in recent years it has become important to learn the full 24-hour behavior of patients with certain illnesses, especially cardiovascular and pulmonary, in order to uncover heretofore unknown danger zones requiring therapeutic interventions.

Sleep in mammals is a special example of a more generalized phenomenon, namely a periodicity or cyclic variation timed by internal clocks of uncertain nature; sleep, however, is basically a neural phenomenon. Circadian rhythms (when the periods of oscillation approximate the period of the earth's rotation) are quite precise in many organisms and are relatively independent of variables except for sensitivity to light. It is likely that the internal clock depends upon the hypothalamus for its viability.

The newborn infant shows cycles of rest and activity of about 90 minutes' duration, and during the first year or two of life, these cycles gradually shift to the ordinary daily rhythm of adult life, although 90 minute undulations can still be noted during sleep. In the adult, modern studies of psychophysiology have indicated not only that sleep can be divided into five stages, but also that there are recurring sleep cycles and that during sleep the brain and the peripheral nervous system under its control, undergo continuous oscillations and activity with a periodicity approximating 90 minutes. Deep sleep is often normally associated with sinus bradycardia in the range of 45-50 beats per minute. The change in heart rate during onset of sleep is interesting in that the cardiac rate decreases progressively throughout the night reaching its nadir at about the sixth hour. In addition to slowing of sinus rate during sleep, there is also a fall in cardiac output, respiratory rate and arterial blood pressure. In normal young adults, the fall in blood pressure reaches its nadir within one and a half to two and a half hours after the onset of sleep. The heart rate and cardiac alterations are mediated by changes in sympathetic and parasympathetic neural outflow and are abolished after cardiac denervation. Thus, the partial sympathetic withdrawal that occurs during sleep may be the basis, because of lessened sympathetic discharge, of the normal sinus bradycardia which is seen. There is movement of extravascular water in the blood on assumption of the recumbent position and water excretion by the kidney is lowered during the night. There is alteration in breathing patterns during sleep, with Cheyne-Stokes oscillations seen not infrequently, and a reduction in alveolar ventilation occurs with its consequent slight rise in CO₂ in arterial blood.

These facts emphasize that nocturnal problems in cardiopulmonary diseases have bases in normal fluctuations. In critical states, major organ systems—brain, coronary, renal, may move into hypoperfused status during sleep. The subject with respiratory insufficiency may accumulate carbon dioxide to a critical level which makes for a somnolent day and further hypoventilation unless assisted breathing is used. Left ventricular failure, as is well known, may reach dangerous levels in bed at night and diuresis becomes imperative to prevent this.

Most recently, attention to malfunction of the sinoatrial node during sleep has become an important diagnostic move. Little information exists concerning the performance of the damaged sinoatrial node during sleep, but since there exists the normal tendency to lower SAN activity during sleep, it would not be surprising to find accentuations of the normal behavior at this time, producing abnormalities which could have been cryptic because of the whipping up of the performance of endogenous catecholamines while the subject was awake. Indeed, the diagnosis of a failing SA node may only be suspected when a subject has peculiar central nervous system symptoms and these are evaluated by 24-hour ECG monitoring. Monitoring for shorter periods would be insufficient to uncover the dangerous bradycardia manifest only in sleep.

Thus, it is now important to include a survey of sleep performance, when feasible, in subjects with cardiopulmonary diseases, since this restful period may in fact contain some real danger zones.

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When to Hospitalize the COPD Patient

Empirical: founded on practical experience but not proved scientifically (Stedman's Medical Dictionary, 22nd Ed.)

Scientific proof of the methods used in managing clinical problems often lags behind both recognition of need and availability of potential modalities of treatment; this is clearly shown in the...
care of patients with chronic obstructive pulmonary disease (COPD). Our concepts of pathophysiology and management\(^1\) have come a long way since the question of when to hospitalize the COPD patient was addressed in a similar article in 1966,\(^2\) yet little objective information has appeared to shed light on this problem. However, with better understanding of the natural history of COPD, and important treatment advances in the last 11 years, a review of clinical experience and objective data bearing indirectly on this subject is worthwhile.

Hospitalization for the patient with COPD may be examined in four general circumstances: acute respiratory failure; unrelated illness; initiation of a comprehensive care program; and clinical deterioration, short of frank acute respiratory failure, under outpatient care. Acute respiratory failure is a well-defined clinical entity in which the necessity of inhospital therapy is clear. Mechanical ventilation, airway management, cardiopulmonary monitoring, aggressive respiratory therapy, and continuous nursing care must be available, preferably in a respiratory intensive care unit.\(^3,4\) The efficacy of vigorous management is well established in this otherwise fatal situation: survival of 66 to 76 percent of episodes is reported in large series from several centers\(^5,6\) despite variations in regimen. Hospitalization of the COPD patient for emergency surgery, trauma, or other serious illness is hazardous but unavoidable. With elective surgical procedures, morbidity and mortality increase with the degree of ventilatory impairment,\(^7\) so that careful assessment of surgical necessity is important. Preoperative respiratory care measures can lower the complication rate,\(^8\) although they can generally be carried out at home.

Progress in pulmonary rehabilitation has provided indirect information on advantages and disadvantages of hospitalization. Of the pilot programs begun a decade ago and studied since in detail, some utilized an initial period of intensive inpatient investigation and treatment.\(^9\) Cited advantages\(^10\) included: better detection and easier treatment of complicating illness; establishment of the "best" baseline functional status for each patient's subsequent follow-up; emphasis on the severity of illness as a stimulus for patient compliance; easier arrangement of a home care plan; and close contact with staff and other patients, promoting stronger therapeutic relationships, better knowledge of individual needs, and interpatient esprit de corps. Hospitalization afforded logistical advantages over repeated outpatient visits and offered patients with physical disability and socioeconomic problems a maximum of contacts with a minimum of inconvenience. Problems with third party payment for numerous initial outpatient visits made inpatient status the only means by which some individuals could enter the program. Reported results are from pulmonary rehabilitation programs with considerable variations in patient population and program design.\(^9\) Thus, no meaningful comparisons are possible between inpatient and outpatient initial treatment regimens with respect to subsequent mortality or rate of functional deterioration.

The case for inpatient therapy for COPD patients is weakened by several established disadvantages. Potent among these is colonization with hospital flora. Although infection with gram-negative bacilli other than \(H\) influenzae is distinctly unusual in outpatients, on admission to the hospital this changes abruptly. Johanson and associates\(^11\) documented colonization with gram-negative organisms in 45 percent of all patients admitted to a medical intensive care unit; half of these occurred in the first 24 hours, with one-fourth of all colonized individuals developing clinical infection. Hospital-acquired infections are more frequent in the elderly and the chronically ill, and among patients with tracheal intubation, the presence of sputum, and the use of antimicrobial drugs.\(^11\) Patients with COPD often meet all these criteria.

Hospitalization may be harmful because of some of the same factors cited as advantages. Interruption of the home environment and emphasis on severity of illness can exacerbate the "neurotic triad" of depression, conversion tendencies, and excessive somatic concern.\(^10\) Hospital costs are important regardless of the source of payment. Although rehabilitation programs stress maintenance of physical activity, and inpatient protocols include civilian dress, communal dining, and other efforts to promote activity, the hazards of immobilization in the chronically ill—particularly pulmonary thromboembolism—must be considered. In addition, clinicians recognize an entity which might be called "nosocomial deterioration," in which the condition of the elderly or chronically ill patient goes downhill in the hospital for no obvious reason.

Ten years' experience with rehabilitation has produced considerable data on short- and long-term results,\(^12\) although there is debate over the clinical importance of some of the parameters measured.\(^13,14\) Without doubt, several of the things we include under "quality of life" can be improved, yet these are difficult to quantitate for skeptical review.\(^12\) Regardless of whether hospitalization is utilized at the start of rehabilitation, subsequent hospital needs can be substantially reduced.\(^15\) Even so, patients with COPD do still need hospitalization, yet little
data and no controlled studies are available on just when these hospitalizations should take place.

The need for such studies is most clear when patients deteriorate under outpatient management, but are not yet in overt respiratory failure. Several factors may be involved: 1) progression of underlying disease; 2) complications of underlying disease; 3) illness in other systems; 4) inadequate therapy; 5) complications of therapy; and 6) psychosocial factors. An "expected" rate of loss of pulmonary function in severe COPD can be estimated from longitudinal studies, and approximates 50-60 ml per year for FEV₁; factors other than progression of the underlying disease process should be considered when more rapid decline is observed. Among "complications," cor pulmonale, formerly a main reason for hospitalization in COPD patients, can now be managed effectively at home with oxygen and other measures, markedly reducing the need for inpatient therapy. Despite traditional emphasis on prompt antibacterial therapy, intercurrent respiratory infection is still of uncertain significance in the natural history of COPD, and no evidence supports the use of inpatient, parenteral antibiotics over oral preparations in exacerbations thought to be infectious in origin.

Insufficient vigor in outpatient respiratory therapy is a tempting explanation for clinical deterioration. Again, scientific proof is lacking. While inpatient chest percussion and postural drainage in stable patients may produce transient improvement in sputum expectoration and some measures of pulmonary function, no studies have detected measurable long-term effects. Certainly, respiratory therapy maneuvers are important when clearance of secretions is a major clinical problem, yet these maneuvers must ultimately be achieved at home in a condition likely to be lifelong.

With increasing knowledge of theophylline pharmacology and availability of serum levels, hospitalization for deterioration because of insufficient therapeutic effect or toxicity should be avoidable. Likewise, drug reactions, iatrogenic electrolyte disturbances, and patient confusion in the face of multiple medications and schedules, are reasons for hospital admission which are avoidable if recognized. Patients often deteriorate because of social and emotional factors not obviously related to their illness, problems which can be identified and dealt with in the outpatient setting.

Inhospital therapy is not necessarily to be avoided at all costs, yet cost and the logistics of providing treatment for patients numbering millions mean that hospitalization must be infrequent. None of the factors mentioned as favoring or discouraging hospitalization is absolute, and existing data cannot be applied to all practice situations. An empirical approach—relying upon personal experience and the practical experiences of others in the absence of scientific proof—is entirely appropriate. Since effective management of nearly all aspects of this disease is now possible without hospitalization, the decision of when to admit the COPD patient must be made individually, and predicated on both sufficient understanding of the problem and adequate resources for treating it outside the hospital.

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Intoxication with Quinidine

The article by Shub and associates elsewhere in this issue of Chest (see page 173) is an unusual but dramatic example of intoxication with quinidine in a patient attempting suicide with this drug. The total dose of quinidine ingested, 117 mg/kg of body weight, is well within the range of lethal doses for quinidine. The maximum serum concentration of quinidine recorded was 21.4 mg/L. Intoxication in this patient with a preexisting normal cardiovascular system was manifested by severe peripheral vasodilation refractory to α-adrenergic agonists, marked hypotension with reduced renal perfusion, coma, generalized seizures, respiratory depression, and various arrhythmias, including ventricular tachycardia. The patient's hemodynamic status was stabilized by use of the intra-aortic balloon pump. Renal perfusion and urinary flow increased, and the serum concentration of quinidine declined, albeit with a slow half-life of approximately 13 hours. This interesting and instructive case report provides the framework for considering more commonly encountered forms of intoxication with quinidine.

Quinidine has been known for years as a useful and potent antiarrhythmic drug. Various manifestations of intoxication with quinidine, including death, have been recognized for as long as the drug has been employed clinically. One of the more dramatic forms of intoxication with quinidine is “quinidine syncope,” which may occur in as high as 5 percent of the patients receiving quinidine. There are at least three causes of quinidine-induced syncope. One is hypotension, accentuated by standing; this results from the action of quinidine on the peripheral vasculature. Studies of intoxication with quinidine in the dog demonstrated a vasodilator effect of quinidine which, at its peak, could not be overridden, even by huge doses of α-adrenergic agonists (such as noradrenaline); however, vasoconstriction could be produced by the infusion of angiotensin. The pharmacologic basis for the vasodilator effect of quinidine was demonstrated later to be blockade of α-adrenergic receptors. The effect of administration of quinidine will be exaggerated in diabetic patients and in other patients with impairment of the autonomic nervous system, in patients who are hypovolemic, and in patients receiving other vasodilator drugs. If the hypotension persists for any length of time, catastrophic damage to the heart or central nervous system may result. This form of quinidine-induced syncope is usually associated with relatively large doses of quinidine and can be ameliorated with reduction of the dosage of quinidine.

Another cause of quinidine-induced syncope is paroxysmal ventricular tachycardia or fibrillation resulting from the effect of quinidine on the impulse-forming and conducting tissues of the heart. Paroxysmal ventricular tachycardia or ventricular fibrillation induced by administration of quinidine has several intriguing and clinically important characteristics. These paroxysms are frequently self-limiting but repetitive; they often occur after only moderate doses of quinidine and are not preceded by significant widening of the QRS complex, one of the electrocardiographic hallmarks of intoxication with quinidine. Administration of lidocaine is useful in controlling these arrhythmias. Ventricular tachycardia and ventricular fibrillation usually cease when the serum concentration of quinidine drops to 1 or 2 mg/L; however, paroxysmal ventricular tachycardia or ventricular fibrillation may reappear, even if therapy with quinidine is reinstituted in a reduced dosage.

The third form of quinidine-induced syncope results from an idiosyncratic reaction characterized by bronchoconstriction, vasomotor collapse, and respiratory arrest. Such idiosyncratic reactions are rare in our experience.

Other severe forms of intoxication with quinidine include thrombocytopenic and nonthrombocytopenic purpura. Therapy with quinidine rarely is associated with the development of antibodies against the patient's platelets. Quinidine also has a direct effect on hepatic synthesis of vitamin K-dependent clotting factors. In combination with warfarin (Coumadin), therapy with quinidine may produce severe hemorrhage. Administration of quinidine may exaggerate defects in neuromuscular transmission and occasionally bring the underlying disorder to light, as in myasthenia gravis. Cinchonism is not