whereas regular inhaled antiasthmatic therapy succeeded. Finally, there may be a link between rheumatoid arthritis and methotrexate-induced airway obstruction, which perhaps could be demonstrated by including airway responsiveness testing when monitoring rheumatoid arthritis patients on low maintenance doses of this drug.

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New Forceps for Biopsy of Peripheral Airways

To the Editor:

Although functional studies have indicated a principal role of the peripheral airways in the obstructive impairment of pulmonary diseases, there have been few morphologic and biochemical studies supporting this idea. Only indirect evidence from autopsied lungs has been obtained, but it still remains unclear how these findings directly reflect in vivo situations. It may be possible to obtain histologic specimens of the peripheral airways by means of open lung biopsy, but this invasive procedure has little or no merit in patients, especially those with obstructive pulmonary diseases.

Transbronchial lung biopsy (TBLB) via a flexible bronchoscope is available even for patients with impaired lung function, making it possible to obtain specimens of both the large airways and the alveolar regions. Peripheral airways lack cartilage and are accompanied by muscular pulmonary arteries. Attempting TBLB of peripheral airways with the use of conventional forceps necessarily causes serious or fatal bleeding. Therefore, to date, TBLB using conventional forceps has not been useful for obtaining specimens of peripheral airways for histologic or biochemical examination.

For this reason, we developed new forceps (3 mm in external diameter) for the biopsy of peripheral airways. As shown in Figure 1, we can insert these forceps in the closed position via a flexible bronchoscope using an x-ray television monitor, and then open and close the forceps to cut the airway wall. In this way, we can obtain tissue specimens of peripheral airways without any involvement of the accompanying pulmonary arteries.

Segmental bronchial biopsy using conventional forceps (FB 19C, Olympus, Tokyo) and peripheral airway biopsy using the new forceps (Machida, Tokyo) via a flexible bronchoscope (P10, Olympus, Tokyo) were performed on six patients with stable bronchial asthma (two women and four men, aged 64 ± 4 [SE] years [range, 54 to 80 years]) and three control patients with a coin lesion on a chest radiograph (all men, aged 56 ± 14 years [range, 22 to 80 years]). Using these forceps, we obtained specimens of the peripheral airways large enough for histologic examination without any complications (2 × 3 to 3 × 5 mm).

The biopsy specimens were processed for paraffin sectionings and stained with hematoxylin-eosin and elastica-Goldner’s stain. All specimens contained epithelium, basement membrane layer, and submucosal layers with various degrees of cell infiltration. Measurement of basement membrane layer thickness and cell counts in submucosal regions were performed with a digitizing tablet coupled to a computer. The thickness of the basement membrane layers in segmental bronchi from bronchial asthma patients showed significantly larger values than those from the control patients (13 ± 2 μm vs 6 ± 1 μm), whereas there were no significant differences between those from peripheral airways of the bronchial asthma and control patients (7 ± 1 μm vs 6 ± 2 μm). Total cell, lymphocyte, and eosinophil counts from both segmental bronchi and peripheral airways from bronchial asthma patients all showed significantly larger values than those from the control patients.

This preliminary report suggests that a thicker basement membrane is a histologic finding particular to large airways, but not to peripheral airways. Autoradiographic examination and receptor binding assay of the tissue specimens of peripheral airways in various lung diseases are now in progress. Thus, these newly developed forceps enable us to obtain histologic and biochemical findings about the peripheral airways, and to directly compare various functional data. They will be a powerful tool for the understanding of the obstructive impairment in lung diseases.

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FIGURE 1. New forceps for biopsy of peripheral airways. Forceps can be inserted via a flexible bronchoscope in closed position and then opened and closed to obtain a tissue specimen.
Reduced Mortality Rates in Severe Adult Respiratory Distress Syndrome

To the Editor:

The adult respiratory distress syndrome (ARDS) is a diffuse and severe pulmonary inflammation that is frequently associated with multiple organ dysfunction. Important contributory factors to the high mortality rate when treating severe ARDS are the aggressive therapies required, such as mechanical ventilation with high airway pressures and inspiratory oxygen concentrations, which can contribute to the progression of lung disease. The recently published European Collaborative ARDS Study enrolled 583 patients and reported an overall mortality rate of 59 percent associated with ARDS. The mortality rate rose to 69 percent in 403 patients who fulfilled entry criteria for group B in that study, specifically, PaO₂ of less than 75 mm Hg with an FiO₂ greater than 0.5 plus positive end-expiratory pressure (PEEP) of 5 cm H₂O.

A specific therapy for reducing or preventing this general inflammatory reaction of the lungs is, as yet, unknown. For this reason, today's therapy is limited to procedures that predominantly support and maintain pulmonary function (eg, pressure-limited, controlled mechanical ventilation with PEEP), controlled or permissive hypercapnia, variable positioning of the patient, particularly in the prone position, and aggressive dehydation. Should these procedures fail to improve impaired gas exchange, the risk of iatrogenic damage increases; at this point, extracorporeal gas exchange by means of venovenous extracorporeal membrane oxygenation (ECMO) provides an alternative form of treatment. In the past, this invasive procedure required almost complete systemic anticoagulation using heparin, which often led to severe hemorrhagic complications. In such circumstances, surgery was seldom successful. It has now become possible to employ extracorporeal systems in which blood-contacting surfaces are coated with covalently bound heparin, greatly reducing the need for systemic anticoagulation.

From April 1989 to March 1992, 44 ARDS patients were transferred to our intensive care unit for treatment including venovenous ECMO. Their mean age was 32 ± 12 (SD) years (range, 16 to 60 years). Only patients fulfilling the following criteria were accepted: (1) typical findings of severe ARDS and (2) presence of a severe persisting and progressive defect of arterial oxygenation for at least 48 h, requiring mechanical ventilation with an FiO₂ of 0.6 or more and PEEP of 10 cm H₂O or more leading to a PaO₂ of less than 80 mm Hg. Excluded were patients with immunosuppression and advanced malignant disease. The expected overall mortality rate in our patients was estimated to be at least 70 percent. We derive this figure from the European Collaborative ARDS Study evaluating patients fulfilling entry criteria for group B.

When patients did not respond to conventional therapy and had life-threatening hypoxemia (PaO₂ <50 mm Hg at an FiO₂ of 1.0 and PEEP of ≥5 cm H₂O for ≥2 h), venovenous ECMO was immediately started ("fast-entry" criteria according to the ECMO study by Zapol et al). The other patients were initially treated with the use of ventilatory and adjunctive procedures for 24 to 120 h. When this treatment had failed and our "slow-entry" criteria (Table 1) remained to be fulfilled, we assumed their chances of survival to be almost nil and instituted venovenous ECMO. Table 2 shows our patients' survival rates according to their treatment groups. All of the survivors were discharged from the hospital without need for any further respiratory support.

<table>
<thead>
<tr>
<th>Table 1—Slow-Entry Criteria for Venovenous ECMO*</th>
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<td>After 24 to 120 h of maximal therapy, four of the following criteria must be fulfilled:</td>
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<tr>
<td>PaO₂/FiO₂ &lt;150 mm Hg at PEEP ≥10 cm H₂O</td>
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<tr>
<td>PaO₂ ≥60 mm Hg at Vt ≥200 ml/kg and PIP ≥40 cm H₂O</td>
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<tr>
<td>Intrapulmonary right-to-left shunt ≥50% at FiO₂ of 1.0</td>
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<tr>
<td>Extravascular lung water ≥15 ml/kg</td>
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<tr>
<td>Total respiratory compliance ≥30 ml/cm H₂O and/or recurrent pneumothoraces with bronchopleural fistula</td>
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<td>*Ve = expired volume per minute; PIP = peak inspiratory pressure.</td>
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<th>Table 2—Outcome of Treatment of Severe ARDS</th>
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<tr>
<td>Treatment</td>
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<tr>
<td>Non-ECMO</td>
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<tr>
<td>&quot;Fast-entry&quot; ECMO</td>
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<tr>
<td>&quot;Slow-entry&quot; ECMO</td>
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<td>Total</td>
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*Combined survival rate for "fast-entry" ECMO and "slow-entry" ECMO was 60%.

The results of our ARDS treatment to date, including venovenous ECMO with heparin-coated systems, suggest that the high mortality rate among ARDS patients can be improved when all of the presently available therapeutic measures are applied.

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