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t over the 5-year interval
to secondary myopathic

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drome are character-
those caused by other
clinical onset for the
is 4 months,[6] 9–18
forms,[7] and 38 years
-onset form.[8] Clinical
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A. genes tend to cause
the age of 8–9 years,
s point awaits further

PATIENTS WITH S.M.A.
SET

Walking unaided	Latest age able to run yr
No*	16
Yes	13
Yes	16
Yes	15
Yes	20–23

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unger brother has a wad-

11-year-old boy who had had clinical features of muscle weakness and scoliosis for at least 5 years before the development of obvious calf hypertrophy.

3 of the 4 index patients we described (cases 1, 2, and 3) were traced as part of a major study of S.M.A. which comprised 102 cases in North-East England. Male cases of the new syndrome resemble X-linked Becker muscular dystrophy, a more common condition.

We recognised other cases of this newly identified syndrome within reported case series of S.M.A. Bundey and Lovelace[2] described two brothers with adolescent-onset S.M.A. with calf hypertrophy, and other examples are known.[9] The X-linked recessive inheritance noted in cases 3 and 4 of the current series emphasises the need to consider this syndrome in the differential diagnosis of Becker muscular dystrophy. This newly described syndrome should also be considered when simple male cases of S.M.A. are found within otherwise unaffected families. Several examples of X-linked recessive S.M.A. of late onset, but without hypertrophy of calves, are also known.[14,15]

The apparent homogeneity of cases with this syndrome is further evidence for a broadening of differential diagnosis in cases of apparent muscular dystrophy.

We thank Prof. J. Walton and Prof. D. A. Shaw for permission to quote from case notes of patients who have been under their care.

Requests for reprints should be addressed to J. P., Department of Child Health, Royal Children's Hospital, Brisbane, Australia 4029.

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NON-OCCUPATIONAL EXPOSURE TO ASBESTOS AND MALIGNANT MESOTHELIOMA IN FEMALES

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Summary A study of the occupational histories of 52 females with malignant mesothelioma and certain of their relatives, carried out to measure the risk of this disorder attributable to indirect asbestos exposure, showed that a significantly greater number of husbands and fathers of cases than of controls worked in asbestos-related industries, and the relative risk for this factor was 10. The frequency of parental cancer, especially gastrointestinal malignancy, was also significantly greater for cases than for their controls. This raises the possibility of a genetic predisposition to malignant mesothelioma.

Introduction

THE occupational hazards of working with asbestos are well established,[1] but the hazards of exposure to asbestos in the general environment is unclear. Although there is no convincing evidence that indirect exposure contributes to the occurrence of mesotheliomas, there have been numerous reports of this rare tumour in individuals exposed at home to dusty clothing or to a source of asbestos air pollution (e.g. mines, factories) in the neighbourhood.[3–9] We assessed the possibility that household exposure might be a major risk factor for females with malignant mesotheliomas.

Methods

All female residents of New York State (excluding New York City), aged 20 years and more, who died with histologically confirmed malignant mesothelioma between 1967 and 1977 and were reported to the Bureau of Vital Records of the State Health Department, were included in a case-control study. For each patient 1 matched control who died in the same year and of a cause other than cancer was selected from the records of the above Bureau by the following criteria: same 5-year age group at death, sex, race, and county of residence (where possible the same census subdivision, as defined by the U.S. Bureau of Census, Washington, D.C.). Cases and controls were also matched for marital status at the time of diagnosis, the information being obtained from their medical records. Where more than one individual satisfied the criteria, a table of random numbers was used to select a control. Field investigators used a set questionnaire to obtain occupational histories for all patients, controls, and their fathers and husbands up to the time of diagnosis. Occupational histories of mothers and sibs of patients and controls were also obtained, but not analysed. Additional information on exposure was obtained from medical records, industrial reports, and on-site visits to the homes of patients and controls. Medical, personal, family, and residential histories were also obtained. Where possible the homes of patients and controls up to the time of diagnosis were plotted on maps which showed the locations of industries using asbestos in New York. Classification by social status was by the main occupations of the husbands of patients and controls or of patients themselves (if single) and graded according to that used for census purposes (high—professionals, managerial staff; low—labourers, and farm, service, and private household workers).

For statistical purposes, patients and their matched controls were subdivided according to whether their occupations were asbestos related (as defined by Hamilton and Hardy[16]) or not. The occupations of their fathers and/or husbands were subdivided according to whether exposure was to asbestos or to other pneumoconiosis-inducing particles (e.g. silica). In each instance the frequencies of the two cells which showed dissimilar histories were tested using the binomial $p = q = \frac{1}{2}$ (where p equals the probability of success and q the probability of failure) for small frequencies and the McNemar χ^2 test for large frequencies.

Results

65 females were reported to have died from malignant mesotheliomas during the 11-year study period, but only 52 (32 pleural and 20 peritoneal) were histologically confirmed. The mean age at diagnosis for the confirmed

CLINICAL DATA OF FIFTEEN FEMALE PATIENTS WHO HAD MALIGNANT MESOTHELIOMA IN NEW YORK STATE (EXCLUDING NEW YORK CITY) BETWEEN 1967 AND 1977, AND THEIR EXPOSURE TO ASBESTOS

Patient	Age at diagnosis (yr)	Year of diagnosis	Site* of mesothelioma	Type of asbestos exposure				Possible duration of exposure† before diagnosis (yr)
				Occupational			Residential	
				Patient	Husband	Father		
A	52	1971	P	Textile worker				5
B	85	1974	Pl	Shoemaker	Shoemaker			21
C	79	1974	Pl	Textile worker	Brake-lining worker			23
D	54	1975	Pl	Textile worker				2
E	52	1973	P	Textile worker				1
F	67	1974	P	Milliner				25
G	66	1969	Pl		Pipe fitter			6
H	40	1968	Pl		Brake-lining worker		Brake-lining company	15
I	44	1973	Pl		Heat insulation worker			18
J	31	1969	Pl		Heat-electric wire worker			14
K	51	1974	P		Heat insulation worker	Elevator insulation worker		15
L	30	1974	Pl		Heat insulation worker			5
M	75	1975	Pl			Electric wire insulation worker	Electric wire cable company	15
N	77	1975	Pl		Brake-lining worker			10
O	52	1973	Pl				Asbestos factory	18

* P—Peritoneal, Pl—Pleural
† Exposures during different periods were added.

cases was 60·2 years (range 22–86 years), and all were Caucasian. The accompanying table summarises data on the 15 patients who could be said to have had some exposure to asbestos before diagnosis. 6 patients (A–F) worked in asbestos-related occupations, whereas none of their matched controls had positive histories. However, there were 2 instances of reverse exposure; that is the controls worked with asbestos textiles for 3–7 years but their cases did not ($P=0·1$). The median age at diagnosis for patients A–F was 60·5 years (mean 64·8 years).

10 patients (B, C, and G–N) had husbands and/or fathers who worked in asbestos-related occupations, whereas their matched controls did not. All these patients routinely hand-laundered their husbands' (or fathers') clothing. Patients G–N were either housewives or were employed as secretaries and clerks in non-asbestos-related industries. In only one instance did the case's husband and father not have positive occupational histories, while her matched control's husband worked in the heat insulating industry for 20 years of their married life ($P=0·006$). The estimated relative risk of mesothelioma for this pattern of exposure to asbestos is 10 with a 95% confidence interval of 1·42 to 37·40. If the two instances (patients B, C) where both the patients and their husbands worked in asbestos-related occupations are excluded, the probability (8 or more out of 9) is 0·02. The median age at diagnosis for the 10 patients with this type of exposure was 58·5 years (mean 57·8 years).

17 patients had fathers and/or husbands whose occupations were associated with pneumoconioses other than asbestosis, but the relatives of their controls were not. None of these cases or their matched controls had histories of asbestosis or other pneumoconioses. For 12 patients the reverse was true (relatives of cases not exposed to other forms of pneumoconioses, controls exposed, $P>0·05$).

85% of cases and 73% of controls had lived in the same county for 20 years before death, and there was no significant difference between these people and those who had lived for less than 20 years in the same county. 2 patients (H and M) lived within 3·6 km of factories using asbestos in New York State for 20–27 years before diagnosis. Another patient (O) lived approximately 1·2 km from an asbestos textile factory for 18 years in Leeds, England. Interestingly, her sister worked in this factory for 5 years and had a pleural mesothelioma in 1973. None of the controls lived within 8 km of asbestos factories. Patients H and M also had relatives who worked with asbestos.

There was no difference between subjects and controls in their race, religion, duration of married life before death, other illnesses requiring hospital admission, personal histories, and socioeconomic status. 17 patients had mothers or fathers who had other malignancies, but the parents of their matched controls did not, whereas the reverse occurred in 5 pairs, i.e., parents of cases had no malignancies, and those of controls did ($P=0·008$). We found no evidence suggesting that affected parents worked in asbestos-related occupations. Gastrointestinal malignancies were commonest (mothers—stomach 2; intestine 2; fathers—intestine 3). The parents of only 2 controls had similar histories. There were no mesotheliomas among the parents of patients or their controls. The mean age at diagnosis of patients whose mothers or fathers had a history of cancer was 55·9 years (median 53 years). This was lower than the mean age for the 13 study patients who had no parental history of cancer (62·3 years), but the difference was not statistically significant (t test, $P>0·05$). Husbands in the two groups did not differ significantly in their cancer histories ($P=0·1$). In 24 instances the spouses of both the patient and matched control were interviewed, whereas for the other 28 pairs another first-degree relative (parent or sib

CANCER RESEARCH UNIT UNIVERSITY OF NEWCASTLE UPON TYNE

Possible duration of exposure† before diagnosis (yr)
5
21
23
2
1
25
6
15
18
14
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18

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parent or sib

was contacted. The two groups of responders did not differ in their answers to the question of asbestos-related occupations in that both groups gave an equal proportion of positive responses.

Discussion

Our results suggest that women run the risk of malignant mesothelioma not only if they work in asbestos-related industries but also if they are indirectly exposed to environmental asbestos. The husband's occupation was clearly the most important risk factor, but 6 of our patients also lived in environments where more than one source of exposure was likely. The importance of other non-occupational exposures varies with the types of industry (e.g., asbestos mines[3] and factories,[4] shipyards, etc.[11-13]) present in an area and their proximity to homes. Residential exposure might be especially important in large cities,[4] whereas in less densely populated areas such as New York (excluding New York City) this might not be a significant risk factor.

It is not clear whether a dose-response gradient exists for malignant mesotheliomas. Studies of workers in the chrysotile mining and milling industry in Quebec[14] and in factories manufacturing asbestos products[15] suggest that only highly exposed groups have an increased risk for lung cancer and mesotheliomas. In addition Whitwell et al.[16] found that dried lung tissue of patients who died of this disorder contained over 100 000 asbestos fibres per gram. But our findings on indirect exposure and those of other occupational studies[13,17-19] support the suggestion that the incidence of mesothelioma is not related simply to the magnitude of dust exposure. The physical properties of certain types of asbestos might partially alter the actual dose of asbestos to which a person is exposed. For example, the incidence of mesothelioma in people who work with chrysotile asbestos is considerably lower than that in those exposed to crocidolite or amosite,[20] possibly because chrysotile fibres are curly and more readily arrested in the upper respiratory tract.[20] Pulverisation of chrysotile fibres does produce a higher incidence of mesotheliomas in animal experiments.[21] Industrial operations which enhance the probability of entry to the periphery of the lung, such as those which promote aerosol formation, might be another dose-modifying factor which influences the pathological response to asbestos. Unlike most forms of dust, particles the size of droplet nuclei settle very slowly, and most are carried along in the inhaled air.[22] Insulation workers appear to have a higher risk of mesothelioma than factory workers making asbestos products. This might be due to the aerosol effect which can occur when insulating cement powders are mixed with water. Interestingly 5 of our patients had husbands and/or fathers employed in the insulating industry. In contrast, the high frequency of asbestosis in textile workers[18] might be related to the high droplet-nuclei index (volume count/setting count) which occurs when spun fibre is woven into asbestos fabric.

The unusually high frequency of cancer among the parents of mesothelioma patients is difficult to interpret. It could merely indicate that mesothelioma patients come from cancer-prone families. Experimental studies suggest that the histological response to asbestos varies with different animal species,[23-25] and in man genetic factors might alter susceptibility to mesothelioma. This possibility gains some support from the fact that the mean age at diagnosis of patients with a parental history of cancer was somewhat lower than that for all other study patients. Although many questions about the pathophysiology of asbestos-related disorders remain unresolved, it seems clear that simple preventive measures, directed at how and where work clothes are laundered, might greatly reduce the frequency of malignant mesothelioma.

Requests for reprints should be addressed to N. J. V.

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CLOSTRIDIUM DIFFICILE AND THE ÆTIOLOGY OF PSEUDOMEMBRANOUS COLITIS

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Summary Bacterial isolates from 5 patients with pseudomembranous colitis (P.M.C.) were screened for toxin production. Strains of *Clostridium* from 4 patients produced in vitro a toxin similar to that found in P.M.C. fæcal suspension. These were identified as *C. difficile*. Use of the strains from 2 patients induced a fatal enterocolitis when inoculated orally into hams-

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11-year-old boy who had had clinical features of muscle weakness and scoliosis for at least 5 years before the development of obvious calf hypertrophy.

3 of the 4 index patients we described (cases 1, 2, and 3) were traced as part of a major study of S.M.A. which comprised 102 cases in North-East England. Male cases of the new syndrome resemble X-linked Becker muscular dystrophy, a more common condition.

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NON-OCCUPATIONAL EXPOSURE TO ASBESTOS AND MALIGNANT MESOTHELIOMA IN FEMALES

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Summary A study of the occupational histories of 52 females with malignant mesothelioma and certain of their relatives, carried out to measure the risk of this disorder attributable to indirect asbestos exposure, showed that a significantly greater number of husbands and fathers of cases than of controls worked in asbestos-related industries, and the relative risk for this factor was 10. The frequency of parental cancer, especially gastrointestinal malignancy, was also significantly greater for cases than for their controls. This raises the possibility of a genetic predisposition to malignant mesothelioma.

Introduction

THE occupational hazards of working with asbestos are well established,[1] but the hazards of exposure to asbestos in the general environment is unclear.[2] Although there is no convincing evidence that indirect exposure contributes to the occurrence of mesotheliomas, there have been numerous reports of this rare tumour in individuals exposed at home to dusty clothing or to a source of asbestos air pollution (e.g. mines, factories) in the neighbourhood.[3-9] We assessed the possibility that household exposure might be a major risk factor for females with malignant mesotheliomas.

Methods

All female residents of New York State (excluding New York City), aged 20 years and more, who died with histologically confirmed malignant mesothelioma between 1967 and 1977, and were reported to the Bureau of Vital Records of the State Health Department, were included in a case-control study. For each patient 1 matched control who died in the same year and of a cause other than cancer was selected from the records of the above Bureau by the following criteria: same 5-year age-group at death, sex, race, and county of residence (where possible the same census subdivision, as defined by the U.S. Bureau of Census, Washington, D.C.). Cases and controls were also matched for marital status at the time of diagnosis, the information being obtained from their medical records. When more than one individual satisfied the criteria, a table of random numbers was used to select a control. Field investigators used a set questionnaire to obtain occupational histories for all patients, controls, and their fathers and husbands up to the time of diagnosis. Occupational histories of mothers and sibs of patients and controls were also obtained, but not analysed. Additional information on exposure was obtained from medical records, industrial reports, and on-site visits to the homes of patients and controls. Medical, personal, family, and residential histories were also obtained. Where possible the homes of patients and controls up to the time of diagnosis were plotted on maps which showed the locations of industries using asbestos in New York. Classification by social status was by the main occupations of the husbands of patients and controls or of patients themselves (if single) and graded according to that used for census purposes (high—professionals, managerial staff; low—labourers, and farm, service, and private household workers).

For statistical purposes, patients and their matched controls were subdivided according to whether their occupations were asbestos related (as defined by Hamilton and Hardy[10]) or not. The occupations of their fathers and/or husbands were subdivided according to whether exposure was to asbestos or to other pneumoconiosis-inducing particles (e.g. silica). In each instance the frequencies of the two cells which showed dissimilar histories were tested using the binomial $p = q = \frac{1}{2}$ where p equals the probability of success and q the probability of failure for small frequencies and the McNemar (χ^2) test for large frequencies.

Results

65 females were reported to have died from malignant mesotheliomas during the 11-year study period, but only 52 (32 pleural and 20 peritoneal) were histologically confirmed. The mean age at diagnosis for the confirmed

CLINICAL DATA OF FIFTEEN FEMALE PATIENTS WHO HAD MALIGNANT MESOTHELIOMA IN NEW YORK STATE (EXCLUDING NEW YORK CITY) BETWEEN 1967 AND 1977, AND THEIR EXPOSURE TO ASBESTOS

Patient	Age at diagnosis (yr)	Year of diagnosis	Site* of mesothelioma	Type of asbestos exposure				Possible duration of exposure† before diagnosis (yr)
				Occupational			Residential	
				Patient	Husband	Father		
A	52	1971	P	Textile worker				3
B	85	1974	Pl	Shoemaker	Shoemaker			21
C	79	1974	Pl	Textile worker	Brake-lining worker			23
D	54	1975	Pl	Textile worker				2
E	52	1973	P	Textile worker				1
F	67	1974	P	Milliner				25
G	66	1969	Pl		Pipe fitter			6
H	40	1968	Pl		Brake-lining worker		Brake-lining company	15
I	44	1973	Pl		Heat insulation worker			18
J	31	1969	Pl		Heat-electric wire worker			14
K	51	1974	P		Heat insulation worker	Elevator insulation worker		15
L	30	1974	Pl		Heat insulation worker			5
M	75	1975	Pl			Electric wire insulation worker	Electric wire cable company	15
N	77	1975	Pl		Brake-lining worker			10
O	52	1973	Pl				Asbestos factory	18

* P—Peritoneal, Pl—Pleural
† Exposures during different periods were added.

cases was 60·2 years (range 22–86 years), and all were Caucasian. The accompanying table summarises data on the 15 patients who could be said to have had some exposure to asbestos before diagnosis. 6 patients (A–F) worked in asbestos-related occupations, whereas none of their matched controls had positive histories. However, there were 2 instances of reverse exposure; that is the controls worked with asbestos textiles for 3–7 years but their cases did not ($P=0·1$). The median age at diagnosis for patients A–F was 60·5 years (mean 64·8 years).

10 patients (B, C, and G–N) had husbands and/or fathers who worked in asbestos-related occupations, whereas their matched controls did not. All these patients routinely hand-laundered their husbands' (or fathers') clothing. Patients G–N were either housewives or were employed as secretaries and clerks in non-asbestos-related industries. In only one instance did the case's husband and father not have positive occupational histories, while her matched control's husband worked in the heat insulating industry for 20 years of their married life ($P=0·006$). The estimated relative risk of mesothelioma for this pattern of exposure to asbestos is 10 with a 95% confidence interval of 1·42 to 37·40. If the two instances (patients B, C) where both the patients and their husbands worked in asbestos-related occupations are excluded, the probability (8 or more out of 9) is 0·02. The median age at diagnosis for the 10 patients with this type of exposure was 58·5 years (mean 57·8 years).

17 patients had fathers and/or husbands whose occupations were associated with pneumoconioses other than asbestosis, but the relatives of their controls were not. None of these cases or their matched controls had histories of asbestosis or other pneumoconioses. For 12 patients the reverse was true (relatives of cases not exposed to other forms of pneumoconioses, controls exposed, $P>0·05$).

85% of cases and 73% of controls had lived in the same county for 20 years before death, and there was no significant difference between these people and those who had lived for less than 20 years in the same county. 2 patients (H and M) lived within 3·6 km of factories using asbestos in New York State for 20–27 years before diagnosis. Another patient (O) lived approximately 1·2 km from an asbestos textile factory for 18 years in Leeds, England. Interestingly, her sister worked in this factory for 5 years and had a pleural mesothelioma in 1973. None of the controls lived within 8 km of asbestos factories. Patients H and M also had relatives who worked with asbestos.

There was no difference between subjects and controls in their race, religion, duration of married life before death, other illnesses requiring hospital admission, personal histories, and socioeconomic status. 17 patients had mothers or fathers who had other malignancies, but the parents of their matched controls did not, whereas the reverse occurred in 5 pairs, i.e., parents of cases had no malignancies, and those of controls did ($P=0·008$). We found no evidence suggesting that affected parents worked in asbestos-related occupations. Gastrointestinal malignancies were commonest (mothers—stomach 2, intestine 2; fathers—intestine 3). The parents of only 2 controls had similar histories. There were no mesotheliomas among the parents of patients or their controls. The mean age at diagnosis of patients whose mothers or fathers had a history of cancer was 55·9 years (median 53 years). This was lower than the mean age for the 35 study patients who had no parental history of cancer (62·3 years), but the difference was not statistically significant (t test, $P>0·05$). Husbands in the two groups did not differ significantly in their cancer histories ($P=0·1$). In 24 instances the spouses of both the patient and matched control were interviewed, whereas for the other 28 pairs another first-degree relative (parent or sib)

was contacted. The two groups of responders did not differ in their answers to the question of asbestos-related occupations in that both groups gave an equal proportion of positive responses.

Discussion

Our results suggest that women run the risk of malignant mesothelioma not only if they work in asbestos-related industries but also if they are indirectly exposed to environmental asbestos. The husband's occupation was clearly the most important risk factor, but 6 of our patients also lived in environments where more than one source of exposure was likely. The importance of other non-occupational exposures varies with the types of industry (e.g. asbestos mines[3] and factories,[4] shipyards, etc.[11-13]) present in an area and their proximity to homes. Residential exposure might be especially important in large cities,[4] whereas in less densely populated areas such as New York (excluding New York City) this might not be a significant risk factor.

It is not clear whether a dose-response gradient exists for malignant mesotheliomas. Studies of workers in the chrysotile mining and milling industry in Quebec[14] and in factories manufacturing asbestos products[15] suggest that only highly exposed groups have an increased risk for lung cancer and mesotheliomas. In addition Whitwell et al.[16] found that dried lung tissue of patients who died of this disorder contained over 100 000 asbestos fibres per gram. But our findings on indirect exposure and those of other occupational studies[13,17-19] support the suggestion that the incidence of mesothelioma is not related simply to the magnitude of dust exposure. The physical properties of certain types of asbestos might partially alter the actual dose of asbestos to which a person is exposed. For example, the incidence of mesothelioma in people who work with chrysotile asbestos is considerably lower than that in those exposed to crocidolite or amosite,[20] possibly because chrysotile fibres are curly and more readily arrested in the upper respiratory tract.[20] Pulverisation of chrysotile fibres does produce a higher incidence of mesotheliomas in animal experiments.[21] Industrial operations which enhance the probability of entry to the periphery of the lung, such as those which promote aerosol formation, might be another dose-modifying factor which influences the pathological response to asbestos. Unlike most forms of dust, particles the size of droplet nuclei settle very slowly, and most are carried along in the inhaled air.[22] Insulation workers appear to have a higher risk of mesothelioma than factory workers making asbestos products. This might be due to the aerosol effect which can occur when insulating cement powders are mixed with water. Interestingly 5 of our patients had husbands and/or fathers employed in the insulating industry. In contrast, the high frequency of asbestosis in textile workers[18] might be related to the high droplet-nuclei index (volume count/setting count) which occurs when spun fibre is woven into asbestos fabric.

The unusually high frequency of cancer among the parents of mesothelioma patients is difficult to interpret. It could merely indicate that mesothelioma patients come from cancer-prone families. Experimental studies suggest that the histological response to asbestos varies with different animal species,[23-25] and in man genetic factors might alter susceptibility to mesothelioma. This possibility gains some support from the fact that the mean age at diagnosis of patients with a parental history of cancer was somewhat lower than that for all other study patients. Although many questions about the pathophysiology of asbestos-related disorders remain unresolved, it seems clear that simple preventive measures, directed at how and where work clothes are laundered, might greatly reduce the frequency of malignant mesothelioma.

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CLOSTRIDIUM DIFFICILE AND THE ÆTIOLOGY OF PSEUDOMEMBRANOUS COLITIS

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Summary Bacterial isolates from 5 patients with pseudomembranous colitis (P.M.C.) were screened for toxin production. Strains of *Clostridium* from 4 patients produced in vitro a toxin similar to that found in P.M.C. faecal suspension. These were identified as *C. difficile*. Use of the strains from 2 patients induced a fatal enterocolitis when inoculated orally into hams-