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MESOTHELIOMA IN AN AGRICULTURAL COMMUNITY OF INDIA: A CLINICOPATHOLOGICAL STUDY

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Mesothelioma is an uncommon neoplastic condition. Its association with asbestos exposure is well established, but it occurs even in non-industrial workers, and naturally there must be some other factors in its ætiology than asbestos exposure. In this report, five patients with primary mesothelioma, all belonging to a rural agricultural community with no chance of any asbestos exposure, have been documented. There was one common interesting observation, in that all five patients were associated with sugar-cane farming or an allied trade. Whether this observation is coincidental or has any ætiological bearing on mesothelioma needs further investigation. Its histopathological features, symptomatology, diagnosis, and treatment are discussed, with a brief review of the literature.

MESOTHELIOMA is an uncommon neoplastic condition arising from the pleura and also rarely from other serous membranes. Its incidence has been reported to range between 0·02% and 0·2% of all autopsies, with a 2 : 1 male preponderance (Borrow *et alii*, 1973). After Wagner published an account of the first documented case of primary diffuse mesothelioma in 1870, only relatively few case reports appeared in the literature till 1960 (Oels *et alii*, 1971). However, the past 15 years have seen many series published, though none of them could really be called large, except those of Wagner *et alii* (1960), Oels *et alii* (1971) and Borrow *et alii* (1973). Mesothelioma is of special interest because of its known induction by occupational exposure to asbestos (Grundy and Miller, 1972). Exposure to asbestos as an important causative factor has also been supported by the experimental production of mesothelioma by Wagner (1962). However, its exact ætiology is still unsettled, as it is also found in non-industrial workers. Furthermore, its morphology is still not well understood, and its histopathological picture and biological behaviour have been the subjects of controversy. There is no satisfactory treatment for malignant mesothelioma.

This presentation is based on the experience in the management of five cases of mesothelioma belonging to the non-industrial rural communities of India, treated at the Wanless Hospital, Miraj Medical College, Miraj, Maharashtra, between January 1974 and March 1976, and aims at elucidating its ætiology and pathology and updating its therapy and prognosis.

CLINICAL RECORDS

CASE 1.—A 35-year-old agriculturist engaged in intensive sugar-cane farming was hospitalized with principal complaints of chest pain and dyspnœa of four months' duration. On examination his chest was normal in shape and size. There was a dull percussion note in the left lower and middle lung fields, with markedly diminished breath sounds. Skiagrams of the chest revealed a large mass continuous with the cardiac shadow and occupying most of the left hemithorax. Thoracocentesis and endoscopy were unproductive.

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a homogeneous opacity of the entire left hemithorax with shift of the mediastinum to the right (Figure 2). The pleural fluid contained no organisms or malignant cells.

Hospital course.—The patient underwent left thoracotomy. There was dense adhesion between the lung and the pleura, which was markedly thickened (2·5 cm to 10 cm), nodular and firm, and gave the appearance of diffuse tumours encasing the collapsed lung. This was more pronounced in the lower part of the thoracic cavity and over the diaphragm and the mediastinum. The tumour mass extended to the



FIGURE 2: Case 3; postero-anterior skiagram of the chest showing complete opacification of the left hemithorax and shift of the mediastinum to the right.

right side across the retrosternal space and completely filled the cardiophrenic and costophrenic angles. Subtotal removal of the pleural mass (approximately 2,500 gm) was done to free the lung, but the decorticated lung failed to expand. It appeared to be involved by the tumour, and there was extensive air leak, necessitating left pneumonectomy. His postoperative course was stormy. Subsequently he received a course of radiotherapy and chemotherapy (cyclophosphamide) and responded well. He is still doing well since his surgery in June 1975.

Morbid anatomy.—The specimen consisted of big tumour masses, weighing 2,500 gm. The largest piece measured 12 cm × 7 cm × 3 cm and was composed of several small and large nodules. The cut surface showed a greyish white homogeneous appearance, with areas of necrosis. The left lung with the main bronchi measured 11 cm × 7·5 cm × 7 cm. Small and large greyish-white nodules were present all over its surface. Its cut surface showed one greyish-white oval growth with central necrosis measuring 2·5 cm × 2 cm, with several similar areas of smaller size. Another area of the lung showed spread of the tumour from the surface to the depth of the lung along the bronchus. Microscopically, the sections of the pleural masses showed tumour cells arranged in tubular fashion or formation of papillary processes on the cores of connective tissue. The tumour cells were cuboidal, columnar or polyhedral in shape, and contained hyperchromatic nuclei (Figure 3). Many acini contained hyaline eosinophilic material. The stroma of the tumour consisted of abundant acellular fibrous tissue. The sections from the lungs showed metastatic deposits. These deposits were well circumscribed

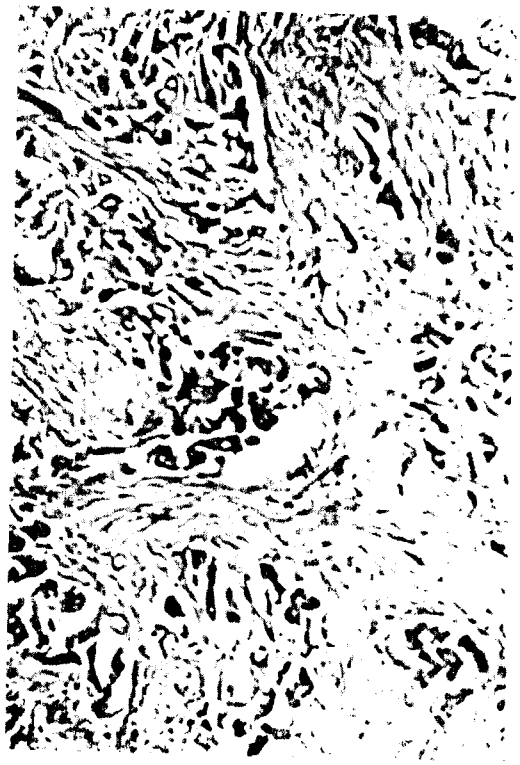


FIGURE 3: Case 3; photomicrograph of section from the tumour mass showing tubulopapillary type of mesothelioma (haematoxylin and eosin, × 350)

and were separated from the lung parenchyma by a layer of lymphocytic tissue. The bronchi were normal. There was no evidence of asbestos bodies or asbestos-like bodies. A diagnosis of diffuse metastasizing mesothelioma of the pleura (tubulopapillary type) was made.

Hospital course.—At operation a huge mass, partly solid and partly cystic, was found. It was continuous with the pericardium and occupied most of the left side of the chest. It was well encapsulated except in one area where it was adherent to the upper lobe of the left lung. The entire left aspect of the pericardium appeared involved and incorporated in the mass, of which the major part was actually lodged in the pericardial cavity. The left upper lobe was intimately adherent to the tumour



FIGURE 1: Case 1; photomicrograph of section from the main tumour mass showing mesothelioma (hæmatoxylin and eosin, × 350).

and was stretched over it, while the lower lobe was compressed and collapsed. For complete extirpation of the tumour with a good surgical margin, the entire left aspect of the pericardium, left phrenic nerve and left upper lobe had to be sacrificed in continuity with the tumour. The patient's postoperative course was uneventful, and he has remained well since his surgery in January 1074.

Morbid anatomy.—The specimen consisted of a large, greyish soft tissue mass, 30 cm × 25 cm × 20 cm in size, with part of the lung and pericardium attached to it. It had a variegated appearance, with fleshy areas alternating with necrotic and hæmorrhagic areas. It was well circumscribed, except in the area where it was adherent to the lung. Microscopically it was composed of spindle-shaped cells, arranged in strands with interlacing bundles and, in some areas, with a whorled pattern. The tumour cells showed eosinophilic cytoplasm with elongated hyperchromatic nuclei. In places there was a proliferation of mesothelial cells forming a glandular pattern (Figure 1). Areas of necrosis and myxoid degeneration of stromal cells were also seen. Infiltration of pulmonary tissue with tumour giant cells in the alveoli was present. Lung sections did not reveal asbestos bodies or asbestos-like bodies. A histopathological diagnosis of malignant mesothelioma (tubulopapillary variety) was made.

CASE 2.—A 35-year-old housewife in a rural family engaged in sugar-cane farming was hospitalized with exertional dyspnœa and evening rise of temperature of one month's duration. She had one episode of hæmoptysis during this period. On examination there was a bulge in the left side of the chest. The trachea was shifted to the right. No apical impulse was palpable. There was an impaired percussion note with diminished breath sounds in the lower part of the left side of the chest. Skiagrams of the chest revealed a large mass in the lower part of the left lung field.

Hospital course. At exploration a large tumour, measuring 30 cm × 15 cm × 15 cm, and occupying the posterior and lower areas of the left thoracic cavity, was found. The parietal pleura was involved in the mass, which was easily freed by extrapleural dissection. There was no chest wall involvement. The tumour was adherent to the lower lobe of the left lung, but the upper lobe appeared free. The tumour was resected in continuity along with the left lower lobe. She made an uneventful recovery and has remained well since her operation in February 1074.

Morbid anatomy. The specimen consisted of a large tumour 30 cm × 15 cm × 15 cm, with the left lower lobe and part of the parietal pleura attached to it. It had a variegated appearance. It was well circumscribed except in one area. Microscopic sections revealed a tumour composed of spindle shaped cells with nuclei which had pointed ends. The cells were arranged in a whorled pattern and in places in an interlacing manner. A few glandular structures were also seen. The sections from the lung showed hæmorrhagic areas and areas with inflammatory cell infiltration. They were free from tumour. Also, the sections showed no evidence of asbestos bodies. A histological diagnosis of benign mesothelioma was made.

CASE 3.—A 27-year-old sugar-cane farmer was admitted to hospital with complaints of breathlessness, left sided chest pain and anorexia, dating back for eighteen months. At the time of admission, his breathlessness had become quite severe. He had also had recurrent pleural effusion, for which he had had repeated thoracocenteses at another institution, and also received a course of antituberculosis therapy, apparently without any bacteriological or other indication. On examination the trachea was shifted to the right. The respiratory movements were markedly restricted, and there was stony dullness on the left-side of the chest. Breath sounds were absent in this area. Chest skiagrams revealed

CASE 4.—A 54-year-old sugar-cane farmer was transferred to the cardiothoracic unit for exploratory surgery for a recurrent and persistent right-sided pleural effusion. His symptoms had commenced three months previously, when he developed right sided chest pain and breathlessness. He was treated by his physician with antituberculosis drugs, without any apparent benefit. On examination, the respiratory movements were restricted on the right-side, and a dull percussion note with succussion splash was also present. Breath sounds were absent in the right lung field. He had several thoracocenteses before and after admission. The pleural effusion reappeared rapidly each time. The pleural fluid contained no organisms or malignant cells. Skiagrams of the chest revealed a right-sided pleural effusion. Skiagrams taken following thoracocentesis showed obliteration of the cardiophrenic angle and thickening of the right cardiac border, and the radiological sign of scalloping was present over the diaphragmatic and mediastinal pleura.



FIGURE 4: Case 4; photomicrograph of section from the tumour showing fibrous type of mesothelioma (haematoxylin and eosin, × 350).

Hospital course.—The patient underwent right thoracotomy. The pleural cavity contained about 1,000 ml of straw-coloured fluid. There was a diffuse and nodular growth of the mediastinal and diaphragmatic pleura, the thickness of which varied from one to two centimetres. Multiple small deposits were seen over the lung surface and the parietal pleura. A rounded deposit, 3 cm × 2 cm in size, was present on the medial aspect of the right upper lobe near the fissure. One large deposit was found on the chest wall, involving the latissimus dorsi muscle at the site of a previous thoracocentesis. Multiple biopsy specimens were obtained from the various sites. His postoperative course was unremarkable. He has received a course of radiotherapy and chemotherapy (cyclophosphamide). He has remained well since his surgery in August 1975.



FIGURE 5: Case 5; postero-anterior skiagram of the chest showing massive pleural effusion on the right side.

Morbid anatomy.—The biopsy specimens were greyish white and soft. Microscopically, the sections showed a tumour composed of dense collagenous tissue enclosing several clusters of tumour cells (Figure 4). In places, focal collections of chronic inflammatory cells were seen. The findings were similar in all the specimens. The specimen from the chest wall deposit was greyish white and homogeneous. Microscopic sections from the deposit showed thick fibrous tissue with skeletal muscle. There were areas of granulation tissue with congested capillaries and lymphocytic infiltration. There were many cystic areas lined by single cell and multiple cell layers, with hyperchromatic nuclei with pleomorphism. Their cytoplasm was scanty and cosinophilic. They were mainly present in the fibrous tissue, but had invaded the muscle in many places. A histological diagnosis of malignant mesothelioma (fibrous type) was made.

CASE 5. A 30-year-old male chemist in a sugar factory was hospitalized with a cough of 15 days'

duration and breathlessness for three days. He had already received some outside treatment, but his dyspnœa worsened and he developed a right-sided pleural effusion. On examination, the entire right hemithorax was dull with absent or diminished breath sounds. Chest skiagrams revealed a massive right-sided pleural effusion (Figure 5). Thoracocentesis following his hospital admission yielded 1,250 ml of hæmorrhagic fluid, but the pleural space filled again rapidly and later he required daily tapping. The pleural fluid contained no organisms or malignant cells.



FIGURE 6: Case 5: photomicrograph of section from the tumour showing bimorphic type of mesothelioma (hæmatoxylin and eosin, × 480).

Hospital course.—In view of the rapid reaccumulation of pleural fluid, he underwent right exploratory thoracotomy. The entire pleural space was filled with hæmorrhagic fluid. The lung appeared collapsed and bound down by fibrinous and tumour deposits on its surface. A hard and nodular tumour mass was present over large areas of the posterior and lower parietal pleura and in the angle between the diaphragm and the posterior chest wall. Innumerable small tumour deposits on all aspects of the visceral and parietal pleura were seen, more so in the lower portion of the chest cavity. With the diagnosis of inoperable diffuse mesothelioma, he was treated by radiotherapy and cyclophosphamide. His response to this regimen was poor. His dyspnœa continued to increase and his general condition started to deteriorate. Meanwhile, he developed several nodules in the scalp, one of which was excised for biopsy, which proved it to be a metastatic mesothelioma. As he was going downhill, he was permitted to leave hospital at the request of his relatives.

Morbid anatomy.—Microscopically, the sections showed a tumour consisting of sheets and groups of epithelial cells which were polygonal with scanty cytoplasm, which was granular and eosinophilic with clear margins. The nuclei in the majority of cells were large and occupied most of the cell space. They were vesicular with prominent nucleoli. In some areas, the cells were pleomorphic with hyperchromatic nuclei, and nucleoli could also be easily made out. Many abnormal mitotic figures with a few tumour giant cells were seen. Areas of necrosis and hæmorrhage in the surrounding areas were also present. Fibrous tissue separated the groups of tumour cells, but in areas where the epithelial cells were typically malignant, the stromal cells were also malignant, resembling sarcoma (Figure 6). A histopathological diagnosis of malignant mesothelioma of bimorphic or mixed type was made.

Microscopic examination of the metastatic deposit in the scalp revealed a tumour mass covered by normal skin. The tumour was pressing the basal cell layer, and in many places it had destroyed it. The tumour consisted of spindle cells with pleomorphic hyperchromatic nuclei. Many tumour giant cells of bizarre type were seen. They were scattered in every conceivable fashion. The histopathological picture was consistent with metastasis from the pleural mesothelioma.

DISCUSSION

Mesothelioma is a rare tumour, and its frequently unpredictable clinical behaviour makes it a complex therapeutic problem. Classically, it has been divided into two groups. The first group consists of solitary, "benign" tumours which are surgically resectable and carry a good prognosis, whereas the second group comprises diffuse "malignant" tumours which spread locally in a progressive manner, carry an unfavourable prognosis and end fatally in less than a year (Urschel and Paulson, 1965).

Site of Origin

The pleura is the commonest site of origin of this tumour, but it can also originate, though less frequently, from the peritoneum, pericardium and other serous membranes. In this series, four patients had pleural mesotheliomas and one had a pericardial mesothelioma. From our review of the literature, it would seem that there has been much

confusion and controversy regarding the origin and nature of this lesion. Its histological variability from a sarcomatous to a carcinomatous appearance has also contributed to the prevailing confusion. The time-honoured concept that this tumour originates as an endothelioma has been discarded. However, Robertson (1924) and Willis (1967) did not believe that these tumours existed, and according to them, they represented metastases from an occult, unrecognized or latent primary source, possibly in the lung. Klemperer and Rabin (1931) felt that the solitary type originated from the subpleural connective tissue and its diffuse variety from the pleural surface.

Occupational Exposure, Ætiology and Histogenesis

The ætiology of mesothelioma remains largely unsettled. However, Brown and Johnson (1951) and many other workers believed that it resulted from the histological reaction secondary to the irritation and inflammatory process in the pleura. This concept certainly supports the clinical association of pulmonary asbestosis with mesothelioma (Wagner *et alii*, 1960; Hourihane, 1964; Selikoff *et alii*, 1964), as does the experimental production of mesothelioma by instillation of asbestos dusts into the pleural cavity of rats (Wagner, 1962). But in none of our five patients was there any chance of occupational exposure to asbestos, as they all belonged to the rural community, having association with sugar-cane farming and related trades. Four patients belonged to the non-industrial farming community, engaged in sugar-cane farming and the making of jaggery (gur) and molasses (indigenous sugar-cane products). The fifth patient was a chemist in a local sugar factory. This observation provides one more possibility in the unsettled ætiology of this lesion. Whether the association of sugar-cane farming and allied trades has any ætiological bearing or not remains wide open for speculation. In the process of preparing jaggery and molasses, dried and crushed sugar-cane is used as fuel, and emits irritating fumes. It is difficult to say at this stage if these fumes could irritate the pleura and promote an inflammatory process. However, since mesothelioma has been produced experimentally by instillation of asbestos dust into the pleural space of rats (Wagner, 1962) and by the use of diatomaceous earth and polyurethane (Hueper, 1964), it is quite possible that the dust or fumes from the burnt or burning sugar-cane could also produce irritation and an inflammatory process in the pleura and result in the production of a mesothelioma. This certainly calls for a critical analysis of all cases reported from the sugar-cane growing areas and necessitates a lookout for any new case coming from these areas, before one can blame sugar-cane as one of the ætiological factors. Also, some experimental work in laboratory animals may be essential to prove this point. In this regard, we have reviewed seven autopsy cases, five reported by Aikat *et alii* (1974) and two by Kshirsagar *et alii* (1971), and three documented cases reported by Reddy (1950), Reddy *et alii* (1973), and Chandurkar *et alii* (1975), and found that all these cases also came from the non-industrial rural community. However, it is not clear from the case histories whether or not any of these patients was associated with sugar-cane farming, but two autopsy cases reported by Kshirsagar *et alii* (1971) and the case of Chandurkar *et alii* (1975) did come from Maharashtra, a belt of intensive sugar-cane farming in India. This observation, along with our finding in five patients intimately associated with sugar-cane farming or an allied trade, indicates that there must be a factor in the non-industrial rural areas connected with farming responsible for inducing mesothelioma in the same way as asbestos is. Further investigations are required to prove this point.

The histopathological variation of mesothelioma can be explained ætiologically or embryologically. The pleural cavity is lined by somatopleura and splanchnopleura, both of which develop from the mesoderm, and therefore both epithelial and endothelial structures could develop either separately or in combination (Urschel and Paulson, 1965). Utilizing the tissue culture technique of Maximow, Stout and Murray (1942) and Sano *et alii* (1950) confirmed the mesothelial origin of these tumours, and Stout and Murray (1942) demonstrated the transformation of mesothelial tissues into fibroblasts with the production of collagenous material. They also showed that a benign mesothelioma can produce epithelial cells in tissue culture. Sano *et alii* (1950) demonstrated

that the malignant variety of mesothelioma can also produce epithelial cells which ordinarily are not seen in the sections. Later, Manguikian and Prior (1963) confirmed that the reaction of mesothelium to injury could be in the form of cuboidal, columnar and epithelial patterns accompanied by papillary processes. Thus the multipotentiality of the tumour is demonstrated on a cellular basis and is confirmed by its clinical behaviour. It has been seen that many of the benign mesotheliomas appear malignant histologically, while some of the clinically malignant mesotheliomas have a benign histological appearance (Urschel and Paulson, 1965).

Symptomatology

The classical presenting features of a patient with mesothelioma are chest pain, breathlessness and cough, but patients may also have less frequent complaints such as loss of weight, weakness, fever, abdominal symptoms, chills, sensation of fullness and tightness in the chest, and backache. In the patients described in this report, breathlessness and loss of weight (all five patients) and chest pain (four patients) were the most frequent complaints. However, fever with chills and hæmoptysis were present in one patient (Case 2).

Physical examination of a patient with diffuse mesothelioma usually reveals signs of pleural effusion or a large intrathoracic or mediastinal mass. Occasionally, clubbing of the fingers and features of osteoarthropathy may be present. In this report, three patients had massive pleural effusions (Cases 3, 4 and 5), which reappeared immediately after thoracocentesis. The pleural fluid was blood-tinged in one patient (Case 5). No evidence of clubbing or pulmonary osteoarthropathy was present in any of our patients. Metastatic nodules were found on the chest wall in Case 4, apparently at the site of one of several thoracocenteses, and on the scalp in Case 5. The metastatic nodule on the chest wall illustrates how this tumour can spread along the track made by needle puncture. The scalp nodules in Case 5 were metastatic deposits. Distant metastasis in mesothelioma is unusual, as normally it spreads locally and involves the surrounding structures by direct extension (Urschel and Paulson, 1965).

Diagnostic Methods

Besides a detailed clinical history, physical examination, and routine investigation including skiagrams of the chest, diagnostic modalities such as thoracocentesis, pleural biopsy, and ultimately exploratory thoracotomy, are available to establish the final diagnosis. Skiagrams of the chest, if pleural effusion is not present, would reveal the intrathoracic or mediastinal mass if present and would show the radiological sign of scalloping (Urschel and Paulson, 1965). Thoracocentesis could be helpful in more than one way. In addition to recovering pleural fluid for bacteriological, biochemical and cytological studies, it clears the way for a better skiagram in which without it the intrathoracic mass or the radiological sign of scalloping could be masked by the effusion. Needle biopsy of the pleura is a bedside procedure and if done properly can provide the diagnosis. The use of a manually operated high-speed drill is an improvement over an ordinary needle biopsy. However, the disadvantage of needle biopsy is that it provides only a small piece of tissue, which makes the definitive diagnosis difficult in these histologically variable tumours (Urschel and Paulson, 1965). Endoscopy has no role in the diagnostic work-up, and lymph node biopsy is usually not called for. Whenever these diagnostic modalities fail to yield a histological diagnosis, exploratory thoracotomy becomes necessary. In all five patients in this report, exploratory thoracotomy was done with a view to diagnosis and possible surgical treatment.

Pathological Features

In the cases described in this report, the tumour was of pleural origin in four patients and of pericardial origin in one (Case 1), in whom it gave rise to a large mediastinal mass which encroached into the left hemithorax and involved the left upper lobe. three patients had recurrent and persistent pleural effusion (Cases 3, 4 and 5), and repeated bacteriological and cytological studies were unrewarding in all five.

Gross pathological features vary according to the type of the tumour. The solitary type is often encapsulated, pedunculated, and easily removable, whereas the diffuse or malignant mesothelioma is characterized by findings ranging from multiple papillary projections on

the visceral and parietal pleural surfaces to the encasement of the entire lung in a thick rind of tumour tissue involving the visceral pleura with similar findings in the parietal pleura (Urschel and Paulson, 1965). The appearance of the tumour, in general, consists of thickened visceral or parietal pleura with dense fibrous, firm, pink, white or yellowish-white nodules or plaques. In our Case 1, the tumour originated from the pericardium, grew to become a big mass, and infiltrated the upper lobe of the left lung. It had a variegated appearance. In Case 2, the tumour was also variegated in appearance. Though the lower lobe was stuck to it, it was well circumscribed. In Case 3, the tumour was really diffuse and extensive. It had encased the left lung and also infiltrated it. The parietal pleura was also markedly thickened and nodular and had obliterated the cardiophrenic and costophrenic angles. In Cases 4 and 5, the gross appearances were more or less the same. The lesion was on the right side in both. There was diffuse and nodular growth over the mediastinal, diaphragmatic and posterior parietal pleura, with multiple small deposits everywhere. In Case 4 there was a metastatic deposit on the chest wall, and in Case 5 there were multiple metastatic nodules in the scalp.

In this series, there were four diffuse malignant mesotheliomas and one benign mesothelioma, though this was not localized. Histologically, there were two cases of tubulopapillary type (Cases 1 and 3). Two patients (Cases 2 and 4) fell into the histological category of fibrous mesothelioma. One of these tumours (Case 2) was benign. Bimorphic or mixed histological features were present in Case 5. Thus the cases in this report belonged to the three principal histological types of mesothelioma, viz., tubulopapillary, fibrous and bimorphic (Oels *et alii*, 1971). In the tubulopapillary variety, there is an attempt at acinar and papillary formation with occasional sheets of epithelium-like cells. The fibrous mesothelioma consists of spindle cells and collagenous fibres and resembles fibrosarcoma. The bimorphic variety is really a mixed type and presents a varied mixture of epithelial and fibrous elements. The interesting feature of the biological behaviour of mesothelioma is that its benign histopathological appearance does not necessarily mean that the tumour is indeed benign, and similarly its malignant picture does not necessarily correspond with its benign behaviour (Urschel and Paulson, 1965).

Distant metastasis is uncommon in mesothelioma. In our cases, evidence of metastasis, by direct extension or by hæmatogenous spread to remote areas, was found in four patients. In Case 3 the tumour deposits were found in lung tissue, apparently due to direct extension, and in Case 1 the pericardial mesothelioma had invaded the lung by direct extension. The tumour deposit on the chest wall along the needle track of a thoracocentesis, seen in Case 4, is an interesting finding and brings the hazard of the needle puncture of a tumour into sharp focus. The only example of distant metastasis was seen in Case 5. Clagett *et alii* (1952), Kshirsagar *et alii* (1971), and Reddy *et alii* (1973) found no evidence of distant metastasis in their cases. Generally, metastasis in a case of mesothelioma is by direct extension, but occasional lymph node metastasis has been reported in isolated cases, particularly in the tubulopapillary variety (Whitewell and Rawcliffe, 1971). The finding of metastatic deposits in the scalp in Case 5, who had the bimorphic type of malignant mesothelioma, is definitely an unusual finding.

In three cases in this report, pulmonary resection became necessary, providing an opportunity to examine the pulmonary tissue for evidence of asbestos or asbestos-like bodies, and apparently none was found. Urschel and Paulson (1965) also were unable to demonstrate asbestos fibres in any of their cases.

Treatment and Prognosis

Treatment of diffuse mesothelioma in general is not satisfactory, but for the localized variety, surgical excision is the preferred therapeutic modality. However, the treatment of a case of malignant mesothelioma is frustrating. There have been no cures. Isolated instances of survival of four to six years have been reported (LeRoux, 1962; Urschel and Paulson, 1965; Porter and Cheek, 1968). However, malignant mesotheliomas have been treated by thoracotomy and biopsy, followed by radiotherapy and chemotherapy. Earlier, pleuro-pneumonectomy was advocated, even if it was subtotal, to accomplish an obliterative reaction and prevent reformation of pleural

fluid (Urschel and Paulson, 1965). The current trend is to treat these patients with closed tube thoracostomy. As an alternative to surgical excision, radiotherapy and chemotherapy have been used. Wide variation in results and survival times makes any critical evaluation difficult. Nevertheless, radiotherapy is recommended when excisional surgery is impossible or incomplete (LeRoux, 1962; Porter and Cheek, 1968). Urschel and Paulson (1965) also noted improvement in many of their patients following radiotherapy. In this review, the result of surgical extirpation with a good surgical margin has been quite good in two patients (Cases 1 and 2), but in a third patient (Case 3), in whom even with pleuropneumonectomy the resection of the tumour was incomplete, surgical treatment had to be supplemented with radiotherapy and chemotherapy. In the remaining two patients the tumour was not resectable on exploration. Radiotherapy in conjunction with chemotherapy (cyclophosphamide) proved quite beneficial in Cases 3 and 4. They experienced considerable improvement in their general condition, with relief of pain, and there was reduction in the size of the mass. These patients are still doing well, ten and eight months respectively following their diagnosis. However, there was no response to radiotherapy and chemotherapy in our Case 5. Actually, the patient started going downhill and had already developed distant metastases. Two patients, Cases 1 and 2, who had satisfactory extirpation of their tumours, are doing well and have remained asymptomatic 26 and 24 months respectively since their surgery, with no evidence of recurrence or dissemination.

The prognosis in malignant mesothelioma is poor. Most patients die within a year or two from the time of diagnosis. The prognosis is worst in patients with the bimorphic variety of the tumour. The variation in survival has so far ranged from four months to five years (Urschel and Paulson, 1965).

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