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NEW CONCEPTS IN OBSTRUCTIVE AIRWAYS DISEASE

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Pathophysiology of Asthma and Chronic Obstructive Pulmonary Disease (COPD)

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Asthma

"Asthma is a disease characterized by an increased responsiveness of the trachea and bronchi to various stimuli and manifested by a widespread narrowing of the airways that changes in severity either spontaneously or in response to therapy."[1] The airway narrowing is the end result of some combination of bronchial muscle contraction, tissue inflammation, mucosal edema, and luminal occlusion by cellular debris and thickened secretions. During the last decade, basic and applied research has shed light on the physiology of the above changes and has led to breakthroughs in therapy and the more rational use of older and newer therapeutic agents, both separately and together.

Anatomy

The nasal passages, the oropharynx, and the large, and some smaller, bronchi are extensively provided with a variety of receptors which respond to temperature and irritating stimuli of many types. The sensory signals emanating from these receptors and others are transported to the central nervous system by the vagus nerve. The motor innervation of the bronchi is via the vagus (cholinergic) and sympathetic trunks (adrenergic), both of which affect bronchomotor tone and secretions.

The epithelium of the intrathoracic airways is covered with a "mucociliary blanket" which facilitates the removal of particulate material; mucus is secreted by glandular epithelial cells. Ciliated epithelium constantly moves the mucus layer from peripheral to central airways, where cough and expectoration eliminate the trapped particles from the respiratory tract.

The multiple branching airways of the lung, as far distal as the respiratory bronchiole, are surrounded by bands of smooth muscle. Proportionately greater amounts of muscle are present in small bronchioles relative to large and medium bronchi, and constriction of this musculature can virtually occlude the airway.

Physiology

For any given flow rate, airways resistance is dependent on the cross-sectional area through which the gas is flowing, that is, the larger the cross-sectional area the less the resistance and vice versa. Bronchial smooth muscle contraction can markedly increase resistance and this can be augmented by compromise of the airway's lumen by secretions, cells, and other factors. Stimulation of the vagus nerve in-

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duces bronchial smooth muscle contraction and increases mucus secretion; sympathetic nerve stimulation has a minimal opposite effect.

The relative "tone" of bronchial smooth muscle, that is, the balance between muscle contraction and relaxation, is controlled by the intracellular ratio of the cyclic nucleotides. High levels of cyclic adenosine monophosphate (cAMP), induce relaxation, and conversely, increased levels of cyclic guanosine monophosphate (cGMP), induce contraction. Beta agonists (isoproterenol, ephedrine, terbutaline, among other drugs) appear to increase levels of cAMP by stimulation of the enzyme adenylcyclase; corticosteroids may work in this fashion as well. Methylxanthines, such as theophylline, appear to prevent the breakdown of cAMP by the enzyme phosphodiesterase and thus increase intracellular cAMP levels. Vagal stimulation in turn stimulates cAMP production, causing bronchoconstriction.[2]

Pathophysiology

A large population of mast cells containing a variety of preformed "mediators" of hypersensitivity such as histamine are normally found in the pulmonary interstitium; these cells can synthesize from precursors other mediators such as a slow-reacting substance of ananphylaxis (SRS-A). Both of these substances are powerful bronchoconstrictors and may increase cell membrane permeability, leading to mucosal edema. Additionally, these mediators increase bronchial receptor sensitivity thus enhancing neurogenic-induced bronchoconstriction. Other mediators can cause inflammatory changes in bronchi and attract and activate phagocytic cells.

In extrinsic (allergic) asthma, mast cells are sensitized by the attachment of antigen-specific IgE to their surface. If an appropriate antigen, such as pollen, fixes to the IgE, the various mediators are released and/or synthesized.[3] The rate of release/synthesis of mediators is governed by the cAMP/cGMP ratio in the mast cell, and is thus subject to pharmacologic manipulation as has been discussed.

In other types of asthma (adult onset, intrinsic, aspirin-induced, and other forms) immunologic mechanisms do not play a dominant role. Some suggested mechanisms causing the airway hyperreactivity in these types of asthma are:

B-adrenergic blockade: A decreased response to beta agonist drugs has been noted in many asthmatics. It is possible that either congenital defects in adenylcyclase production or recurrent infections could induce this blockade.

Cholinergic dominance: This hypothesis presupposes that the vagus nerve in the asthmatic is easily stimulated via the irritant receptors, leading to an enhanced bronchoconstrictive response (the "twitchy vagus" theory). Cortical (emotional) components may act via this pathway. Whether the vagus hyperreactivity is a primary or secondary defect is in question. Histamine, for example, increases irritant-receptor sensitivity and indirectly plays a role in vagally mediated bronchoconstriction.

Adrenergic amine deficiency: This hypothesis presupposes that in response to bronchoconstrictive stimuli, the adrenal medulla should release additional epinephrine to partially modify this response (epinephrine acting as a beta agonist). In the asthmatic, this response is impaired.

Smooth muscle abnormalities: Asthmatics are known to have hypertrophied bronchial musculature. Whether or not the muscle is also innately more reactive is undecided.

Alpha-adrenergic hyperresponsiveness: Some asthmatics have been shown to have an exaggerated response to phenylephrine (a pure alpha agonist) in organs other than the lung. It is thus hypothesized that naturally occurring alpha agonists (which increase mast cell and bronchial musculature intracellular cGMP) can induce bronchoconstriction.

Much is still to be learned about asthma. Apparently, in all individuals, many factors play a role in the pathogenesis of the disease, some factors being dominant and others seeming less significant. It is the clinician's responsibility to determine in his patient which factors predominate and to tailor the treatment to these findings.

Chronic Obstructive Pulmonary Disease (COPD)

Emphysema and bronchitis constitute the major disease entities which fall under the heading of Chronic Obstructive Pulmonary Disease (COPD). Although emphysema and bronchitis will, for discussion purposes, be considered separately, they occur concomitantly in most

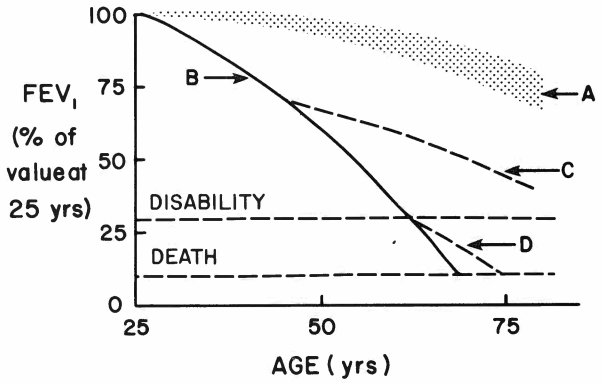
patients with COPD. Only a small percentage of patients will have "pure" emphysema or "pure" bronchitis.

"Classic" Findings in Far-Advanced Emphysema and Bronchitis

Emphysema is defined as destruction of terminal alveolar capillary units with enlargement of the remaining air spaces. Etiologically, it is causally related to cigarette smoking and certain genetic disorders such as alpha 1 antitrypsin deficiency. In addition, there is some evidence that recurrent childhood pulmonary infections predispose smokers to emphysema.

The typical patient with far-advanced emphysema is 45 to 50 years of age and complains of dyspnea on mild exertion. Unless an associated bronchitis is present, cough and sputum production do not occur. Physical examination reveals a thin, cachectic patient with an increased respiratory rate, using his or her accessory muscles of respiration, an increase in anteroposterior chest diameter, a tympanitic chest percussion note, and decreased breath sounds. Laboratory results are unremarkable and the chest radiograph shows a vertical, small heart with clear, hyperinflated lung fields; the EKG shows low voltage. Pulmonary function tests are consistent with hyperinflation, decreased flow rates and diffusing capacity and airway collapse. Mild hypoxemia ($PaO_2 > 55$ torr) and normocapnea ($PaCO_2 < 45$ torr) are common findings. Because of the labored breathing and lack of cyanosis this type of patient has been termed the "pink puffer." As lung destruction is the basic problem, most therapeutic interventions are nonrewarding, but teaching the patient to purse-lip breathe may lessen the dyspnea and decrease the respiratory rate.[1]

Chronic bronchitis is defined as an increase in sputum production two to three months out of the year for two years in a row. Patients with this condition usually are cigarette smokers and/or have been exposed to industrial or air pollutants. Their chief complaint is a cough productive of sputum, often described as "a cigarette or morning cough." The bronchitic patient shows no evidence of weight loss, has a normal chest AP diameter but may have, on auscultation, wheezes, rhonchi, and early inspiratory rales. In addition, signs of right ventricular failure (jugular venous distention, hepatomegaly, and peripheral edema) may be present. Polycythemia and, in certain cases, either sputum or blood eosinophilia may be found on routine laboratory analysis. Carbon dioxide retention ($PaCO_2 > 45$ torr) and hypoxemia ($PaO_2 < 55$ torr) are found on arterial blood gas analysis; pulmonary function tests reveal decreased flow rates which may respond to bronchodilators. Chest radiography shows an enlarged heart (mainly right ventricle) with increased bibasilar lung markings; the EKG may show right ventricular hypertrophy. Because of the cyanosis and the peripheral edema, these patients have been termed "blue bloaters." Treatment consists of antibiotics for recurrent pulmonary infections, diuretics and digitalis for the right heart failure and supplemental oxygen for the hypoxemia.



Fig—Decreases in FEV_1 with age in nonsmokers, nonsusceptible smokers and susceptible smokers. This graph depicts fall in FEV_1 in one particular susceptible smoker. Other smokers will have different FEV_1 loss rates thus reaching the "disability" line at different ages. See text for explanation and discussion.

Which Patients are at Risk of Developing Symptomatic COPD?

The patient with far-advanced COPD responds poorly to treatment and the average life expectancy after severe symptoms ensue is 3½ to 5 years.[2] It would be advantageous to predict which patients who smoke may develop far-advanced disease as it is now known that 90% to 95% of all smokers are either not susceptible or minimally susceptible to the effect of cigarette smoke; that is, life-long smoking does not lead to symptomatic lung disease as described above. Most cigarette smokers have normal or near normal FEV_1s compared to age-

matched nonsmoking controls (Line A, Figure).[3] A small percentage of patients, however, may be susceptible to cigarette smoke and if FEV_1s are performed yearly (after age 40), there will be a marked decline in the FEV_1 per year (Line B, Figure) compared to normal values (Line A, Figure). If these patients continue to smoke, they will become symptomatic and disabled at a relatively early age; if they stop smoking, the FEV_1 decline will slow (Line C, Figure), but impaired pulmonary functions may be demonstrable, although the patient may be asymptomatic. If smoking is stopped late in the course of the disease (that is, by the time disability occurs), although the FEV_1 decline will improve, death will ensue in a relatively short period of time (Line D, Figure). Therefore, FEV_1s should be performed yearly in all cigarette smokers > 40 years of age. If a marked loss of FEV_1 occurs (> 60 to 70cc/sec/yr), an aggressive approach to cessation of smoking should be instituted.

The Figure is modified by permission from the *British Medical Journal* (1 : 1645–1648, 1977).

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Diseases Which Mimic Asthma and Chronic Obstructive Pulmonary Disease (COPD)

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The American Thoracic Society defines *asthma* as a disease characterized by increased responsiveness of the trachea and bronchi to various stimuli and manifested by widespread narrowing of the airways that changes in severity either spontaneously or as a result of therapy.[1] In this context asthma is a physiologic diagnosis. It is most often recognized when a patient complains of episodic wheezing and dyspnea and most often confirmed by the demonstration of variable airways obstruction on spirometric testing.

Chronic bronchitis, on the other hand, is characterized by excessive mucous secretion in the bronchial tree and manifested by chronic or recurrent productive cough present on most days for a minimum of three months in the year and for not less than two successive years.[1] Therefore, chronic bronchitis is a clinical diagnosis of exclusion, dependent upon a constellation of nonspecific symptoms. *Emphysema* is an alteration of the lung characterized by an abnormal enlargement of air spaces distal to the terminal bronchioles with destructive changes of the alveolar wall.[1] Confirmation of emphysema may be difficult because it is dependent upon lung anatomic findings or the appearance of obvious bullae on chest roentgenogram; moreover, it is recognized that chronic bronchitis and emphysema occur together and it may be difficult to predict which of these conditions is the dominant cause of chronic airways obstruction in an individual patient. To circumvent this difficulty, clinicians have preferred to use the term "chronic obstructive lung disease" (COPD) with the understanding that this term implies the probable coexistence of both bronchitis and emphysema.

From a practical standpoint, clinicians customarily respond to specific "signals" for the detection of asthma or COPD. Common examples are a patient's complaint of wheezing episodes, the demonstration of airways obstruction on spirometric testing, or detection of hypercapnia on arterial blood gas analysis. Appropriate interpretation of these signals requires not only knowledge of the definitions of asthma and COPD but also an awareness that there are numerous other diseases which can produce these signals and thereby mimic asthma or COPD.

The purpose of this report is to review and demonstrate, by case reviews, diagnostic pitfalls in the approach to patients with diseases which mimic asthma or COPD.

CASE 1. A 20-year-old white female college student complained of an exacerbation of coughing, mucopurulent sputum, and wheezing in April 1974. She had experienced numerous identical episodes since 1967 and had noted gradually progressive exertional dyspnea. In 1967, because of wheezing, a physician had diagnosed "asthma" and prescribed a compound containing theophylline and glyceryl guaiacolate. She was referred to an allergist who detected cutaneous hypersensitivity to multiple allergens and administered desensitization injections. Despite these interventions, her symptoms continued. Past medical history revealed undiagnosed chronic diahrrea during childhood. A physical ex-

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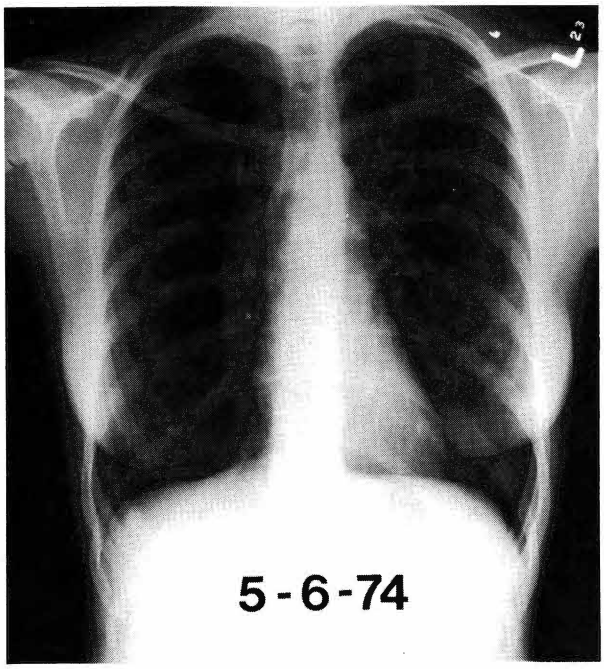

Fig 1—Posteroanterior chest roentgenogram of case 1 showing faint reticular densities in all lung fields and increased subcardiac air.

amination revealed a well-developed and well-nourished female. There were inspiratory crackles in the upper lung fields, diffusely diminished vesicular sounds, and mild digital clubbing. The chest roentgenogram (Fig 1) showed scattered coarse reticular densities and subcardiac air. Physiologic studies revealed a forced vital capacity of 3.05 liters (predicted value, 3.54 liters), a one-second forced expiratory volume of 1.68 liters/sec (predicted value, 2.44 liters/sec), and a maximum mid-expiratory flow of 0.96 liters/sec (predicted value, 2.98 liters/sec). Sweat chloride values exceeded 60mEq/liter on three occasions, thus confirming the diagnosis of cystic fibrosis.

Comments: There is evidence to suggest that differences in genetic factors or penetrance may influence the course of cystic fibrosis.[2] Some patients may not develop the typical wasted and chronically-ill appearance and because of this, cystic fibrosis may be easily overlooked in adolescents or young adults. Futhermore, over 20% of cystic fibrosis patients may remain unrecognized when they reach the age of seventeen.[2] Case 1 is an example of this. Misdiagnosis resulted in inappropriate and expensive attempts to provide protection from presumed pulmonary allergens. Earlier institution of correct treatment, consisting of aggressive chest physiotherapy and prompt attention to specific airway bacterial pathogens, may have improved her long-term prognosis. Because cystic fibrosis is the most common cause of chronic airways obstruction in young adults,[2] it represents an important simulator of asthma and COPD.

CASE 2. A 58-year-old female nurse complained of progressive wheezing and dyspnea in December, 1978. She denied smoking cigarettes, previous atopy, allergic rhinitis, or asthma and had experienced excellent health until June, 1978, when she developed episodic "tightness" in her chest. This worsened in November, 1978, causing her to seek medical attention. Asthma was diagnosed and she was given a bronchodilator which temporarily relieved her symptoms. In December she was hospitalized with severe wheezing and fever. Her past history revealed that she had converted to a positive tuberculin test in 1977. She had refused to take prophylactic isoniazid. A physical examination revealed an elevated temperature (102 F), tachypnea, use of accessory muscles of inspiration, and expiratory prolongation of her breath sounds; bilateral diffuse expiratory wheezing was present. The total leukocyte count was 16,100 cells/cu mm with 78% mature neutrophils, 7% band forms, 6% lymphocytes, 3% monocytes, and 6% eosinophils. The absolute eosinophil count was 5056 cells/cu mm. A chest roentgenogram (Fig 2) revealed a "ground glass" infiltrate in the left upper lobe. Serologic tests for antibody titers to Mycoplasma pneumoniae, Q fever, psittacosis, and a variety of viral agents known to infect the respiratory tract were low. *Mycobacterium tuberculosis* was not present on sputum smears or cultures. Arterial PO_2 was 54 torr, PCO_2 32 torr, pH 7.47 units. After five days of intravenous aminophylline her wheezing cleared. Physiologic studies revealed a forced vital capacity of 2.17 liters (pre-

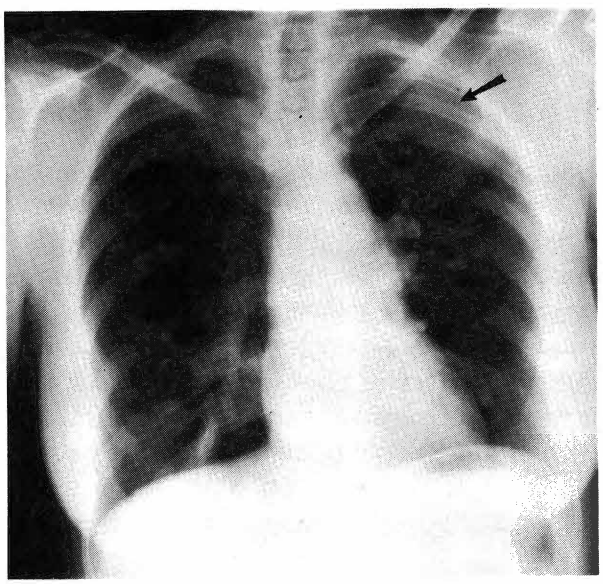

Fig 2—Posteroanterior chest roentgenogram of case 2 showing ill-defined "ground-glass" infiltrate (*arrow*) in left upper lung field.

dicted value, 2.43 liters), and one-second forced expiratory volume of 1.55 liters/sec (predicted value 1.78 liters/sec). The left upper lobe had cleared completely on roentgenogram but was replaced by a similar infiltrate in the left mid-lung field. Because of these migratory infiltrates associated with eosinophilia, Löffler syndrome was suspected. Twenty days after admission her chest roentgenogram was normal. Physiologic studies revealed a forced vital capacity of 2.27 liters, a one-second forced expiratory volume of 1.78 liters/sec; arterial PO_2 was 78 torr, PCO_2 36 torr, pH 7.41 units.

Comments: Löffler pneumonia is the mildest disorder in a group frequently described as "pulmonary infiltrates with eosinophilia" or "PIE syndromes." The spectrum of PIE syndromes also includes more debilitating disorders such as chronic eosinophilic pneumonia (CEP) or potentially fatal disorders such as polyarteritis nodosa.[3] Although the etiology and pathogenesis of Löffler pneumonia are unknown, recent detailed pathologic descriptions of a single case have shown striking similarities to CEP.[4] Therefore, distinction between the two may have to be made on clinical grounds. Löffler syndrome is a self-limited form producing mild illness, whereas CEP is prolonged and may result in severe restrictive impairment, occasional obstructive impairment and large ventilation-perfusion imbalances.[3] CEP will resolve rapidly with corticosteroid therapy, but relapses are common. Löffler pneumonia rarely requires corticosteroid therapy. The PIE syndromes may be associated with obstruction, wheezing, and peripheral eosinophilia,[3] thereby simulating asthma as occurred in case 2.

CASE 3. In February 1975, on the eve of a skiing trip, a 59-year-old male sorting machine mechanic developed chills and fever. These were followed by malaise and dyspnea. Seven days later a dry cough developed. Two weeks following the onset of the illness, he was hospitalized because of persistent symptoms and an abnormal chest roentgenogram showing coarse, bibasilar linear infiltrates. After an unrevealing, noninvasive work-up, he underwent a right lower lobe open biopsy, which was interpreted as showing nonspecific inflammatory changes and fibrosis. The acute illness apparently resolved. During his convalescence, physiologic studies revealed moderately severe obstruction. He was told that he had COPD related to his long-term smoking habit. However, he had smoked cigarettes only occasionally and had been able to play tennis and ski prior to his illness in February. Since then he was dyspneic on exertion and unable to perform sports activities. In October, 1976, he sought another opinion. A physical examination revealed a few scattered posterior wheezes and moist rales with a well-healed right thoracotomy scar. Chest roentgenogram showed postsurgical blunting of the right costophrenic angle but was otherwise normal. The physiologic studies (Table I) continued to show moderately severe obstruction, obstructive air trapping, and severe reduction in diffusing capacity. Histopathologic sections of his previous biopsy were obtained and a Van Giesson stain was performed (Fig 3). This revealed numerous remnants of bronchial wall elastin, unrecognized on earlier hematoxylin and eosin staining, which indicated severe bronchiolitis obliterans.

Comments: Bronchiolitis with bronchiolitis obliterans is a well-recognized sequela of acute viral infections in infants and children. Among children less than 2 years old, respiratory syncytial virus accounts for most cases.[5] Because of their severe and potentially fatal obstructive complications, adenovirus types 3, 7 and 21 are another important, although much less frequent, cause of bronchiolitis in this age group.[5] On the other hand, acute viral bronchiolitis is rarely diagnosed in adults. The occasionally recognized case of bronchiolitis obliterans can usually be attributed to inhalation of a toxic substance, with resultant chemical injury, or to a syndrome of rapidly progressive airway obstruction which is sometimes seen in rheumatoid arthritis.[6] However, as a diagnosis by exclusion, viral bronchiolitis obliterans seemed likely in case 3. The patient denied toxic inhalation and had no chemical or serological evidence of rheumatoid arthritis. His prodromal symptoms were suggestive of a viral infection. His subsequent clinical course further supported this. Although the pathogenesis and pathologic lesion in his illness

TABLE 1
Physiologic Studies in a 59-Year-Old Male with Bronchiolitis Obliterans

	PRE-DRUG	POST-BRONCHODILATOR	PREDICTED
Vital capacity, liters	2.50	2.58	4.64
FEV_1, liters/sec	1.53	1.53	3.29
Total lung capacity, liters	5.28	—	7.03
Residual volume, liters	2.79	—	2.39
Diffusing capacity, ml/min/torr	15.8	—	27.7

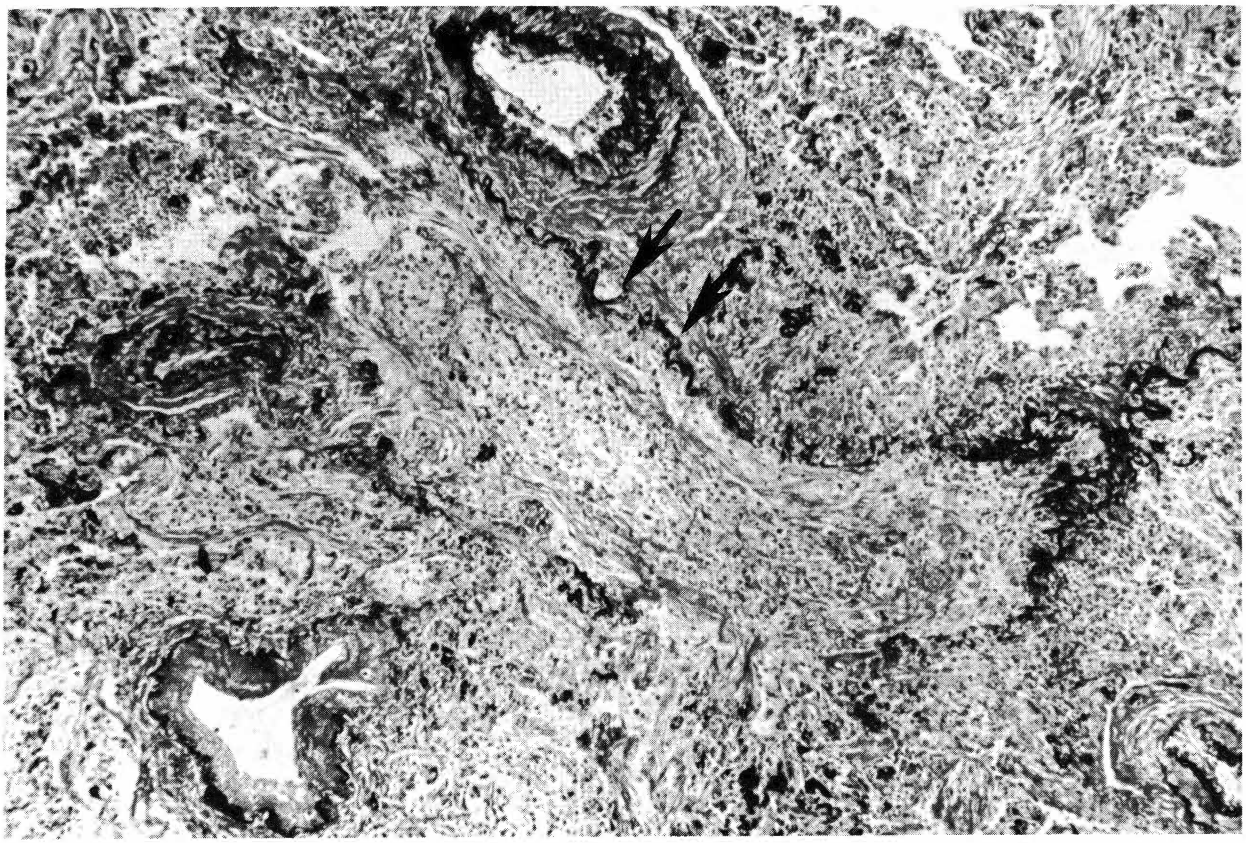

Fig 3—Histopathologic section of lung biopsy from case 3 showing remnants of bronchiolar wall elastin enmeshed in fibrous tissue. The findings are diagnostic of bronchiolitis obliterans (Van Giessen stain × 100).

were quite different from those of COPD related to chronic cigarette smoking, his long-term prognosis and hope for benefit from pharmacologic therapy are uncertain because the natural history of bronchiolitis obliterans in adults is not well known.

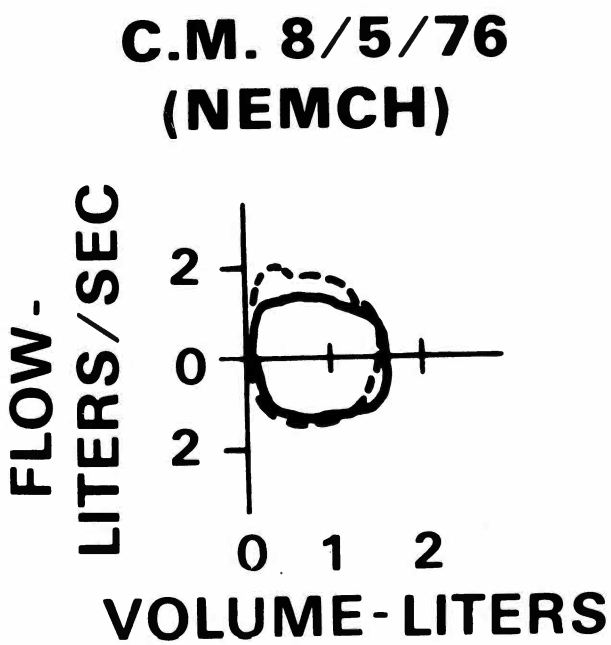

Fig 4—Flow-volume curve in case 4 showing flattening of both inspiratory (lower curve) and expiratory (upper curve) loops. The dotted line is a superimposed curve from the same patient while breathing 80% helium.

CASE 4. A 12-year-old white male was treated for asthma for six years because of wheezing and dyspnea. On a routine visit, inspiratory stridor was detected. Spirometry showed mild obstruction (one-second forced expiratory volume 70% of predicted). Because of his stridor, a flow-volume curve was performed to screen for upper airway obstruction. Both the inspiratory and expiratory limbs of this curve were flattened indicating nonvariable upper airway obstruction (Fig 4). A contrast tracheogram revealed an area of extreme tracheal narrowing extending from the level of the thyroid cartilage to the carina (Fig 5). An anomalous right upper lobe bronchus communicated with the trachea at the level of the thoracic outlet. The finding of anomalous bronchial drainage in conjunction with the tracheal stenosis suggested that all findings were of congenital origin.

Comments: Tracheal stenosis is usually associated with postinflammatory scarring because of pressure necrosis from indwelling endotracheal or tracheostomy tubes. Its occurrence as a congenital abnormality in a youth long suspected of having allergic asthma underscores the importance of correctly timing abnormal breath sounds. Earlier failure to recognize an in-

spiratory component to this patient's "wheezing" misled the clinicians caring for him. Prolonged, and perhaps unnecessary, bronochodilator therapy exposed the patient to expensive and potentially toxic medications. The extent of the abnormality precluded surgical correction. However, after a correct diagnosis was made, close attention to clearance of secretions and recognition of a permanently limited exertional tolerance helped the patient and his family to cope with his condition.

CASE 5. A 36-year-old black male complained of exertional dyspnea and massive swelling of his lower extremities in March, 1979. These symptoms were of 12 months' duration and had progressed to the extent that he was short of breath with minimal exercise such as dressing himself. He noted frequent nocturia, intermittent orthopnea, and was hypersomnolent during the day. A physical examination revealed massive obesity. His height was 5 feet, 9 inches; his weight was 344 pounds. The thyroid gland was not palpable and there were no changes in hair texture or quality of his voice. The chest was clear to auscultation. Heart sounds were faint with an S_4 gallop. Pitting dependent edema to the level of the umbilicus was present. Serum urea nitrogen, glucose, and electrolytes were normal as were the urinalysis and total leukocyte count. Hemoglobin was 19.7 gm%. An electrocardiogram showed right axis deviation. Serum free thyroxine was normal. A chest roentgenogram revealed cardiomegaly. The arterial PO_2 was 38 torr, PCO_2 was 56 torr, pH 7.36 units. Supplemental oxygen, digoxin, and furosemide were administered. Physiologic studies (Table 2) showed mild restriction and no evidence of obstruction. During sleep, the patient was observed to snore loudly between apneic spells. This phenomenon was documented by simultaneous sleep recordings of electroencephalogram, electrocardiogram, intraesophageal pressure (an estimate of intrapleural pressure), and air flow at the mouth (Fig 6). While in stage II non-rapid-eye movement sleep, he demonstrated numerous prolonged apneic spells during which he continued to have phasic inspiratory efforts, as manifested by persistent swings in intrapleural (intraesophageal) pressure. This confirmed the diagnosis of obstructive sleep apnea.

Comments: Disordered control of breathing during sleep may produce prolonged nocturnal hypoxemia and hypercapnia. These, in turn, may cause nocturnal pulmonary hypertension and gradual "resetting" of the central chemoreceptor response to CO_2. Eventually, chronic hypercapnia and cor pulmonale will occur. Although the precise sequence leading to chronic cor pulmonale and hypercapnia are unknown, at least three distinct pathophysiologic mechanisms may produce a ventilatory sleep disorder. The first, and most common, occurs in patients with COPD in whom exaggerated deterioration in arterial oxygenation and CO_2 retention may accompany the normal decrease in alveolar ventilation during sleep. The second occurs in patients with congenital or acquired defects in brain stem chemoreceptor or respiratory integrative functions. They develop apneic spells during sleep because respiratory drive from the cortex normally ceases, but the brain stem control mechanisms are unable to maintain normal ventilation.[8] The third results from intermittent upper airway obstruction, which leads to alveolar hypoventilation interrupted by loud snoring spells. Patients with anatomic defects of the upper airway, such as mandibular malformations or tonsillar hypertrophy, are predisposed to this condition.[8] However, the majority of patients with obstructive sleep apnea have no recognizable anatomic defect, and the precise mechanism for their intermittent upper airway obstruction remains unknown.[8] They tend to be obese. Because their sleep pattern is interrupted by frequent hypoxic spells with arousal, they tend to be hypersomnolent during the day. By the time they seek medical attention, they are usually experiencing cardiorespiratory failure. It is apparent that these patients have the cardinal features of what was formerly called the "Pickwickian syndrome." Case 5 is an example of this phenomenon. Often these patients are diagnosed as having COPD because they have chronic CO_2 retention and are assumed to have chronic diffuse airway obstruction. Misdiagnosis of such patients may result in grave therapeutic errors. The prognosis for untreated obstructive sleep apnea is poor, but the condi-

TABLE 2
Physiologic Studies in a 36-Year-Old Male with Obstructive Sleep Apnea

	OBSERVED	PREDICTED	%PREDICTED
Vital capacity, liters	3.60	5.07	71
FEV_1, liters/sec	3.00	3.94	76
FEV_1/vital capacity, %	83	78	—
Maximum mid-flow, L/sec	3.26	4.14	79

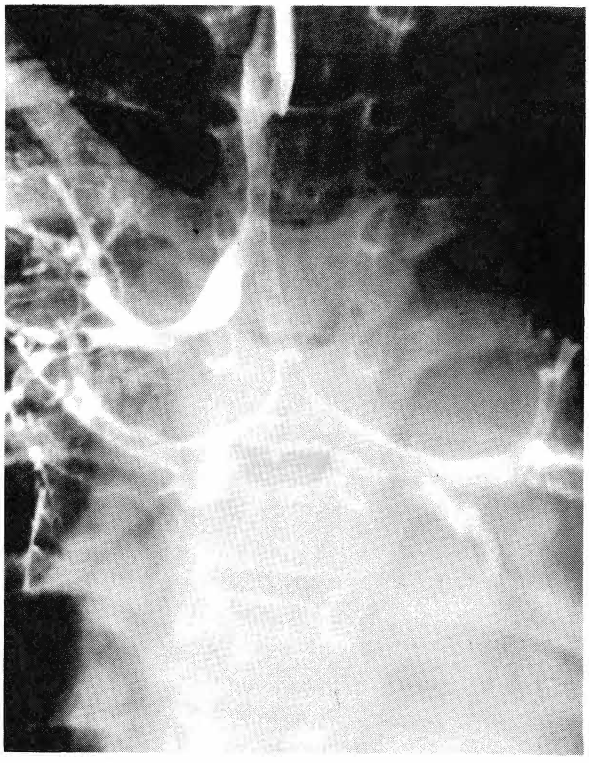

Fig 5—Tracheogram from case 4 showing long segment of narrowed trachea well outlined by contrast material. Right upper lobe bronchus branches from trachea above the carina indicating congenital anomalous bronchial tree with tracheal stenosis.

tion may be alleviated by the performance of a tracheostomy to allow for a patent airway during sleep.

In addition to the examples discussed in this report, there are other lung disorders which may cause obstructive airways disease or CO_2 retention (Table 3), either as an occasional complication or as a dominating feature.

Kyphoscoliosis can produce chronic CO_2 retention and cor pulmonale. However, the mechanisms initiating this are obscure because restriction, rather than obstruction, is the predominant mechanical abnormality.[9] Advanced tuberculosis may also cause chronic CO_2 retention. Again, the precise mechanism is ill-defined although inflammatory bronchial stricture with subsequent obstruction may play a role.[9] Because both of these diseases are easily recognized, confusion with asthma or COPD should rarely occur.

"Occupational asthma," on the other hand, may be difficult to distinguish from the more common allergic asthma of atopic individuals. In the former, patients experience reversible airways obstruction after exposure to specific organic volatile compounds or fibers.

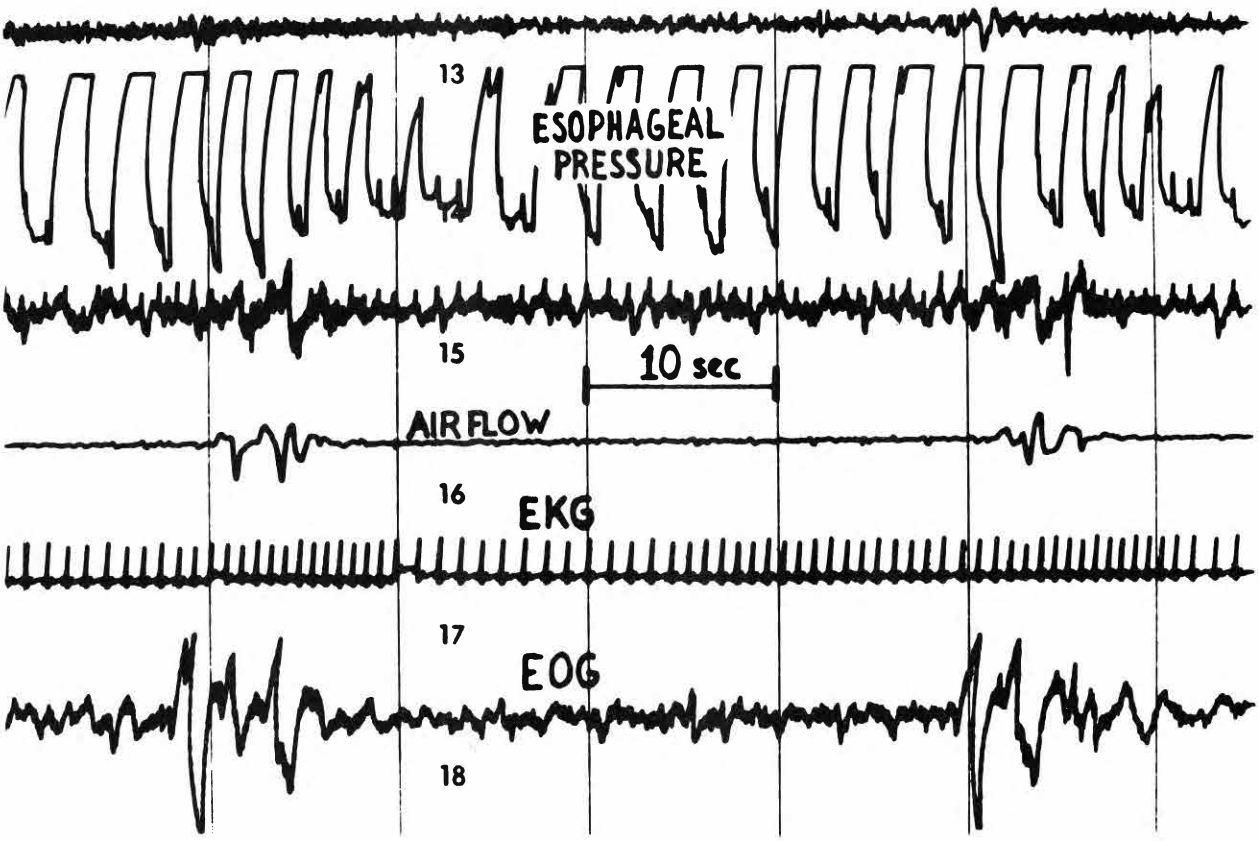

Fig 6—Sleep recording from case 5 showing continued inspiratory attempts (phasic esophageal pressure) during apneic spell as indicated by absence of mouth or nasal air flow. Unlabled channels are electroencephalograms. "EOG" is electrooculogram showing absence of rapid-eye-movements during this apneic spell.

Although reaginic antibody may be a factor, predisposition to the development of occupational asthma may be unrelated to the previous atopic status of affected individuals.[10] A number of compounds have been implicated, common examples of which are toluene diisocyanate, used in the manufacture of polyurethanes, and cotton or hemp dusts, encountered in the milling and carding processes of textile industries.[10]

Noninfectious, granulomatous inflammatory diseases of the lung may produce chronic airways obstruction and thereby create diagnostic confusion, especially because these diseases more commonly produce restrictive defects. Histologically, granulomatous bronchiolitis is almost invariably seen in allergic alveolitis and sarcoidosis. It is not surprising, therefore, that as many as 25% of patients with these disorders have reduced one-second forced expiratory volumes when expressed as a ratio of the forced vital capacity.[11,12] On occasion, obstruction is the dominant mechanical deficit in these patients and can occur with equal frequency in those with or without a smoking history.

Lymphangioleiomyomatosis is an exceedingly rare disease of women in childbearing years in which hyperplastic nodules of atypical smooth muscle cause obstruction of pulmonary lymphatics, venules, and bronchioles. These, in turn, produce episodic chylothorax, hemoptysis, and progressive obstructive airways disease.[13] In addition, chest roentgenograms in this condition show reticular markings associated with supernormal radiographic lung volumes. Although this constellation of clinical findings is distinctive, the disease is so rare that the diagnosis is often not made without open lung biopsy. Unfortunately, the prognosis for women with lung involvement is poor with most patients dying within ten years of the onset of symptoms.[13]

Respiratory compensation for severe metabolic alkalosis may result in "chemically justifiable" CO_2 retention in order to minimize elevation in pH. This well-known phenomenon is overlooked with surprising frequency by noninternists who may be less familiar with interpreting arterial blood gas data and may automatically attribute CO_2 retention to ventilatory failure. Carried to its full extent, such an error in logic may produce a corresponding error in treatment. Fortunately, most clinicians recognize the phenomenon before instituting therapy for acute respiratory failure.

TABLE 3
Conditions Which Mimic Asthma or COPD

1. Upper airway obstruction*
2. Sleep apnea syndromes*
3. Cystic fibrosis*
4. Kyphoscoliosis
5. Advanced tuberculosis
6. Pulmonary infiltrates and eosinophilia (PIE)*
7. Bronchiolitis obliterans (viral, toxic inhalation, rheumatoid)*
8. Industrial asthma
9. Sarcoidosis
10. Allergic alveolitis
11. Lymphangioleiomyomatosis
12. Severe metabolic alkalosis

* Discussed in comments of case reports

Table 3 represents only a partial list of diseases which may mimic asthma or COPD. As illustrated by the case reports, correct interpretation of wheezing, obstruction, and CO_2 retention depends not only on a knowledge of their differential diagnosis but also on obtaining an accurate history and physical examination. Special studies, such as the flow-volume curve illustrated in case 4, are merely confirmatory data. These special studies are appropriate only when clinical and screening laboratory data suggest a specific diagnosis. Therefore, the availability of such studies in many medical centers has not diminished the important role of basic bedside clinical skills in the diagnosis of obstructive lung disorders.

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Chronic Obstructive Pulmonary Disease: Outpatient Management

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Chronic obstructive pulmonary disease has become one of the more common problems which face physicians both in inpatient and outpatient settings. The incidence of the disease and increase in mortality have been documented in a number of studies as have other lung diseases, indicating a general rise in pulmonary disorders over the past several decades.[1-3] Two types of disease are classified under the heading of chronic pulmonary disease: chronic bronchitis and pulmonary emphysema. Chronic bronchitis is defined as a clinical syndrome of cough and sputum production for three consecutive months over two consecutive years, and pulmonary emphysema is defined as the histological expansion and destruction of the terminal respiratory units, with loss of structural elements. The etiologies associated with these diseases probably are multiple and are beyond the scope of this discussion; however, two of the causal factors are a hereditary predisposition such as is seen in alpha$_1$-antitrypsin deficiency and the continued irritation of respiratory tissues by various air pollutants including tobacco smoke.[4]

The following discussion of a therapeutic program for those who suffer from chronic obstructive pulmonary disease is directed toward the possibility of maintaining a patient in an outpatient status because of the need to minimize health care costs.[1-6]

The pathogenetic mechanisms of respiratory distress associated with chronic obstructive pulmonary disease share several common denominators (Fig 1). The primary problem is airways or bronchial obstruction, thus the physician should attempt to relieve this condition to prevent the cascade of effects that may occur later in the course of the illness. Obviously, bronchial irritation and infection lead to bronchial edema, spasm and hypersecretion with resulting bronchial obstruction. This can cause a number of difficulties the more important of which are problems of pulmonary infection and atelectasis, ventilation-perfusion disturbances with consequent hypoxemia, hypercapnea, and ultimately cardiovascular death, primarily from arrhythmias. The series of steps that can be taken to avoid the natural progression of these problems to mortality are outlined in the Table.

A major concern for patients with chronic pulmonary illness is the necessity of being reassured that their physician is taking an active interest in the treatment and follow-up care of their case. While there is no total cure for people with chronic pulmonary disease, a reasonable lifestyle can be maintained in most cases where the physician is ready to present an optimistic outlook and offer encouragement in those aspects of treatment that require the patient's cooperation. Such guidance is an important therapeutic factor in combating this illness and provides significant satisfaction to the physician for the time and interest expended.

Patients with chronic pulmonary disease must avoid respiratory irritants; first of all they must stop smoking. There is ample evidence that while people who have pulmonary impair-

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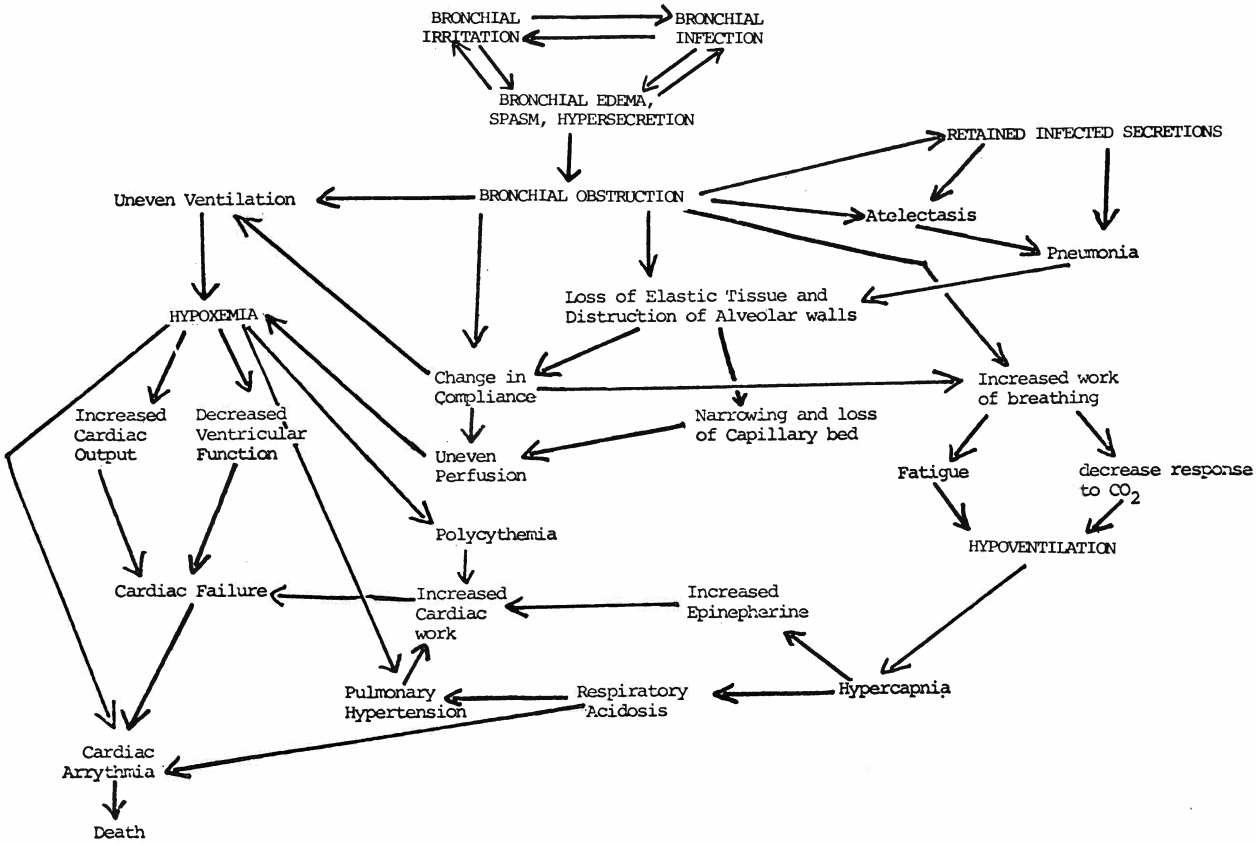

Fig 1—Pathogenesis of respiratory failure in chronic obstructive pulmonary disease. Remediable aspects in capitals.

ment and stop smoking continue to have an FEV_1 that is less than predicted for their size and age, the rate of decline in lung function is significantly slowed.[7] This is one of the more difficult aspects of treatment to accept and many patients deny that not smoking is of value. It is important that the physician continue to encourage these people not to smoke, and to maintain follow-up of those who will not stop. In addition to cigarette smoking, patients should avoid other known environmental respiratory irritants as well as any inhaled allergens if they are known and can be documented. One of the most important aspects of a therapeutic program is to provide these patients with a home that is as free from irritants and allergens as possible: pets should be kept outdoors; dust generators should be removed from the bedroom, as this is where the patient spends the most time; nonallergenic pillows and bedclothes should be purchased; and all animal and cotton products should be removed from the bedroom if possible and only synthetic, nonallergenic fibers used in rugs, upholstered furniture, draperies, and other items. Consideration should be given to purchasing an air filter for the bedroom as well as one for the entire home if simpler measures are ineffective.

The atmospheric environment should be controlled at between 40% and 60% relative humidity. In addition to this, patients with chronic pulmonary disease should drink large quantities of liquid each day to assist in liquefying the great amount of thickened secretions that their lungs produce; a good rule of thumb is 12 to 14 glasses of water daily or an adequate amount of water to dilute urine to the point that it looks like water. A vaporizer at times of increasing respiratory secretions such as with an upper respiratory infection may also be useful.

Bronchial drainage measures should be practiced using a simple four-position technique; three of these positions are illustrated in Figure 2.[5] The patient lies with hips elevated above the shoulders in each position (in addition to face-up) for 5 minutes twice daily. If a family member can be taught chest percussion and/or vibration, this can assist in the removal of the increased tenacious secretions. The next procedure is to teach the patient pursed-lip breathing which requires that the patient exhale through

pursed lips as though he or she were whistling. This will slow respiratory rate and may maintain airways in an open position for a longer time during exhalation, thus decreasing air-trapping and improving ventilation-perfusion relationships.

Since many severe pulmonary difficulties begin with upper respiratory infections, these chronically-ill patients should be instructed to keep antibiotics such as tetracycline or ampicillin in their home, and to start on these drugs as they develop either an upper respiratory infection or a change in sputum color or quantity which suggests an increase in infection. The patient's physician should then be called and, depending upon the degree of difficulty the patient is having, the physician should have a Gram stain and/or culture done of the patient's sputum.[3]

The regular use of bronchodilators is a cornerstone of therapy for chronic pulmonary disease.[3,5,6] Patients must be encouraged to take their drugs daily even though their condition is quiescent. The newer anhydrous aminophyllin preparations are generally the best available. The addition of sympathomimetics such as terbutaline or metaproterenol is appropriate if further bronchodilation is needed. Inhaled bronchodilators are also helpful, but they should be used infrequently, as these drugs are easily overused. Patients taking inhaled drugs must be given careful instructions with a demonstration of their proper use. The nebulizer is positioned just distal to the open mouth and a deep breath, followed by complete exhalation, is accomplished to time appropriately the introduction of the medication at the beginning of the next inspiration; at the onset of this inspiration the medication is nebulized via the open mouth. The patient holds his or her breath for as long as possible following a maximal inspiration and slowly exhales through pursed lips. This process should be repeated two to three times with two to three puffs of bronchodilator each time. Patients should be taught to monitor their pulse rate and rhythm when taking this type of medication and to discontinue its use if they develop any arrhythmia or tachycardia.

Another classification of drugs considered for therapeutic use is the adrenal corticosteroids which may be given either in inhaled or oral forms with the inhaled form producing fewer side affects. The introduction of steroid therapy should be based upon indication of failure of the above-mentioned bronchodilators and antibiotic therapy, or evidence of a clear-cut allergic disorder shown by either nasal or sputum eosinophilia or severe irritation by known allergens. The goal of steroid therapy should be to use the drugs in their inhaled form and if that is impossible to use minimal amounts of the oral drugs on alternate days to decrease side effects.[8]

Another drug available for use is cromolyn sodium; patients with definite allergic abnormalities or evidence of allergic-oriented disease are more likely to respond to this drug. There is no place for the use of either sedatives or tranquilizers in the treatment of chronic respiratory dis-

TABLE
Chronic Obstructive Pulmonary Disease: Outpatient Management

1. Physician interest and frequent follow-up
2. Avoidance of respiratory irritants
3. Maintenance of adequate humidity and hydration
4. Practice of bronchial drainage measures
5. Control of infection
6. Regular use of bronchodilators
7. Use of oxygen
8. Use of steroids
9. Control of heart failure
10. Other drugs
11. Active exercise reconditioning
12. Patient and family education

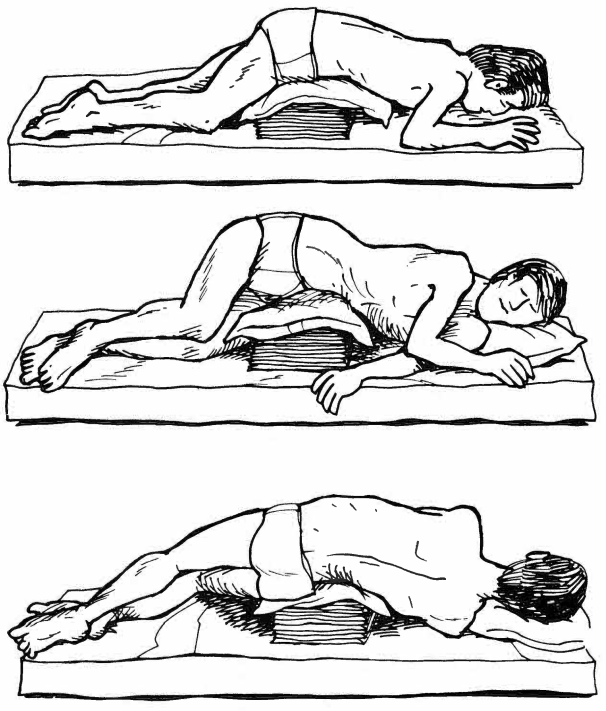

Fig 2—Basic positions for bronchial drainage.

ease. These patients are generally anxious, agitated, and frustrated because of their illness and/or the hypoxemia and/or hypercapnia which are associated with the disease. They are quite sensitive to most tranquilizers, particularly the benzodiazepams (Valium, Librium, among others), and these drugs should be avoided. A possible drug for use is hydroxozine (Atarax, Vistaril) which at least in parenteral form does have some bronchodilator effect and may be taken as a last resort in small doses (10 mg, t.i.d.) after all other possibilities have been exhausted.

Many patients will have observable evidence of right heart failure or cor pulmonale which should respond to the therapeutic regimen suggested above; if they do not, first, diuretics should be tried, and if they are unsucessful, digitalis may be used. Digitalis generally does not improve right heart failure as much as left heart failure, although it does have some effect. It is important to avoid drugs which block the effectiveness of beta adrenergic stimulation, particularly propranolol which is a beta 1- and 2-blocker, as they will make the bronchodilators less effective. An effective beta 1-blocker drug may be available in the not-too-distant future which will permit bronchial dilatation while controlling cardiac arrhythmias without producing the kind of problem one regularly sees with beta 1- and 2-blockade.

Active exercise reconditioning is of great importance for patients with chronic pulmonary disease.[1–3,5,6] They should begin with a regular walking program in which goals are set, such as walking a number of blocks (or other measured distance) daily in a specified period of time, with a planned increase in the rate of walking or a decrease in the amount of time it takes to cover a certain distance. In addition to this, having an exercise bicycle for indoor use during inclement weather is of extreme importance. Exercise with nasal oxygen may increase the exercise tolerance of the patient and permit more rapid progress; its use in the outpatient setting has been demonstrated to be of significant value in reducing pulmonary hypertension and improving the psychological status of chronically hypoxemic patients.[9]

In conclusion, an educational program in which the family as well as the patient is provided with information concerning the etiology of the disease is very important; a similar one which explains the pathogenetic mechanisms involved in the illness, what the course and prognosis are likely to be, as well as the rationale for all therapeutic measures introduced, is also very helpful. This type of approach will assist most patients to improve and function more effectively.

Figure 2 is reprinted with permission from Dr. Irwin Kass.

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Recent Advances in the Management of Chronic Airway Obstruction

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Recent advances in our understanding of the natural history of chronic airway obstruction have identified aspects of this process that may enhance the morbidity and mortality of patients with a progressive increase in airway resistance. These advances have helped us to be more specific in the investigation and quantitation of the disease in the pulmonary function laboratory and to be more precise in our therapeutic management. Experience has taught us that the most useful measurement with which to characterize the degree of disease and its rate of progression is the forced expired volume in one second (FEV_1). The comprehensive studies of Dr. Charles Fletcher in London have demonstrated that the single most important therapeutic factor is avoidance of all airway irritants.[1] The application of aggressive bronchial hygiene in patients with obstructive airways disease may produce an initial improvement in the FEV_1 but will not in itself alter the rate of decline in pulmonary function. As the degree of airway obstruction increases, a number of interrelated physiologic abnormalities develop including hypoxemia, hypercarbia, polycythemia, cor pulmonale, and eventually, acute or chronic respiratory failure. These abnormalities account for most of the morbidity in this condition and the majority of patients who develop them have a high degree of airway obstruction. It is not unusual, however, to see patients with a moderate degree of airway obstruction who also manifest these problems. The purpose of this paper is: (1) to review the relationship between a progressive increase in airway obstruction and the associated physiologic abnormalities, and (2) to discuss the therapeutic interventions that show promise of reducing the morbidity from these accelerated physiologic abnormalities.

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Hypercarbia and Airway Obstruction

In order to identify those patients whose clinical condition is significantly worse than anticipated from their level of airway disease, we need a readily applicable laboratory marker such as the elevated arterial carbon dioxide tension ($PaCO_2$). Several years ago, the relationship between airway obstruction characterized by the FEV_1 and the $PaCO_2$ was investigated.[2] It was noted that when the FEV_1 was 1500 cc or greater, the $PaCO_2$ was normal ($PaCO_2 < 44$ mm Hg). When the FEV_1 fell below one liter, the patient was as likely to have an elevated $PaCO_2$ as he was to have a normal $PaCO_2$, and when the FEV_1 was 500 cc or less, the $PaCO_2$ was almost always in excess of 44 mm Hg. Hypercarbia has been identified as an adaptive response in those patients who must balance the increased work of breathing against adequate carbon dioxide clearance and, indeed, this may be true in patients with severe airways disease. Such a state, however, has two major disadvantages; increased arterial hypoxemia and promotion of metabolic alkalosis, which contribute to a cycle of events that leads to premature metabolic deterioration. We have identified patients with moderate obstructive airway disease whose hypercarbia, previously attributed to the

airway disease, was in fact, related to conditions amenable to medical management. Furthermore, there are patients who have severe obstructive airway disease whose hypercarbia is made worse by these same factors. These conditions include respiratory disturbances during sleep, metabolic alkalosis, and respiratory muscle weakness.

Respiratory Alterations During Sleep

Recent studies using an ear oximeter have clearly demonstrated that gas exchange is not stable from moment to moment during the day and that a single arterial puncture is not satisfactory to describe an individual's blood gas composition, particularly during exercise and during sleep. Healthy adults develop periodic breathing during light sleep with an overall reduction in minute ventilation of one to two liters. Rapid eye movement (REM) sleep may include apneas of 15 to 20 seconds in normal individuals. Accompanying these episodes, there is an elevation in $PaCO_2$ of 4 to 8 mm Hg and a reduction in arterial oxygen tension (PaO_2) of 3 to 10 mm Hg. In patients with chronic obstructive airway disease, similar fluctuations are found but with more profound blood gas disturbances that are not directly related to the degree of respiratory impairment when awake. There are three major abnormalities of respiration that may occur during sleep. These are (1) hypoventilation, (2) central apnea, and (3) obstructive apnea. Patients with chronic airway obstruction may suffer from any of these entities; however, the two former problems are far more common than obstructive apnea. Episodes of hypoventilation causing hypoxemia and hypercapnia are usually brief but have been reported to last up to one hour. Alterations in chest wall mechanics and airway tone during REM sleep may increase these episodes. Normal, brief central apneas may be prolonged by alterations in the ventilatory control of the central nervous system. An increase in hypoxic drive produces a Cheyne-Stokes breathing pattern. Depression of either the hypoxic or hypercapnic drives may prolong the apneic spells.

Spells of nocturnal hypoxemia have been demonstrated to cause episodic pulmonary arterial hypertension, fluid retention, and polycythemia. It has been suggested that recurrent arterial hypoxemia during sleep produces a sustained elevation of the pulmonary arterial pressure and cor pulmonale. A major factor contributing to the prolongation of these episodes of hypoxemia is the depression of the central ventilatory response to hypercarbia. As the $PaCO_2$ rises, respiratory acidosis develops and repeated and prolonged bouts of acidosis stimulate a compensatory metabolic alkalosis. This renal adjustment to hypercarbia is a "compromised adaptation" in which the respiratory acidosis is buffered by an increase in serum and extracellular bicarbonate, but this elevated bicarbonate in turn promotes a readjustment of the respiratory control mechanism favoring perpetuation of the hypercapnic state. This effect of an elevated serum bicarbonate on the respiratory control mechanism has been demonstrated in patients with and without respiratory compromise.[3] Nocturnal hypercapnia in a patient with modest airway disease may initiate progressive elevation of the serum bicarbonate which in turn will alter the respiratory control of the central nervous system and lead to a sustained elevation of arterial carbon dioxide tension during the waking hours. Furthermore, such an alteration prolongs the nocturnal apneic spells increasing both the arterial hypoxemia and hypercapnia.

This unfortunate situation may be magnified by the administration of chloride-depleting diuretics that are often given for fluid retention. Clinical experience has impressed upon us the fact that patients with moderate-to-profound arterial hypoxemia respond poorly to large doses of diuretics until their arterial oxygenation has been improved, which alone is often sufficient to promote a diuresis. The interrelationships among these abnormalities that occur during sleep are shown in Figure 1. There are several points in this cycle in which the physician may intervene. The most quickly reversible problem is diuretic-induced alkalosis. When we encounter a patient with a marked elevation in serum bicarbonate who has been on chloride-depleting diuretics, we discontinue the diuretic therapy and treat the patient with either a carbonic anhydrase inhibitor such as acetazolamide or by the administration of ammonium chloride. The effect of reducing the serum bicarbonate in a group of patients with severe obstructive lung disease whose metabolic alkalosis was in excess of that appropriate for the arterial carbon dioxide tension has been reported.[4] In these patients diuretic therapy was discontinued and

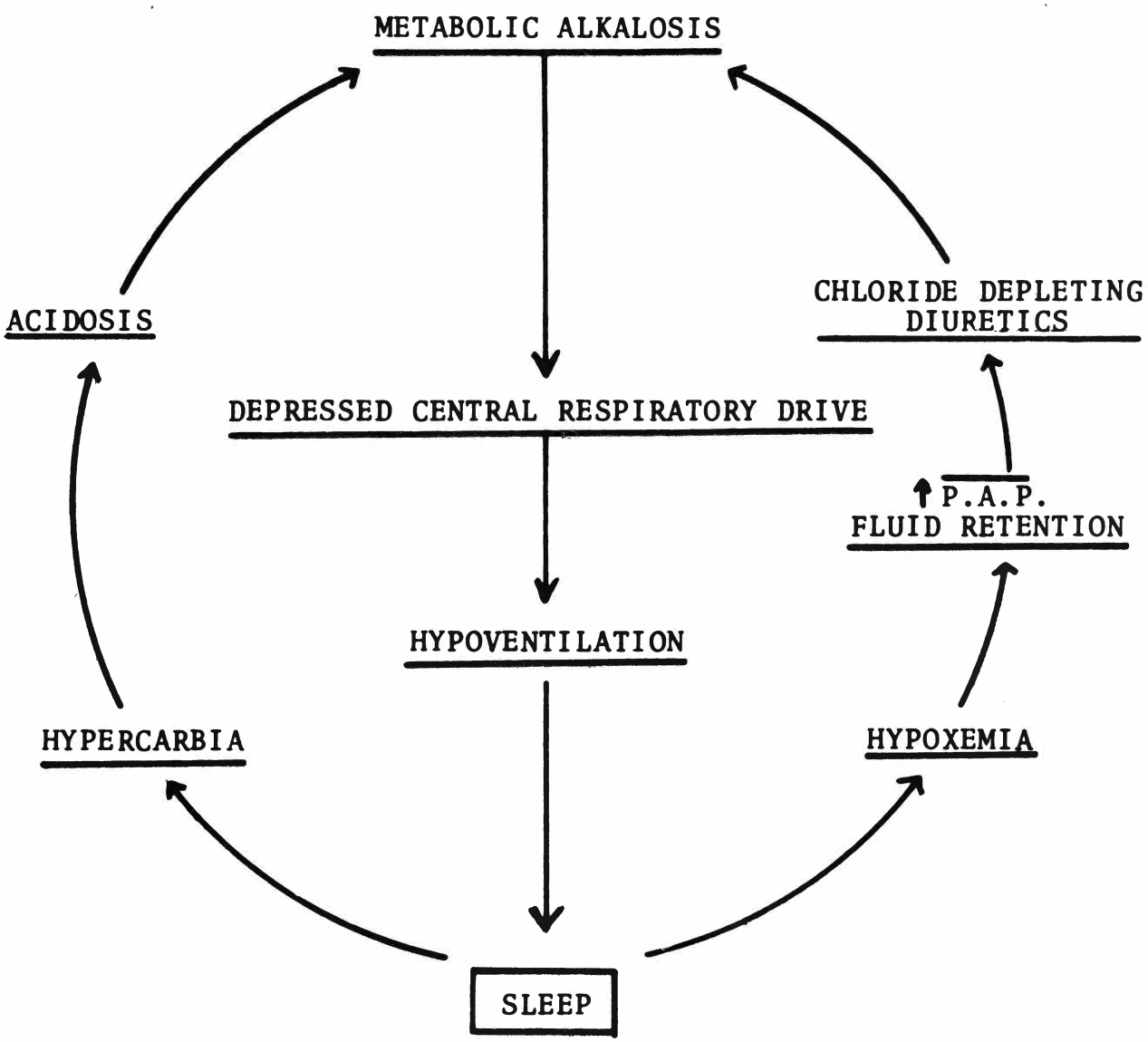

Fig 1—Abnormalities of gas exchange during sleep.

acetazolamide 500 to 750 mg/day in divided doses or ammonium chloride 3 to 6 gm/day in divided doses was administered until the serum bicarbonate, $PaCO_2$ and arterial pH stabilized. The effect of this therapy on the arterial blood gas composition of 11 patients is summarized in Table 1.

Following the line of reasoning that a central control mechanism may be abnormal in patients with prolonged nocturnal hypoventilation, a number of physicians in this field have been investigating the use of medroxyprogesterone. This agent has been used in an attempt to increase minute ventilation in a variety of pulmonary problems with variable success. The most striking benefit seems to occur in those patients whose apneic spells are limited to hypoventilation on a central basis. Impressive improvement in arterial blood gas composition has been reported in patients with obesity hypoventilation[5] and chronic airway obstruction.[6] While correction of metabolic alkalosis and the use of progesterone can be of significant benefit to these patients, the administration of low-flow oxygen during sleep may be a necessary addition, especially for patients whose PaO_2 when awake is less than 60 mm Hg. The effect of nocturnal ox-

TABLE 1
Blood Gas Values Before and After Correction of Metabolic Alkalosis

	Before Correction	After Correction
HCO_3 mmol/L	36.9 ± 1.7	28.1 ± 1.0
$PaCO_2$, torr	60.8 ± 2.6	47.6 ± 2.2
PaO_2, torr	52.4 ± 3.1	69.1 ± 2.1

TABLE 2
Hypoxemia During Sleep in 10 Patients with C.O.A.D. on Room Air and Supplemental O_2

	S_aO_2 Breathing Room Air			S_aO_2 on 2L. O_2		
	AWAKE	ASLEEP	CHANGE	AWAKE	ASLEEP	CHANGE
Mean	95	68	−26	97	86	−11
S.D.	4	12	11	2	9	8

ygen therapy has been described in a group of patients with moderate airway obstruction (Table 2)[7] The data here are in terms of arterial oxygen saturation (S_aO_2) and not PaO_2. The mean waking arterial oxygen saturation was 95% while the mean sleep saturation was 68% (a value associated with pulmonary arterial hypertension and polycythemia). The administration of low-flow oxygen to this group of patients significantly improved the oxygenation during sleep.

Abnormalities of ventilation during sleep remains a fertile field for investigation and the application of therapeutic modalities. We at the Medical College of Virginia are most interested in the documentation of breathing disturbances during sleep in patients believed to have accelerated physiologic deterioration. In conjunction with the Department of Neurology, we have developed a Sleep Study Center in which the presence of episodes of hypoventilation, central apnea or obstructive apnea may be readily determined and correlated with the stage of sleep. It is believed that after careful documentation of these abnormalities and the application of appropriate therapy, we may significantly reduce the morbidity that develops in the group of patients with moderate airway obstruction and premature carbon dioxide retention.

Respiratory Muscle Weakness

A great deal has been learned about the function of the respiratory muscles in recent years. The ability of patients with obstructive airways disease to sustain ventilation and avoid hypercapnic respiratory failure depends upon the strength and endurance of the respiratory muscles. The major causes of muscle failure in obstructive airways disease are (1) hyperinflation of the lung, (2) increase in airway resistance increasing the work of breathing, and (3) generalized muscle weakness. The development of respiratory muscle failure may be divided into two phases; muscle hypertrophy and muscle atrophy.

In the early stages of airway obstruction,

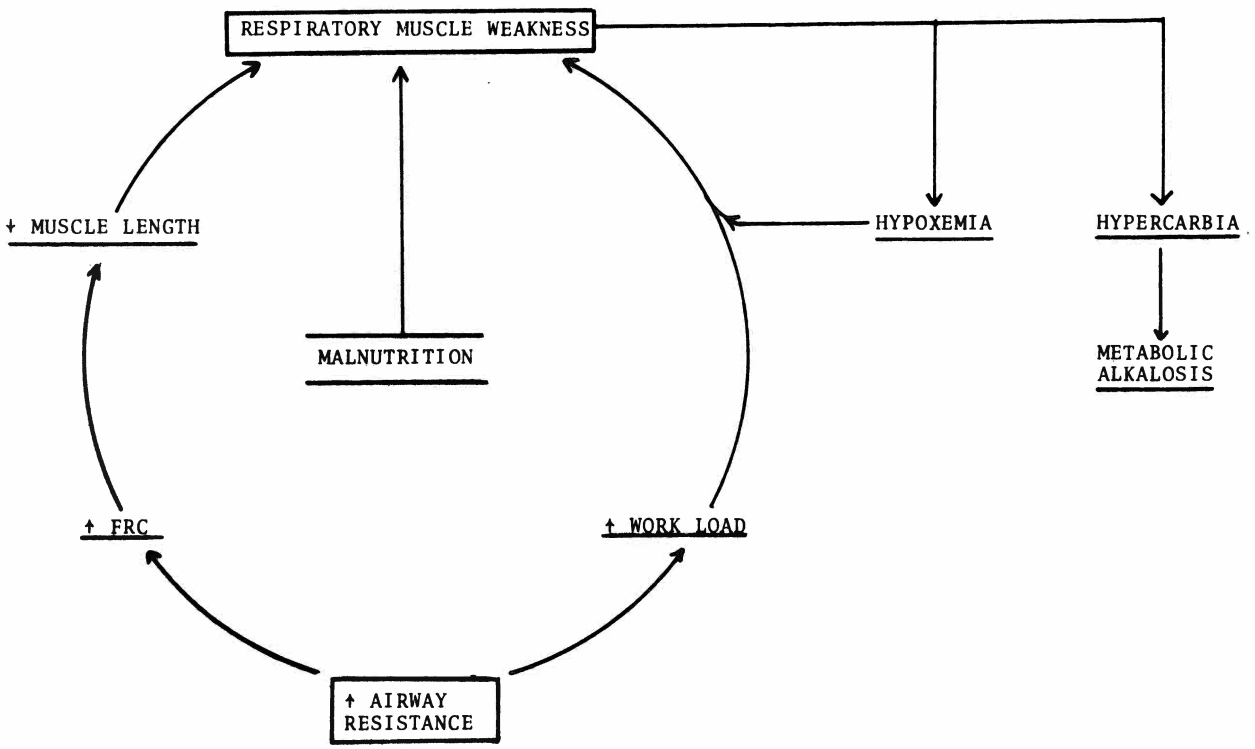

Fig 2—The development of muscle weakness.

hyperinflation of the lung pushes down on the diaphragm shortening its resting length; as the muscle is progressively shortened, the ability to develop contractile force is reduced. At the same time, the increase in airway resistance and the increase in required minute ventilation increase the demands on this compromised muscle. In this early stage, it appears that there is hypertrophy of the diaphragmatic muscle. As the disease progresses, some patients begin to lose weight, most frequently because of inadequate diet, or an inability to eat a complete meal because of dyspnea. These patients develop a negative nitrogen balance and their loss in general muscle mass is shared by the diaphragm, to the point of producing hypercapnic respiratory insufficiency. In the Pulmonary Function Laboratory we test inspiratory and expiratory muscle strength with a pressure manometer but the presence of this problem can often be suspected during the physical examination by noting generalized muscle tone, evidence of recent weight loss and asynchronous breathing. Asynchronous breathing develops when the diaphragm becomes so weak that it no longer acts as an inspiratory muscle with depression of the abdominal contents and protrusion of the abdomen during inspiration. Instead, it becomes passive and is sucked up into the chest when the accessory muscles of inspiration are called into play causing retraction of the abdomen during inspiration. The events leading to this condition are seen in Figure 2.

There are a number of points of therapeutic intervention. The increased airway resistance may be treated with bronchodilators and aggressive airway hygiene to mobilize secretions. Hypoxemia may be reversed with supplemental oxygen, and malnutrition may be treated by ensuring an adequate diet. Frequently, several small feedings, high in protein content, are necessary in patients who become dyspneic during eating. Two other forms of therapy are currently under investigation and may add significantly to our management of these patients. One is breathing training and exercise programs; the other is the use of intermittent mechanical support. The former may be useful in those patients whose condition is caused by purely mechanical factors while the latter is reserved for those who have developed evidence of diaphragmatic atrophy. When a patient with evidence of marked muscle weakness is placed on either positive pressure ventilation or in the tank respirator, there is a marked decrease in inspiratory muscle contractile effort and relief of dyspnea. Many physicians now feel that periodic rest for this overworked muscle combined with an adequate diet will improve the patient's ability to sustain ventilation. Patients with this problem are currently being managed at home with Drinker-type tank respirators in which they may sleep or spend several hours per day. The initial result of this therapy has been a marked reduction in the amount of hospitalization these patients require.

TABLE 3
Investigation of Hypercapnia

Pulmonary Function Tests
- $FEV_1 > 800$ cc
- $\downarrow PaCO_2$ with Hyperventilation

Metabolic Alkalosis
1) Review diuretic use
2) Seek history of sleep disturbance
3) Obtain sleep study
4) CO_2 response curve

Muscle Weakness
1) Obtain diet and weight history
2) Examine for:
   a) Paradoxical abdominal motion
   b) Deltoid wasting
   c) Use of accessory muscles
3) Request static muscle pressures
4) Inspiratory/expiratory chest X-rays

In summary then, there are a number of factors, previously often unnoticed, that complicate the clinical picture of chronic obstructive airway disease. With the recent advances in our knowledge and diagnostic techniques, we may more precisely define patients whose deterioration is premature. Premature deterioration may be suspected when the $PaCO_2$ is elevated in an individual whose FEV_1 is in excess of 800 cc and who is able to reduce the $PaCO_2$ with voluntary hyperventilation. The presence of sleep abnormalities, metabolic alkalosis or muscle weakness may then be confirmed by further investigation as outlined in Table 3. Appropriate therapeutic intervention may produce significant improvement in the patient's condition and reduce the frequency of hospitalization.

Table 1 is adapted by permission from the *Canadian Medical Association Journal* (117:900–903, 1977).

Table 2 is adapted by permission from *Annals of Internal Medicine* (86:725–730, 1977).

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Pre- and Postoperative Care of Pulmonary Patients Undergoing Nonthoracic Surgery

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Introduction

A variety of pulmonary complications occur in patients during and following nonthoracic surgery. These may include hypoxemia, atelectasis, bronchitis, pneumonia, and respiratory failure. The incidence of these complications is high and remains a major cause of morbidity and mortality in the postoperative state. Even so, this morbidity may be underestimated since hypoxemia, the most common pulmonary complication, exerts its influence throughout many organ systems through inadequate tissue oxygenation.

Physiologic Alterations Following Surgery

Predictable alterations occur in the pulmonary system in all patients undergoing surgery and general anesthesia regardless of age or underlying illness; the major impairment is a reduction in lung volume.[1] Total lung capacity and all its subdivisions (vital capacity, residual volume, functional residual capacity, and other factors) are decreased; in addition, expiratory flows (FEV_1) are reduced to a similar degree. These changes occur during the operative procedure, are maximal within the first 24 hours and slowly resolve over five to ten days. The magnitude of decline is related to the location of the surgical procedure; operations on the upper abdomen generally result in reductions of 50% to 60%. Following lower abdominal procedures, lung volumes and flows decrease by 25%. There is no change in pulmonary function following operations on the extremities or the head and neck area.

With the change in volume, the lung becomes less distensible (reduced compliance), airways close and alveoli collapse, especially in dependent portions of the lung. Because of these abnormalities, there are areas in the lung in which ventilation is reduced but perfusion continues, resulting in hypoxemia. This decrease in arterial oxygen tension approximates 20 torr following upper abdominal surgery in normal persons.

Postoperatively, the respiratory rate increases and tidal volume decreases, although total minute ventilation is unchanged. Periodic deep inspirations, such as with sighs and yawns, are less frequent also. This unvarying pattern of respiration leads to alveolar collapse and a progressive decline in compliance and arterial oxygen tensions. These changes in respiratory pattern have been ascribed to postoperative pain and poor motion of the diaphragm. However, administration of narcotics to alleviate pain accentuates these changes as patients are reluctant to cough or take periodic deep breaths. This leads to retention of secretions, eventual atelectasis, and occasionally, pneumonia.

Because of tissue repair and healing, the metabolic rate is increased following operative procedures, resulting in an increase in respiratory demands approximating 15% to 25%. In addition, the work of breathing is increased because of the fall in lung compliance. Thus, in the postoperative state, the respiratory system

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TABLE 1
Characteristics of Patients at High Risk for Postoperative Complications

1. Advanced age (>65)
2. Obesity
3. Past or present smoker
4. Mucous hypersecretion
5. Abdominal operation
6. Postoperative $FEV_1 < 1.02$
7. $CO_2 > 46$ torr

is called upon to meet greater demands at a time when it is temporarily impaired. These pathophysiologic events result in a small risk of complication in normal patients and a much greater risk in patients with preexisting pulmonary disease.

Factors Predisposing to Postoperative Complications

Table 1 lists characteristics which predispose patients to postoperative complications.[2] Elderly patients have smaller lung volumes and flow rates. Obesity decreases pulmonary compliance and reduces lung volumes and arterial oxygen tensions. Mucous hypersecretion (whether from smoking or other causes) reduces flow rates and predisposes to atelectasis and infection. Abdominal operations have significant effects on lung volumes as noted above. However, the most important factor contributing to postoperative complications is chronic obstructive lung disease. The vital capacities and flow rates are low in these patients, their work of breathing is increased and they are hypoxemic. In addition, a number of other features in the patient with chronic lung disease add to the excessive risks for postoperative complications. These include mucous hypersecretion, abnormal mucociliary clearance mechanisms, and a propensity toward bronchospasm. In addition, a small percentage of patients have an elevated arterial carbon dioxide tension indicative of far-advanced pulmonary dysfunction.

Preoperative Evaluation

Preoperative evaluation consists of the identification of those clinical features, functional abnormalities and operative considerations which are likely to lead to respiratory complications. Many predisposing factors can be identified by history and physical examination (age, weight, smoking, dyspnea, cough, and other findings). Similarly, operative factors such as the site of incision and the expected duration of anesthesia should be identified in consultation with the anesthesiologist and surgeon. Finally, an objective evaluation of lung volumes, air flow and gas exchange should be made. While many pulmonary function tests are available, simple spirometry and arterial blood gas evaluation are the most readily available and practical. The level of pulmonary dysfunction is best evaluated with the FEV_1, although other spirometric tests have been used.[3] An FEV_1 less than one liter per second may be associated with carbon dioxide retention; thus, a predicted postoperative FEV_1 greater than this is desirable. A reasonable estimate of the postoperative FEV_1 can be derived by multiplying the patient's preoperative value by the decline expected based upon the location of the operation. As an example, if the patient's preoperative FEV_1 were 2 liters and the contemplated operation were a gastrectomy, one might expect a 60% reduction in FEV_1. Thus, the estimated postoperative FEV_1 would be 800 cc and the patient's risk of respiratory failure high. Arterial blood gas analysis identifies patients with preexisting carbon dioxide retention and serves as a guide to oxygen supplementation.

Preventive Measures

Identification of patients at high risk is useful only if measures are available which may prevent complications. Fortunately, specific pre- and postoperative maneuvers in the high-risk patient have reduced the incidence of postoperative complications from 66% to 21%.[4] A treatment program outline for preoperative, intraoperative, and postoperative care is presented in Table 2. For convenience, patients with COPD have been divided into four groups according to certain general characteristics; however, individual patients may fit into more than one category thus requiring more complex treatments as suggested in each specific category.

The first group includes patients with obstructive defects and also patients whose ventilatory capacities are reduced from other causes such as restrictive defects, advancing age, obesity, or other factors. Patient education is very important; a knowledgeable patient is more likely to cooperate with difficult or uncom-

TABLE 2
Prevention of Postoperative Pulmonary Complications
COPD

	Group 1 Obstructed	Group 2 Hypersecretion	Group 3 Bronchospastic	Group 4 CO_2 Retention
PREOP	Instruction Minimize premedication	Stop smoking Percussion and drainage Hydration Antibiotics ?	Stop smoking Bronchodilators, aminophylline Beta agents, steroids	Treat cor pulmonale Correct metabolic alkalosis
INTRAOP		PM operation	Maintain bronchodilators	Insert arterial line Monitor arterial blood gases Avoid overventilation
POSTOP	Mobilize early Inspirometer Supplemental O_2 Care medication	Continue preop program Sputum smears	Maintain bronchodilators	Continue ventilator Maintain arterial blood gases ICU

fortable postoperative maneuvers aimed at protecting the respiratory system. Respiratory therapists can be employed to teach deep breathing maneuvers and coughing techniques. The patient can be instructed in the use of an inspirometer, a device to encourage maximum deep inspirations. Preoperative medications should be minimized; narcotics, benzodiazepams and other sedative drugs reduce respiratory drive and result in the unvarying respiratory pattern which may lead to alveolar and airway collapse, a fall in compliance and arterial hypoxemia. The patient should be encouraged to sit and walk as soon as possible postoperatively and the inspirometer should be used frequently. Supplemental oxygen should be administered until the patient has demonstrated the ability to maintain normal arterial oxygen tensions breathing room air. In addition, postoperative medications which could potentially suppress respiration should be given judiciously.

Those patients with mucous hypersecretion constitute group 2. The major postoperative respiratory complication in this group is atelectasis. Cessation of smoking will significantly reduce the amount of bronchial secretions. The duration of abstinence necessary for a significant change in the volume of secretions is highly variable; however, a period of five to seven days is usually sufficient. Every effort should be made to provide sufficient time prior to an operative procedure for clearing of the airways. Chest percussion and postural drainage accelerate the clearing process, and hydration aids in liquefying and mobilizing secretions from the tracheobronchial tree.[5] Gram stains or culture of tracheobronchial secretions may reveal pathogenic organisms which should be treated with appropriate antibiotics. Operations should be scheduled for the afternoon; the morning is used in a vigorous attempt to remove any secretions which may have accumulated during the preceding night. In the postoperative period, good tracheobronchial toilet should be maintained. In addition, sputum smears should be evaluated on a regular basis to guide antibiotic usage.

Patients with bronchospasm (group 3) should also stop smoking, as cigarette smoke alone or in consort with other stimuli often induces bronchospasm. Bronchodilators should be administered preoperatively in therapeutic doses. Aminophylline and beta adrenergic agents are first-line drugs. Systemic steroids may be necessary in patients who have required their use in the past. Steroids must be given in those patients who require them on a routine basis for adequate bronchodilatation.

Patients in group 4 are those whose preoperative arterial carbon dioxide tensions are elevated and those who are likely to develop elevations because of the expected decline in their pulmonary function following surgery. Because the etiology of the respiratory failure is known (surgery) and improvement likely, the episodes should be managed with little difficulty. Preoperatively, cor pulmonale should be treated with diuretics and the administration of supplemental oxygen to correct pulmonary hypertension and relieve right heart failure. Diuretic and steroid administration may produce metabolic alkalosis which should be corrected since it depresses respiratory drive. During the

intraoperative period, an arterial line should be inserted for repeated measurements of arterial blood gases. The physician can then make appropriate changes in the ventilator settings to maintain adequate levels of arterial oxygen tension and baseline levels of arterial carbon dioxide. In particular, intraoperative hyperventilation should be avoided, as it leads to relative hypoventilation in the postoperative period as body tissue stores of carbon dioxide are replaced. In the postoperative period, ventilatory support should continue until the patient has demonstrated the ability to maintain his own ventilation. This type of care is given preferably in an intensive care unit where acute exacerbations of chronic respiratory failure are best managed.

Conclusions

The patient evaluation and respiratory care program outlined here provides a measure of protection for patients with preoperative pulmonary dysfunction. Such a program can be instituted with equipment now available and little added time, and if done routinely and diligently, leads to a reduction in postoperative complications. In addition, patients who in previous years might have been considered "too sick" for operation can now be managed through a postoperative period without significant morbidity and/or mortality.[6]

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Pulmonary Rehabilitation in a Community Hospital

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Pulmonary rehabilitation programs seem to have come into vogue along with the national craze for exercise. This paper will discuss the feasibility of a rehabilitation program in a community hospital. In order to do that, we will first address several questions: "Does pulmonary rehabilitation really work?"; "If so, how?"; and "Is it safe?" Having answered those questions, we will discuss some of the details of setting up a rehabilitation program.

"Does Pulmonary Rehabilitation Really Work?"

Several investigators have shown significant improvement in exercise tolerance following pulmonary rehabilitation programs consisting of a number of treatment modalities which include bronchodilator therapy, antibiotic therapy, oxygen, postural drainage, somatic (exercise) reconditioning, and breathing retraining.[1-4] Petty et al[5] showed not only an increased exercise tolerance but also improved survival, reduction in hospital days and improved psychological status in patients completing a rehabilitation program. Pierce and associates[6] have shown that, following exercise training, maximal oxygen consumption was higher and, at any given level of exercise, minute ventilation, oxygen consumption and heart rate were lower even though there was no improvement in ventilatory function or lung volumes. Others have confirmed the beneficial effects of reconditioning without breathing retraining.[7-11]

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Although there is general agreement that exercise reconditioning is effective, even in patients with severe chronic obstructive pulmonary disease, there is no consensus regarding the value of breathing retraining. The studies appearing in the literature consist of several treatment modalities applied simultaneously; thus it is impossible to separate the relative effects of breathing retraining. Pursed lip breathing and abdominal augmentation can affect a decrease in minute ventilation and respiratory rate and an increase in tidal volume as well as an improvement in blood gas tensions.[12-14] Motley[15] found that slow deep breathing led to a reduction in the ratio of dead space to tidal volume and an increase in the oxygen saturation in most patients with emphysema. Following a program of breathing retraining, Sinclair reported a reduction of inefficient spinal and shoulder girdle movement during respiration.[16]

At the University of California at Irvine we have recently completed a study that was designed to separate the relative effects of somatic reconditioning and breathing retraining. Results of this study have been submitted elsewhere for publication. Our program was divided into four phases: selection of patients, optimizing medical therapy, somatic reconditioning, and breathing retraining. Eleven patients with severe type A chronic obstructive pulmonary disease were selected for this study. Optimal medical management using bronchodilators, oxygen, diuretics and ionotropics where appropriate was achieved and stabilized prior to entering the study. The patients were then exercised on a treadmill on an outpatient basis three times weekly in pairs with one patient resting

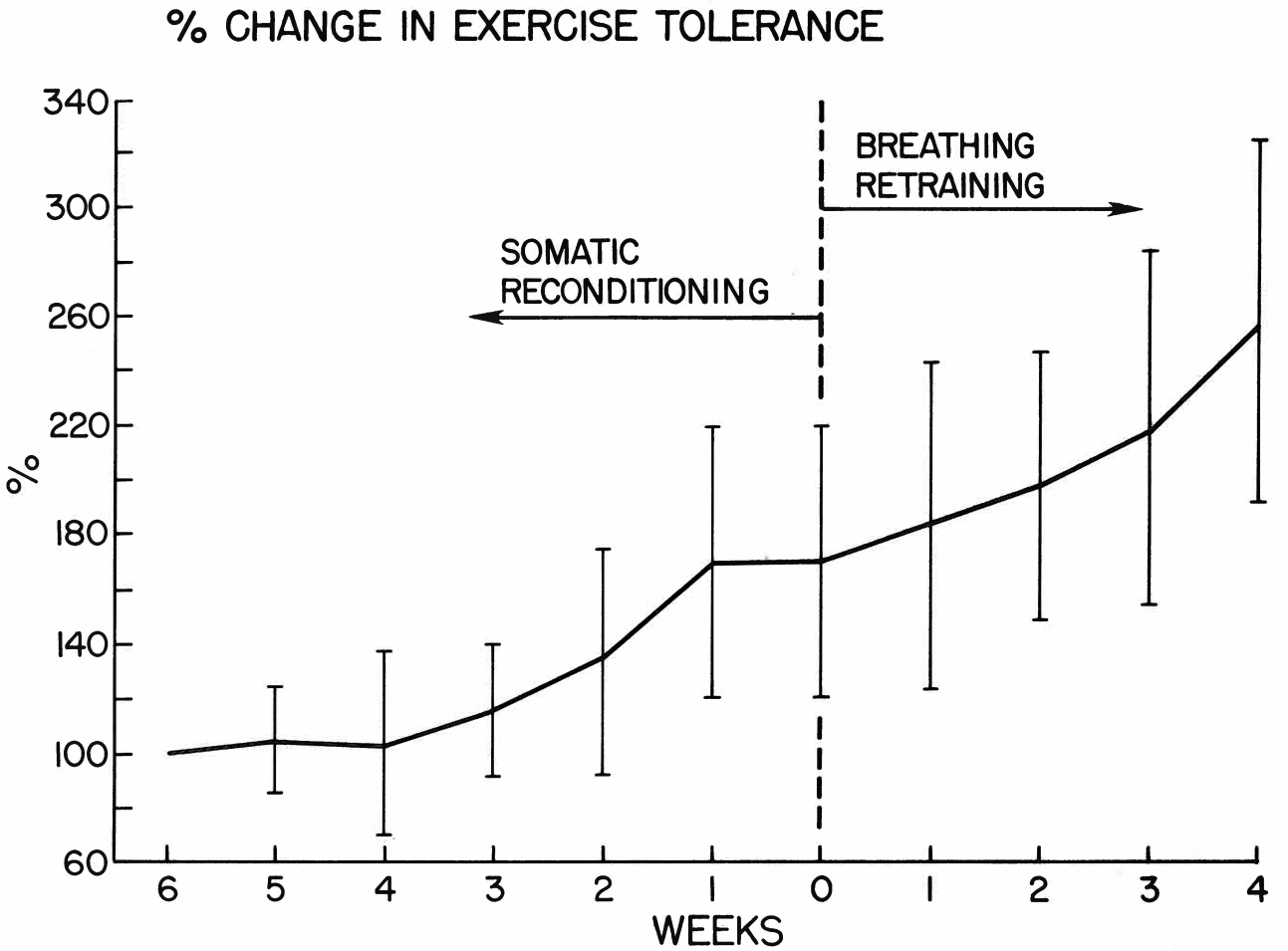

Fig 1—Mean percent change in maximal exercise tolerance for all 11 patients over the entire study period. Time O is determined to be the point at which breathing retraining has begun.

while the other was exercising. The total exercise session for two men would last one hour with each man exercising for approximately 25 minutes. Each exercise session consisted of a warm-up period at slow speeds, a stress period during which the patient would be encouraged to top his previous maximal tolerance, rest, and then several longer exercise periods at lower workloads. The rest periods were long enough to let the patient's pulse and respiratory rate return to baseline levels. The patients continued exercising until their maximal exercise tolerance was stable for at least four consecutive sessions.

After the somatic reconditioning phase of the program was completed, a program of breathing retraining was begun. Breathing retraining consisted of education about chronic obstructive lung disease, pursed lip breathing,[12,13] expiratory abdominal augmentation,[14] synchronization of movement of the abdomen and thorax using magnetometry and biofeedback, relaxation techniques for the accessory muscles[17] using electromyography and biofeedback, and psychological reassurance. Attempts were made to teach the patients to integrate these breathing retraining techniques into their activities of daily living. Breathing retraining was continued until all the techniques were well learned and were used without prompting during exercise as well as at rest.

There was significant improvement in exercise tolerance with somatic reconditioning alone (Fig 1). The average percent improvement in estimated oxygen consumption, which is a measure of work tolerance, after somatic reconditioning was 71% [0.97 ± 0.41 liters/min to 1.52 ± 0.43 liters/min ($p < 0.005$)]. What was surprising, however, was that there was an additional 39% increase in exercise tolerance after breathing retraining [1.52 ± 0.43 liters/min to 2.12 ± 0.61 liters/min ($p < 0.025$)]. The patients differed in their response to the program. Some improved minimally after

exercise reconditioning but markedly after breathing retraining. Others improved more after exercise reconditioning. The mean improvement from baseline levels after completion of the program was 126%. These results indicate that somatic reconditioning and breathing retraining are beneficial aspects of a program of pulmonary rehabilitation.

"If So, How?"

Based upon earlier work, the improvement after exercise reconditioning was expected. It is generally accepted that this improvement is due to a combination of improved neuromuscular coordination and acclimatization to walking on a treadmill, improved utilization and distribution of delivered oxygen, and improved effort due to motivational factors.[1,6,7,9]

The improvement after breathing retraining is more difficult to explain and has not been previously reported in the literature; it could not be attributed to any improvement in resting pulmonary function since none was found. Most previous workers have not found any change in resting pulmonary function[1,6-8] following a program of pulmonary rehabilitation, and our study substantiated these findings.

Arterial blood gas studies showed that the PaO_2 did increase significantly from the reconditioning to the retraining phase. This indicates better ventilation-perfusion relationships following breathing retraining. We could not, however, attribute the improvement observed in exercise tolerance to this increase in PaO_2 alone, since the improvement in oxygen content would not be great enough to account for the improvement in exercise tolerance. Arterial blood gas studies also showed that there was a significant decrease in the base excess after breathing retraining compared to both the baseline period and the reconditioning period. This indicates that the patients were willing to exercise beyond their anaerobic threshold following breathing retraining. This would increase exercise tolerance; however, it is again unlikely that this would account for all the improvement we observed.

The heart rate did not change significantly during the study (Fig 2). However, the respiratory rate decreased significantly following breathing retraining both at rest and after maximal exercise. When examined further it became apparent that the decrease in respiratory rate

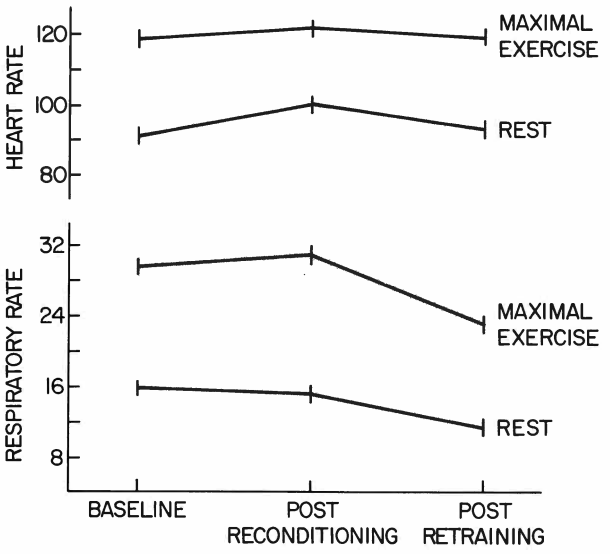

Fig 2—Heart rate and respiratory rate at rest and after maximal exercise measured at the beginning of the study, after somatic reconditioning and after breathing retraining.

was due to an increase in tidal volume, because minute ventilation did not change significantly. Cherniack[18] has shown that there is a decreased efficiency of the respiratory muscles and a high oxygen cost of increased ventilation in patients with emphysema. It has been suggested that breathing retraining may decrease the work of breathing by lowering the respiratory rate and relaxing accessory muscles.[1,16] The most likely explanation for the improvement demonstrated by our study after breathing retraining is increased efficiency of the respiratory muscles so that there is less relative increase in the oxygen cost of increasing ventilation during exercise, thereby freeing more oxygen for distribution to the peripheral tissues.

This study also showed that sophisticated and expensive magnetometry monitoring is not necessary for the purpose of synchronizing chest and abdominal movement. We found that patients corrected their own phase lag following somatic reconditioning and that the magnetometry and biofeedback techniques were not needed.

Ten of the 11 patients responded to a questionaire that was sent to them at the conclusion of the study. All felt that they had benefited from the study (8 answered "very much" and 2 answered "a lot"). Their comments regarding how they benefited are interesting. In response to the question "What can you do now that you could not do before the program?" two persons said that they could re-

sume work, two said they were able to travel (one having completed a cross-country trip), one began to play golf again, one reported the ability to shop for himself, and one related he was able to walk up a small hill to a recreation center that he had not been able to climb for the previous three years. Four patients suggested that the most important benefit of the program was learning that they could recover from a stressful situation, thereby decreasing their sense of panic. These findings, suggestive of subjective improvement, are similar to almost every study of pulmonary rehabilitation that has appeared in the literature.[1,4,7,10] This improvement may be secondary to the physiologic changes already described, or it may represent benefits obtained by the patients from the amount of attention rendered to them by members of the rehabilitation team. In any event, it seems to be a real and consistent finding following programs of pulmonary rehabilitation.

TABLE
Comprehensive Respiratory Care: Factors to Consider

I. General
  A. Environmental factors
    1. avoid inhalation of pollutants, including cigarette smoke
    2. avoid occupational hazards
    3. consider climate (altitude, temperature, humidity, smog)
  B. High fluid intake, unless contraindicated by presence of cardiac disease
  C. Yearly influenza shot
  D. Pneumococcal vaccine shot
II. Medications
  A. Bronchodilators
    1. sympathomimetics (prefer beta$_2$ stimulators)
    2. theophylline types
  B. Expectorants
    1. water
    2. glyceryl guaiacolate
    3. other
  C. Antimicrobials (early antibiotic therapy for pulmonary infections)
  D. Corticosteroids
  E. Digitalis
  F. Diuretics
  G. Cromolyn sodium
  H. Other
III. Respiratory Therapy
  A. Aerosol devices
    1. cartridge inhaler
    2. hand-held nebulizer
    3. compressor-driven nebulizer
    4. Intermittent positive pressure breathing
  B. Humidification devices
    1. vaporizer/humidifier
    2. all-purpose nebulizer (heated or cool mist)
    3. ultrasonic nebulizer
  C. Oxygen systems
    1. high-pressure gas cylinders (stationary or portable)
    2. low-pressure liquid systems (stationary or portable)
    3. concentrators
  D. Air purifiers
IV. Physical Therapy
  A. Somatic (exercise) reconditioning
  B. Breathing retraining
  C. Percussion and postural drainage
V. Occupational Therapy
  A. Activities of daily living
  B. Energy conservation
  C. Adaptive equipment
VI. Nutrition
VII. Psychosocial Evaluation and Recommendations for Vocational Rehabilitation
VIII. Patient and Family Education

"Is It Safe?"

No complications of exercise were observed in our study; indeed, not a single study has reported deterioration of cardiopulmonary function following a program of pulmonary rehabilitation. There has been no precipitation of right cardiac failure; to the contrary, a fall in mean resting pulmonary artery pressure along with a rise in arterial oxygen partial pressure has been reported.[19]

How to Set Up a Program in a Community Hospital

Equipment and Physical Plan

Approximately 400 sq ft is needed to house a rehabilitation program, one easily accessible from a hospital entrance or the parking area. The room should be divided so that there is an area where patients can exercise and an area where the physician can examine prospective patients. Since patients will be exercising rather strenuously, the room must be well ventilated.

We elected to use a treadmill to recondition our patients. We chose this because treadmill walking more closely approximates day to day activity than bicycle ergometry. A cardiac monitoring system, complete with recorder, is mandatory, as is a fully equipped resuscitation cart. Oxygen is, of course, available and we try to have several different types on hand to instruct the patients in their use. A Hewlett-Packard ear oximeter is an excellent way of measuring oxygen saturation noninvasively.[20] This essentially negates the need for arterial line

monitoring. The ear oximeter attaches to the patient's ear and gives continuous saturation readouts at rest, while exercising and during recovery. All of the equipment described above can be obtained for less than $15,000.

Personnel

The rehabilitation team consists of a medical director, a rehabilitation specialist who may be a registered nurse, a respiratory therapist or a physical therapist, a social worker, and in some instances an occupational therapist and a psychologist. The medical director performs a complete history and physical on all candidates referred to the program. He also supervises and interprets the exercise stress test and the pulmonary function tests, and documents the degree of the patient's disability. A useful checklist illustrating the comprehensive approach to the patient with chronic obstructive pulmonary disease is shown in the Table. Various aspects of this program can be implemented by the physician directly; however, many aspects, including techniques of avoidance of cigarette smoke, nutritional information and family education, are better performed by other members of the rehabilitation team. The physician sees the patient at the conclusion of the program and at scheduled follow-up sessions at 6 weeks, 6 months, 12 months, 18 months and 24 months after completion of the program.

Pulmonary Stress Testing

Stress testing can be performed on either a bicycle ergometer or on a treadmill. Cardiac status and oxygen saturation are monitored continuously. The test consists of graded exercise with the patient walking at each level for three minutes. Since most of our patients have severe exercise limitation, we have arbitrarily elected to begin our stress testing at much lower workloads than the accepted protocols for cardiac disease. The patient is started at 1 mph and a 0% grade for three minutes. The speed is then increased by 1 mph every three minutes until the patient reaches 3 mph at a 0% grade for three minutes at which point the grade is increased to 6%. The grade is then increased by 2% increments every three minutes until the patient reaches his maximal exercise tolerance. The patient is then allowed to recover until his heart rate and respiratory rate have returned to baseline levels. If the patient's saturation falls below 88%, the test is repeated with oxygen in place administered by nasal cannula and started at 2 liters/min. The stress test is repeated, increasing the oxygen by increments of 1 liter/min, until the patient's saturation remains above 88% at maximal exercise.

The typical patient with severe chronic obstructive pulmonary disease will stop exercising at a heart rate that is well below his predicted maximum. Additionally, he will show some desaturation with respect to oxygen. If the patient stops exercising when his heart rate has reached his predicted maximum, one must consider either primary cardiac disease or extreme deconditioning as the cause of the patient's exercise limitation.

The stress test as described above is a valid indicator of the need for home oxygen. Patients who desaturate severely with maximal exercise are also likely to need oxygen during sleep and meals. An exact prescription can be written based on the oxygen saturation as observed during the treadmill stress test.

The Program

Many different types of programs exist. We feel that six weeks is a reasonable length of time to accomplish both somatic reconditioning and breathing retraining. We also favor an outpatient program as opposed to inpatient rehabilitation, as outpatient rehabilitation enables the patient to incorporate the techniques taught into his activities of daily living. In addition, there is more time in a six-week program than in a two-week inpatient program for problems of day-to-day living to become apparent to the patient and the rehabilitation team. Our patients come to the hospital three times a week for one hour sessions. Each patient has a partner, and indeed the support of a partner seems to be a very important part of the psychological reassurance. Somatic reconditioning and breathing retraining are begun simultaneously and are enforced throughout the program. Breathing retraining emphasizes primarily pursed lip breathing, accessory muscle relaxation, abdominal augmentation and psychological reassurance. The program is tailored to the individual patient utilizing the expertise of physical therapy, occupational therapy and social services as indicated by the weekly reviews of each patient's case.

In conclusion, rehabilitation has been shown to be an effective and safe art of medical practice that can return a patient to his highest possible functional capacity. Pulmonary rehabilitation programs should include careful and optimal medical management, somatic reconditioning, and breathing retraining which can be performed in a community hospital without expensive or invasive monitoring. If properly carried out, such programs will result in increased exercise tolerance, improved sense of well being, and reduced hospitalization.

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Newer Drugs and Their Use in the Treatment of Bronchial Asthma

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The current knowledge of pathophysiology and new medications, as well as the better use of old ones, has significantly improved the therapy and prognosis of patients with bronchial asthma. However, it should be understood that drug therapy is beneficial only when aggravating or precipitating agents have been eliminated from the patient's environment; these include allergens, such as dust, mold, pollens and other irritants, infection, exercise, psychological disturbances, certain drugs (aspirin), and stimulation of irritant receptors in the respiratory tract.

There are five major classes of drugs used in treating bronchial asthma: (1) adrenergic agents, (2) xanthines, (3) corticosteroids, (4) cromolyn sodium, and (5) parasympatholytic agents. Some adrenergic agents, such as terbutaline and metaproterenol, offer advantages over others, such as epinephrine, isoproterenol and ephedrine. Among the xanthines the measurement of theophylline blood levels has resulted in the more effective use of aminophylline and other theophylline compounds. The development of a topical steroid, beclomethasone, has been useful in treating steroid-dependent chronic asthmatics. The drugs described below are prescribed to eliminate wheezing and dyspnea; however, other types of therapy such as antibiotics for infections, hyposensitization for allergic factors, and counseling for emotional disturbances should also be considered.

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Adrenergic Drugs

Adrenergic agents reduce bronchial obstruction by activating the enzyme adenylcyclase, which increases cyclic adenosine monophosphate (cAMP) in bronchial smooth muscle and mast cells. Adrenergic drugs have alpha- and beta-stimulating effects. The stimulation of alpha receptors causes vasoconstriction. Beta receptors are divided into $beta_1$ and $beta_2$ receptors. The stimulation of $beta_1$ receptors causes cardiac stimulation; stimulation of $beta_2$ receptors is responsible for bronchodilatation, as well as other effects. Terbutaline and metaproterenol are primarily "$beta_2$-selective," but they also stimulate the heart minimally.

Terbutaline (Brethine; Bricanyl), which comes in tablets and ampules is, as noted above, a selective $beta_2$ agent. The most common side effect is tremor, which is caused by stimulation of $beta_2$ receptors in the skeletal muscle. It is recommended that this drug be started at 2.5 mg every eight hours. Tremor may disappear after continuation of the medication; thereafter the dose can be increased to 5 mg every eight hours. However, it should be kept in mind that an injection dose of 0.25 mg of terbutaline may also cause a significant degree of cardiac stimulation.

Metaproterenol (Alupent) is available as a syrup, in tablets and as an aerosol; tremor is a common side effect. The usual oral dose is 10 to 20 mg q.8.h.

Isoetharine (Bronkosol; Bronkometer) is available as an aerosol.

Epinephrine and ***isoproterenol*** have been used for a long time in the management of

patients with bronchial asthma. Epinephrine has both alpha- and $beta_1$- and $beta_2$-stimulating effects. Isoproterenol stimulates both $beta_1$ and $beta_2$ receptors. Epinephrine may also improve symptoms by constricting vessels in the bronchial mucosa, thus decreasing edema. However, epinephrine increases blood pressure, and large doses of this agent or isoproterenol can cause angina pectoris and cardiac arrythmias. It has been observed that cardiac stimulation may increase blood flow in some regions of the lung where there may be poor ventilation. This may cause lowering of arterial O_2 tension.

Ephedrine. This drug was the first adrenergic agent used and it stimulates both alpha and beta receptors. However, its bronchodilatation activity is less than that of the new $beta_2$ agents. Ephedrine may increase blood pressure and may cause CNS stimulation (insomnia, nervousness). It may be responsible for urinary retention in patients with some degree of prostatic obstruction. Ephedrine and isoproterenol have more $beta_1$ (cardiac stimulation) than the newer medications. Insomnia, palpitations, and anxiety limit their use in bronchial asthma.

Xanthines

Theophylline is 1,3 dimethylxanthine. Methylxanthines increase intracellular cAMP by inhibiting phosphodiesterases, enzymes responsible for the breakdown of cAMP. Theophylline has been used for many years in combination with ephedrine and a sedative. The combination medications provide one fourth to one half the proper dose of theophylline and less bronchodilatation.

Aminophylline is theophylline ethylenediamine and is used more often than theophylline itself. Since the difference between therapeutic and toxic doses of theophylline compounds may be narrow, it is desirable to start with a small dose and increase it as required. Plasma theophylline levels should be obtained if patients do not respond to the usual doses; the optimum serum level is between 10 and 20 μg/ml.[1] Patients with chronic liver disease should be treated carefully, since theophylline is detoxified in the liver. Serum theophylline levels greater than 20 μg/ml are usually associated with toxic side effects, such as nausea, vomiting, anorexia, headache, tachycardia and CNS irritation. Levels greater than 30 to 40 μg/ml may lead to serious cardiac arrythmias and seizures.

An oral loading dose of approximately 5 to 6 mg/kg of aminophylline, anhydrous theophylline, or elixophylline will supply therapeutic theophylline levels within 30 to 45 minutes and will usually be effective against a mild-to-moderate degree of bronchospasm. In cases of severe bronchospasm 6 mg/kg aminophylline should be given intravenously in a drip over 20 minutes.

The usual recommended intravenous (IV) maintenance of theophylline is 0.9 mg/kg/hr aminophylline. Serum theophylline levels should be checked at 18 to 24 hours and proper adjustments made as needed. In patients with congestive heart failure or liver disease, the dose should be reduced by half or more if indicated. In elderly people intravenous maintenance of theophylline is 0.7 mg/kg/hr.

For long-term maintenance of theophylline an average-size adult patient with bronchial asthma requires approximately 800 to 1200 mg/day aminophylline. The serum levels should be checked after three days on this therapy, and proper adjustments should be made to maintain levels between 10 to 20 μg/ml. The slow-release preparations of theophylline can be given every 12 hours and can be effective against early-morning bronchospasm.

Corticosteroids

Steroids are very useful in the treatment of asthma but should be used only when conventional bronchodilating agents fail to relieve bronchospasm. Some of the undesirable side effects of steroids include acne, peptic ulcer, osteoporosis, growth retardation, hypertension, adrenal suppression and opportunistic infections. The exact mechanism of steroid action in asthma is not definitely known. Large doses appear to potentiate beta agonists and cause bronchodilatation. As soon as symptoms are relieved with up to 60 to 80 mg/day of prednisone or prednisolone, the dose is tapered to the smallest effective dose, 5 to 10 mg/day or 10 to 20 mg every other day.

Beclomethasone dipropionate (Vanceril) is a topically active, inhaled steroid (50 μg/puff, 8 to 20 puffs per day). When used properly it has no, or only minimal, systemic effects and is especially useful in steroid-dependent chronic asthmatics. It is most effective

when the patient is relatively free of asthma. The usual dose is two puffs four times a day. The patient continues to take all previous medications. If the patient improves after two weeks, steroids should be decreased slowly. If no improvement takes place, the dosage may be increased to four puffs four times a day and then decreased after two weeks of symptomatic improvement. Sixteen hundred micrograms or greater per day causes adrenal suppression. By proper administration of beclomethasone in many steroid-dependent asthmatics, the steroid dose can be significantly reduced and even discontinued. The main possible adverse effects of this agent are nasopharyngeal candidiasis and, in patients who have been on long-term systemic steroids, adrenocortical insufficiency as adrenal suppressive doses of corticosteroids are decreased. Oral candidiasis can be minimized by rinsing the oral cavity after each use with plain water; if candidiasis occurs, nystatin (Mycostatin) rinse three times a day will eradicate the infection.

Cromolyn Sodium

Cromolyn blocks the release of chemical mediators from the sensitized mast cells; it has no antihistamine, bronchodilator or anti-inflammatory characteristics and should not be used during an acute asthmatic attack. It has only prophylactic value. The main indication in the asthmatic appears to be as a steroid-sparing agent. It is most useful in young patients with extrinsic or exercise-induced asthma. The usual dose is 20 mg four times a day by a special inhaler.[2] If after four weeks of therapy, no improvement occurs, the drug should be discontinued. The adverse side effects include cough, throat irritation, skin rashes, occasionally bronchospasm, and eosinophilic pneumonia.

Parasympatholytic Agents

A parasympatholytic agent, such as ipratropium (SCH-1000/Atrovent, 40 μg/puff) may give bronchodilatation in asthma and chronic bronchitis. It is not available in the United States at the present time.

Combination of Drugs

A beta agonist such as terbutaline can be given with theophylline, and lower doses of the two together may be as effective or less toxic than higher doses of either drug alone. Oral bronchodilating agents are usually continued when patients receive corticosteroids or cromolyn sodium.

Indications of Severity of Bronchial Asthma

Significant reduction in FEV_1 (less than 1.0 liter) associated with one or more abnormalities such as marked scalene muscle contractions, mental confusion, pulse rate greater than 130/min, pulsus paradoxus greater than 10 mm Hg, marked overdistension of the lungs on chest x-ray, central cyanosis, arterial PCO_2 greater than 40 mm Hg, pneumothorax, or pneumomediastinum, indicate a severe attack of asthma.[3] If FEV_1 is less than 25% predicted, there is a tendency to CO_2 retention. Pulsus paradoxus of more than 10 torr is associated with FEV_1 less than 25% predicted; scalene muscle contractions and intercostal retractions suggest FEV_1 less than 1.0 liter.[4]

Patients with these abnormalities should be hospitalized immediately, and receive proper therapy (IV aminophylline, high doses of steroids, supportive and specific care).

Status asthmaticus is defined as a severe asthma attack unresponsive to inhaled or injected sympathomimetic amines. The cornerstone of management of status asthmaticus is the administration of IV aminophylline and large doses of corticosteroids. Supportive care and specific therapy for any complication should also be undertaken.

Indications for Intubation and Mechanical Ventilation in Asthma.

1. Arterial PCO_2 over 50 to 60 torr in the absence of chronic hypercapnea.
2. An arterial PO_2 under 60 torr on 6 liters of O_2 by nasal cannula.
3. Evidence of marked increase in the work of breathing judged by physical examination, even in the presence of near-normal arterial gas studies.
4. Respiratory arrest.

It should be emphasized that during the acute episode of an asthma attack, there is a lowering of arterial PO_2 and PCO_2. Perfectly normal PCO_2 such as 40 torr indicates fatigue of the patient and the necessity of aggressive therapy.

Treatment Failures

Patient compliance and understanding are important for the successful management of

asthma. Hidden environmental hazards should be eliminated. Not every wheezing represents bronchial asthma; left-sided heart failure, chronic obstructive pulmonary disease, pulmonary emboli, hypersensitivity pneumonitis, mediastinal node compression, foreign body in a large bronchus, or bronchial carcinoid can be responsible for diffuse wheezing masquerading as asthma. Finally, inadequate medication may be the cause of failure to improve. Readings of serum theophylline at the level obtained one hour after a dose has been given, and one hour before the next dose, are helpful indications of whether an adequate amount has been given. There is a tendency to underuse corticosteroids in severe acute respiratory failure. It is better to overuse the steroids for a short period than to have the patient suffer cardiac, respiratory or neurologic damage if complications arise.

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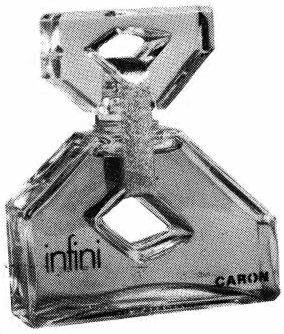

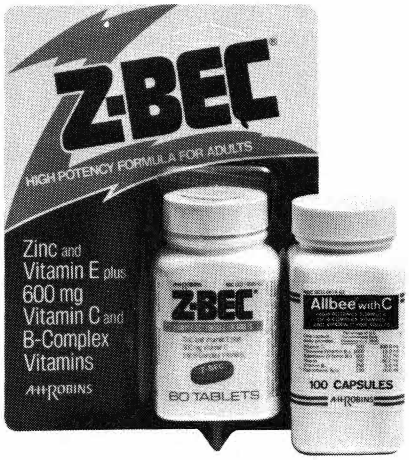

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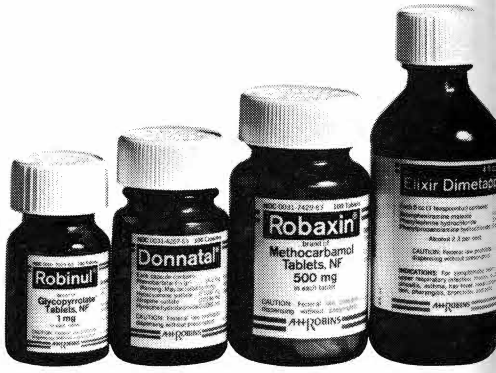

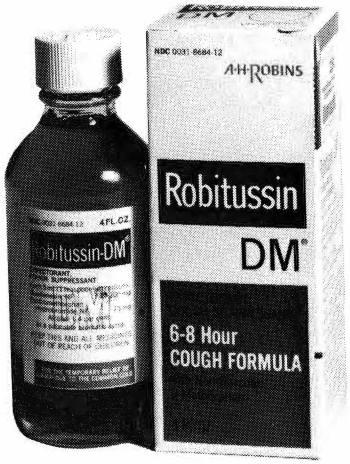

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Program for the Thirty-Second Annual Stoneburner Lecture Series

New Concepts in Outpatient Management of Chronic Obstructive Pulmonary Disease and Asthma

Presented by

the Pulmonary Division and the Department of Continuing Medical Education

Friday, April 6, 1979

Pathophysiologic Concepts in COPD
FREDERICK L. GLAUSER, M.D.

Pathophysiologic Concepts in Acute Bronchial Asthma
ROBERT A. FASOLI, M.D.

Mimickers of Asthma and COPD
GEORGE W. BURKE, III, M.D.

Overview of the Outpatient Management of COPD
JAMES P. BAKER, M.D.

Newer Treatment Modalities in COPD
JAMES A. MATHERS, JR., M.D.

Preoperative Evaluation of Patients with COPD and Asthma
PAUL FAIRMAN, M.D.

Saturday, April 7, 1979

Does Pulmonary Rehabilitation Really Work?
RAYMOND CASCIARI, M.D.

A Pulmonary Rehabilitation Program in a Community Hospital
RAYMOND CASCIARI, M.D.

Newer Drugs and Their Use in the Treatment of Asthma
ORHAN MUREN, M.D.

Home Oxygen Use in COPD: Do's and Don't's
JAMES P. BAKER, M.D.

The Role of Pulmonary Function Testing in the Outpatient Management of COPD in Asthma
FREDERICK L. GLAUSER, M.D.

INTRODUCTION

The 32nd Stoneburner Lecture Series, "New Concepts in the Outpatient Management of Chronic Obstructive Pulmonary Disease and Asthma," was presented on April 6 and 7, 1979, to an audience consisting principally of family practitioners and internists. The conference explored new concepts about COPD and asthma which have emerged from basic and clinical research during the last decade. In particular, practical management related to drug treatment, pulmonary rehabilitation, pulmonary function testing, pre- and postoperative care, and the use of oxygen were emphasized.

James P. Baker, M. D., Chairman, Department of Medicine, Eastern Virginia School of Medicine, and a former member of the Pulmonary Division at the Medical College of Virginia, was the Stoneburner Lecturer. He reviewed and updated the modern outpatient management of chronic obstructive pulmonary disease. Raymond Casciari, M.D., Director of the Rehabilitation Center, St. Joseph's Hospital, Anaheim, California, and Clinical Instructor of Medicine at the University of California, Irvine, talked about his experience in establishing a pulmonary rehabilitation program in a community hospital. In addition, Dr. Casciari stressed the physiological benefits derived from rehabilitation.

The Medical College of Virginia Pulmonary faculty and selected pulmonary fellows actively participated in the preparation of the lectures. The audience's response was excellent as evidenced by the many questions asked and the excellent post-program evaluation.

The Pulmonary Division would like to thank the Department of Continuing Medical Education for planning this symposium.

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THE THIRTY-SECOND ANNUAL STONEBURNER LECTURE SERIES

New Concepts in Outpatient Management of Chronic Obstructive Pulmonary Disease and Asthma

Presented by the Pulmonary Division and the Department of Continuing Medical Education

FREDERICK L. GLAUSER, M.D., *Guest Editor*