

FILE NAME: Brakes (BRK)

DATE: 1972

DOC#: BRK03y

DOCUMENT DESCRIPTION: W2dzNj1-f ! NÚŕÖfŜ π tŜNÚ2yŜI-f a Šă2úKŜt2YI-

## CURRENT CLINICAL CONCEPTS

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### PERITONEAL MESOTHELIOMA

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The filmy mesothelial layer that lines the abdominal cavity and envelopes its contents is exceedingly vulnerable to secondary involvement by a multitude of neoplasms taking origin both within the abdomen and at distant sites. The only cancer primary to the peritoneal surface, however, is the mesothelioma. Recognition of this tumor seems to be unique to the latter half of the 20th century by virtue of either the astuteness or creativity of our pathologists and also by virtue of the sometimes less than wholesome nature of our environment. The remarkably rapid increase in the rate of occurrence of these neoplasms makes it seem likely that they will be an increasingly frequent clinical challenge to the gastroenterologist in the years ahead.

#### Incidence

Prior to the last decade, reported cases of peritoneal mesotheliomas were exceedingly rare, and in 1960 Winslow and Taylor<sup>1</sup> were able to cull only 13 reasonably documented cases from the literature. In the 11 subsequent years, up to this writing, this total has swelled to at least 169 cases in the English literature alone.<sup>1-11</sup> Much of this increase can undoubtedly be attributed to improved pathological recognition, but retrospective studies of necropsy material employing current pathological criteria would also indicate that a

substantial portion of this increase is real.

The incidence of mesotheliomas has a striking relationship to the dominant occupation of the population studied. In Canada, where a large proportion of the populace is engaged in rural pursuits, the average rate of occurrence is 0.1 case per 100,000 of population per year<sup>6</sup>; among heavy industry workers in Dutch provinces, the rate is 1 per 100,000<sup>11</sup>; and in Dutch shipyard workers, it is found to be 100 per 100,000.<sup>11</sup>

The peritoneum is host to mesotheliomas less commonly than is the pleura. In series of mesotheliomas collected from single sources, 257 cases were primary to the pleura, 128 to the peritoneum, and 7 cases seemed to have tumors primary to both surfaces.<sup>1, 4, 6-9, 11, 12</sup> From the standpoint of incidence, as well as etiology and pathology, however, mesotheliomas should best be considered as a whole, regardless of their site of origin.

#### Etiology

With the possible exception of lung cancer, there is no malignant neoplasm for which the relationship of environmental factors to carcinogenesis has been so clearly established as in the mesothelioma.

The first link in this chain of evidence was forged by Wagner and co-workers<sup>13</sup> who demonstrated a remarkable predilection for the development of mesotheliomas among asbestos miners in South Africa. Since then, a number of other studies have associated both pleural

Received January 31, 1972.

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346

*Custodian* Depo. No. 28  
Date 4/29/83 by AAC

and peritoneal mesothelioma with asbestos exposure. Particularly vulnerable occupations are shipyard workers, asbestos textile manufacturing, brake lining installation, insulation workers, and sack repair workers.

With specific regard to peritoneal mesotheliomas, 54 of 84 adequately documented cases<sup>3, 5, 7-9, 11</sup> have had either known occupational exposure to asbestos or demonstration of asbestos bodies of significant number in lung tissue.

A clinching bit of etiological evidence has come from the induction of tumors of mesothelioma histology after inoculation of experimental animals with asbestos fiber.<sup>14</sup> Under these conditions all three varieties of asbestos fiber—amosite, chrysotile, crocidolite—have proved equally carcinogenic.

The duration of exposure has varied widely in mesotheliomas presumed related to asbestos, ranging from less than 1 year<sup>3</sup> to over 50 years.<sup>15</sup> There is uniformly, however, a very long induction period which in several series has averaged between 33 and 43 years,<sup>10, 13, 16</sup> measured from the time of initial asbestos exposure. With the widespread industrial use of asbestos materials in the mid 20th century, it is entirely possible that the years ahead may demonstrate a far more alarming increase in the occurrence of mesothelioma than that which we are already witnessing.

It should be noted that not all mesotheliomas are related to asbestos exposure—the proportion of such patients is related to the occupational pattern of the particular region studied. In McEwen et al.'s<sup>17</sup> study of Scotland, where a large proportion of the population is employed in shipyard industries, 83% gave a positive history of occupational exposure; in the London Hospital series,<sup>7</sup> where occupations were more varied, 38% gave a positive history; and in MacDonald et al.'s<sup>8</sup> Canadian series, only 20% of male patients had an occupational exposure to asbestos and female mesothelioma patients had no greater exposure than control subjects. It is apparent that other, as yet unelucidated etiological factors, may

induce this neoplasm. Of particular interest in this regard is the recent demonstration by Chabot and associates<sup>18</sup> of induction of typical mesotheliomas in the chicken by a strain of MC29 avian leukemia virus.

### Pathology

The histological appearance of the peritoneal mesothelioma is so variable, and in its variability it so closely simulates other recognized neoplasms, that some have challenged the existence of this tumor as a pathological entity. Indeed, many pathologists will still only make the histological diagnosis of "probable mesothelioma" with confirmation resting on such factors as the failure to demonstrate some other primary neoplasm at autopsy or a history of occupational exposure.

The pathological classification employed by Whitwell and Rawcliffe<sup>11</sup> is quite typical of those used in other reports:

1. *A tubulo-papillary form.* These are quite similar to secondary adenocarcinomas and are characterized by branching acini lined by low columnar or cuboidal cells. In contrast to adenocarcinoma, Mucicarmine stains seldom reveal evidence of mucin production; but staining reactions do demonstrate a hyaluronidase—labile mucopolysaccharide around the tumor cells, indicating the presence of hyaluronic acid. A transition zone between normal and neoplastic mesothelium may provide convincing evidence of a peritoneal site of origin.

2. *An undifferentiated polygonal cell type.* Here, uniform eosinophilic polygonal or round tumor cells occur in solid sheets resembling a medullary type of adenocarcinoma. Mitotic figures, however, are quite rare.

3. *A sarcomatous type.* This variety may be indistinguishable from a fibrosarcoma or fibromyxosarcoma. There is a spindle cell, fibroblastic appearance with arrangements in bands or whorls; and multinucleated giant cells may be seen.

4. *A mixed type.* This may contain any of the above elements, and with this mix-

ture histological diagnosis is simplified. The only confusion that may exist is with a primary carcinosarcoma or a malignant synovioma.

Grossly, peritoneal mesotheliomas present in two basic forms. One is with a large tumor mass, usually in the upper abdomen, and discrete smaller nodules scattered over larger areas of the visceral and parietal peritoneum. The other form is that of diffuse nodules and plaques that coat the abdominal cavity and envelope and matt together the abdominal viscera. There is characteristically a striking contrast between the massive abdominal involvement and the minimal visceral invasion and metastatic dissemination. When invasion does occur, it is usually only superficial and tends to follow fascial planes. Large tumors in the abdomen may invade through the diaphragm and involve the diaphragmatic pleural surface. Frequently, death occurs as a result of abdominal involvement alone before there is any detectable metastasis. Nodal metastasis is uncommon and is essentially never observed with the pure sarcomatous form. When metastasis occurs from the mixed histological variety, the metastatic lesions are usually of the tubulo-papillary architecture. Observed sites of blood-borne metastatic spread have included most commonly the liver and lungs, and more infrequently, the adrenals, thyroid, kidneys, pancreas, and bone.

#### Clinical Presentation and Diagnosis

Among 118 reported cases of peritoneal mesothelioma where sex is stated,<sup>1, 2, 3, 5-8</sup> men outnumbered women at a ratio of 67:51. The proportion of men tended to be higher in regions where occupational exposure seemed to play a strong etiological role. The median age at diagnosis was 53 years with a range of from 13 to 92 years of age. Sixty-three per cent of cases occurred between ages 45 and 65.

The most frequent initial symptom is abdominal pain which may be specified as epigastric or right upper quadrant burning, vague and nonlocalized abdom-

inal discomfort, obstructive cramping, or severe paroxysms. Sometimes pain is aggravated by micturition or defecation. Severe weight loss is almost universal, and usually by the time the patient seeks medical assistance, abdominal distention is also evident. Nausea and vomiting, bowel obstruction, and fever are less common complaints.

The most common physical sign is ascites which has been observed in almost 90% of reported cases. A palpable abdominal mass is a much less frequent presenting finding (16%). Occasionally, the disease is first evidenced as an extrarectal or pelvic mass, and rarely it has been first diagnosed incidentally on pathological examination of a hernia sac. Many patients will have respiratory signs and digital clubbing associated with their pulmonary asbestosis.

In company with a variety of other mesenchymal tumors, the mesothelioma has been found rarely to be associated with symptomatic hypoglycemia. Thirteen such cases have been reported,<sup>19</sup> and in 5 the primary tumor has been peritoneal. In some of these, however, the precise diagnosis of mesothelioma may be challenged under today's pathological criteria. It has been evident in these patients that the hypoglycemic syndromes are not related to increased levels of circulating insulin and some other hypoglycemic factor is probably involved. As is true with most of the other non-islet cell hypoglycemic tumors, this factor (or factors) has not been clearly identified. Prominent theories include production of an insulin-like substances by the tumor, irritation of splanchnic nerves, excessive consumption of glucose by the tumor, and an induced disorder of hepatic glycogenolysis.

#### Diagnosis

There are no specific laboratory or roentgenological findings which characterize the peritoneal mesothelioma, and although a clinical impression of abdominal carcinomatosis is usually reached, the specific diagnosis cannot be made

without laparoscopic biopsy and histological interpretation.

Examination of ascitic fluid may be helpful. Occasional mesothelioma may be viscous. Cytology usually reveals atypical epithelial cells, but this finding is not specific and co-wo high acid fast, sterile fluid is strongly suggestive. In some cases, a peritoneal approach, with sufficient diagnostic value.

Unfortunately, the disease has lagged in its etiology and diagnosis. In some instances, and presumably, it has been recorded always well at the time of autopsy, systematic examination of the peritoneum is attempted in all cases. In view of the high incidence, organized therapeutic programs seem to be indicated in regions where the disease is endemic.

Palliative therapy, particularly of severe ascites,

Although survival has been reported in mesothelioma, it follows a progressive and relentless course.

without laparotomy or autopsy. Needle biopsy alone will not provide the pathologist with adequate tissue for definitive interpretation.

Examination of aspirates of peritoneal fluid may be of some diagnostic assistance. Occasionally, the ascitic fluid in mesothelioma patients has been described as viscid. Cytological examination will usually reveal an abundance of mesothelial cells with some atypical forms, but this finding is nonspecific. Thompson and co-workers<sup>23</sup> have suggested that a high acid mucopolysaccharide level in sterile fluid with a nondiagnostic cytology strongly suggests mesothelioma. This approach, however, has yet to be put to sufficient clinical trial to prove its diagnostic value.

### Treatment

Unfortunately, our ability to treat successfully the peritoneal mesothelioma has lagged far behind our knowledge of its etiology and epidemiology. Although some instances of surgical cure of localized and presumed benign mesotheliomas have been recorded, the malignant variety is always well beyond any hope of resection at the time of diagnosis. Radiation therapy, systemic chemotherapy, and instillation of various cytotoxic substances into the peritoneal cavity have all been attempted in a rather haphazard fashion and all have been conspicuous failures. In view of the apparent rapid increase in incidence of this neoplasm, more organized therapeutic trial programs would seem to be clearly indicated, particularly in regions where the mesothelioma is endemic.

Palliative management consists primarily of analgesia and measures to relieve ascites.

### Prognosis

Although occasional long term survivals have been reported with pleural mesotheliomas, the peritoneal variety follows a more virulent course with progressive inanition and debility and frequent complicating bowel obstruction.

Death has uniformly been reported to occur in less than 12 months after the diagnosis is established.

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