The results obtained in this series of cases are similar to those reported by other investigators. We are aware of only one series larger than this one—that of Mestitz *et al.*⁸ in England. These authors reported on 188 patients with pleural effusion with only 2% having inadequate specimens as compared with 20% in the present series. If the cases with inadequate specimens are removed from each study, then Mestitz *et al.* obtained specific histological results in 55% of their patients compared with 50% of our patients. Trivial complications (subcutaneous haematoma and small pneumothorax) occurred in only two of their patients, and they regarded haemorrhagic disease as the only contraindication to needle biopsy.

Summary

In a series of 185 patients with pleural effusion 256 needle biopsies of the parietal pleura gave a yield of specific findings in 61% of patients with tuberculous effusion and 59% of patients with neoplastic effusion. A majority of patients with cardiac effusion had unsatisfactory specimens, whereas a majority of patients with other diseases had histological evidence of non-specific pleuritis.

In cases of tuberculosis the yield of effusion cultures is much less than the yield of biopsy, but in cases of neoplasm the yield of cell block approximates the yield of biopsy. Since each procedure may yield a diagnosis when others do not, all diagnostic methods should be used in the study of pleural effusion.

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In the July issue of *The Chiropodist*, the journal of the Society of Chiropodists, members are urged not to keep silent on the subject of their patients' footwear. The editorial says, "Should a chiropodist refuse to give more than a single treatment to corns which are produced by bad footwear? . . . The idea seems to be deeply rooted, particularly in the feminine mind, that to consider comfort when buying a pair of shoes is a sign that she is falling into the ultimate sin, that of growing old! . . . Even when we cannot persuade our patients away from the extravagant fashion entirely, . . . we may be able to suggest that a shoe which is suitable for the dance floor or for a dress occasion is not the best shoe to wear to the office or in which to do the shopping. . . . Even if it is difficult for us to make our voice heard, never let it be said that we failed for want of trying."

PLEURAL BIOPSY IN DIAGNOSIS OF THORACIC DISEASE

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In recent years needle biopsy of the pleura has proved a useful aid to diagnosis in thoracic disease. It is a simple and safe procedure which normally causes no more discomfort to the patient than a simple aspiration. Possible complications are bleeding into the pleural cavity, pneumothorax, lung or liver trauma, infection, and bleeding from an intercostal vessel. In practice they are unusual if the operation is carried out with due care.

Various needles have been used for this operation. Harvey and Harvey (1958), using a Franseen needle, obtained positive histological proof of carcinoma or tuberculosis in 14 (35%) out of 41 pleural biopsies, while Pagel and Goldfarb (1960), using a Harefield needle, obtained positive proof of tuberculosis in 13 (50%) out of 26 cases. Better results were reported by Welsh (1958), who obtained histological proof of carcinoma in 14 (82%) out of 17 cases using a Vim-Silverman needle, while Weiss (1961) obtained positive biopsies in 16 (66%) of his series of 24 cases with the same type of needle.

However, Leggat (1959) used both the Vim-Silverman needle and the Harefield needle (Abrams, 1958) in his series of 22 biopsies, and was of the opinion that it was much more difficult to obtain a satisfactory specimen with the former. Mestitz and Pollard (1958) reported on a series of cases using the Harefield needle, and later gave a more detailed report on their results (Mestitz, Purves, and Pollard, 1958). In their series 228 pleural biopsies were carried out on 200 patients, most of whom had an effusion at the time of the investigation. They established the diagnosis in about 80% of tuberculous and 60% of malignant effusions by this means, and concluded that it is by far the most reliable diagnostic technique when tuberculosis is suspected. They also thought that it should be part of the initial investigation of every patient with a pleural effusion of uncertain aetiology. The latest series in the British literature would appear to be that of Hampson and Karlish (1961), who used the Harefield needle in all their cases. They performed 136 biopsies on 118 cases with pleural effusion, and the results were diagnostic in 24 (75%) out of 32 cases of pulmonary tuberculosis and in 25 (62.5%) out of 40 cases of malignant effusion. These workers suggest that an effusion should not be regarded as of unknown origin unless pleural biopsy has been carried out, preferably at the initial aspiration.

Method

In the present series the Harefield needle was used in all cases. It was felt that this was the best instrument available, in view of the high percentage of positive results, the absence of complications reported (Mestitz

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and Pollard, 1958; Mestitz *et al.*, 1958; Abrams, 1958), and the fact that it allows an aspiration of a pleural effusion and a punch biopsy of the parietal pleura to be performed in one operation. It also has the advantage of resecting a piece of tissue consisting of intercostal muscle and adjoining pleura, approximately 3 mm. long and 4 mm. in diameter, which is punched out and is therefore likely to be undistorted and adequate for histological study.

The method we used was that described by Abrams (1958). As a considerable amount of pressure is required to introduce the biopsy needle, we make an initial track with a trocar and cannula or an aspiration needle; this also minimizes the danger of forcing the needle in too quickly (thereby damaging the lung). Most patients were premedicated with pethidine or "pethilorphan" 50 mg. intramuscularly, and only a few experienced pain. Three of the elderly patients felt faint during the procedure, and for this reason one of us always performs the biopsy prior to aspiration. (If the biopsy is performed first and only a poor specimen obtained, a further biopsy can be taken with little danger of lung damage.)

Results

A total of 83 pleural biopsies were performed on 79 cases admitted to Plaistow Hospital Chest Unit from March, 1958, to September, 1961. Pleural biopsy was performed in all cases with pleural effusion when the diagnosis was in doubt.

Biopsies Performed in Absence of Pleural Effusion

Seven biopsies were carried out in the absence of a pleural effusion in 1958, and in all cases no pleura was obtained. In three of these cases hepatic parenchyma, intercostal nerve trunk, and lung tissue respectively were reported. In view of the potential dangers revealed by these reports, it was decided to abandon pleural biopsy in the absence of fluid. We agree with Abrams (1958), however, that should the pleura be radiologically adherent and feel thickened on insertion of a needle, pleural biopsy in the absence of fluid is a reasonably safe procedure, and may lead to a definite diagnosis. Only one pleural biopsy was performed under these conditions, and this saved the patient from a thoracotomy.

A woman aged 64 had had dull right-sided chest pain for three weeks and exertional dyspnoea for four months on admission. She had lost 3 stone (19 kg.) over the previous year. On examination she looked ill and wasted; there was no clubbing or lymphadenopathy. Clinically, the percussion note was dull on the right side, but there was no mediastinal shift and the breath sounds were equal on both sides. Her chest x-ray picture showed loss of translucency over the whole of the right lung, which on a lateral view appeared maximal anteriorly. Bronchoscopy showed no abnormality. Three pleural aspirations were attempted but no fluid was obtained. Anteriorly, however, the pleura felt thickened to the point of a needle and a biopsy was therefore taken; this showed infiltration with an oat-cell carcinoma.

Biopsies Performed in Presence of Pleural Effusion

Seventy-six biopsies were performed on 71 cases in the presence of an effusion, and pleura was obtained on 63 occasions (83%). The biopsy results were divided into five groups according to the histological diagnosis: tuberculous pleurisy, malignant infiltration, acute or subacute inflammatory, non-specific, and inadequate. The results obtained are shown in Table I.

TABLE I.—*Correlation Between Final Diagnosis and Biopsy Diagnosis Taken in Presence of a Pleural Effusion*

Final Diagnosis	No. of Cases	No. of Biopsies	Biopsy Results				
			Acute or Subacute Inflammatory	Tuberculous	Malignant	Non-specific	Inadequate
Malignant ..	35	36	1	—	25	4	6
Tuberculous ..	15	18	2	5	2*	6	3
Pneumonic ..	14	14	—	—	—	10	4
Empyema ..	3	3	3	—	—	—	—
Pulmonary infarction ..	2	3	1	—	—	2	—
Malignancy and tuberculosis ..	1	1	—	—	1	—	—
Traumatic ..	1	1	—	—	—	1	—
Total ..	71	76	7	5	28	23	13

* Misdiagnoses.

The methods by which the definitive diagnosis was reached in the cases of tuberculosis and malignancy are shown in Tables II and III respectively. The only complications that arose were a small pneumothorax in one case and haemorrhage from an intercostal vessel in another. Biopsies were not performed if the effusion was known to be secondary to congestive cardiac failure or hypoproteinaemia. Patients with clear radiological evidence of tuberculosis or with small lymphocytic effusions were excluded from this series.

Tuberculous Pleurisy

Eighteen biopsies were performed on 15 cases—12 patients had one biopsy and three had two. In 15 (83%) of the biopsies an adequate specimen was obtained. In the three cases with two biopsies the histology was non-specific. In five cases (28%) the histology was diagnostic, but positive cultures were obtained in only two of these. All these positive histological findings were obtained within a fortnight of admission and thus enabled an early diagnosis to be made. No patient had received antituberculosis drugs prior to the first biopsy.

TABLE II.—*Means by Which Definite Diagnosis was Reached in 15 Cases of Tuberculous Effusion*

Pleural biopsy ..	..	..	5
Positive culture ..	..	..	6
Response to chemotherapy ..	..	..	4

Tuberculosis and Malignant Disease

There was one case of malignant disease and coexistent pulmonary tuberculosis, which demonstrates the value of pleural biopsy in correcting an initially incorrect clinical diagnosis. Thus the diagnosis must be reviewed if a patient thought to have a tuberculous pleural effusion fails to respond to chemotherapy. This applies even when the sputum has shown tubercle bacilli and especially if the organisms be found sensitive to those antituberculosis drugs which the patient is receiving.

Case 1.—A man aged 55 was admitted to hospital with diarrhoea and vomiting. He had suffered from a cough for years. On examination he was found to be anaemic and wasted. There was no lymphadenopathy or finger-clubbing. His chest x-ray film showed some tuberculous infiltration in the right upper zone and a left-sided pleural effusion. One gastric lavage and one laryngeal swab were positive on culture for tubercle bacilli. The pleural biopsy, however, showed malignant infiltration of the pleura. In spite of antituberculosis chemotherapy his condition gradually deteriorated and he died three months later. At necropsy an adenocarcinoma was found at the periphery of the lung with infiltration of the muscles of the chest wall.

In two cases subsequently proved to have tuberculosis the pleural biopsy report was incorrect. These were the

only two biopsies out of 63 where pleura was obtained in which the misdiagnosis was made on histological grounds. However, in both these cases there was excellent response to antituberculosis chemotherapy and in one case a positive culture was obtained from the pleural fluid six weeks after taking the biopsy. One case has been followed up for three years, the other for four years. Both patients have gained weight and there was no evidence of development of malignancy on their most recent chest x-ray films.

Malignant Disease

Thirty-six pleural biopsies were done on 35 patients with a malignant pleural effusion (Table III). In the patient who had two biopsies the first showed some acute inflammatory changes, while the second showed malignant infiltration. Of these 36 biopsies, 25 (69%) showed malignant infiltration of the pleura, one showed

TABLE III.—Means by which Definite Diagnosis was Reached in 35 Cases of Malignant Effusion

Bronchoscopy	..	..	..	..	6
*Pleural biopsy	..	..	..	..	25
Lymph-node biopsy	..	..	..	..	2
†Clinical evidence of metastases	..	..	..	..	2

* One patient had bronchial carcinoma and tuberculosis, and one patient had ovarian carcinoma with pulmonary metastases.

† One patient had breast carcinoma with pulmonary metastases.

an acute inflammatory reaction, and four showed non-specific changes. This group comprised 33 cases with primary bronchial carcinoma, one case of ovarian carcinoma with pulmonary metastases, and one case of carcinoma of the breast with lung metastases two years after radical mastectomy.

In peripherally situated neoplasms associated with malignant effusion bronchoscopy is often negative, a definite diagnosis being made on pleural biopsy alone. Nine patients who were shown to have malignant infiltration of the pleura on biopsy were bronchoscoped, and in five of them nothing abnormal was seen.

A pleural biopsy may on occasions give evidence of unsuspected disease. This generally arises when the patient has some associated lung condition which could produce the pleural effusion. This is illustrated by the following case.

Case 2.—A man aged 49 was known to have had bilateral lung cysts since 1954. In December, 1958, he developed left-sided pleuritic chest pain, rapidly increasing exertional dyspnoea, and a persistent non-productive cough. He had gained weight. On examination he was found to be in congestive cardiac failure and there was evidence of a left-sided effusion. Chest x-ray examination showed a large emphysematous bulla in the right upper zone, a small bulla in the left upper zone, and a small left basal effusion. The pleural aspirate was blood-stained but contained no neoplastic cells. The pleural biopsy showed evidence of squamous-cell carcinoma. At thoracotomy there was extensive infiltration of the pleura with carcinoma.

Other Diagnoses

Pneumonias.—Fourteen biopsies were performed on 14 cases of pneumonia with pleural effusion. In four no pleura was obtained, and in 10 the pleura showed non-specific changes.

Empyema.—In three cases of empyema the pleural biopsy showed inflammatory tissue. It was concluded that a pleural biopsy showing inflammatory changes may help in making a definite diagnosis and to exclude a carcinoma, but other features of the case must be considered. These include the medical history, the

clinical and haematological findings, and the character and culture results of the pleural fluid.

Pulmonary Infarction.—Three pleural biopsies were performed on two cases of pulmonary infarction: the histology showed non-specific changes.

Traumatic.—One pleural biopsy was performed on a case of traumatic haemothorax. It showed organizing fibrous blood clot, an appearance consistent with recent traumatic haemorrhage.

Operators

The biopsies were performed by 14 different doctors—either the senior house officer looking after the patient or one of us. It was found that the technique called for a certain amount of skill, which was usually acquired in time. Some operators, however, obtained a higher percentage of adequate biopsies than others after performing the same number of biopsies. An experienced operator obtained a good specimen of pleura in approximately 85% of pleural biopsies performed. Others, who failed to master the technique, achieved only 40%.

Discussion

Tuberculous Pleurisy.—In our cases of tuberculous pleural effusion, pleural biopsy was diagnostic in only 28% of cases. This comparatively low figure may be due in part to the fact that many biopsies were performed within the first few weeks of the appearance of the effusion. Hampson and Karlsh (1961) believe that in the early stages of tuberculous effusions negative results may be obtained, since time has not been allowed for the formation of the characteristic tubercles; they suggest that if a negative biopsy report is obtained in a case of suspected tuberculous effusion a second biopsy should always be performed two weeks later. Another possible cause of a negative biopsy in these cases is previous antituberculosis chemotherapy (Misra and Sharma, 1959). However, in our series the first biopsy was performed prior to chemotherapy in all cases subsequently proved to have pulmonary tuberculosis. Needle biopsy of the pleura in the case of tuberculous pleural effusion more often gives positive results than culture of the pleural fluid (Weiss, 1961). In these cases the condition may be diagnosed by pleural biopsy, and treatment instituted long before results of culture can be obtained.

Malignant Disease.—In the case of neoplastic pleural effusion the results were diagnostic in 69% of our cases subsequently proved to have malignant disease. This compares favourably with the reports of other workers (Leggat, 1959; Hampson and Karlsh, 1961). No reliance, however, can be placed on a negative biopsy, since a malignant plaque on the pleura may easily be missed. On the other hand, there is also a danger of making a false diagnosis of malignancy by the misinterpretation of actively proliferating cells in the presence of an inflammatory process; this was so in two of our cases, but the biopsy report was disregarded in the face of clinical and radiological evidence against malignancy. Hampson and Karlsh (1961) state that a useful diagnostic feature is that pleural cells are often found to be ramifying among the intercostal muscle fibres in the case of malignant disease. These workers also point out that in cases where well-differentiated tumour deposits are seen it was sometimes possible to give an opinion on the site of the primary growth.

In conclusion, therefore, our results confirm the fact that biopsy of the pleura, using the Harefield needle, is a safe and useful aid in the diagnosis of thoracic disease.

Summary

We report our experience with punch biopsy of the parietal pleura in 71 patients with a pleural effusion, seven patients without an effusion, and one patient with a thickened and adherent pleura. We found that this procedure established the diagnosis of tuberculous effusion in 28% of cases and malignancy in 69%. In the case of tuberculous effusion, pleural biopsy was almost as often positive as culture of the pleural fluid and the results were obtained more quickly. A firm diagnosis of malignant effusion could often be obtained from pleural biopsy alone, and thus avoided subjecting an ill patient to bronchoscopy or open pleural biopsy. It is a simple and safe procedure in the presence of a pleural effusion or an adherent pleura. We do not advise biopsy where there is no fluid and the pleura is non-adherent.

Pleural biopsy should be performed in all cases where the cause of the pleural effusion is not firmly established, and on occasions may correct an incorrect clinical diagnosis.

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Preliminary Communications

Observation of Compatible and Incompatible Foetal Red Cells in the Maternal Circulation

It is generally agreed that under natural conditions the Rh sensitization of an Rh-negative mother can take place only when Rh-positive foetal erythrocytes enter her circulation during pregnancy or around the time of parturition. It is also known that Rh sensitization is less likely to occur if the Rh-positive cells of the foetus are incompatible in the ABO sense with the mother's plasma, and it is customary to explain this by supposing that these ABO-incompatible cells are removed from the maternal circulation much more rapidly than ABO-compatible cells and before they can effectively stimulate the formation of Rh antibodies. Finn *et al.* (1961), who have discussed the problem fully, did not detect foeto-maternal microtransfusions in women who bore an ABO-incompatible baby, and thought it unlikely that such an event would be detectable.

We have examined 635 mothers in whom the ABO and Rh groups of both mother and baby were known.

Two films were made of the mother's capillary blood, one 24 hours after the other, and both within the first 60 hours after delivery. These were examined for foetal cells by the method of Kleihauer *et al.* (1957). The magnitude of any "spill" was assessed by counting the foetal cells detected amongst an estimated 50,000 maternal cells, and making corrections for maternal and foetal haematocrit, maternal blood volume (all estimated values), and the proportion (about 80%) of recognizable foetal cells found in foetal blood by the acid lysis technique. Artificial mixtures confirmed the rough accuracy of these corrections.

The results (see Table) indicate that within 60 hours of delivery a foeto-maternal spill could be detected in 28.7% of the mothers, but that the leak was a very small one in the majority. These results are comparable with those of Zipursky *et al.* (1959) and Finn *et al.* (1961). But it is also apparent that spills were detectable when the baby's erythrocytes were incompatible with the mother's serum with respect to their ABO groups. In this finding we differ from the conclusion of Finn *et al.*

Incidence of Foeto-maternal Spill in the First 60 Hours Post Partum

	ABO Relation of Child's Cells and Maternal Serum		Total
	Compatible	Incompatible	
Total examined ..	535	100	635
Positive for foetal cells ..	166 (31%) ($\chi^2=8.185$; $P<0.01$)	16 (16%)	182 (28.7%)
Volume of spill:			
Under 0.5 ml. ..	107 (20%) ($\chi^2=3.93$; $0.05>P>0.02$)	11 (11%)	118 (18.6%)
0.5 to 0.9 ml. ..	35	3	38
1 to 9.9 ml. ..	20	2	22
10+ ml. ..	4	0	4

However, ABO incompatibility certainly affects the outcome of the foeto-maternal bleed. In the first place, spills of incompatible blood were detected with only about half the frequency observed when the blood was compatible, and large spills of 10 ml. or more have not yet been found with incompatible blood. In the second place, the examination of two films from each of 155 mothers who had been shown to have received an accidental transfusion of foetal blood allowed us to observe any changes that might occur in the number of transfused cells persisting in the mother's blood over a 24-hour period (the remaining 17 positive findings were based on a single film). When the foetal blood was compatible, as happened in 141 cases, both films were usually positive, and among these mothers there were only 28 (18%) whose blood showed foetal cells on the first day and none on the second. However, after the 14 labours producing an incompatible baby, the film had become negative on the second day in eight cases, or more than 50%. The observed difference in the persistence of foetal cells in the mother's circulation into the second post-partum day is very unlikely to have arisen by chance ($\chi^2=8.98$, for 1 d.f.; $P<0.01$). Apart from this, there was no discernible difference in the amount of circulating foetal blood as between the first and the second day in either type of delivery. The period of observation was short, but it does seem, as expected, that incompatible foetal cells have a shortened life in the maternal circulation; nevertheless they can be detected, and they should be sought for early in the puerperium.

Foetal cells can be found in the maternal bloodstream during pregnancy. We have not yet determined