Pathophysiology of Asthma and Chronic Obstructive Pulmonary Disease (COPD)

ROBERT A. FASOLI, M.D.

Pulmonary Division, Medical College of Virginia, Health Sciences Division of Virginia Commonwealth University, Richmond, Virginia

FREDERICK L. GLAUSER, M.D.

Associate Professor of Medicine and Chief, Pulmonary Division, Medical College of Virginia, Health Sciences Division of Virginia Commonwealth University, Richmond, Virginia

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-

Correspondence and reprint requests to Dr. Frederick L. Glauser, Box 93, Medical College of Virginia, Richmond, VA 23298.

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

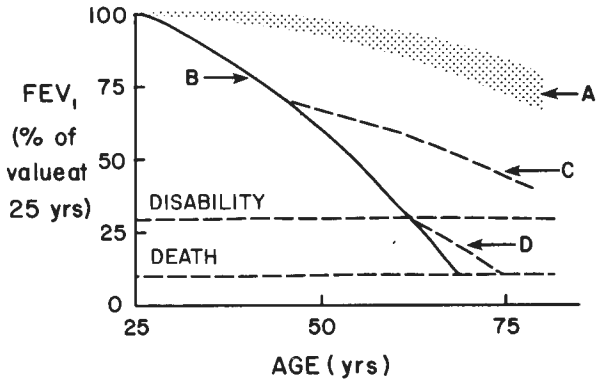
patients with COPD. Only a small percentage of patients will have "pure" emphysema or "pure" bronchitis.

"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).

REFERENCES

Asthma

1. BEALL GN, HEINER DC, TASHKIN DP, ET AL: Asthma: New ideas about an old disease. *Ann Int Med* 78:405–419, 1973.
2. AUSTEN, KF, ORANGE RP: Bronchial asthma. The possible role of the chemical mediators of immediate hypersensitivity in the pathogenesis of subacute chronic disease. *Am Rev Resp Dis* 112:423–436, 1975.
3. WEISS EB: Bronchial asthma. *Ciba Clinical Symposium 27*(1 and 2), 1975.

COPD

1. BURROWS B, EARLE RH: Course and prognosis of chronic obstructive lung disease. *N Engl J Med* 280:397, 1969.
2. HUGH-JONES P, WHIMSTER W: The etiology and management of disabling emphysema. *Am Rev Resp Dis* 117:343–378, 1978.
3. FLETCHER C, PETO R: The natural history of chronic airflow obstruction. *Brit Med J* 1:1645–1648, 1977.