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iminary nature and the investigations in Britain are far from com-
ed. However, we have been able to show evidence of asbestos exposure
least as many cases of mesothelioma of the pleura and peritoneum as
been diagnosed in South Africa.

ıe South African finding has been confirmed that the association is
asbestos exposure, and not necessarily with asbestosis. In a number
ses the actual exposure has been slight, in one case three months of
r lagging, and the latent period between initial exposure and diagnosis
nor is again about 40 years.

Sully Hospital near Cardiff, Roger Seal has diagnosed six cases of
al mesothelioma. The histories of these patients have been followed
tail by members of Professor A. L. Cochrane's Epidemiological Unit,
n five of the six cases, there has been a definite history of asbestos
ure.

Newcastle-upon-Tyne, T. Ashcroft of Professor A. G. Heppleston's
tment, has found 13 histologically diagnosed cases, and evidence of
os exposure in 11. In Portsmouth, R. D. Clay has found evidence of
os exposure in two out of his three cases.

Britain's main ship-building areas — Belfast, Tyneside, Merseyside,
ydeside — we have not yet investigated Clydeside but two cases have
eferred by P. D. Stewart at Dunbarton. The most disturbing fact
t during the investigation new cases in increasing numbers have
eported from all these areas.

Britain, it has not been possible to obtain positive, clear evidence im-
ng a single type of asbestos as in South Africa, since the majority
s have been exposed where several types of asbestos were used. How-
lefinite evidence of crocidolite exposure has been established in a
ty of cases, and no indisputable case of pure chrysotile exposure has
n discovered.

EPIDEMIOLOGY OF MESOTHELIAL TUMORS IN THE LONDON AREA

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Introduction

In recent years, the association between exposure to asbestos dust and cancer of the lung, and other malignant neoplasms has been the subject of much research (Brit. Med. Journal, 1964). Wagner, Sleggs and Marchand (1960) described the occurrence of mesothelioma of the pleura in those exposed to crocidolite asbestos in the mining districts of South Africa, and have stimulated further studies of patients suffering from this tumor (Glyn Owen, 1964; Fowler *et al.*, 1964).

The present investigation concerns patients in whom a diagnosis of mesothelioma had been made at the London Hospital. All the post-mortem and biopsy specimens held in the Pathology Department in which a diagnosis of mesothelioma had been made in the past 50 years have been reviewed by Hourihane (1965). In 83 cases the diagnosis was confirmed. The series consists of 41 men of whom 31 had pleural and 10 peritoneal tumors, and 42 women of whom 25 had pleural and 17 peritoneal tumors. The aim of this study has been to establish the occupational histories of these patients and to trace any other possible exposure to asbestos.

There were four surviving patients at the outset of the investigation, but these have subsequently died. The earliest date of death in the series was 1917, 10 died before 1950, 33 between 1950 and 1959 and the remaining 40 in the past four and a half years. The youngest died at the age of 33 and nearly half were dead before the age of 55 (TABLE 1).

The ward notes of 65 of these patients were available; they give a picture of a disease with a consistent symptomatology. Among those with pleural tumors, the commonest symptom present was the rapid onset of extreme shortness of breath due to the formation of a massive pleural effusion. Pain was a prominent feature, either described as a dull ache, sometimes due to invasion of ribs or vertebrae, or sometimes sharp and radiating, suggesting nerve involvement. Tumors in the chest wall were not uncommon, occurring either in previous operation scars or by direct invasion of the chest wall. The symptomatology of the peritoneal tumors was more varied. In some patients the presenting symptom was pain on defecation or micturition; diffuse upper abdominal pain was very common and swelling of the abdomen due to ascites was always present terminally. The treatment was varied; pneumonectomy, decortication of the lung, deep

TABLE 1
AGE AT DEATH OF PATIENTS WITH MESOTHELIAL TUMORS

Age	Males	Females
<34	1 (2.4%)	1 (2.4%)
35+	9 (21.4%)	5 (12.2%)
45+	12 (29.3%)	12 (29.3%)
55+	11 (26.2%)	16 (37.0%)
65+	8 (19.0%)	7 (17.1%)

X-ray therapy, instillation of radioactive gold and cytotoxic drugs were used alone or in combination, but appeared to have little effect on the course of the disease. Half of the patients suffering from pleural mesothelioma died within one year of the onset of symptoms, a further third within two years and only one survived for more than three years. The course of those with peritoneal tumors appeared to be even more rapid; 14 of the patients died within six months of the onset of symptoms.

Sources of Information

In addition to the ward notes, some of which gave good occupational histories, there were three other sources of information: (1) the patient's general practitioner; (2) the records of a large asbestos factory making textiles, insulating materials, and other goods, where it was known that some of the patients had been employed; and (3) personal interviews with patients or their surviving relatives.

As a first step, the general practitioners were contacted with an explanatory letter asking them to complete a form giving details of the patients and their immediate relatives' occupations. Within two months 65 per cent of the doctors had replied. In two cases a hitherto unknown exposure to asbestos was revealed, in others the name and address of a surviving relative was given, but in the majority the doctor was unable to give information as, on the death of the patient, the notes had been returned to the local executive council of the National Health Service, where they were destroyed within a period of three years.

The asbestos factory keeps a file with detailed records of all employees since it started to operate in 1913. The names of all patients were checked with these files. Nine men were identified without difficulty and nine married women after their maiden names had been ascertained from relatives. The exact dates of employment of these 18 patients, and the jobs they had done, were obtained from the factory files.

The four patients alive at the beginning of the investigation were interviewed personally. A few relatives were contacted by post, but the relatives of 68 patients were interviewed by one of us at their homes situated mostly in the East End of London, Barking, or Dagenham. Not only was an occupational history of the patient, the spouse, sons and daughters and father taken, but past addresses were also recorded. The interviews lasted for at least an hour, as to recall events of thirty or forty years ago it was often necessary to explore the histories of all members of the family, their illnesses and difficulties.

A Control Series

A control series of patients was also examined to determine the proportion of in-patients of the London Hospital who may normally be expected to be exposed at their work or in other ways to asbestos dust. They were selected from the patients in the medical and surgical wards of the hospital during the early summer of 1964. Each patient in the mesothelioma series who had been traced was matched with a control patient of the same sex, born in the same five year period. As there was a dearth of male patients over 75 years of age in the hospital, a sample of six patients of

TABLE 2
TYPES OF EXPOSURE TO ASBESTOS OF 76 PATIENTS WITH MESOTHELIOMA AND 76 CONTROLS*

Type of exposure	Mesothelioma series†	Control series‡
Employed at one asbestos factory Delivered goods to factory	18) 1) (25.0%)	1 (1.3%)
Employed at other asbestos factories	5 (6.6%)	1 (1.3%)
Insulators and laggers	7 (9.2%)	4 (5.3%)
Relative worked with asbestos	9 (11.8%)	1 (1.3%)
Dockers handling asbestos cargo	0	2 (2.6%)
No history of exposure to asbestos	36 (47.4%)	67 (88.2%)

*7 cases of mesothelioma could not be traced and are omitted from this table.

† Positive exposures to asbestos.

‡ Positive histories. $\chi^2 = 27.11$, $P < .001$ for Mesothelioma versus Control series.

this age and older was taken from a neighboring geriatric hospital. The same interviewer and techniques were used for the mesothelioma and control series but for the latter, in which the patient rather than a relative was seen, it was much easier to obtain detailed and accurate histories. Subsequent analysis of the jobs showed that, according to the Registrar General's classification, there was no significant difference in the social classes of the two series.

Results

No information about past domestic and occupational histories was available in seven patients with mesothelial tumors, six of whom had died before 1950, one as early as 1917 and another in 1922. Among the remaining 76, 40 (52.6 per cent) gave a history of exposure to asbestos, compared with only nine (11.8 per cent) of the control series (TABLE 2). This difference is statistically highly significant ($\chi^2 = 27.11$, $P < .001$).

Occupational Exposures (Mesothelioma Series)

There are particularly accurate details available of the 18 mesothelioma patients who had worked at a large asbestos factory. Eleven started work before 1933 (the date when the asbestos regulations controlling the manufacture of asbestos goods and the protection of asbestos workers became effective) and seven later, but none after 1943. This factory originally used crocidolite asbestos with small amounts of chrysotile; amosite was first introduced in 1926.

Among the nine women the period of employment was usually short, varying between six months and two years, with only one working as long as six years. Among the nine men the period of employment was usually much longer, only three were employed for less than two years, three for between five and 14 years and three for more than 20 years. In one woman it was not possible to verify the actual job. The occupations of the remaining 17 employees and the type of asbestos used are shown in TABLE 3. All had used crocidolite asbestos. Only the first four occupations listed are scheduled as requiring medical supervision under the Asbestos Regulations of 1931.

Four patients in the mesothelioma series were working at other factories, making all types of asbestos goods. One patient had been employed in a wagon works sawing asbestos sheets for partitions. Except for one patient, a woman employed in insulating electrodes with crocidolite, the types of asbestos used in these factories are not known.

The heating engineers and laggers were all men: five had been employed in dockyards on ship repairs, one in a power station, and one specialized in installing hospital sterilizing equipment. All were consistently employed

TABLE 3
JOBS OF 17* PATIENTS EMPLOYED AT ONE ASBESTOS FACTORY

Statutory obligations	Job	Males	Females	Material
Subject to regulations	Spinning	0	4	Crocidolite
	Carding	1	1	Crocidolite
	Clothing and weaving	1	0	Crocidolite Chrysotile Amosite
	Disintegrating and opening	2	1	Crocidolite Chrysotile Amosite
Not subject to regulations	Filter making for ARP masks	2	0	Crocidolite
	Manufacturing of preformed pipe insulation	1	1	Crocidolite
	Manufacturing of brake linings	1	0	Crocidolite
	Rubber compounding	0	1	Crocidolite Chrysotile
	General laborer	1	0	Crocidolite Chrysotile Amosite

*Employment history not available for one female patient.

in this type of work for more than 20 years, but their exposure to asbestos was intermitttent.

Exposure of Relatives (Mesothelioma Series)

The group of nine, seven women and two men, whose relatives worked with asbestos, are of particular interest. The most usual history was that of the wife who washed her husband's dungarees or work clothes. In one instance we were told that the husband, a docker, came home "white with asbestos" every evening for three or four years and she brushed him down. The two men in this group, when boys of eight or nine years old, had sisters who were working at the asbestos factory where others of this series were employed. One of these girls worked as a spinner from 1925

:o 1936. In 1947 she died of asbestosis. The press report of the inquest ıtates, "she used to return home from work with dust on her clothes." Her ɔrother had no other exposure to asbestos, he started work as a shop as-ıistant, then became a sawyer of iron girders until 1948 when he worked ıs a loader of groceries in the docks for five years (but never on dusty :argoes) and then returned to sawing iron girders. He died in 1956.

Types of Exposure of Control Series

Two of the control series had worked in asbestos factories; four as aggers; the husband of another was employed at the large asbestos fac-:ory for three years, and two dockers gave histories of handling asbestos :argoes from time to time throughout their working life.

The diagnoses of these patients have been grouped into eight categories (TABLE 4). The patients with a positive history of exposure are scattered throughout the various diagnostic groups. The individual diagnoses of these patients do not suggest that exposure to asbestos could in any way be related to the disease which had caused their admission.

TABLE 4
DISEASE GROUPS OF PATIENTS IN CONTROL SERIES

Disease group	Number of patients	Number with exposure to asbestos
Cardiovascular disease	21	3
Metabolic disease	9	0
Reticuloendothelial disease (including anemias)	8	2
Gastrointestinal disease (excluding cancers)	6	2
Respiratory disease (excluding cancers)	3	0
All neoplasms	18	1
Other diseases	11	1
Total	76	9

Neighborhood Exposures

Among the 36 affected patients, and the 67 patients in the control series, who had neither an occupational exposure nor a relative living in the home working with asbestos, there is a further group who could have been exposed to asbestos dust because they lived in the immediate vicinity of an asbestos factory.

The factory where more than a fifth of the series were employed opened in 1913, having been situated nearer the City of London for the previous seven years. There were three affected female patients living within half a mile of the factory during the seven years it was in production at its first site. At the time it opened they were children between five and seven years old. At the present site, there were eight patients living within a half mile radius of the factory. One, a male, was born within a quarter of a mile of the factory in 1922 and remained at the same address for 16 years. The other seven were females and aged between six and 13 when the factory opened. They remained in the area for only between three and seven years, except for one who remained at the same address until she died 48 years later.

Among the control series, there is one man who between the ages of seven and 14 lived near the factory at its previous site, and three women and one man who lived near its present site. One of the women was 22 years of age when she moved into the neighborhood in 1915. She disliked it and, when interviewed, complained impartially about the dust from the asbestos factory and the rats in the house.

Thus, among those with no occupational or domestic exposures to asbestos there are 11 (30.6 per cent) of the patients in the mesothelioma series and five (7.6 per cent) in the control series who lived within half a mile of the factory at its present and previous sites (TABLE 5). The difference in the proportion of the patients in the two series who lived in the

TABLE 5
RESIDENCE OF PATIENTS WITH NO OCCUPATIONAL OR DOMESTIC EXPOSURE TO ASBESTOS

Category	Lived within 1/2-mile of asbestos factory		Lived more than 1/2-mile from asbestos factory		Total
Mesothelioma series	11	(30.6%)	25	(69.4%)	36
Control series	5	(7.5%)	62	(92.5%)	67

$\chi^2 = 7.85$, $P < .01$

vicinity of the factory and had no other exposure to asbestos is statistically significant ($\chi^2=7.85$, $P<.01$).

Including the 11 patients who lived near the asbestos factory there are 51 who had been exposed to asbestos. In 39, exposure first occurred before 1930, in the remaining 12, before 1943. The interval between first exposure and onset of symptoms varied between 16 and 55 years (mean 37.5). The duration of exposure also varied widely, ranging from five weeks to over 50 years.

Discussion

Among those traced in the mesothelioma series there are 15 men and 10 women in whom no evidence could be found of an exposure to asbestos. A chief source of information was a history taken from a surviving relative. A surprising amount of information was obtained, but in some of those interviewed the memory may have been defective, or they may not have known of short periods of exposure during the youth of the deceased. One of the patients was eventually identified as having worked at the large asbestos factory for five weeks in 1941, but this was before he married and his widow did not know of this episode. A colored man born in South Africa worked as a merchant seaman for much of his life; he may have been exposed in the asbestos mines or to cargoes carried at sea, but it was not possible to get any details of his life in South Africa or his work at sea. There is also evidence that some of these 25 patients may have lived close to other asbestos factories in the London area.

It is of interest that both industrial and nonindustrial exposures were recognized. Among the men the exposure was predominantly industrial: 22 worked in asbestos factories or as laggers, two were exposed at home, and one lived near the asbestos factory; whereas among the women only 10 worked in asbestos factories and a further 17 had nonindustrial exposures, seven in the home and 10 living near asbestos factories.

In this series there is no evidence that the patients with peritoneal tumors differed in the type of exposure they experienced from those with pleural tumors. A higher proportion of women were affected by peritoneal tumors, but the difference was not statistically significant.

The recent increase in the number of cases diagnosed at the hospital may be partly due to mounting interest in the disease and partly to the long interval between first exposure and development of the tumor. Those exposed between 1915 and 1925 might be expected to die from about 1950 onwards. Asbestos imports in the United Kingdom have mounted steeply since 1932 (Leathart, 1964) and its uses are becoming very diversified in industry. The increasing proportion of the population exposed to asbestos during the past 30 years may be expected to give rise to an increasing occurrence of mesothelial tumors.

There seems little doubt of the risk of both occupational and domestic exposure of asbestos. Wagner *et al.* (1950) described patients with no other exposure except living as a child in the vicinity of the asbestos mines. A high incidence of asbestos plaques of the pleura has been found in the population living near an anthophyllite mine in Finland (Kiviluoto, 1960). More evidence is required of an increased risk to the population living in the neighborhood of asbestos factories or other areas, such as dockyards, where asbestos is used in quantity.

The occurrence of tumors after exposure of less than a year's duration strongly suggests that personal factors are important in the etiology of this disease. There is a need for studies of whole populations where more is known about the duration and type of exposure of all at risk, so that dose–response relationships can be evaluated.

Summary

Two groups of patients who have attended a large hospital in the East End of London have been examined to determine their exposure to asbestos.

The first consisted of 83 patients in whom the diagnosis of mesothelioma had been confirmed at autopsy or by biopsy. In all but seven, past occupational and domestic histories were obtained. In 22 patients the tumor was peritoneal in origin, in 61 pleural. The earliest recorded death was 1917, but only 10 of the series died before 1950. Fifty-five per cent of the males and 42 per cent of the females died under the age of 55. The interval between first exposure and development of terminal illness ranged between 16 and 55 years (mean 37 years).

The second group consisted of 76 patients of the same hospital, matched by sex and date of birth with those traced in the first series.

Of the patients suffering from mesotheliomata 52.6 per cent had been exposed to asbestos, as compared to 11.8 per cent of the control series. The difference in the proportion of patients with known exposures in the two series is highly significant ($\chi^2 = 29.1$, $P < .001$). Three main types of exposure were recognized: work in factories manufacturing asbestos textiles, insulating materials, and other products; employment as laggers or insulators; and exposure to dust brought home by relatives working with asbestos. Eighteen of those employed in factory work and four whose relatives were working with asbestos were employed at one factory. This factory opened in 1913 and was, until recent years, a heavy user of crocidolite; all those whose records could be traced worked with this type of asbestos.

Among the 36 patients with mesotheliomata, with no positive occupational history and no relatives living at home who worked with asbestos, there were 11 who lived within half a mile of an asbestos factory; five of the control series also lived in the same area. The difference in the pro-

portion of patients in the two series is also statistically significant ($\chi^2 = 7.85$, $P < .01$).

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DISCUSSION

THOMAS F. MANCUSO (*University of Pittsburgh, Pittsburgh, Pa.*) Dr. Newhouse's work and observations, and those of Dr. Wagner brin out a striking resemblance between the accumulating data on asbestos an those on beryllium. Years ago, the first cases of berylliosis (then an unusu disease) were identified in a tuberculosis sanitorium. This is brought t mind by recent observations concerning mesotheliomas, made in a sani torium in South Africa, as reported by Wagner and his co-workers. Dr Hardy observed berylliosis in household members of the families of beryl lium workers, and subsequent studies demonstrated the release of berylliu in the laundering and handling of work clothes of beryllium workers. Simi larly, Dr. Newhouse has observed mesotheliomas among the relatives i the household of asbestos workers, who had laundered their work clothe The resemblance continues with biological effects of air pollution. Beryll osis was observed among resident nonemployees within a certain radiu of beryllium manufacturing plants in Ohio and Pennsylvania, and Dr Newhouse and Wagner have reported mesotheliomas, and Kiviluoto pleur plaques, of residents living within a certain radius of asbestos factory an mining operations.

The second point I should like to make is the evidence provided by Dr Newhouse and Dr. Wagner and by other speakers, of the very long late period between initial exposure to asbestos and the development of mes theliomas and lung cancer. The latent period may average 37 years a extend to 60 years. There is also some evidence of the effect of duratio of employment.

In view of these observations, it would seem inadvisable now to calculat mortality rates upon a population which includes the younger age grou such as recording the observed and expected deaths for the combined age 25-64. It would be more appropriate to utilize a minimum age of 35, a least in the U. S. and to extend the upper age group. We intend to tak this into consideration in our future studies.

In Dr. Newhouse's study, we have a good illustration of what can b accomplished by retrospective studies, by personal contacts and interview even though many years have elapsed. It is evident that because of th long latent period, much of the future work pertaining to mesotheliom will follow a similar approach.

I should also like to emphasize the importance of all biological effec of asbestos, not just the relationship to malignancy or the extent of a bestosis, but other related effects such as bronchitis, bronchiectasis, em physema, cor pulmonale, chronic pneumonia, etc. This in effect, point out the advisability of studying multiple causes of death in industri health studies of asbestos workers, otherwise the extent and significan