual incidence of deficiency may be presumed to be higher. Other causes of anæmia in pregnancy include thalassæmia, chronic pyelonephritis, infection and unexplained hæmolysis.

One patient with megaloblastic anæmia was observed to have a low serum vitamin B_{12} level, but laboratory investigations and her response to small doses of folic acid indicated that her disturbance of vitamin B_{12} metabolism was secondary to folate deficiency.

A scheme is outlined for the prevention, diagnosis and treatment of anæmia in pregnancy.

THERE is a widely held belief that anæmia in pregnancy is a problem of small importance in Australia, because of a uniformly high standard of living and good nutrition. A review of the patients attending the antenatal clinic of the Department of Obstetrics and Gynæcology of the University of Western Australia demonstrates that anæmia is a common and serious complication of pregnancy, and one which is not receiving sufficient attention from medical practitioners.

MATERIALS AND METHODS

Seven hundred and forty patients presented themselves at the clinic of the Department of Obstetrics and Gynæcology, University of Western Australia, for antenatal supervision during the year 1967. All were wives of labourer-class husbands earning not more than about $45 (Australian) per week. Seventy-six (10%) were found to have hæmoglobin concentrations of less than 10 gm/100 ml at some stage of pregnancy or the puerperium, and their anæmia was not the result of hæmorrhage.

Hæmatological Investigations

Hæmoglobin concentrations were estimated by the oxyhæmoglobin method and the packed cell volume by the Hawksley microhæmatocrit (Dacie and Lewis, 1963). Particular attention was paid to the percentage of neutrophil polymorphs with five or more lobes to the nucleus (Chanarin *et alii*, 1963) as a measure of folate deficiency. Bone-marrow specimens were collected from the right anterior iliac crest, and methanol-fixed smears were stained with May-Grunwald and Giemsa stain and for intracellular iron (Hutchison, 1953).

Serum folate activity was assayed with the use of *Lactobacillus casei* as the test organism (Davis and Kelly, 1962), and the serum vitamin B_{12} level using *Euglena gracilis* (Nicholas and Pitney, 1958), the lower limits of normal were taken to be 2·7 ng/ml and 160 pg/ml respectively.

Hæmoglobin electrophoresis was carried out on cellulose acetate by a modification (Lau, L. S., and Pryor, D. S., personal communication) of the method of Graham and Grunbaum (1963); the percentage of hæmoglobin A_2 was measured by elution and the upper limit of normal was taken as 4%.

The serum iron level, total iron binding capacity and percentage saturation of the total iron binding capacity were measured by the method of Kok and Wild (1960). The limits of normality during the third trimester of pregnancy were taken as serum iron, 60 to 180 μg/100 ml, total iron binding capacity, 200 to 630 μg/100 ml, with saturation, 14% to 40% (Ventura and Klopper, 1951).

Iron deficiency was diagnosed on the criteria of a hypochromic blood picture (in the absence of thalassæmia), a high total iron binding capacity, a low serum iron level, low percentage saturation of the total iron binding capacity, and absent or scanty intracellular iron in the bone-marrow; patients were classified as (i) iron deficient, (ii) sideropenic, but with another major cause of anæmia, or (iii) iron sufficient. Similarly, the patients were classified as having (i) folate deficiency as a major cause of anæmia when there was a macrocytic blood picture, more than 7% hypersegmented polymorphs, low serum folate activity or megaloblastic change in the bone marrow, (ii) folate deficiency as a secondary contributory cause of anæmia, when there was another major cause of anæmia, but when there was also 4% to 6% hypersegmented polymorphs, low serum folate activity or minimal changes in the bone marrow towards megaloblastosis, and (iii) folate sufficiency.

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FATAL CASES OF ACUTE HEPATITIS ASSOCIATED WITH OCCUPATIONAL EXPOSURE TO ASBESTOS IN VICTORIA

NASAL SPEECH, ADENOIDECTOMY AND THE HYNES' PHARYNGOPLASTY

ADVANTAGES OF WOOLLEN CLOTHING

A NEW HEMOSTATIC VASOCONSTRICTOR AGENT FOR THE CONTROL OF BLEEDING