Treatment of Dyspnea with Psychotropic Agents

Dyspnea is the most disabling symptom of chronic obstructive pulmonary disease (COPD). The severity of the sensation is related to the degree of airflow obstruction. Although much of the obstruction is not reversible with standard bronchodilator treatment, it is possible that commonly employed drugs may have extrapulmonary actions which reduce dyspnea. Theophylline strengthens diaphragmatic contraction and increases cardiac output, but the clinical significance of these observations has not been fully determined.

Active investigation into the precise mechanisms which produce the sensation of dyspnea is being carried out in the areas of respiratory physiology, neurophysiology and psychophysics. The perception of respiratory muscle effort appears to be quantitatively related to the intensity of the sensation of dyspnea. Patients with COPD also have reduced perception of resistive and elastic loads, but no alteration in the sensation of inspired volume during nonloaded breathing or of respiratory muscle force during static inspiratory maneuvers. This has led to the suggestion by Gottfried and colleagues that these reductions in respiratory sensation are due to impaired processing of separate signals. The complex, multidimensional nature of these perceptions may explain why the understanding of dyspnea has remained elusive.

The hypothesis that dyspnea might be reduced by pharmacologic alteration of signal processing in the central nervous system has attracted a number of investigators. Benzodiazepine derivatives were initially reported to hold some therapeutic promise. However, subsequent studies, including that by Man and colleagues in this issue (see page 832) have shown no significant benefit and considerable side effects with the use of these agents. Promethazine, a phe-nothiazine with antihistamine and sedative properties, has also been reported to improve dyspnea and exercise tolerance in normal individuals. Patients with COPD may also benefit, albeit to a very modest degree.

The effects of narcotics on respiratory drive are well known. The concept of dyspnea as a "pain equivalent" regulated by endogenous opiates is supported by the observation that naloxone, an opiate antagonist, restores blunted ventilatory load responses in COPD patients. It has also been suggested by Woodcock and associates that narcotics may improve dyspnea by decreasing oxygen consumption out of proportion to minute ventilation. Although acute administration of dihydrocodeine reduces dyspnea by up to 20 percent, long-term opiate treatment has variable effects on breathlessness and is associated with significant side effects, most notably increases in Pco2, which probably outweigh the potential benefits. The observed improvements in dyspnea with these agents are modest at best and probably due to nonspecific sedation. The concomitant reduction in minute ventilation is a potentially serious adverse effect in patients with marginal pulmonary function and the use of such drugs cannot be routinely recommended in patients with severe COPD. Better understanding of the mechanisms of dyspnea is needed in order to identify specific therapeutic interventions in the pathways which produce this uncomfortable sensation.

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REFERENCES
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Clinical Aspects of Pulmonary Amyloidosis

Amyloidosis (AL) results from the extracellular deposition of fibrils derived from the light chain of a monoclonal immunoglobulin and is a disorder of plasma cells. When sought for aggressively by immunolectrophoresis and immunofixation, monoclonal protein will be found in the serum or urine of 90 percent of the patients with amyloidosis. Immunoglobulin-derived amyloidosis may be systemic or localized. The lower respiratory tract is unique in that both systemic and localized deposits can occur. Many patients undergo extensive noninvasive investigation before the proper diagnosis is made. A definite diagnosis requires biopsy of an affected tissue and demonstration of amyloid deposits defined by their green birefringence when viewed under polarized light after Congo red staining.

Systemic disease generally, but not always, portends an unfavorable prognosis, with median survivals of approximately one year; a figure that has not improved during the last ten years. Involvement of the respiratory tract is common in systemic AL, but only in the minority is it of clinical significance because the clinical findings usually are dominated by cardiac involvement and symptomatic congestive heart failure. In a review at Boston University, only one patient died of severe lung involvement. The reason is that in most pulmonary involvement there are small deposits in the vessel walls and alveolar septa, which may not disrupt gas diffusion.

The localized forms of pulmonary amyloidosis are varied and, in contradistinction to the systemic form, have a good prognosis. Tracheobronchial forms, when noted as pseudotumors, are generally incidental findings at bronchoscopy. Diffuse narrowing resulting in bronchial obstruction can be treated successfully with endoscopic laser resection, and excellent results have been achieved, although repeated resections may be necessary later. Pulmonary amyloidosis (AL) also may present as a single (occasionally multiple) pulmonary nodule which cannot be distinguished radiographically or clinically from malignancy or granulomatous infection. In these instances, a diagnosis may be made on the basis of transbronchial biopsy or transcutaneous needle aspiration. Thoracotomy and resection are unnecessary because many patients will show little or no progression when followed up for years. The report by Cordier and colleagues in this issue of Chest (see page 827) solidifies these concepts in a single report of 21 patients seen during a 15-year period. All diagnostes were confirmed pathologically. They also described two patients with senile pulmonary amyloidosis. This form of amyloidosis is not immunoglobulin derived. The prevalence of senile amyloidosis exceeds 20 percent in patients more than 85 years old and represents an incidental finding at autopsy. Three additional patients had amyloidosis associated with malignancy. Their clinical courses were not affected by the amyloidosis. No patient had secondary (AA) amyloidosis involving the respiratory tract.

Two of the 21 patients had interstitial amyloidosis, and these constitute to the clinician the most important subpopulation of patients with pulmonary amyloidosis. Both patients died as a result of pulmonary

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<tr>
<td>Nodular tracheobronchial (pseudotumoral)</td>
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<td>Diffuse tracheobronchial (submucosal plaques)</td>
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<td>Nodular parenchymal</td>
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*AL = immunoglobulin-derived amyloid; AA = amyloid derived from amyloid A protein; AE = amyloid associated with medullary thyroid carcinoma; and AS = senile cardiac amyloid.