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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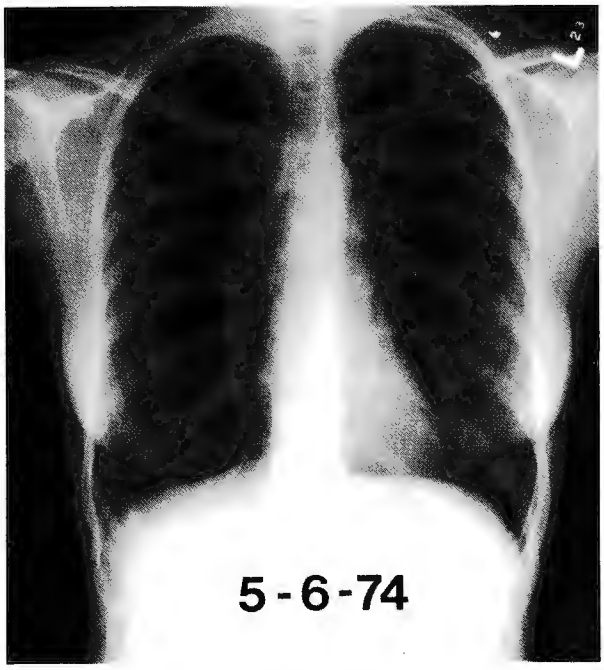

Fig 1—Posteroanterior chest roentgenogram of case 1 showing faint reticular densities in all lung fields and increased subcardiac air.

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-

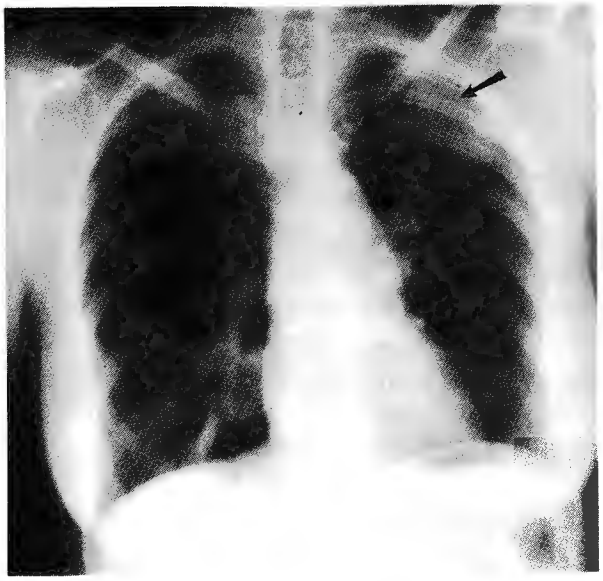

Fig 2—Posteroanterior chest roentgenogram of case 2 showing ill-defined "ground-glass" infiltrate (*arrow*) in left upper lung field.

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

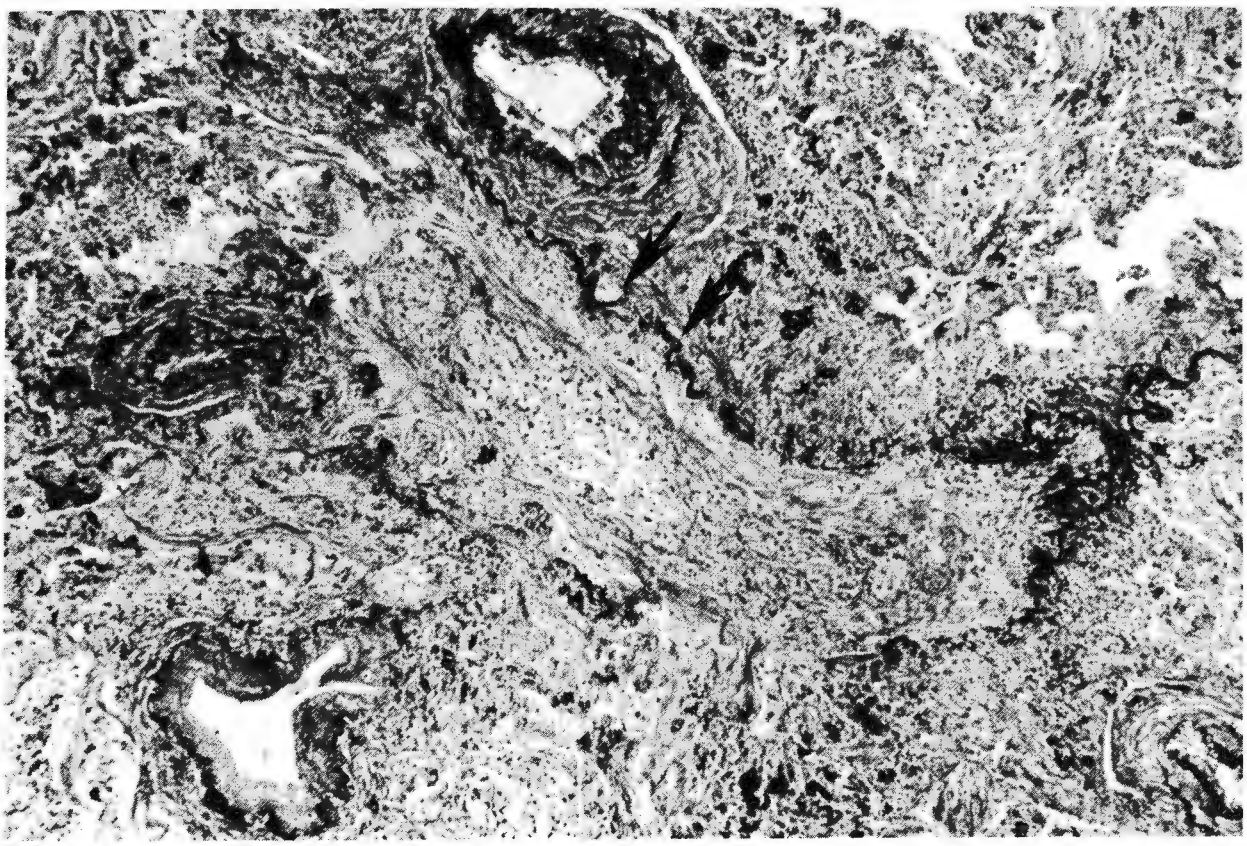

Fig 3—Histopathologic section of lung biopsy from case 3 showing remnants of bronchiolar wall elastin enmeshed in fibrous tissue. The findings are diagnostic of bronchiolitis obliterans (Van Giessen stain × 100).

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.

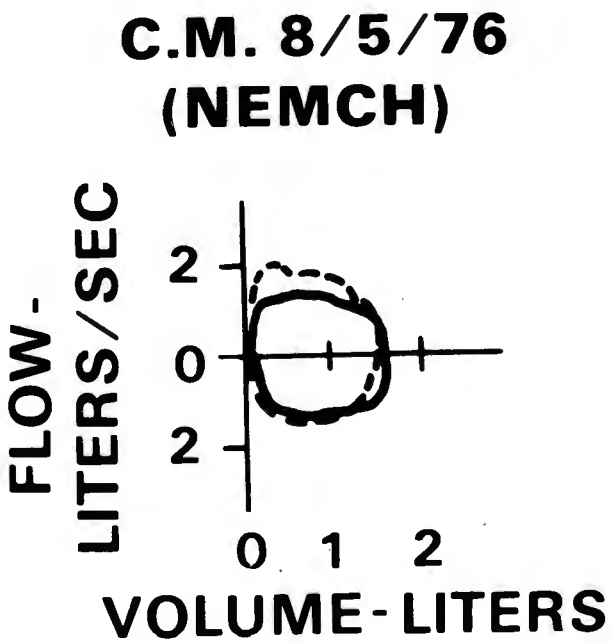

Fig 4—Flow-volume curve in case 4 showing flattening of both inspiratory (lower curve) and expiratory (upper curve) loops. The dotted line is a superimposed curve from the same patient while breathing 80% helium.

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 electroencephologram, 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.

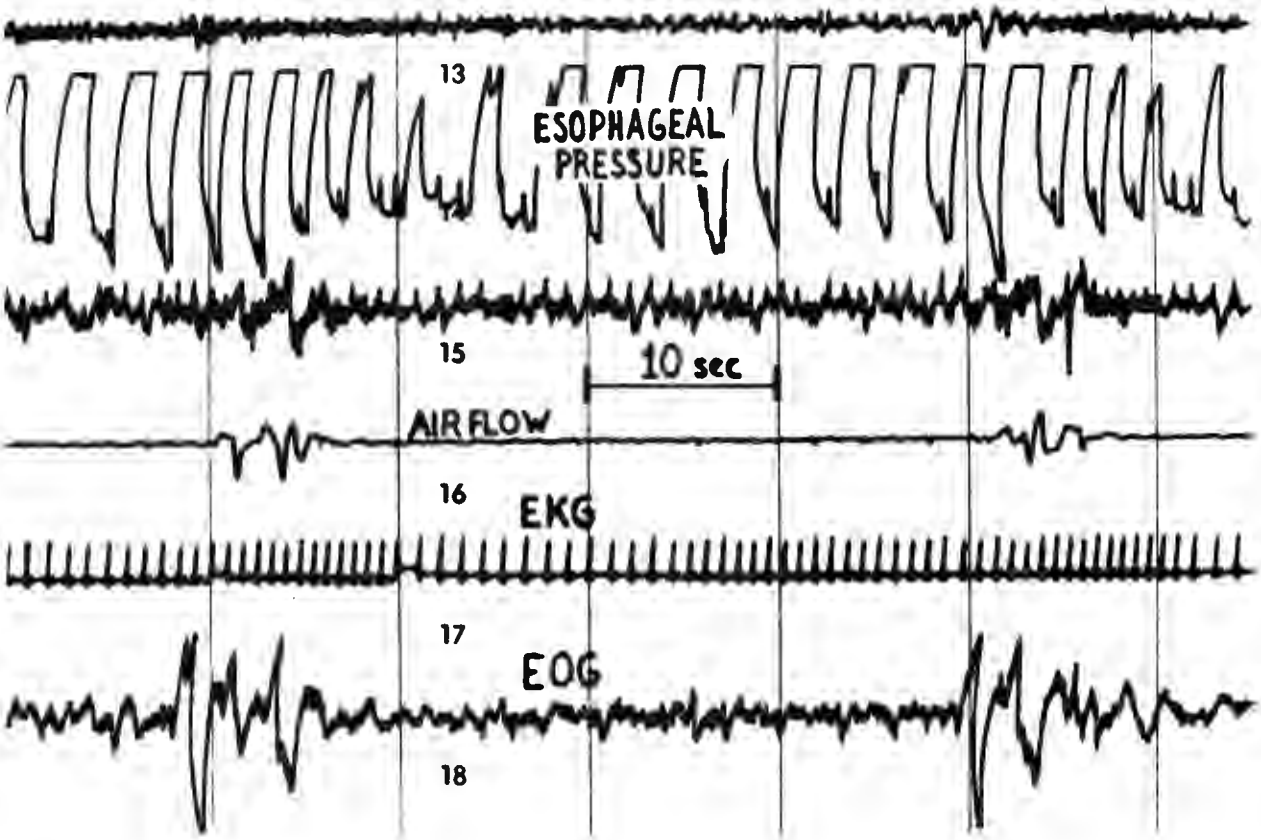

Fig 6—Sleep recording from case 5 showing continued inspiratory attempts (phasic esophageal pressure) during apneic spell as indicated by absence of mouth or nasal air flow. Unlabled channels are electroencephalograms. "EOG" is electrooculogram showing absence of rapid-eye-movements during this apneic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