Transpleural Lung Biopsy by the Thoracoscopic Route in Patients with Diffuse Interstitial Pulmonary Disease*

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Thoracoscopy was carried out in 81 cases of diffuse pulmonary disease in order to obtain lung tissue for biopsy. After we established artificial pneumothorax, the thoracoscope was introduced under local anesthesia, multiple biopsy specimens (ø 3 mm) were obtained under visual control, and an underwater sealed drain was left in place. The method was used to determine the cause of x-ray shadowing and respiratory distress in 26 immunocompromised patients. Within 2-48 hours, all biopsy specimens provided sufficient microbiologic and morphologic information to guide management, eg, specific antimicrobial drugs, decreasing or intensifying immunosuppression, or cytostatic therapy. Thoracoscopy was tolerated better than fiberoptic bronchoscopy, especially in hypoxic patients. Persisting or recurring pneumothoraces were seen in four patients and was not a major complication. In one very ill patient, the spleen was punctured accidentally before biopsy specimens were taken. Of 63 nonimmunocompromised patients, a histologic diagnosis was obtained in 57 (90 percent). In most of these patients, previous biopsy procedures had produced inconclusive results. Also in this group persisting or recurring pneumothoraces were seen in four patients, but closed eventually in a conservative way.

F requently confronted with immunocompromised patients who develop diffuse pulmonary infiltrations and rapidly progressive respiratory distress, we were dissatisfied with the methods currently available to obtain a diagnosis solid enough to rely upon for management and therapeutic approach. In such patients, good microbiologic and morphologic information is badly needed to define the pathologic process, to estimate its reversibility, to choose between intensifying or reducing immunosuppressive therapy, and to identify possible opportunistic pathogens for selection of an appropriate antimicrobial regimen.

Open chest surgery under general anesthesia is hazardous for many such patients since it often leads to prolonged artificial respiration connected with risks of multiple infections and the problem how to wean the patient from the ventilator. Transbronchial fiberoptic biopsy under local anesthesia may yield useful information in patients with diffuse interstitial pulmonary disease. Although the method is successful in 80 to 90 percent of cases of sarcoid-osis,[1,2] it is less successful (40 percent) in fibrosing alveolitis,[3] and in many other types of diffuse pulmonary disease the specimens obtained are too small for adequate pathologic studies.[4] In contrast to earlier reports,[5,6] we found fiberoptic bronchoscopy of poor diagnostic value in immunocompromised patients because of frequent oropharyngeal contamination of aspirates and insufficient amount of biopsied tissue for morphologic investigations. Transthoracic needle core and drill biopsies produce small specimens also, and their complication rate is rather high to balance the average yield.[7]

In our department, thoracoscopy (pleuroscopy) under local anesthesia has been practiced for many years in patients with pneumothorax and pleural disease, and since 1975 we have extended the thoracoscopic approach to patients with diffuse pulmonary disease to obtain biopsies of lung tissue.

METHODS

About 30 minutes after premedication (usually with atropine 0.5 mg, droperidol 2.5 mg and fentanyl 0.05 mg intramuscularly) the patient is brought into a horizontal lateral (right or left) position, with the head down to prevent possible air emboli reaching the brain (Fig 1A). Usually we choose the 4th or 5th intercostal space in the mid-axillary line for entrance. To obtain adequate local anesthesia, infiltration with 10 to 15 ml lidocaine 2 percent up to the pleura is sufficient. After having established an artificial pneumothorax (300 to 600 ml) by using a needle connected to a manometer, an incision of 1.5 to 2 cm is made. Sub-
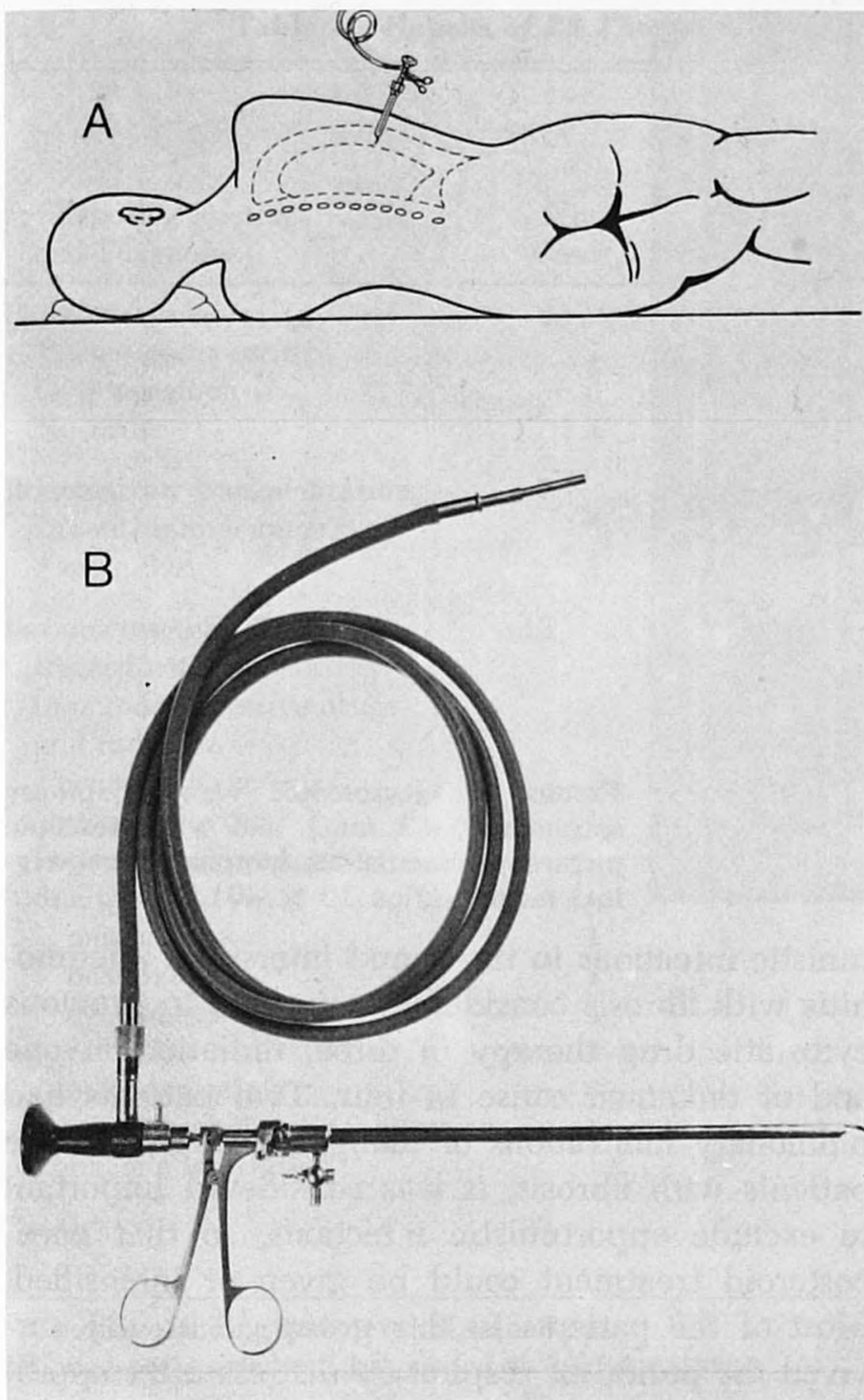
FIGURE 1. Position of the patient and instruments used.

cutaneous tissues, including the parietal pleura, are bluntly dissected, and the thoracoscope (Storz, Tuttlingen, West Germany) is introduced via a trocar (0.9 mm). In this way, the lung surface can be inspected and multiple biopsies from the superficial lung tissue can be taken under visual control. The instruments used are shown in Figure 1B. The forceps, in open position, is dipped into the pulmonary tissue (Fig 2A), is closed and subsequently withdrawn (Fig 2B). A piece of tissue with a diameter of approximately 3 mm is torn off when withdrawing the forceps from the pleural cavity into the trocar (Fig 2C). Biopsies can be taken from any site. Inspection thereafter shows a shallow lesion, which may bleed slightly. Abundant bleeding is not observed, because superficial lung tissue contains only capillary vessels and the specimen is not cut away but torn off. Usually we take eight to ten biopsy specimens. A drain is left in the trocar and sealed under water. We never apply active suction by which air-flow tends to keep the holes open. We prefer fast closure of the lung over fast elimination of the pleural air.

After collection, the biopsy specimens are immediately sent to a number of laboratories (pathology, microbiology, parasitology, mycology) which are notified in advance to ensure optimal care for the material obtained.[8]

Macroscopic (Fig 3A) and microscopic views (Fig 3B) of a representative transpleural biopsy specimen (0.3 mm) show that the size of the sample is much larger than obtained by transbronchial biopsy.

RESULTS

Thoracoscopic lung biopsy was performed in two categories of patients: immunocompromised individuals in whom a rapid diagnosis was mandatory, and in non-immunocompromised individuals being investigated for diffuse pulmonary disease of unknown origin.
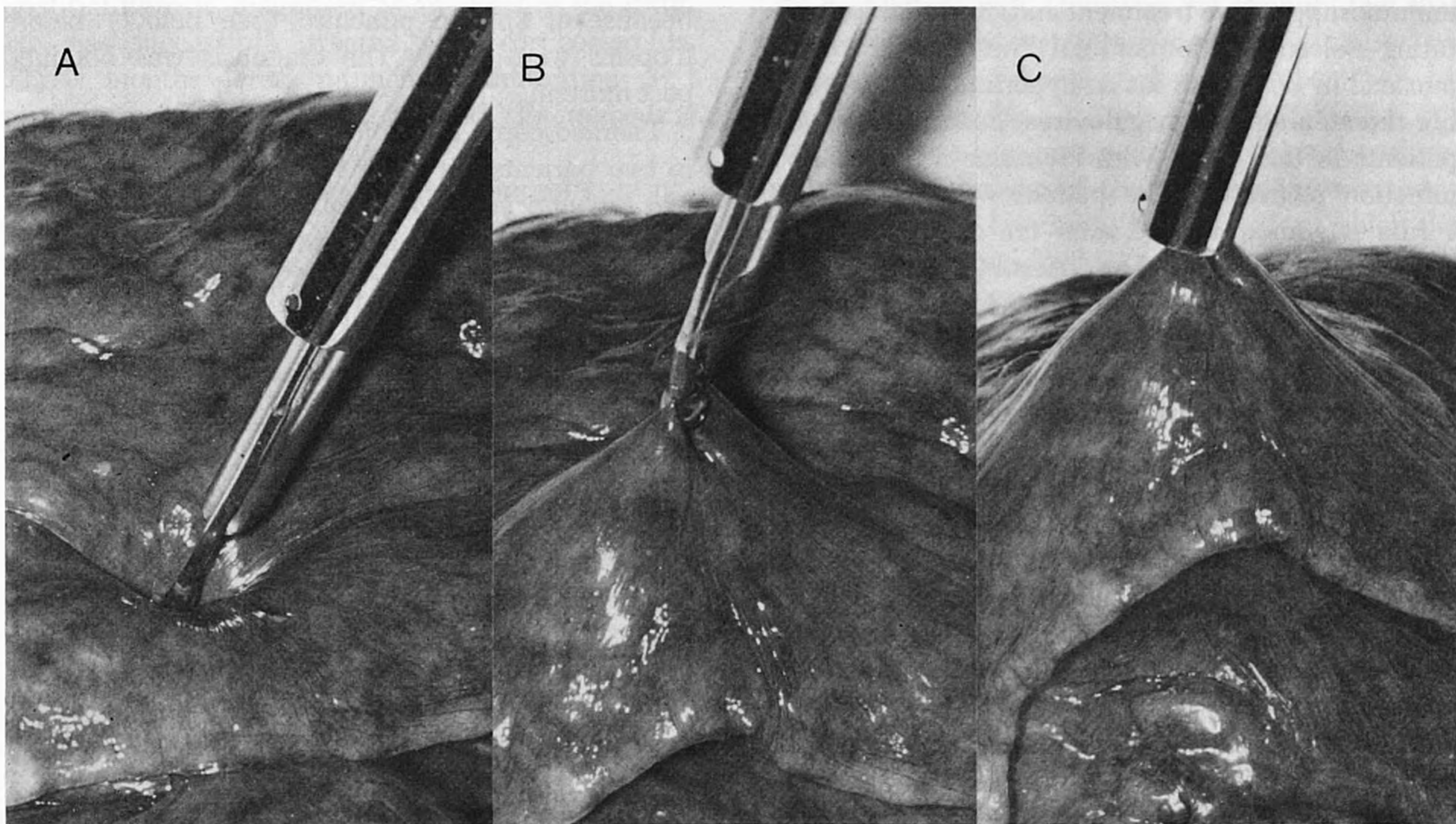

FIGURE 2. Biopsy of lung tissue through the thoracoscope. For explanation see text.
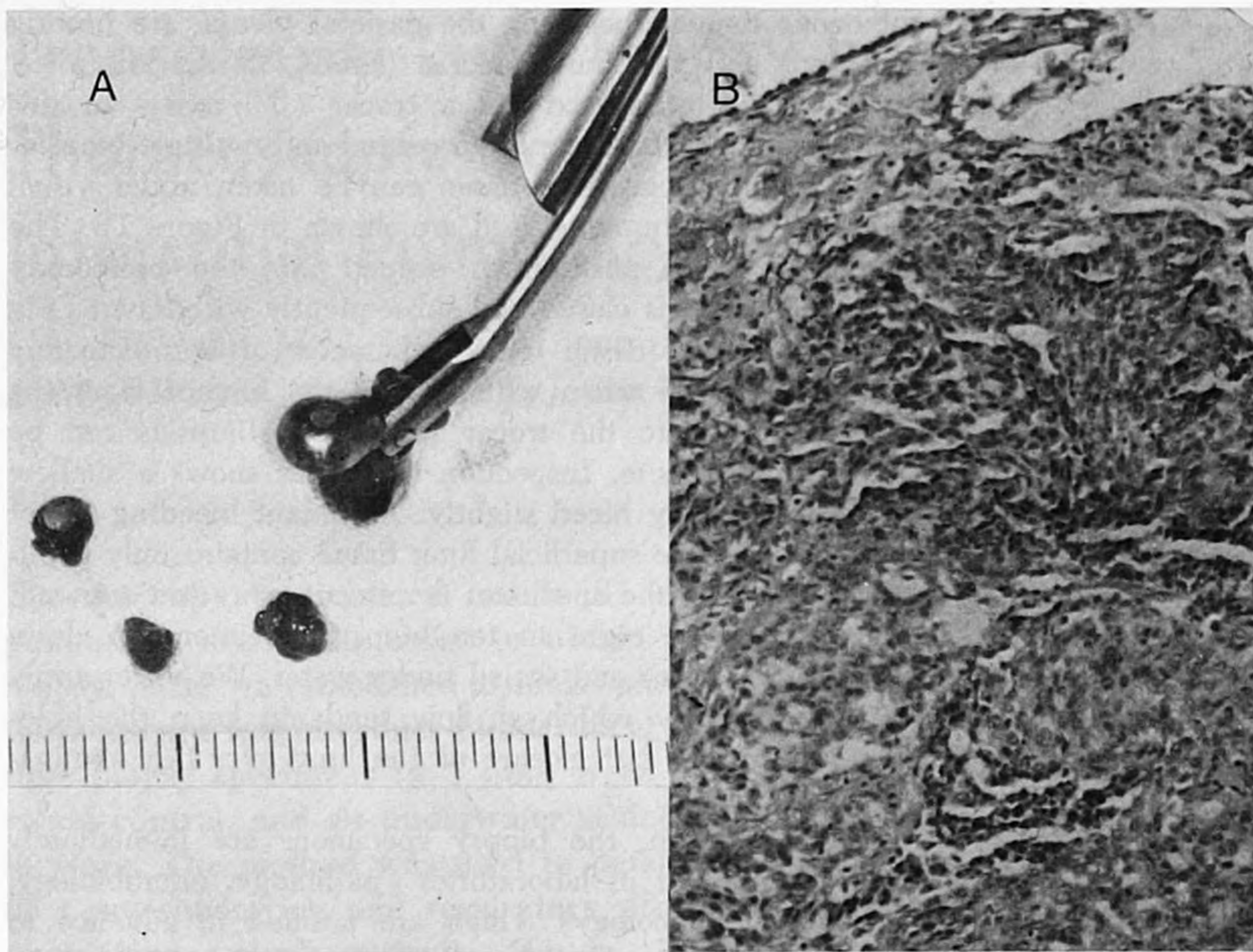
FIGURE 3. Macroscopic view of biopsy specimens (ø 3 mm) and a microscopic picture carcinomatous lymphangitis (original magnification 10 × 40).

Immunocompromised Patients

Biopsies were performed for 28 episodes of diffuse pulmonary infiltration in 26 immunocompromised patients, whose underlying diseases are listed in Table 1. Results of the biopsy procedure, clinical outcome and complications are presented in Table 2.

In all eight patients who developed diffuse pulmonary disease after renal transplantation, infections caused by opportunistic pathogens were demonstrated. These findings resulted in reducing immunosuppressive treatment and, if available, instituting selective antimicrobial therapy, *eg*, cotrimoxazol in Pneumocystis or hyperimmune serum in life-threatening cytomegalovirus pneumonitis.[9] All patients in this group with Pneumocystis or CMV-infection recovered. The patient with diffuse Nocardia pneumonitis died after ten days in spite of administration of several antimicrobial drugs.

Most of the patients with bone marrow graft for acute leukemia[10] showed severe interstitial pneumonitis with fibrosis,[11] considered to be caused in part by previous irradiation and cytostatic drugs and in part resulting from a graft-vs-host reaction. This condition was lethal in four of the six patients despite intensive immunosuppressive treatment. Autopsy was performed in three patients and yielded no other diagnosis than idiopathic interstitial fibrosis. In addition, the patient with extensive Aspergillus-pneumonia after bone marrow transplantation also died.

In the other 13 patients, with various types of malignant or other diseases (Table 1), who were treated with cytostatic and immunosuppressive drugs, thoracoscopic lung biopsy revealed opportunistic infections in three, and interstitial pneumonitis with fibrosis considered to be due to previous cytostatic drug therapy in three, radiation in one and of unknown cause in four. Two patients had pulmonary infiltrations of malignant origin. In the patients with fibrosis, it was considered important to exclude opportunistic infections, so that corticosteroid treatment could be given or intensified. Most of the patients in this group (8 of 13) survived the period of respiratory distress after appropriate therapy. In the patient with leukemic pulmonary infiltration, the procedure was terminated because of splenic puncture (see below) before biopsies were taken. The diagnosis was obtained post mortem.

Thoracoscopic lung biopsy was performed twice in two patients, on different occasions. One patient had *Pneumocystis carinii* infection two months after renal transplantation and exhibited a cytomegalovirus infection six weeks later. The other patient had been treated with cyclophosphamide because of

Table 1—*Underlying Disorder(s) in 26 Immunocompromised Patients*

Renal transplantation	8
Bone marrow transplantation	7
Leukemia	3
Wegener's granulomatosis	2
Hodgkin's disease	2
Angioimmunoblastoma	2
Systemic lupus erythematosus	2
Breast carcinoma	1
Small-cell bronchial carcinoma	1

Table 2—Results of 28 Thoracoscopic Lung Biopsies in 26 Immunocompromised Patients

Predisposing Factors and Diagnoses	No. Cases	Negative Findings in Fiberoptic Biopsy*	Diagnosis by Thoracoscope	Confirmation at Autopsy	Recovery	Duration of Drainage, days (Mean and Range)	Complications (No. Patients)
Renal transplantation	8		8		7	2.8 (1-8)	
Pneumocystis carinii	2	1			2		
Cytomegalovirus	5				5		Pneumothorax (1)
Nocardia	1	1		1			
Bonemarrow transplantation	7		7		2	8.0 (3-28)	
Interstitial pneumonitis	6			3	2		Pneumothorax (1)
Aspergillus	1	1					
Various diseases (Table 1) treated with cytostatics, immunosuppressive drugs and radiation	13		12		8	3.5 (1-7)	
Pneumocystis carinii	2			1			
Cytomegalovirus	1				1		
Interstitial pneumonitis due to:							Pneumothorax (1)
methotrexate	1				1		
busulfan	1	1			1		
cyclophosphamide	1				1		
radiation	1	1			1		
unknown origin	4	1			2		Pneumothorax (1)
Angio immunoblastic infiltration	1				1		
Leukemic infiltration	1†			1†			Splenic puncture (1)
Total	28	8	27	6	17	4.4 (1-28)	Pneumothorax (4) Splenic puncture (1)

*A positive finding was never obtained.
†Biopsy not carried out because of splenic puncture.

Wegener's granulomatosis. First, he developed interstitial fibrosis, diagnosed as an effect of the drug. He was successfully treated with corticosteroids. Three months later, pulmonary infiltration and respiratory distress recurred, and *Pneumocystis carinii* was found by biopsy.

Although most of these immunocompromised patients, especially the patients who had bone marrow or kidney grafts, showed intense x-ray film shadowing and suffered from respiratory distress which needed oxygen-supply, the artificial pneumothorax and the thoracoscopy were well tolerated and caused less discomfort than was caused by tracheal anesthesia for previous fiberoptic bronchoscopy in several of them. Nearly all these patients received oxygen by nasal route or mask and thoracoscopy was usually performed without increasing the oxygen supply they had already. We had no opportunity to monitor blood gas levels during the procedure. However, heart rate and blood pressure were monitored and showed no major changes.

While we have not considered hypoxia to be a contraindication for thoracoscopy, we always have refused hypercapnic patients. In spite of this policy, artificial respiration was needed in three patients at 12 hours, two and five days after thoracoscopy. All died eventually. However, we strongly feel that progression of the respiratory distress was caused by the underlying pulmonary disease, rather than by the biopsy procedure.

Using an underwater-sealed chest drain without suction, re-expansion of the lung usually was completed within a few hours or days, after which the drain was clamped for another day and subsequently, after x-ray examination, removed. The duration of chest drainage was 1-21 (mean 4.4, median 3.0) days. In three patients, re-expansion of the lung took more than eight days and in two others, pneumothorax recurred after removal of the drain. This complication only caused some discomfort in three patients, but to some extent hampered management in two others, who went on artificial respiration.

Many of the patients were thrombocytopenic and showed a bleeding tendency. In such cases platelet transfusions were given shortly before the procedure. We have accepted a maximal bleeding time (Ivy[12]) of seven minutes. In no patient did lung biopsy cause more than superficial bleeding. However, in one patient puncture of the spleen occurred

accidentally which caused a peritoneal hemorrhage. This patient was so distressed that it was not possible for him to assume a strict horizontal position. In trying to establish artificial pneumothorax, the spleen was punctured, probably because the patient had a large leukemic spleen which pushed the diaphragm upwards. After this experience, we have not accepted any patients who were not able to lie down completely horizontally.

Most patients had granulocytopenia as well, but no infections occurred at the site of the biopsy or chest drain after the procedure.

In all 27 patients in whom lung tissue was obtained, a diagnosis was available within 48 hours, in many of them even within two hours (by microbiologic studies and frozen tissue sections). Receiving treatment directly guided by the diagnosis, 17 survived the acute and critical period of severe respiratory disease. Most of the lethal cases were patients with progressive, diffuse interstitial pneumonitis and fibrosis, occurring two to four months after bone marrow transplantation and not responding to high doses of corticosteroids.

Nonimmunocompromised Patients

Along with growing experience in immunocompromised patients, the biopsy technique was applied

as a diagnostic procedure in diffuse pulmonary disease in other patients.

Results in a group of 63 non-immunocompromised patients, with diffuse interstitial pulmonary disease in which a diagnosis was desirable and other investigations, including fiberoptic bronchoscopy in 33, had failed to yield a diagnosis, are given in Table 3. In some of these patients, especially those with pneumoconfosis, sarcoidosis and carcinomatous lymphangitis, the lung surface showed small irregularities which helped us choose the site of the biopsies. In 57 patients, thoracoscopic biopsy was sufficient to obtain a diagnosis. The procedure was considered to be nonconclusive in six patients, and was followed by open chest surgery in five of them. This added essential information in three patients, with Wegener's disease, pulmonary veno-occlusive disease, and tuberculosis, respectively. In two others, one patient with allergic alveolitis and one with histiocytosis X, the thoracoscopic biopsy proved to have been sufficient in retrospect, because open biopsy yielded the same information as was already obtained by thoracoscopy. One patient with inconclusive thoracoscopic biopsy was considered to have multiple pulmonary microemboli as indicated by serial scintigraphy, and further diagnostic measures were abandoned.

Thus, in more than 90 percent of our nonimmuno-

Table 3—Thoracoscopic Lung Biopsy in 63 Non-immunocompromised Patients

	No. Patients	Negative Findings in Fiberoptic Biopsy*	Diagnosis by Thoracoscope	Diagnosis by Thoracotomy	Duration of Drainage, Days (Mean and Range)	Complications
Fibrosing alveolitis	17	6	17	—	4.1 (2-9)	Pneumothorax (1)
Focal fibrosis	7	3	7	—	5.1 (2-14)	Pneumothorax (1)
Allergic alveolitis	2	2	1	1	3.0 (3-3)	—
Histiocytosis X	6	3	5	1	8.5 (4-14)	Pleuritis (1) Pneumothorax (1)
Pneumoconiosis	7	4	7	—	4.0 (2-7)	Pneumothorax (1)
Sarcoidosis	7	5	7	—	4.3 (2-9)	Wound infection (1)
Lymphangitic carcinoma	5	4	5	—	3.4 (4-4)	—
Eosinophilic pneumonia	3	2	3	—	2.3 (2-3)	—
Granulomatous and vascular disease	6	3	3	2	4.1 (3-8)	—
Hemosiderosis	1	—	1	—	10	—
Tuberculosis	1	—	—	1	6	—
Muscular cirrhosis	1	1	1	—	1	—
Total	63	33	57	5	4.5 (1-14)	Pneumothorax (4) Infection (2)

*Positive findings have only been obtained in patients with sarcoidosis (6), fibrosing alveolitis (2) and malignant lesions (4). These 12 patients are not listed in this table, because no thoracoscopy was performed in them.

compromised patients, a diagnosis was obtained using the thoracoscopic biopsy technique. No patient had a serious complication. In four patients, a pneumothorax persisted over eight days or recurred, and in two patients, minor wound infections were seen; all of these were handled satisfactorily in a conservative way. The mean duration of pleural drainage after thoracoscopic lung biopsy was 4.5 days (median three days). Pneumothorax persisting over a week was mainly seen in patients with low compliances (under 120 ml/cmH2O).

DISCUSSION

Thoracoscopy was introduced in 1910 by Jacobaeus[13] as a way to study the pleura. In the following decades, the method was used to destroy pleural adhesions which prevented collapse treatment for cavitating tuberculosis, in use then. In several European centers, the technique has been used ever since to examine collapsed lungs in spontaneous pneumothorax and to apply an irritant in the pleural cavity to achieve pleurodesis.[14] Since 1953, the technique has been to obtain biopsy specimens of pleural tissue under visual control.[15-17] Moreover, thoracoscopists were able to provide diagnostic information in mediastinal disease (tumors, cysts) by puncture or biopsy under direct inspection of the mediastinum surface, which had been made accessible after an artificial pneumothorax.[18] In 1957, Heine[19] reported a series of patients with diffuse interstitial pulmonary disease in whom, after instillation of air in the pleural cavity, a thoracoscope was introduced and biopsies of the pulmonary tissue were taken under visual control. Independently, Kapsenberg[20] introduced the method in the Netherlands. A new field for thoracoscopy seemed to have been opened, but the technique was not widely accepted, as most pulmonologists preferred open lung biopsy for diagnosing diffuse interstitial lung disease because they feared complications of thoracoscopic biopsy. Moreover, its diagnostic value was doubted because pathologists claimed to need large and deep biopsy specimens for adequate evaluation.

In 1975, one of us (J.D.) was confronted with a young man, about two months after renal transplantation, who was in severe respiratory distress, with high fever and intense bilateral x-ray film shadowing. Anesthesists refused to provide instant general anesthesia to this patient and the severe hypoxemia (Po2 55 mm Hg under heavy oxygen supply by mask, Pco2 28 mm Hg) made bronchoscopy under tracheal anesthesia extremely unattractive. A lung biopsy was taken by thoracoscopic route. Because the procedure was taken very well,

a diagnosis (*Pneumocystis carinii* infection) was available within hours and recovery was uneventful, we decided to continue practicing thoracoscopy in such patients.

After using the procedure in 28 immunocompromised patients we remain satisfied. Thoracoscopy fits in very easily in the daily endoscopic activities of our chest department, has been carried out even in patients with severe respiratory distress, and is taken surprisingly well. The yield of the biopsies is very high, and reliable microbiologic and morphologic information becomes available at the same time.

In a number of cases (Table 2), rather unspecific interstitial pneumonitis was found. In such patients, however, it was very important to have excluded the presence of opportunistic infections, and this proved to be so at autopsy in three patients. In some, the most likely cause of the interstitial pneumonitis seemed to be the previous cytostatic therapy; in others, such changes seemed to represent activity of the underlying disease, eg, graft vs host reaction in bone marrow transplantation, interstitial malignant infiltration in angio-immunoblastoma or leukemia. Since we have been able to identify specific opportunistic infections, antimicrobiologic treatment could be very selective and restrictive in these patients, thus preventing the appearance of multiresistant microorganisms in the best possible way.

In eight of the 28 immunocompromised patients, fiberoptic bronchoscopy had been performed before thoracoscopy without providing a diagnosis. When comparing fiberoptic bronchoscopy and thoracoscopy, we hold the view that bronchoscopy rather increased respiratory distress and often produced inaccurate or no microbiologic information because of contamination in the conducting airways whereas biopsy specimens in all cases were far too small for adequate pathologic studies. In contrast to bronchoscopy under local anesthesia,[20] thoracoscopy does not substantially affect the arterial Po2,[22] biopsy specimens obtained by thoracoscopy are not contaminated, and proved to be large enough to come to conclusive information in all immunocompromised patients and in at least 90 percent of the non-immunocompromised patients with diffuse pulmonary disease.

When comparing thoracoscopy to open chest surgery in immunocompromised patients, obviously larger specimens can be obtained by the latter method and not only superficial lung tissue can be studied. In these patients, however, general anesthesia and chest surgery carry definite hazards while the results of thoracoscopic biopsy hardly can be improved. No disadvantage was experienced in

obtaining only superficial lung tissue, probably because there was always diffuse alveolar pathology in these patients.

In the nonimmunocompromised group with diffuse pulmonary disease, the situation is different. Most of these patients are in much better condition than the immunocompromised, and hypoxemia, if present, is mild and always easily correctable. In these patients, transbronchial lung biopsy during bronchoscopy is not a burden as it is in patients with respiratory distress, and is considered the first approach especially if sarcoidosis is suspected. That biopsy during fiberoptic bronchoscopy was successful is reflected by the diagnoses shown in Table 3, where sarcoidosis is largely under-represented compared to the type of diagnoses commonly reported in series of patients with diffuse pulmonary disease.

In the beginning of this study, the pathologists had to become acquainted with the amount of tissue becoming available compared to chest surgery. It is relevant to note that in two of five open lung biopsies, in retrospect, the thoracoscopic specimen had delivered the essential information already. Moreover, it turned out that frozen sections could provide fast information. In three of six patients with granulomatous and vascular disease, the diagnosis was not obtained by thoracoscopic biopsy, probably because only peripheral vessels could be studied. On the other hand, biopsies were taken in six patients without roentgenologic lung shadowing but showing dyspnea and grossly decreased diffusion tests (Dco), and in four of them, fibrosing alveolitis was diagnosed.

Complications of thoracoscopy and biopsy of lung tissue can be expected to arise from the reduction of lung volume caused by the artificial pneumothorax. In our experience, this risk was negligible, provided only a partial collapse of the lung was established and patients with hypercapnia were excluded. A further risk is bleeding from intercostal vessels. This risk can be minimized by blunt dissection of the subcutaneous tissues and the parietal pleura, after which the thoracoscope can be introduced smoothly. The chance of a major bleeding from biopsy sites in the lung proved to be small, because the arteries in the superficial lung tissue are tiny and the specimens were torn off and not cut. Thrombocytopenia, and other causes of bleeding tendency, should be corrected. Arbitrarily we chose a bleeding time (Ivy) of seven minutes as a maximum to pursue the procedure, and this policy proved to be safe. Infection of the wound was a minor complication, and seldom met, even in granulopenic patients. In patients with stiff lungs, frequently present in diffuse pulmonary disease, re-expansion took more time than average. Eventually all biopsied lungs closed without surgical intervention, except in three patients who died while being ventilated. This outcome was related to an unfavorable course of the underlying disease.

In our experience, thoracoscopy with transpleural lung biopsy is extremely helpful in diagnosing the cause of diffuse pulmonary disease in immunocompromised patients, causing less of a burden than envisaged in open chest surgery and being equally effective, without major complications, provided strict criteria are observed. It is now our first choice approach in such patients, surpassing fiberoptic transbronchial biopsy. In nonimmunocompromised patients, fiberoptic bronchoscopy is part of our routine, but very often transbronchial biopsy specimens are insufficient to establish a solid diagnosis. Then we proceed to thoracoscopy and transpleural biopsy instead of open chest surgery, which comes last, if still needed.

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