Papers and Originals

Lung Biopsy in the Diagnosis of Diffuse Lung Disease*

J. G. SCADDING,† M.D., F.R.C.P.

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This lecture commemorates Arthur Tudor Edwards, one of the very small group of surgeons who, in the decade following the first world war, established the surgery of intrathoracic organs as a practicable procedure. For one year, 1932-3, I was house officer at the Brompton Hospital to him and his colleague, J. E. H. Roberts, the two leading thoracic surgeons in London. Seeking a possible link between the time when as a young man I was privileged to work for Tudor Edwards and my present interest in the nosology of broncho-pulmonary disease, I propose in this lecture to consider the contribution of surgical biopsy to the diagnosis of widespread lung disease.

I shall exclude from consideration the problem of localized lung disease presenting more or less well-defined radiographic shadows. Dr. E. D. Churchill, the Boston thoracic surgeon, asked to discuss a case of this sort at one of the clinicopathological exercises at the Massachusetts General Hospital in 1951, commented: "I don't know what this is, but I do know what to do about it"; and most physicians would agree that in such a case, once a relatively limited number of investigations have proved inconclusive, thoracotomy is usually indicated, for it may be not only diagnostic but a preliminary to definitive treatment by resection.

The problem posed by those patients who present with radiological or other evidence of widespread lung disease, the nature of which remains undetermined after routine investigations, is more difficult. Lung biopsy can benefit them only by providing information which will lead to more effective medical management or better-based prognosis. In itself it can have no therapeutic effect; it exposes the patient to inevitable discomfort and to some risk, though this should be small. For this reason the number of cases in which I personally have advised lung biopsy is relatively small, amounting to 43 in the past 13 years. I have also had under my care a further 23 patients who were referred to me after surgical lung biopsies had been performed elsewhere. Thus I can report personal observations on 66 patients with diffuse lung disease who were submitted to open lung biopsy (Table I).

Table I.—*Results of 66 Open Lung Biopsies in Diffuse Lung Disease*

Cryptogenic fibrosing alveolitis		27
Extrinsic allergic alveolitis		1
Sarcoidosis		15
Eosinophilic granuloma (histiocytosis X)		5
Malignant disease		4
Primary emphysema		1
Categorization doubtful		8
Alveolar fibrosis (? extrinsic allergic, ? cryptogenic)	3	
Necrobiotic nodules	4	
No evidence of rheumatoid arthritis	3	
Later developed rheumatoid arthritis	1	
Honeycomb lung, unclassifiable	1	
Biopsy not contributory		5
Final diagnosis (after further observation):		
Probable cryptogenic fibrosing alveolitis (1 with coal miner's pneumoconiosis)	3	
Gas transfer defect of undetermined cause: death from myocardial infarction	1	
Glomerulonephritis with lung purpura	1	

In 53 of these cases the histology of the biopsy specimen permitted satisfactory diagnostic categorization. Before considering the 13 in which categorization remained in various degrees of doubt, I will make some observations on the better-defined diagnostic groups.

Cryptogenic Fibrosing Alveolitis

I suggested in 1964 that the term "fibrosing alveolitis" might conveniently be used to refer to a broadly defined group of cases of progressive lung disease characterized by varying combinations of two histological features: thickening of alveolar walls, at first cellular but with a strong and early tendency to fibrosis, and the presence of large mononuclear cells presumably of alveolar origin in the alveolar spaces. This term is being used increasingly (Crofton and Douglas, 1969). These cases have been described under a variety of other names, such as "chronic diffuse interstitial fibrosis of the lungs" and "interstitial pneumonitis." Most are of unknown cause, and may therefore be specified as "cryptogenic." As a result of long-term clinical study of patients who have been submitted to lung biopsy, it has become possible to correlate variations in histological pattern with differences in clinical and radiological picture and in course.

Histologically, there is a range between a "desquamative" pattern, in which the most striking histological finding is the large mononuclear cells filling the alveoli, and alveolar wall thickening and fibrosis are not prominent; and a "mural" pattern characterized chiefly by alveolar wall thickening (Scadding and Hinson, 1967). The desquamative type has been described by Liebow *et al.* (1965) under the title "desquamative interstitial pneumonia," with the implication that it is different in pathogenesis from "other forms of interstitial pneumonia." But Hinson and I considered that the histological evidence was equivocal in relation to possible differences in pathogenesis, since all sorts of intermediate patterns between the desquamative and the mural could be found.

As would be expected, those patients who at biopsy show a desquamative pattern may respond favourably to the suppressive effect of corticosteroid treatment, and a few even improve spontaneously. Those who show a mural pattern respond less to corticosteroids, rarely showing either radiological or functional improvement; but in many of them the disease progresses only slowly, and in some there are long periods of fixed non-progressive disability. Radiologically, the desquamative pattern is characterized either by patchy consolidation or by bilateral basal shadowing above a somewhat raised diaphragm; the mural pattern generally presents widespread discrete small rounded opacities or multiple small ring-shadows, the so-called honeycomb appearance, or a mixture of these. Radiographic honeycombing develops also late in the course of some cases, starting with a desquamative pattern. It has been found to correlate with corresponding structural changes in the lungs.

* Tudor Edwards memorial lecture delivered at the Royal College of Physicians of London on 4 February 1970.

† Professor of Medicine, Institute of Diseases of the Chest, Brompton Hospital, London S.W.3.

Present Series

Of the 27 cases classified as cryptogenic fibrosing alveolitis in the present series of lung biopsies 6 showed a desquamative and 12 a mural pattern, and 8 had features intermediate between these two patterns. The remaining case, classified as "mixed," is of special interest because in different parts of the biopsy specimen there were typical examples of the desquamative and the mural patterns.

Case 1.—A housewife aged 59 complained in July 1968 of increasing breathlessness on exertion. Though at first radiographic changes consisted in only doubtful patchy shadowing in the lower zone of the right lung, both breathlessness and lung shadowing increased steadily over the next three months. In October 1968 she was breathless on the slightest exertion and cyanosed. The total lung capacity was grossly reduced with proportional reduction in vital capacity, as was the carbon monoxide transfer factor. The arterial blood oxygen pressure at rest was 60 mm. and CO_2 pressure 30 mm. Lung biopsy through a small right anterolateral thoracotomy showed a small lung which felt granular; in a wedge removed from the middle lobe the changes of cryptogenic fibrosing alveolitis were found. In some parts there was a typical mural pattern, with severe fibrosis of alveolar walls and very scanty intra-alveolar cells (Fig. 1); elsewhere the changes were characteristic of the desquamative pattern, with lymphocytic infiltration of alveolar walls and alveolar spaces containing many mononuclear cells, mostly of granular type (Fig. 2.) Because this patient already had symptoms from spinal osteoporosis, the use of corticosteroids was considered inadvisable. She was treated with the immunosuppressant azathioprine, and made a favourable response, of a degree compatible with suppression of the "desquamative" element in the lung changes, both radiologically and in objective tests of function (Table II).

TABLE II.—*Case* 1. *Serial Lung Function Tests*

	Predicted	Nov. 1968	Apr. 1969	Nov. 1969
T.L.C. (ml.)	4,130	2,260	2,920	3,750
F.R.C. (ml.)	2,430	1,460	1,520	2,350
V.C. (ml.)	2,610	1,150	1,750	2,100
F.E.V.$_1$ (ml.)	2,080		1,300	1,550
TLco (ml./min./mm. Hg):				
Rest	11·8	3·9	6·9	11·3
Exercise			8·9	11·4

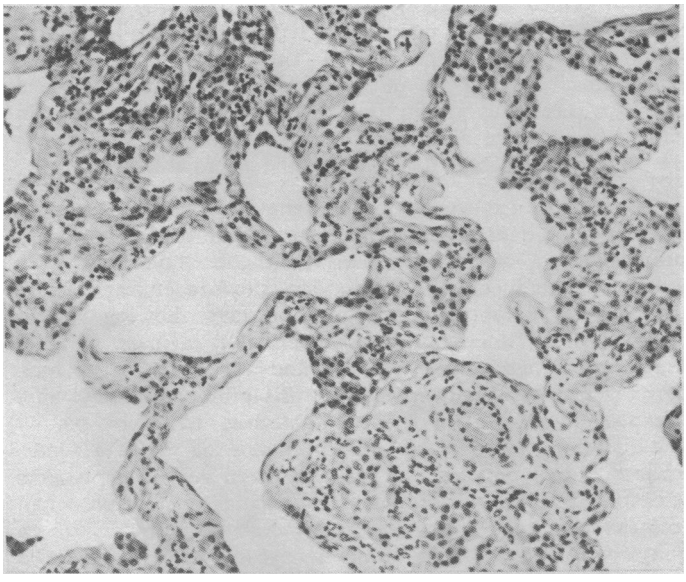

FIG. 1.—Case 1. Lung biopsy: area showing a mural pattern of fibrosing alveolitis. (H. & E. × 130.)

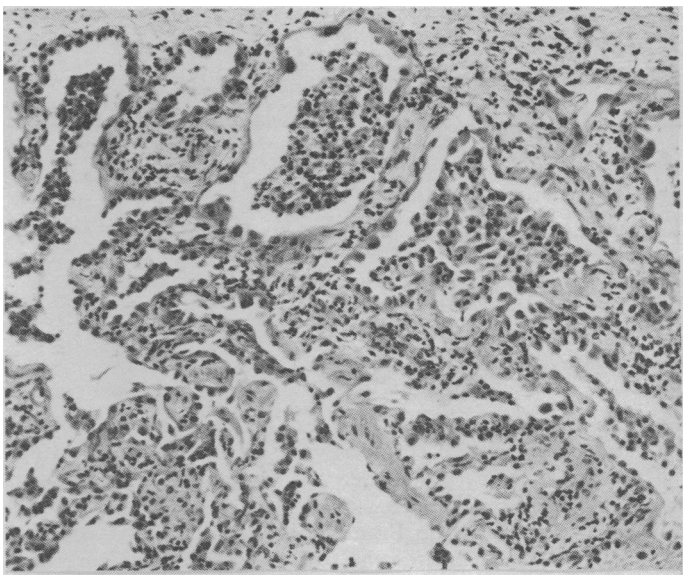

FIG. 2.—Case 1. Lung biopsy: another area showing a desquamative pattern of fibrosing alveolitis. (H. & E. × 130.)

The occurrence of fibrosing alveolitis of the desquamative pattern without radiographic abnormality in the lungs, though rare, is well documented. In such cases diagnosis must remain in serious doubt until biopsy has provided histological evidence. In six patients with a clinical picture and functional defect suggesting fibrosing alveolitis, but with substantially normal radiographic appearances, lung biopsy was advised. In two of these histological changes of the desquamative pattern of fibrosing alveolitis were found. Three showed no specifically identifiable changes, though in two of these, as described below, the subsequent course has been compatible with the clinically suggested diagnosis of fibrosing alveolitis; and one, also mentioned later, had emphysema. I will quote one of the two with a normal lung radiograph who nevertheless had fibrosing alveolitis, intermediate between the desquamative and the mural patterns.

Case 2.—A man aged 57 noticed gradually increasing breathlessness on exertion about the middle of the year 1963. He had had no known exposure to a dust hazard. He had smoked 20 or more cigarettes daily since the age of 16. By September 1964 he was able to climb only one flight of stairs without stopping for breath. No abnormality was found on physical examination. The chest radiograph was normal, apart from some calcified foci at the right hilum and upper zone of the right lung. Function tests showed a maximum voluntary ventilation of 122 l./min., well within the normal range; but gas transfer was much reduced, the T_{LCO} by the steady state method being 8·7 ml./min/mm. Hg, at the high ventilatory rate of 22 l./min. On review in January 1966 his dyspnoea had increased somewhat; there was still no radiographic sign of lung disease, the T_{LCO} had fallen to 6·1 at a ventilatory rate of 23 l./min., and the resting arterial blood P_{O_2} was 87 mm. and P_{CO_2} 32·5 mm. Hg. An open lung biopsy was performed from the lingula, the naked-eye appearance of the lung provoking no comment. Histologically, there were moderate numbers of large mononuclear cells in the alveolar spaces, increase in fibrous tissue and some cellular infiltration in alveolar walls, and prominent lymphoid follicles (Fig. 3). Moderate symptomatic and functional improvement followed the administration of prednisolone, 20 mg. daily, and has been maintained subsequently on smaller doses.

The widespread pulmonary fibrosis, in many instances leading to "honeycombing," that occurs in a few cases of rheumatoid arthritis generally conforms to the mural pattern of fibrosing alveolitis (Scadding, 1969). The diagnosis can be made in most of these cases with sufficient probability on

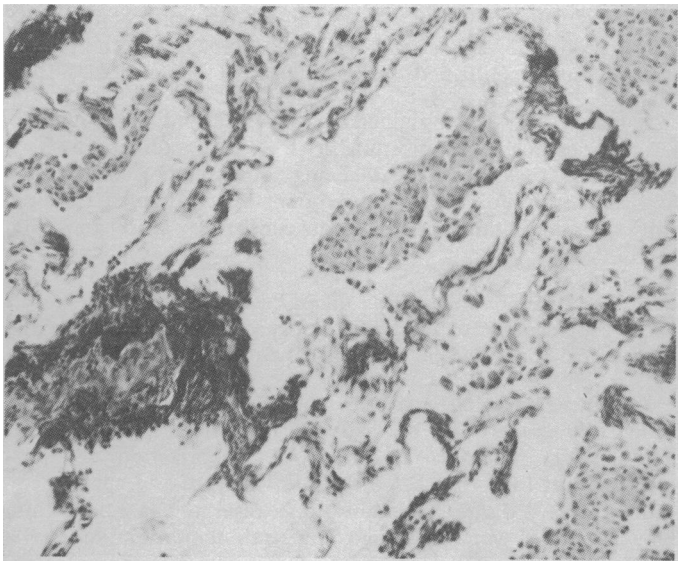

FIG. 3.—Case 2. Lung biopsy in a man with dyspnoea due to a gas transfer defect, whose chest radiograph was normal, showing many large mononuclear cells in alveoli and patchy fibrotic thickening of alveolar walls. (H. & v.G. × 130.)

consideration of clinical, radiological, and lung function findings to obviate the need for biopsy. For this reason I have advised lung biopsy in only one such patient, who had been exposed to a potential dust hazard, so that the result of the biopsy might have had an important influence on the advice given to him. In fact, it showed a typical mural pattern of fibrosing alveolitis, without pneumoconiosis. One other patient in the series reviewed had presented with widespread irregular mottling in the chest radiograph and had had a lung biopsy before he was referred to me. This showed fibrosing alveolitis, predominantly mural, together with active fibrosis of the pleura, in which there were patches of fibrinoid change reminiscent of that seen in necrobiotic nodules. At the time of the biopsy there was no evidence of arthritis. When I saw him, three years later, he was complaining of painful swelling of both ankles and one knee, and tests for rheumatoid factor were strongly positive. Subsequent events in this case have included a pericarditis, a sensory neuropathy mainly in the legs, and the finding of a granulomatous arteritis in a muscle biopsy.

Extrinsic Allergic Alveolitis

Of recent years it has become evident that certain respirable organic dusts can cause widespread changes in the peripheral gas-exchanging part of the lungs, through antigen-antibody reactions principally of the precipitin-mediated type III. "Farmer's lung" was the first of these to be recognized and elucidated immunologically, the source of the antigen being the thermophilic actinomycetes that predominate in mouldy hay (Pepys *et al.*, 1962, 1963). An increasing number of organic dusts, including the spores of some other moulds, dust from pigeon and budgerigar droppings (Barboriak *et al.*, 1965; Hargreave *et al.*, 1966), and pituitary snuff, have been shown to give rise to lung changes similar to, though not in all respects indentical with, those of "farmer's lung." A term by which to refer to the whole group of diseases characterized by tissue-damaging allergic reactions to inhaled dusts in the gas-exchanging parts of the lungs is evidently needed, and Pepys (1967) suggested that "extrinsic allergic alveolitis" might meet this need. So long as it is recognized that this term does not necessarily imply that morbid changes are confined to alveoli, it can be accepted as appropriate. This proviso is necessary, because in some cases bronchioles may be involved; and in some, notably among budgerigar fanciers, an asthmatic element, involving airways, is evidently present. Perhaps this difficulty might be met by referring to "extrinsic allergic bronchiolo-alveolitis."

In its early stage this type of reaction gives rise to a recognizable histological pattern, distinguishable from that of cryptogenic fibrosing alveolitis; it includes granulomatous elements, giant cells, often with inclusions, and conspicuous plasma cell infiltration and lymphoid follicle hyperplasia, as well as some alveolar wall thickening and a variable number of large mononuclear cells in the alveolar spaces. The only patient in whom I advised lung biopsy at this stage of the disease was the first case of pigeon-fancier's lung seen at the Brompton Hospital. In this case the resemblance of the clinical, radiological, and functional picture to that of farmer's lung was obvious, but there was no contact with mouldy hay; contact with the dust of pigeon-lofts was not then recognized as a possible cause of such a syndrome, and the diagnosis was far from clear. The biopsy (Fig. 4) showed the

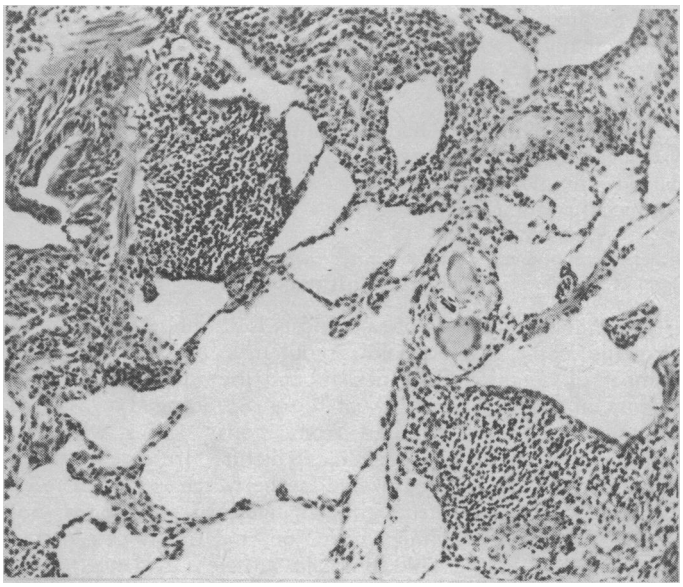

FIG. 4.—Lung biopsy in a case of extrinsic allergic alveolitis in a pigeon-fancier, showing patchy thickening of alveolar walls with plasma cells and lymphocytes and some small collections of histiocytes; two giant cells are seen in one alveolus. (H. & E. × 110.)

histological picture now recognized as that of a relatively early stage of extrinsic allergic alveolitis; but the identification of the pigeon-loft dust as the allergen depended, firstly, on the history of headache, malaise, and tightness in the chest coming on several hours after the periodic cleaning of the pigeon-loft, and, secondly, on immunology.

In general, patients with this sort of lung disease have in their blood serum precipitating antibody to the relevant antigen; and in response to an intracutaneous test with it may show a "dual" reaction (immediate weal-and-flare, followed in four to six hours by a more diffuse brawny oedematous swelling subsiding in 24 hours). In cases of doubt, confirmation can be obtained in the earlier stages of the disease, before lung function is seriously impaired, by cautious challenge tests by inhalation of aerosols of the suspected antigen. Now that the immunology of this group of diseases has been elucidated, the history and immunological tests provide diagnostic evidence, and in my view lung biopsy is indicated only if, after consideration of these data, real doubt remains whether some other disease requiring different treatment has been excluded.

If extrinsic allergic alveolitis progresses to a chronic fibrotic stage it may be indistinguishable from a late stage of cryptogenic fibrosing alveolitis clinically and radiologically, and

even, when the granulomatous element disappears, histologically. A patient with unexplained widespread lung fibrosis must be closely questioned about possible exposure to organic as well as mineral dusts. If he has been exposed intermittently to high concentrations of organic dust, as is usually the case with farmers and often with pigeon-fanciers, he may remember episodes of tightness in the chest, fever, and headache several hours after the heavier exposures; and sometimes radiographic evidence of lung changes developing at these times and resolving completely or partially afterwards leaves little doubt of the diagnosis. The greatest difficulty arises in persons who are exposed persistently to low concentrations of the offending dust and consequently have no history of illnesses after known exposure. This occurs especially in budgerigar-fanciers. They often come under observation only after fibrosis is established; the presence of precipitating antibody in the blood and of positive skin-test reactions may mean no more than contact with the antigen; if the respiratory function is severely reduced, challenge tests are undesirable and may be uninformative. And unfortunately, at this stage, histological changes in the lung are in many cases indistinguishable from those of the late "honeycombed" fibrotic stage of other forms of alveolar fibrosis.

Three patients who had widespread alveolar fibrosis and had been exposed to organic dusts capable of causing extrinsic allergic alveolitis were submitted to biopsy with equivocal results. These cases are considered below.

Sarcoidosis

The clinical diagnosis of sarcoidosis is an inference, from all available data, that sarcoid granulomas are present in a number of organs and tissues, though they may be clinically evident in only one or a few of these (Scadding, 1967a). The amount of support required from biopsy varies with the confidence with which the clinical picture presented by the individual patient is recognizable as one which is known to be associated with such histological changes. In most cases presenting with a diffuse lung infiltration, and finally categorized as sarcoidosis, it is possible to obtain sufficient evidence to justify this diagnosis by procedures less trying to the patient than lung biopsy. The Kveim reaction may be helpful, but can be expected to be positive in only about 30% of such patients; and, as I shall indicate later, doubt may remain even after a positive Kveim test. Moreover, it is wise to reserve judgement about the diagnosis if the finding of non-caseating epithelioid cell granulomas in a single organ is the sole evidence. For these reasons, I consider that lung biopsy should be required only rarely for the diagnosis of sarcoidosis of the lungs.

Of the 15 lung biopsies with a final diagnosis of sarcoidosis, eight were performed before the patient was referred to me. The seven which I personally advised were performed for various reasons.

One patient, a man aged 28, presented with an acute febrile illness with haemolytic anaemia. He was found to have bilateral hilar lymph node enlargement followed by a diffuse pulmonary infiltration, and biopsies of peripheral lymph nodes were uninformative; lung biopsy showed fibrosing sarcoid granulomas. This patient subsequently developed systemic lupus erythematosus (Scadding, 1967a, p. 464).

A 56-year-old man, investigated because of widespread mottling in the chest radiograph, showed a nodule of thyroid tissue in a scalene node biopsy; radioiodine scan of the lungs was negative, and lung biopsy showed typical sarcoid granulomas.

A young woman who was a hairdresser was found to have a widespread lung infiltration without bilateral hilar lymph node enlargement, and it seemed important to exclude hair-spray disease, often misleadingly named "thesaurosis" (Bergmann *et al.*, 1962; Brunner *et al.*, 1963). Lung biopsy and lymph node biopsy both showed sarcoid-type granulomas, and the subsequent course confirmed the diagnosis of sarcoidosis.

A man aged 48 complained of dyspnoea and was found to have widespread fine mottling in the chest radiograph. The Kveim test was equivocal. Lung biopsy showed discrete non-caseating epithelioid and giant-cell granulomas, and subsequent spontaneous resolution confirmed the diagnosis of sarcoidosis.

In one case advantage was taken of an operation for aortic valve replacement to obtain a biopsy of the lung to confirm the clinical diagnosis of sarcoidosis.

In the remaining two patients lung infiltrations were shown by biopsy to be caused by non-caseating epithelioid-cell granulomas, leading to categorization as sarcoidosis; but in both cases the clinical picture and subsequent course have led me to retain some reservations about this. One of these is worth quoting to illustrate the difficulties.

Case 3.—A symptom-free youth aged 19 was found at routine radiography to have enlarged left hilar lymph-nodes, with a small shadow in the lingula and tomographic evidence of small flecks of calcification in both these sites. Six months later he coughed up blood-stained sputum for several days. The tuberculin test was strongly positive, and, though no tubercle bacilli were found, he was thought to be suffering from primary tuberculosis, so was treated for two years with isoniazid and para-aminosalicylic acid. There was slow reduction in the size of the hilar shadow. Nine years later he again coughed up blood. At this time there was evidence of consolidation in the lingula; bronchography and bronchoscopy showed evidence of some smooth narrowing of the proximal part of the lingular bronchus, compatible with the effects of old tuberculous hilar lymphadenopathy. Three years later, when he was 31, he developed a cough, and radiologically there was considerable extension of the mottled shadowing in the left lung, together with a small pleural effusion. At thoracotomy the left lung was found to be infiltrated with white nodules, which were also seen in the parietal pleura. Biopsy (Fig. 5) showed epithelioid and giant-cell granulomas undergoing fibrosis, without caseation. All examinations for tubercle bacilli were negative. A tuberculin test with 1 T.U. gave 16 mm. of induration. A Kveim test showed well-formed epithelioid cell granulomas, and was interpreted as positive. There was no response to two months of further antituberculosis drug treatment, the pleural effusion increasing during this time; improvement followed the addition of prednisolone to the treatment.

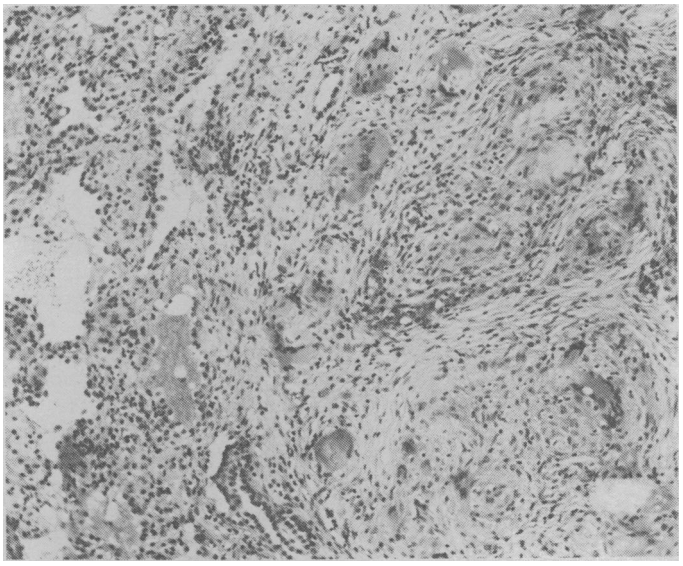

FIG. 5.—Case 3. Lung biopsy, showing fibrosing epithelioid and giant-cell granulomas. (H. & E. × 110.)

I have provisionally categorized this case as sarcoidosis because of the absence of response to antituberculosis drugs, the non-caseating character of the histology, the failure to find tubercle bacilli, and the positive Kveim test. But the unilateral distribution of the lung changes and the absence of any evident extrathoracic changes are points against this diagnosis; and there can be little doubt, in view of the original radiological picture and the persistent strongly positive tuberculin test, that the patient has had a tuberculous infection. The relationship between this and the current illness is a question on which I think it wise to keep an open mind.

In one of the patients submitted to biopsy before she was referred to me the histology had initially been interpreted as that of "interstitial fibrosis of the lungs." The knowledge that she had had widespread mottling in a chest radiograph 30 years earlier, without symptoms, and the finding of a few remnants of epithelioid cell granulomas and some Schaumann conchoidal bodies in the biopsy sections led to the revision of the diagnosis to sarcoidosis at a late fibrotic stage (Scadding, 1968).

One other patient was shown by biopsy to have non-caseating epithelioid cell granulomas in the lung, but nevertheless, for reasons discussed below, was not categorized as a case of sarcoidosis.

Histiocytosis X

Histiocytosis X or eosinophilic granuloma sometimes presents as its principal manifestation a widespread infiltration of the lungs, tending to develop into generalized honeycombing. In some cases this is accompanied by extrapulmonary changes, especially in bone. If bone changes are detected in patients with lung changes of this type, and are shown to be due to eosinophilic granuloma, the inference that the lung changes are of similar histology is acceptable. In the absence of bone changes, rather typical widespread honeycombing in the chest radiograph with relatively slight symptoms may suggest the diagnosis, but lung biopsy is required to prove it. It is well worth while looking for bone changes before proceeding to this. In three of my personal cases the diagnosis of pulmonary infiltration by histiocytosis X was accepted without lung biopsy because the lung changes were associated with histologically confirmed eosinophilic granuloma in bone. Among the five in which the diagnosis was based on the histology of the lung changes there was some difficulty and difference of opinion among pathologists in two, though the diagnosis was finally agreed, and the subsequent course has been compatible with it. In the late fibrotic honeycombed stage of this disease the specific granuloma may be very difficult or even impossible to find, so that histology may well be equivocal, and in the absence of extrathoracic manifestations of this systemic disease diagnosis may be impossible.

Malignant Disease

It should rarely be necessary to perform open lung biopsy for the diagnosis of widespread malignant disease of the lung. Blood-borne metastases often cause scattered large round opacities in the radiograph which present an almost diagnostic appearance. If any of these is of sufficient size, needle biopsy may give adequate diagnostic information, and in this situation I think it is a useful procedure. Malignant disease was found in only four of the cases of widespread lung disease in which I recommended open biopsy, and in all of these the radiographic changes consisted in a fine mottled or reticular pattern. Three proved to have so-called alveolar cell carcinoma, which might well have been metastatic from an unlocated adenocarcinoma, and the fourth was a secondary adenocarcinoma of lymphangitic distribution in the lung.

From a practical point of view, if the radiographic appearance and course are strongly suggestive of widespread metastatic malignant disease, the essential step is to determine whether the tumour is susceptible to hormonal or other systemic treatment. Fortunately, the sites from which such tumours arise—breast, thyroid, prostate, genital tract—are accessible to clinical examination.

Emphysema

The single case in which emphysema was found in the lung biopsy is instructive. In this patient, a woman aged 45 who did not smoke, increasing dyspnoea on exertion was associated with airways obstruction, a large residual capacity, and moderately reduced gas transfer factor, but radiologically there was no evidence of emphysema. Lung biopsy was performed to exclude fibrosing alveolitis or pulmonary vascular disease; it showed only emphysema. Over the next few years radiographic evidence of emphysema appeared in the form of bulla formation in the lower parts of both lungs.

Categorization Doubtful

There were eight cases in which diagnostic categorization remained doubtful even though the histology of the biopsy was grossly abnormal.

Alveolar Fibrosis

Three of these had presented with evidence of widespread fibrosis and had had contact with organic dusts; the differential diagnosis rested between cryptogenic fibrosing alveolitis and extrinsic allergic alveolitis. In one, who had had relatively slight contact with budgerigars, immunological tests were equivocal; the histology favoured cryptogenic fibrosing alveolitis, but did not exclude extrinsic allergic alveolitis; and the subsequent course, for two years after the biopsy, suggested cryptogenic alveolitis. In the second, who had been exposed heavily to budgerigars, the fibrosis was so severe that challenge tests were not considered advisable, so that immunological evidence was inconclusive; the lung biopsy showed severe fibrosis with some features favouring extrinsic allergic alveolitis; and the subsequent course and failure to respond to corticosteroid treatment was non-contributory to diagnosis in view of the irreversible fibrosis evident in the biopsy. In the third case the clinical, immunological, and histological evidence was so confused that it can be summarized only in a brief case report.

Case 4.—A woman aged 31 complained of increasing breathlessness on exertion for 15 months. She had been exposed intermittently to pigeons, her father being a pigeon-fancier. She had suffered for at least six years from adult coeliac disease, of which the presenting feature was anaemia, responding to folate. She was of short stature; the fingers were moderately clubbed; there were persistent fine crepitations at the bases of the lungs. The chest radiograph showed widespread fine mottling. The total lung capacity was reduced to two-thirds of the predicted value, with proportionate reductions in its subdivisions: the F.E.V.1 constituted 60% of the F.V.C.; the CO transfer factor was reduced to one-fifth of the predicted value at rest, but doubled on exercise. Precipitins to pigeon antigens were present in the blood, and bronchial challenge with pigeon serum produced a febrile reaction after four hours, together with a neutrophil leucocytosis. Lung biopsy showed epithelioid cell granulomas of sarcoid type, with considerable fibrosis, but no other changes (Fig. 6). The Kveim test was negative, and there was no response to corticosteroid treatment. In spite of avoidance of avian antigens, her respiratory disability has continued to increase.

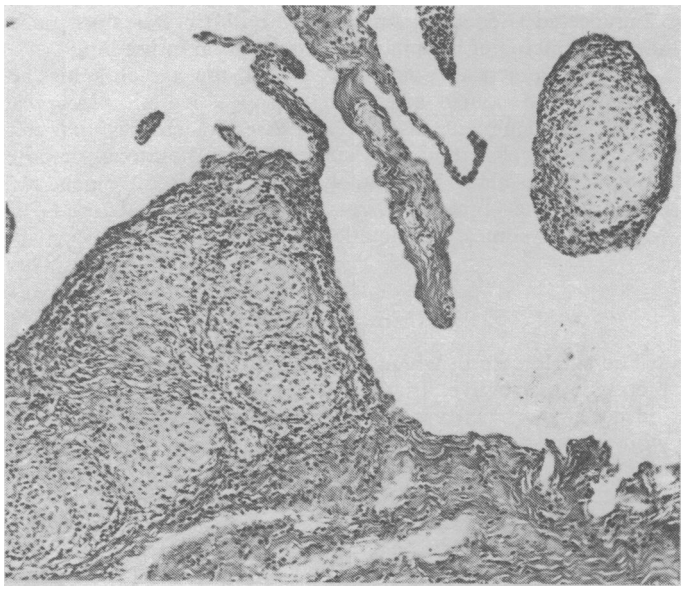

FIG. 6.—Case 4. Lung biopsy, showing well-defined epithelioid cell granulomas, with much fibrosis. (H. & v.G. × 110.)

In this case the clinical and immunological features strongly supported a diagnosis of extrinsic allergic alveolitis, but the lung biopsy was discordant; the absence of evidence of granuloma elsewhere than in the lungs, the failure to respond to corticosteroid treatment, and the negative Kveim test made it difficult to categorize the granulomatous changes in the lung as sarcoidosis; and how, if at all, the coeliac disease fitted into this complex picture remained doubtful.

Necrobiotic Nodules

In four patients lung biopsy was performed for the diagnosis of multiple nodules causing oval or rounded shadows in the chest radiograph; the histology was similar to, though not in every respect identical with, that of the necrobiotic nodules of rheumatoid arthritis. In the absence of clinical evidence of arthritis or other systemic manifestations, and of serological evidence at the time of biopsy, diagnostic categorization was impossible. In one of these cases, which I have reported elsewhere (Scadding, 1969, Case 1), joint symptoms appeared later, and within a year progressed to florid seropositive rheumatoid arthritis, leaving no doubt about categorization. The other three, followed for up to two years after biopsy, have shown neither arthritis nor positive tests for rheumatoid factor, and categorization remains in doubt.

Honeycomb Lung

The remaining case in which categorization remained doubtful illustrates the difficulties presented by established fibrotic honeycombing.

Case 5.—A boy aged 17 complained of breathlessness on exertion. His mother said that he had had respiratory difficulties at birth, and had been kept in an oxygen tent for a fortnight at that time. He had always been more easily breathless than others. Pectus excavatum had become evident during childhood, and at the time of examination was severe. The fingers showed drumstick clubbing. The chest radiograph showed, in addition to the pectus excavatum and consequent displacement of the heart to the left, an abnormal pattern in the middle zones of both lungs. Function tests showed a total lung capacity of less than half the predicted figure, with proportionate reduction of its subdivisions, the vital capacity being 1·7 l., of which 83% was expired in the first second of a forced expiration; the T_{LCO} was 50% of the predicted value, and Pa_{O_2} fell to 70 mm. on moderate exercise, Pa_{CO_2} remaining at 39mm. At operation for correction of the pectus excavatum a portion of the lingula was removed for biopsy. This showed dilated bronchioles and emphysematous spaces throughout, with cellular and fibrous thickening of alveolar walls, and an apparent excess of smooth muscle (Fig. 7). Histologically, this could be described only as a honeycomb lung; the bizarre arrangement of the smooth muscle suggested the possibility of diffuse leiomyomatosis. There was, however, no suggestion of any systemic mesodermal dysplasia, and during the subsequent two and a half years there has been no deterioration in the lungs. It seems likely, therefore, that the "honeycombing" was the end-result of an unidentified disease that was active in childhood or infancy, or even of the neonatal respiratory distress.

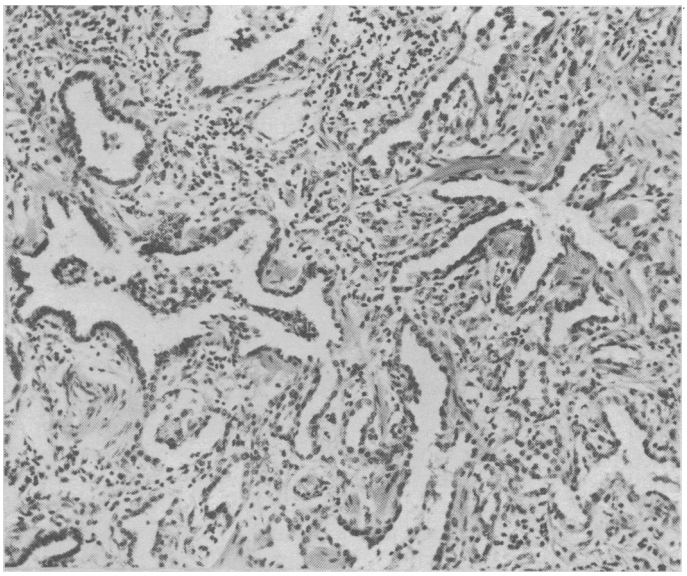

FIG. 7.—Case 5. Lung biopsy, showing fibrotic "honeycombing" with apparent excess of smooth muscle. (H. & E. × 110.)

Biopsy Not Contributory

Of the five patients included in this group, one was a young man who presented with recurrent haemoptyses, and in whom the diagnosis of lung purpura with glomerulonephritis was eventually made on the basis of the clinical course rather than any specific change in the lung biopsy (Scadding, 1958, Case 4).

In the other four cases lung biopsy was performed because of dyspnoea associated with an unexplained defect in pulmonary gas transfer, but showed no changes sufficient to explain this finding. One of these patients died three years later of myocardial infarction, though there had been no evidence of coronary artery disease at the time of the original investigation; necropsy threw no further light on the cause of the gas transfer defect. In the other three cases the subsequent course has been compatible with a diagnosis of chronic fibrosing alveolitis, and the question arises whether the inconclusive findings at biopsy may have been due to a sampling error. Two of these are briefly described.

Case 6.—A man aged 39 had complained of breathlessness on exertion for several years; but it had become notably worse for nine months, so that he was restricted to walking 400 yards (365 metres) at normal pace. He had smoked heavily until two years earlier. Physical examination and the chest radiograph showed no abnormality. Function tests showed a vital capacity of 4·4 l., within the normal range, of which only 52% was expired in the first second of a forced expiration; this indicated some airways obstruction, probably attributable to his previous heavy cigarette smoking, but was insufficient to account for his dyspnoea. The T_{LCO} was reduced to half the predicted value. This suggested the possibility of changes in the gas-exchanging part of the lung.

Accordingly a lung biopsy was performed. The lung looked normal, but felt stiffer than normal. The specimen removed from the tip of the lingula showed only some excess of macrophages in some alveoli, with no significant change in alveolar walls. In spite of these inconclusive findings, treatment with prednisolone was begun, and was followed by almost complete relief of dyspnoea and an improvement of gas transfer factor to above the predicted figure. This patient has now been followed for six years after the biopsy. Reduction of prednisolone dosage was followed by relapse, and in spite of reinstitution of higher dosage he was once again severely disabled. Radiologically, the lower lobes appeared to have contracted, the diaphragm having risen nearly one intercostal space. No firm diagnosis could be made, of course; but it seemed likely that, in addition to a mild cigarette-induced chronic obstructive bronchitis, there is a fibrosing alveolitis of which the excessive alveolar mononuclear cells were the inconclusive evidence at the time of the biopsy.

Case 7.—A coal miner started to become breathless on exertion at the age of 50. A chest radiograph when he was aged 53 showed widespread fine mottling. He was observed to have gross drumstick clubbing, but no other abnormality on physical examination. Function tests showed normal ventilatory function, normal airways resistance, greatly reduced gas transfer factor (7·4 ml./min./mm. Hg by the steady state method), and arterial Po_2 of 66 mm. at rest, falling to 54 mm. on mild exercise. Because of these findings lung biopsy was performed; it showed simple pneumoconiosis only. Nevertheless, over the next few years his disability steadily increased, with further fall in the transfer factor to 3·5 ml./min./mm. Hg; and, radiologically, widespread honeycombing developed in the lungs. There is little doubt that some additional factor, as well as coal miners' pneumoconiosis, was concerned in this, and it seems likely that at the time of biopsy a specimen from some other part of the lung might have shown evidence of this. The occurrence of "interstitial fibrosis" of the lungs as an additional factor in coal miners with pneumoconiosis has been noted by Gaensler *et al.* (1960).

Comments

Method of Biopsy

I do not propose to discuss details of surgical technique, except to note that a limited lateral or anterolateral thoracotomy is generally sufficient. It is important that access should be free enough to permit inspection of the lung and selection of the site, in order to ensure that representative tissue is obtained. An adequate sample is required, since histological changes are not always uniform (see Case 1), and variations in pattern in different parts of the specimen may be important; moreover, examinations other than histological—for example, bacteriological, chemical, or immunological—may be indicated, and special care is required to ensure that the specimen is appropriately handled for each of these.

These considerations have led me to prefer open lung biopsy to any of the methods of needle biopsy for assistance in the diagnosis of diffuse lung disease, a preference which is shared by Gaensler *et al.* (1964).

Mortality and Morbidity

Patients with the sort of diffuse lung changes for which lung biopsy may be advisable commonly have little or no airways obstruction or bronchial hypersecretion; and in the absence of these anaesthesia rarely presents problems and postoperative recovery is generally uneventful. Two patients died within a month of biopsy. One of these was the young man with lung purpura and glomerulonephritis, already mentioned; in the light of current knowledge, I should not now advise biopsy in this case. The other was a woman with alveolar cell carcinoma, who was expectorating large quantities of mucus, which I should now regard as a contraindication to biopsy. One patient had persistent pain in the thoracotomy scar for six months. Apart from this, there was no long-term morbidity.

Contribution of Lung Biopsy to Diagnosis

If our knowledge of medicine were sufficient, the diagnostic process, starting with assessment of the clinical symptoms and signs, should progress through elucidation of the underlying structural abnormalities and disturbances of function to knowledge of the cause or causes of all these phenomena (Scadding, 1967b). Unfortunately, it is only in a few contexts that knowledge is sufficient to permit this process to be carried to completion. If we can get no further than recognition of a previously described combination of symptoms or signs we shall simply categorize the case with others presenting the same syndrome. If it is possible to demonstrate or deduce the underlying morbid anatomical changes or disturbances of function, these more precise and objective criteria displace the symptom-complex as the basis of categorization. And, finally, when the cause of the illness is recognized it is usually adopted as the basis of categorization. However incomplete the diagnostic process, its end-result is expressed in terms of "diseases." We thus have a hierarchy of possible bases for categorization of patients, and consequently for definition of diseases, from clinical description, through abnormalities of structure and of function, to causation. The names of diseases are to be regarded as a convenient shorthand by which we can report in each case the current conclusion of the diagnostic process.

It is to be expected, then, that lung biopsy will provide the evidence on which the ultimate diagnosis is based most frequently in those diseases whose current basis of definition is in morbid anatomical terms. This is exemplified in the group cryptogenic fibrosing alveolitis, and also applies to malignant disease. Though biopsy may occasionally provide the opportunity for demonstration of the causal agent of a disease defined in terms of aetiology, in my series there was no instance of this. This is due largely to selection; I take every step to exclude diseases whose causal agent can be isolated by other procedures before I advise lung biopsy. If a disease defined aetiologically is suspected, but the agent is not demonstrated in the biopsy material, the histology provides only indirect and rarely conclusive evidence. This is exemplified by the group extrinsic allergic alveolitis, where diagnosis ultimately depended on clinical and immunological considerations, the histology being compatible in some instances and equivocal in others. In general, in diseases other than those whose current basis of definition is in terms of morbid anatomy, the evidence from lung biopsy must be considered in conjunction with that derived from other fields of study to permit satisfactory diagnostic categorization.

Because lung biopsy has proved so useful in diffuse lung disease presenting diagnostic problems, there is a danger that it may come to be regarded as a routine procedure in such cases. For this reason I have been critical in my appraisal of it in this lecture; I have emphasized, where appropriate, the possibilities of diagnosis by other means, and have dealt at length with those cases in which for various reasons it did not lead to definitive diagnostic categorization. It should be used selectively.

Two points should be borne in mind in deciding whether to advise it for a patient. Firstly, careful assessment by all other means is desirable to ensure that it is used only in cases where it seems likely to make a useful contribution to diagnosis. Secondly, it must be recognized that knowledge of some diseases, derived in part from correlation of biopsy findings in previous patients with immunological, physiological, and other data, has advanced to such a stage that it is now possible to make a diagnosis with reasonable confidence without biopsy if a patient presents a typical combination of clinically ascertainable findings. For instance, it is now possible to recognize

in this way those patients, usually middle-aged or older, who have a chronic fibrosing alveolitis of mural type; and those with extrinsic allergic alveolitis should be recognizable on a combination of clinical and immunological findings. The avoidance of the need for biopsy is a benefit that these patients can now enjoy, thanks to advances in medical knowledge derived in part from biopsies on earlier patients.

My sincerest thanks are due to Dr. K. F. W. Hinson, both for the instruction and pleasure I have derived from our discussions of clinicopathological correlations in lung disease over many years and for his help in the preparation of this lecture.

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Haemostatic Mechanism in the Uterine Circulation during Placental Separation

JOHN BONNAR,* M.B., CH.B., M.R.C.O.G. ; C. R. M. PRENTICE,† M.B., B.CHIR., M.R.C.P.
G. P. McNICOL,‡ M.D., PH.D., F.R.C.P.(ED., GLASG.) ; A. S. DOUGLAS,§ M.D., F.R.C.P.(LOND., ED., GLASG.)

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Summary: The haemostatic mechanism in the uterus during parturition was investigated in 12 patients being delivered by caesarean section. Detailed sequential study of the blood coagulation and fibrinolytic systems in the uterine circulation showed that placental separation is accompanied by a striking local activation of the clotting mechanism. Uterine vein blood draining the placental site while the placenta was separating showed a pronounced shortening of the whole-blood clotting-time, a significant shortening of other clotting-tests, and a sharp increase in factor VIII activity, though these changes were transitory. After delivery the level of fibrinogen and circulating platelets steadily increased and factor VIII activity remained high.

Activation of the clotting mechanism during placental separation appears to play an essential part in controlling uterine haemorrhage. The subsequent changes in the haemostatic mechanism in the puerperium are likely to predispose to thromboembolic complications.

Introduction

The physiological control of haemorrhage during parturition has been largely considered as a function of myometrial contraction. In a previous study (Bonnar *et al.*, 1970) of normal childbirth changes in the peripheral blood were found which suggested that an activation of the clotting mechanism occurs during delivery. The present report gives the results of an investigation of the coagulation and fibrinolytic systems in the uterine circulation and simultaneously in the peripheral blood during and after placental separation at delivery by caesarean section.

* Present appointment: First Assistant, Nuffield Department of Obstetrics and Gynaecology, Radcliffe Infirmary, Oxford.
† Senior Registrar in Medicine, University Department of Medicine, Royal Infirmary, Glasgow C.4.
‡ Senior Lecturer, University Department of Medicine, Royal Infirmary, Glasgow C.4.
§ Professor of Medicine, University Department of Medicine, Royal Infirmary, Glasgow C.4.

Placental separation presents an acute local challenge to the mechanisms responsible for the control of haemorrhage. The behaviour of the blood-clotting and fibrinolytic systems in the uterine circulation might therefore be expected to reflect closely the events in the uterus during parturition.

Patients and Methods

Twelve patients with haemoglobin levels over 12 g./100 ml. were studied during and after delivery by elective caesarean section. Full consent was given by each patient for the blood samples to be taken as part of an investigation into the causes of haemorrhage during childbirth. After incision of the abdominal wall and exposure of the uterus, blood samples were taken simultaneously from a large vein on the surface of the uterus in the region of the placental site and from an arm vein. A lower uterine segment caesarean operation was then performed. Immediately after delivery of the baby blood samples were taken simultaneously from a vein at the uterine fundus draining the placental bed and from an arm vein, these specimens being obtained while the placenta was separating spontaneously in utero. The placenta was then delivered by gentle cord traction, and at intervals of 5 and 15 minutes after delivery of the placenta, blood samples were taken from veins draining the placental site and simultaneously from arm veins. On closure of the abdominal wall, about 25 minutes after placental delivery, a blood sample was taken from an arm vein. In the postoperative period peripheral blood samples were taken at 24 to 48 hours, 3 to 5 days, 6 to 9 days, and 10 to 14 days after operation. In a few instances blood samples were not obtained at all the times specified owing to the absence of an adequate number of suitable veins.

The blood samples (16-18 ml.) were taken in every case by clean venepuncture into plastic syringes: 2 ml. was used for measuring the whole-blood clotting-time, 9 ml. was mixed with 1 ml. of 3·8% sodium citrate in a plastic tube for coagulation and fibrinolytic tests, 3-5 ml. was added to a plastic tube containing glass beads and 1 mg. of tranexamic acid for assay of fibrin/fibrinogen degradation products, and