Fever, Hepatic Lesions and Ascites

Stenographic reports, edited by Philip E. Cryer, M.D. and John M. Kissane, M.D., of weekly clinicopathologic conferences held in Barnes and Wohl Hospitals are published in each issue of the Journal. These conferences are participated in jointly by members of the Departments of Internal Medicine, Radiology and Pathology of Washington University School of Medicine in St. Louis.

A 54 year old man was admitted to Barnes Hospital on August 1, 1978, because of unexplained fever. He was discharged two weeks later but was readmitted on October 13 because of persistent fever, episodes of chest pain, and dyspnea. An operation was performed on October 26, 1978.

Aside from a history of chronic osteomyelitis from 1946 to 1952, following an automobile accident, the patient was in apparent good health until mid-June 1978 when he noted the onset of headaches, upper abdominal discomfort and weight loss. He lost 30 pounds in weight over a six week period. Daily fevers began in early July. These persisted despite antibiotic therapy. Three weeks prior to his first Barnes Hospital admission he was hospitalized elsewhere. Negative studies there included chest roentgenograms, intravenous urograms, an x-ray series of the upper gastrointestinal tract, a barium enema, bone and liver-spleen scans, a bone marrow examination, pulmonary function tests and a serum protein electrophoresis. Positive findings, in addition to fever, included an erythrocyte sedimentation rate of 48 mm/hour, a platelet count of 521,000/mm^3 and mildly abnormal liver function tests. Laparoscopy disclosed several "3 mm, whitish, umbilicated masses" on the liver surface, but a liver biopsy specimen was normal. The patient was transferred to Barnes Hospital on August 1, 1978.

The patient had never used alcohol or tobacco. He served in the Navy from ages 20 to 23 years and worked in a rock quarry for 23 years thereafter.

Aside from prostatic enlargement, the physical examination was initially within normal limits. This included a temperature of 37.2°C.

Routine serum chemical studies disclosed no abnormalities other than a serum alkaline phosphatase of 261 mIU/ml and a serum glutamic oxaloacetic transaminase (SGOT) of 106 mIU/ml. The hemoglobin level was 11.2 g/dl and the hematocrit value 35.2 per cent. The white blood cell count was 5,600/mm^3 (with a normal differential count) and the platelet count 416,000/mm^3. The erythrocyte sedi-

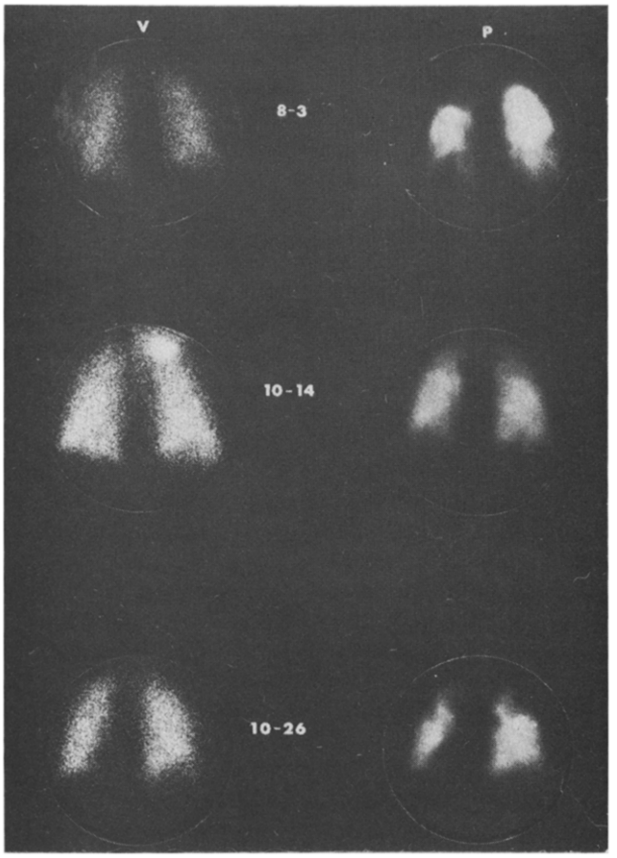

Figure 1. Posterior views of single breath ventilation and perfusion scintigraphs obtained on the dates as shown. The perfusion defects seen on 8-3 in the upper and lower lobes of the left lung and in the lower lobe of the right lung have almost cleared by 10-14. The perfusion images on 10-26 demonstrate new defects in the upper lobes of both lungs.

mentation rate was 103 mm/hour. The arterial oxygen/tension (PO_2) was 75 mm Hg, the carbon dioxide tension (PCO_2) 27 mm Hg and the pH 7.51. Chest films and an electrocardiogram did not reveal any abnormalities. Serologic studies for viral, bacterial and fungal pathogens, drawn on admission, were subsequently reported to be negative. Blood and urine cultures were negative as was a tuberculin skin test (a mumps skin test was positive).

Substernal chest pain, dyspnea and fever (with temperatures to 38.4°C) developed on the second hospital day. Ventilation-perfusion lung scans were interpreted as having a high probability for pulmonary emboli, and heparin was administered. The patient defervesced and remained afebrile throughout the remainder of that hospitalization. Additional studies included negative ultrasonography of the gallbladder and gallium scans. Computed tomographic (CT) scans of the abdomen disclosed fluid anterior to the liver and splenomegaly. Warfarin was substituted for heparin, the patient was clinically stable without further fever or chest pain and with improving liver function tests; he was discharge two weeks after admission.

Over the next six weeks the patient noted increasin fatigue, malaise and dyspnea, episodes of chest pain an recurrent fever. These led to his second Barnes Hospita admission on October 13, 1978. Aside from a tempera ture of 39.5°C, the findings on physical examinatio were unchanged. Liver function tests were normal ventilation-perfusion lung scans demonstrated im provement, and chest films, venograms and intravenou urograms were within normal limits. Abdominal C scans demonstrated only ascites. A paracentesis yielde 600 ml of exudative fluid; cytologic examination of thi fluid was negative. Cultures of blood, urine and asciti fluid were negative.

Dyspnea and fever persisted. Repeat ventilatio perfusion scans on the 13th hospital day revealed nev perfusion defects despite warfarin therapy. Hepari therapy was reinstituted. An operation was performe on the 16th hospital day.

CLINICAL DISCUSSION

Dr. Philip Majerus: The patient, a 54 year old man, wa first admitted to Barnes Hospital in August 1978 fo evaluation of a fever of unknown origin. He had bee well until sometime last summer when headache, ab dominal pain and a progressive 30 pound weight los developed. Four weeks prior to admission, fever tha apparently persisted throughout the patient's remainin course developed. He was given antibiotics, but hi condition did not improve. He was hospitalized else where and underwent an extensive work-up, includin laparoscopy. At laparoscopy his liver was found to b studded with 3 mm white, umbilicated masses whic were biopsied and said to be "benign." The fever per sisted; the patient was transferred to Barnes Hospita where a diagnosis of pulmonary embolism was made and he was discharged. Because he was not doing wel he was readmitted to Barnes Hospital six weeks late He had ascites that was an exudate. The cytologic ex amination of the ascitic fluid was negative. Finally, h had an operation which I assume was an explorator laparotomy. I would like to begin by asking Dr. Biell to discuss the x-ray material of which there is a ver large amount.

Dr. Daniel Biello: The chest films obtained on Augus 3, at the time of the first Barnes Hospital admission, di not show any abnormalities.

On August 10, an abdominal computed tomographi examination was performed. A water density flui collection was distributed about the liver compatibl with ascites. The liver, retroperitoneum, adrenal gland and pancreas were normal. A repeat abdominal com puted tomographic examination on October 24 showe interval development of small bilateral pleural effu sions, but the findings were otherwise unchanged.

The pulmonary scintigraphs are illustrated in **Figur 1.** Those performed on August 3, demonstrated mil

focal obstructive airways disease in the base of the left lung and large segmental perfusion defects in the upper and lower lobes of the left lung and in the lower lobe of the right lung. Thus, there were multiple segmental ventilation-perfusion mismatches which are associated with a high probability for pulmonary emboli. The second pulmonary scintigraphs were obtained on October 14. The lungs ventilated normally. The perfusion to the upper and lower lobes of the left lung and to the lower lobe of the right lung were strikingly diminished, which is compatible with resolving pulmonary thromboemboli. There were no new regions with perfusion defects.

Another episode of chest pain occurred on October 26, and another lung scan was performed. There were several new segmental perfusion defects in the upper lobes of both lungs. Recurrent pulmonary emboli is the most likely diagnosis.

The x-ray series of the upper gastrointestinal tract and the small bowel study showed multiple large diverticula in the duodenum and the jejunum. There was a single dilated loop of small bowel with normal mucosal margins and wall thickness. The transition zone between the dilated small bowel and adjacent normal small bowel was not well defined in this study.

Dr. Majerus: When I first looked over this case, one thing that struck me was that the diagnosis of pulmonary emboli kept getting in the way of figuring out what was wrong with this man. Two different scans were read as "high probability for pulmonary embolism." The diagnosis depended heavily on these data; what is the probability that they were false positives?

Dr. Biello: The scintigraphic diagnosis of pulmonary thromboemboli remains controversial. There is general agreement that the ventilation-perfusion scan is quite sensitive for the detection of emboli. A normal scan virtually excludes thromboemboli from diagnostic consideration. However, there are widely diverging opinions regarding scan specificity. Mismatched ventilation-perfusion defects have been associated with multiple abnormalities including acute pulmonary emboli, previous pulmonary emboli, congenital pulmonary vascular anomalies, vasculitis, radiation therapy, intravenous drug abuse, bronchogenic carcinoma, pulmonary artery sarcoma, lymphangitic carcinomatosis, pneumonia, sarcoidosis, Dirofilaria immitis infestation, hemangioendotheliomatosis, pulmonary venoocclusive disease and obstructive airways disease [1]. I have recently reviewed our past five year experience with pulmonary angiography and pulmonary scintigraphy in patients suspected of having pulmonary thromboemboli. The data show that 92 per cent of the patients with ventilation-perfusion mismatches, such as this patient exhibited, will have angiographically demonstrable pulmonary emboli. Moreover, the episodic appearance and resolution of perfusion defects eliminate many of the abnormalities previously listed from serious diagnostic consideration. Thus, the false-positive rate for a patient with episodic large ventilation-perfusion mismatches would be 8 per cent or less.

Dr. Majerus: In medicine 92 per cent is about as good as you can do. I would think, therefore, that it is very likely that this man did have pulmonary emboli.

This man was sick for several months without anybody being able to get to the bottom of his problem. It is quite clear that the physicians caring for the patient organized the case around a single finding—fever. I think that this is usually the best way to make a diagnosis in a difficult case. In other words, you sort out from the information presented the event or finding that seems to be the most unusual or the most likely to lead to an answer. The major fabric upon which this case hung was "fever of unknown origin." This patient had a fever work-up while pulmonary emboli clouded the picture. To my mind, the finding on which to organize this case was not fever of unknown origin but the "masses" on the liver. There are not a large number of disorders that can cause white masses on the liver. So I would have pursued that as the focus in this case. In the records available, there was no mention of what the biopsy of these white masses showed, and I asked Dr. Daniels if the pathologist could be on my side for a short period of time and tell me what these lesions were.

Dr. Frederick Askin: We were able to obtain the laparoscopic biopsy specimens from the other hospital. The slides showed only normal liver. There was nothing that I could correlate with the clinical impression of "white spots" on the liver surface.

Dr. Majerus: By hindsight, I believe that I would have immediately proceeded to look at those white lesions again.

Let us now turn to a consideration of two findings. We cannot overlook the fact that this patient did have pulmonary emboli. He also had liver function tests which became abnormal and then returned to normal. These findings have to be explained. Dr. Varki, do patients with cancer, which is the most common cause of white spots on the liver, have an increased incidence of thrombosis? If so, what is the incidence in such patients?

Dr. Ajit Varki: The answer to this question is in the affirmative. The literature supports the common clinical impression that patients with clinically evident neoplasms suffer frequent, and sometimes fatal, thromboembolic episodes on both the arterial and the venous sides of the circulation [2–5].

If this is so, what are the possible mechanisms involved? **Figure 2** summarizes some of the major factors that need to be considered. The problem with analyzing the situation is that patients with malignancy often have rather nonspecific reasons to be prone to recurrent venous thromboembolism. These include immobilization due to cachexia, pain and surgery, and direct invasion or obstruction of veins by the tumor itself. But are there more specific mechanisms involved? Certainly, many

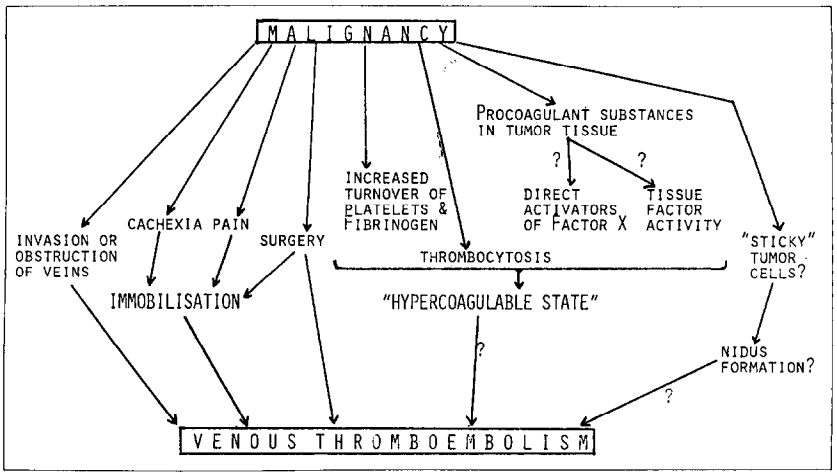

Figure 2. Possible mechanisms predisposing to thromboembolism in malignancy.

abnormalities of the coagulation system have been demonstrated, both in vitro and in vivo. Procoagulant substances such as direct activators of factor X have been identified [3,6,7], especially in mucin-producing adenocarcinomas. Thrombocytosis is a frequent accompaniment of malignancy [8]. Increased turnover rates of both fibrinogen and platelets have been demonstrated in vivo [9]. The suggestion that "sticky" circulating tumor cells can form a nidus for clot formation [10] has little support. However, although any or all of these factors could be theoretically responsible for a "hypercoagulable" state, it is difficult to evaluate their significance with regard to the pathogenesis of recurrent venous thromboembolism in a given patient with malignancy.

In summary, although the exact frequency is variable, in patients with clinically evident metastatic malignancies, the incidence of venous thromboembolism is high. The mechanisms involved may be both specific and nonspecific.

Dr. Majerus: In preparing for this conference, I looked through numerous old clinicopathologic conferences. Discussants generally present a long list of diseases, which sound unlikely, and then carefully exclude them one by one. There really is not much of a list which needs to be constructed in this case.

This man lost 30 pounds in two months, he had fever, he was treated with antibiotics, he had many cultures, many skin tests and many titers, all of which were negative. This history effectively excludes most kinds of infectious disease, with the possible exception of tuberculosis, and he did not have a positive tuberculin skin test. It, therefore, is likely that he suffered from some kind of malignancy. When he was discharged from the hospital for the first time, his discharge diagnosis was "fever due to recurrent pulmonary emboli." In my experience, emboli are not a cause of a 30 pound weight loss and persistent fever. I looked for cases like that and was unable to find any. The evidence that this man had thrombophlebitis is very thin; he had negative venography, and he did not have any abnormalities in his legs, despite his past history of osteomyelitis. Therefore, it is most likely that he had cancer. The house staff also thought that cancer was a likely possibility. Dr. Varki, how useful is it to work up patients for cancer who have unexplained or obscure causes of recurrent thromboembolic disease?

Dr. Ajit Varki: This is obviously a different question. To restate it, what is the chance of finding an occult neoplasm in a group of patients with "idiopathic" venous thromboembolism? The available information is too limited to allow a conclusive answer.

It all began in 1865, when Armand Trousseau stated: "So great, in my opinion is the semiotic value of this phlegmasia as a sign of the cancerous cachexia, that I regard this phlegmasia as a sign of the cancerous diathesis as certain as sanguinolent effusion into the serous cavities" [11]. Well, we know today that bloody effusions do not necessarily imply cancer; and what of this "Trousseau's sign?" **Table I** summarizes the few studies in which an attempt was made to look at the incidence of venous thrombosis as a sign of occult malignancy in a systematic manner. All were retrospective reviews, and all depended upon the clinical diagnosis (with all of its vagaries) of thrombophlebitis.

Ackerman and others [12] looked at 88 cases of idiopathic thrombophlebitis seen at the Mayo Clinic; at five to 10 year follow-up, 5.8 per cent of the patients in these cases turned out to have previously occult neoplasm. However, among 301 consecutive cases of venous thromboembolism seen by Anlyan and associates [13], no clinically occult malignancies became evident on follow-up. On the other hand, in 14.5 per cent of these 301 cases clinically evident neoplasms were already present at the time the thrombophlebitis was diagnosed. In a large retrospective review of the New York Hospital

TABLE I Incidence of Venous Thrombosis as a Sign of Occult Malignancy

Reference	Population Studied	Incidence of Venous Thrombosis: With Clinical Evidence of Malignancy (%)	Incidence of Venous Thrombosis: Occult Malignancy Found Later (%)
Ackerman et al. (1951) [11]	88 cases of "idiopathic thrombophlebitis"		5.8
Anlyan et al. (1956) [12]	301 consecutive cases of venous thromboembolism	14.5	0.0
Lieberman et al. (1961) [4]	1,400 cases of venous thromboembolism (excluding post-op)		2.2
Pineo et al. (1974) [2]	200 nonsurgical cases of venous thrombosis		0.5
	Surgical patients with known carcinoma	33.3	

records, Lieberman et al. [5] noted a 1.8 per cent incidence of occult cancers in all patients with thrombophlebitis. In a more recent series of 200 nonsurgical patients with venous thrombosis, only one patient was eventually found to have a hidden neoplasm [3]. Interestingly, the same group noted a 33.3 per cent incidence of venous thrombosis in patients undergoing surgery for clinically evident neoplasms [3]. We would have to conclude then that the chance of finding an occult malignancy in a patient with idiopathic venous thrombosis is very low and that extensive investigation in this direction is not justified in most cases.

However, running through all the literature on this subject is the oft-repeated statement, not supported by any numerical data, that there are certain unusual features in a case of thrombophlebitis that make one suspect "Trousseau's sign." These are recurrent episodes, migratory character, absence of obvious predisposing factors, unusual sites of involvement, refractoriness to treatment and evidence of systemic disease such as weight loss and high sedimentation rate. Our patient's thromboembolism certainly showed several of these features. I might mention that a quick review of the published clinicopathologic conferences from this institution over the last four years revealed four patients in whom recurrent venous thromboembolism formed a major part of the presenting symptom complex. Of these, three had malignancies, two of which were occult and found only at autopsy!

To conclude my answer to your second question, Dr. Majerus, I have listed those neoplasms that have had the highest (anecdotal) association with venous thrombolism as a presenting sign. These include pancreatic carcinoma, bronchogenic carcinoma, and carcinomas of the gastrointestinal tract and biliary tree (all of which are often mucin-producing), carcinoma of the breast, prostatic carcinoma and renal cell carcinoma (this last can also produce tumor emboli by extension into the vena cava). However, this is a very incomplete list; there are anecdotal reports that could support the association of practically any malignancy with "Trousseau's sign."

Dr. Majerus: The patient had a very occult primary tumor that eluded discovery. Therefore, I would include the possibility of prostatic carcinoma. Prostatic carcinoma can metastasize to the peritoneum. It is not a common cause of thrombophlebitis but it can be a cause of a very occult primary lesion. A gastrointestinal primary tumor in this patient is somewhat unlikely since he was never anemic, and he had all of those various tests which were negative. A renal cell carcinoma growing out through the renal veins and up the vena cava obstructing hepatic veins could explain the findings; yet the various studies were normal including renal sonography and an intravenous pyelogram.

There is a diagnostic clue in the protocol although it is a bogus one. We are told that this man worked in a rock quarry for 23 years. When I read this I thought about poisoning with asbestos. We are also told that he was in the Navy for three years; I have no idea what he did, but people who work in shipyards get asbestosis. Asbestosis is a disease which is associated with the production of mesotheliomas of the pleura and peritoneum, and carcinomas of the lung.

There is an enormous list of substances that contain asbestos. There are two kinds of asbestos; spinning fiber and nonspinning fiber. Asbestos is a fibrous mineral that comes in different lengths. The longer it is, the easier it is to weave into a fabric. The spinning form is used in making brake linings and clutch linings in automobiles, and this is an occupational hazard for people who work in that industry. Asbestos is used in insulation, fireproof materials and hundreds of manufactured products. Whether or not someone has ever been exposed to asbestos is obviously extremely difficult to determine since we are all exposed in some way. What is the incidence of mesothelioma in various people? It is a very rare tumor. There is one case per million people per year in

Canadian farmers [14]. In industrial workers there may be as many as 10 cases per million per year. In shipbuilders who put asbestos around pipes on ships, there may be up to 100 cases per million per year. In insulation workers the incidence has been even higher. The incidence of this very rare tumor varies enormously according to asbestos exposure.

Asbestos exposure can occur in rock quarries [15]. I grew up near the rock quarry where our patient worked. I remember the white building where he operated the scale; it has white powdered limestone tumbling down around it. Yet, I never heard of anybody having any trouble around our neighborhood. So it seemed to me that there was something wrong. I went to the library and checked out a geology book. There are three main types of rock: igneous rocks which are formed from the core of the earth; sedimentary rocks which are swept by oceans and rivers and settle out to form limestone and shale, and then there is an in-between kind called metamorphic rock. Metamorphic rocks occur in areas in which igneous rocks come out of the core of the earth and sedimentary rocks are sitting on the surface. A tremendous amount of pressure forms when this happens. Apparently, sedimentary rocks are then recrystallized under pressure. Marble is limestone that has been recrystallized under enormous pressure. Another metamorphic rock is called serpentine. Serpentine is a recrystallized form of limestone from which comes asbestos.

Having learned this, I called an internist in that community and asked him if he had ever seen a case of asbestosis. He said "no." Then I called several agencies of the Missouri state government to find out if there is asbestos in the quarry in which the patient worked. Finally, I got ahold of the Missouri State Geologist. He told me that there is no chance that there is asbestos in that mine in northern Missouri. He said that there is no serpentine rock there, no metamorphic rock and no asbestos. Upon checking several geology books, I found that he was right. So, I was forced to conclude that I had no clear evidence for asbestos exposure.

Peritoneal mesothelioma is an extremely rare tumor and, in fact, if this was a mesothelioma, this case is one of only about 200 cases of mesothelioma of the peritoneum that have been reported. In reviewing cases of peritoneal mesothelioma, I found that the diagnosis is almost never made clinically. Only about half the cases of mesothelioma reported in the United States are associated with asbestos exposure in the first place. Thus, we have a situation similar to that discussed previously. If you have cancer, you are likely to have thromboembolism. But that does not mean that if you have thromboembolism, you are likely to have cancer. And so it is with mesothelioma. If you have been exposed to asbestos, you are likely to have a mesothelioma. But if you have a mesothelioma, you were not necessarily exposed to asbestos. At Massachusetts General Hospital, which is right down the road from a big shipyard, there have been 36 cases of mesothelioma [16]. In 19 cases, there was no exposure to asbestos. In 17 cases in which the patients were exposed to asbestos, 14 worked in the shipyard. There is no shipyard anywhere near Barnes Hospital that would account for that kind of exposure to asbestos. Thus, asbestos exposure might be even less common in the patients with mesothelioma in Barnes Hospital. The most interesting aspect of this article was that there were 22 cases in which autopsy was performed. In nine of those, the patients had asbestos exposure and at autopsy eight turned out to have mesothelioma. However, of those 13 cases in which there was no history of asbestos exposure and in which the diagnosis antemortem was mesothelioma, only four definite mesotheliomas were found at autopsy! Thus, I concluded I need two answers to this case. If the patient is alive, he has a carcinoma of either the pancreas or the prostate. If he is dead, he has a peritoneal mesothelioma.

PATHOLOGIC DISCUSSION

Dr. Askin: The patient underwent one further diagnostic test, an exploratory laparotomy. At operation, multiple nodules were found studding the peritoneal surface and mesentery. Microscopically, the lesion was a neoplasm composed of cuboidal cells growing in papillary and tubular patterns and invading the underlying tissues (**Figure 3**). The differential diagnosis involved mesothelioma or metastatic adenocarcinoma. Special stains for epithelial mucins were negative; a feature supportive but not diagnostic of mesothelioma. Alcian blue stains demonstrated acid mucopolysaccharides only in the stroma of the tumor and were not considered helpful in this case [17]. However, the tissue was processed for electron microscopy. This study was most helpful in that we could demonstrate that the tumor cells lacked secretory granules but that they did contain large numbers of microfilaments. In addition, the cell surfaces had numerous long microvilli, and the cell borders were connected by abundant desmosomes. Both Wang [18] and Davis [19] have provided evidence that these ultrastructural features are extremely helpful in making a specific diagnosis of mesothelioma.

Mesothelioma is an extremely interesting lesion, and one which has really become accepted as a distinct entity only in the latter half of this century [17,20,21]. The diagnosis still is often one of exclusion, although with strict clinical and pathologic criteria, including electron microscopic study, it should be possible to make an antemortem diagnosis with reasonable certainty.

In reported series of peritoneal mesothelioma [20,22], abdominal pain, intermittent intestinal obstruction and impressive weight loss have been the almost universal presenting features. Ascites has been present in 90 per cent of the reported cases. As with the pleural lesion, many, but not all, of the reported cases of peritoneal mesothelioma have occurred in association with as-

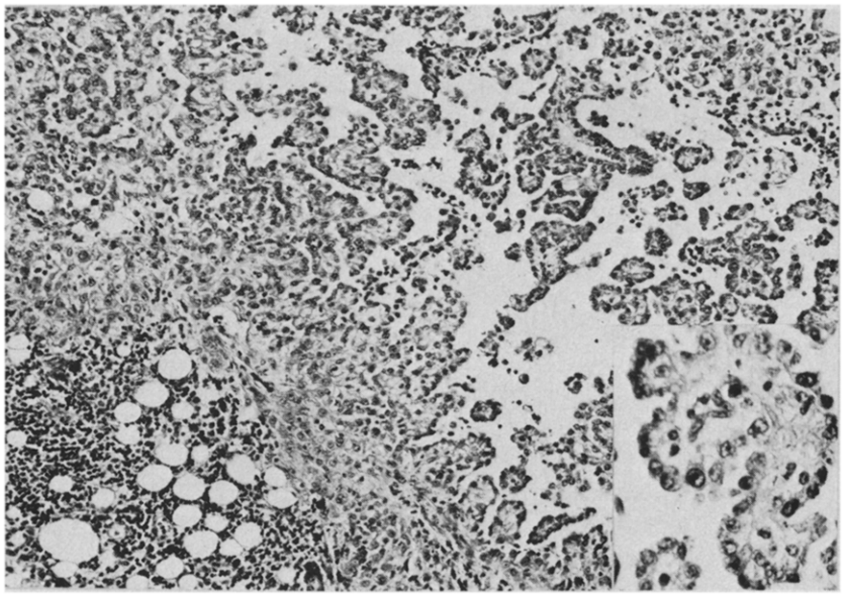

Figure 3. Peritoneal mesothelioma. The photomicrograph shows a papillary neoplasm invading the omental fat. The inset shows cuboidal tumor cells lining a vascular stalk. Special stains for mucins were negative. Hematoxylin and eosin stain; magnification ×150, inset ×350, reduced by 33 per cent.

bestos exposure. In a recent series, patients with peritoneal disease were shown to have had a heavier exposure to asbestos than those with pleural lesions.

The prognosis in a patient with this lesion remains poor, with an average survival of 10 months after the onset of the symptoms [20]. The effect of chemotherapy remains to be determined [21].

In the article to which Dr. Majerus referred [16], the investigators confirmed the dictum that one must be careful to exclude another primary before diagnosing mesothelioma, especially in the absence of a history of asbestos exposure. However, of the nine patients in the study who were considered not to have mesothelioma on the basis of postmortem examination, seven had tumors with epithelial mucins as demonstrated by periodic acid-Schiff staining and probably would not have been diagnosed originally as having mesothelioma if strict criteria had been employed. Electron microscopy was not a part of their study.

Dr. John Daniels: The occupational history was added to the protocol because there was inadequate documentation in the chart. In fact, the patient was in the Navy during World War II and worked in the engine room of a large warship. One of his main duties was repairing broken pipes, a job that required stripping and relining pipes with asbestos insulation. Furthermore, following the war he worked in Navy shipyards stripping ships.

Following the diagnosis, the patient was asked about previous asbestos exposure in a very general manner. He did not associate his Navy years with asbestos exposure and, therefore, denied such an exposure. It was not until I asked very specific questions regarding his service record that this history became obvious. This points to the difficulty of obtaining a good history of exposure to asbestos or other toxins and indicates the need for a systematic detailed history in patients who might have industrial-related diseases.

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