EDITORIALS

The Origins of Cor Pulmonale
A Hypothesis

At some stage in the progression of chronic obstruction of the airways, pulmonary hypertension and cor pulmonale may develop. Numerous studies have suggested that the initiation of pulmonary hypertension is related to the onset of hypoxemia. First, the inhalation of reduced concentrations of oxygen in animals, normal subjects, and patients with obstruction of the airways causes pulmonary vasoconstriction and pulmonary hypertension. Secondly, patients with established pulmonary hypertension and cor pulmonale are usually hypoxemic. Finally, the long-term relief of hypoxemia by continuous therapy with supplemental oxygen at a low rate of flow has been shown to reduce pulmonary vascular resistance and pulmonary hypertension and to relieve right ventricular failure.

All of the observations mentioned have been made with the patient awake while arterial blood was sampled to assess hypoxemia and right cardiac catheterization was done to assess pulmonary hypertension. Recent studies using an accurate ear oximeter have taught us that oxygenation is not stable from moment to moment during the day and that a single arterial puncture may not be satisfactory to describe even oxygenation while the subject is awake. Even more striking are the changes in oxygenation that occur during sleep. Severe drops in saturation have been demonstrated during light sleep and rapid-eye-movement sleep in patients with chronic obstruction of the airways. These decreases may be brief but may last for periods up to an hour. Severe hypoxemia may be present during sleep in the majority of patients with chronic obstruction of the airways, even when such hypoxemia cannot be demonstrated while the subjects are awake.

We have recently shown that episodic nocturnal desaturation in patients with chronic obstruction of the airways may cause episodic nocturnal pulmonary hypertension. This relationship is not surprising, since it has recently also been demonstrated in patients with upper airway obstruction, sleep-induced apnea, and hypersomnolence. In these latter patients, pulmonary arterial pressure increased in a stepwise fashion with repetitive apneic episodes. These observations suggest an origin for cor pulmonale that has been ignored in the past. We propose that patients with chronic obstruction of the airways may initially have well-saturated blood during the day but periodically have desaturation at night. Episodic pulmonary hypertension may occur, which easily reverses when nocturnal desaturation is relieved. Those patients with the most severe, prolonged, or frequent episodes of nocturnal desaturation would be most likely to sustain the greatest degrees of nocturnal pulmonary hypertension, which might ultimately become irreversible. Such patients might be the "blue bloaters," as Flenley has recently proposed. Most would also demonstrate some desaturation during the day, but occasional patients may show only nocturnal desaturation. If this postulate is correct, then nocturnal therapy with supplemental oxygen might have usefulness in more patients than we suspect today. Fifteen hours of therapy with supplemental oxygen (including during sleep) has already been shown to relieve established pulmonary hypertension. Is it possible that prophylactic treatment with supplemental oxygen at night could prevent the development of cor pulmonale in chronic obstruction of the airways?

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The Other Mycobacteria

*Mycobacterium intracellulare*, *M avium*, *M kansasii*, *M fortuitum*, and other species of mycobacteria are well characterized microbiologically. Some are recognized as causing disease in man, but the clinical aspects are poorly understood. Although most of these organisms can be found in the natural environment (unlike the better known *M tuberculosis*), the factors leading to infection and disease in man are enigmatic. The evidence indicates that infection with these mycobacteria is more common than with *M tuberculosis* in many areas of the United States and in some cases exceeds 70 percent of the population, as determined by skin test reactivity. Disease, by contrast, is uncommon. Our understanding of the true incidence of disease is hampered by the fact that there is no nationwide system of reporting and collecting data. Definitive criteria for the diagnosis of disease in distinction to infection alone or colonization have not been established.

Since many strains of mycobacteria are ubiquitous in the environment, their presence in relationship to man is to be expected either as a saprophytic colonization (probably rather common) or as clinically insignificant tissue invasion resulting in infection without disease (very common and indicated by the host's positive delayed hypersensitivity reaction to the specific antigen). When a disease process exists in association with the finding of these mycobacteria, both of the preceding circumstances and the possibility of a direct cause must be considered. Their isolation from diseased tissues which are normally sterile indicates a definite cause-and-effect relationship, provided all other more likely pathogens have been excluded. Results of smear and culture of sputum require careful scrutiny even in the presence of compatible pulmonary disease.

Our experience with human disease caused by these mycobacterial species has prompted our use of the following guidelines in determining when disease exists:

1. The organisms must be isolated repeatedly from the same source over a period of days or weeks. They are nearly always found in all properly collected specimens.
2. The organisms must be isolated in significant numbers. A quantitative culture method is essential. A disease process is usually associated with the isolation of more than a few colonies.
3. A compatible disease process as determined by roentgenogram or other diagnostic procedures must be present. Isolation of organisms from a person otherwise healthy usually has no significance.
4. Other pathogenic organisms have been excluded. *M tuberculosis* disease, for example, is the one most likely to have other mycobacterial species present as colonizers. Mixed infections causing disease can occur, but are uncommon.
5. When an underlying disease process is likely, pathologic examination is helpful to establish the role of a possible mycobacterial pathogen. The diagnosis is established when there are changes compatible with mycobacterial disease, particularly if acid-fast bacilli are present. Likewise, the isolation of the Mycobacterium on culture from tissue is strong evidence of disease.

Even when disease clearly exists, controversy does not end. Whether to treat or not is a difficult decision since most of these mycobacteria are resistant to a variable degree to drugs effective against *M tubercu*