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Bronchial Asthma

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Bronchial asthma, which affects an estimated 6 to 8 million Americans, is a clinical state of heightened reactivity of the tracheobronchial tree to numerous stimuli. Characteristically, episodes of dyspnea and wheezing which are symptomatic of airway obstruction are features of the disorder. In some patients, cough, with or without the production of tenacious sputum, may occur. These symptoms are the result of bronchospasm, bronchial wall edema, and hypersecretion by mucous glands. The asthmatic episodes may be continuous or paroxysmal, and may result in an impairment of respiratory function ranging from a modest degree of disability to life-threatening asphyxiation —status asthmaticus. However, *asthma is reversible,* either spontaneously or through treatment. With a proper therapeutic program, most patients can be helped.

Principal Forms of Bronchial Asthma

Clinically, patients with bronchial asthma have one of several forms of the disease. The most frequently used classification is based largely on known etiologic factors but also considers clinical variations. Although such a combined etiologic-clinical classification is not entirely satisfactory, it has the advantage of aiding the clinician in selecting appropriate therapy for the management of patients.

Extrinsic bronchial asthma, also called *allergic asthma,* usually affects children and young adults. It is characterized by paroxysms of bronchospasm with wheezing, dyspnea, and other symptoms of respiratory distress following exposure to causative allergens (Plate 1). These episodes are of sudden onset and brief duration. During the periods between such acute attacks the patient may be relatively symptom free. Patients with allergic bronchial asthma may have a history of other allergic manifestations such as hay fever or eczema (*atopy*) and usually also have a family history of such atopy. The allergic features of this type of asthma will be discussed in detail subsequently (page 20). At this point, it is sufficient to emphasize that the acute attacks of allergic asthma are often related to exposure to specific allergens and that dermal reactivity to such allergens is frequently significant. Immunoglobulin E (IgE) plays a role (page 24).

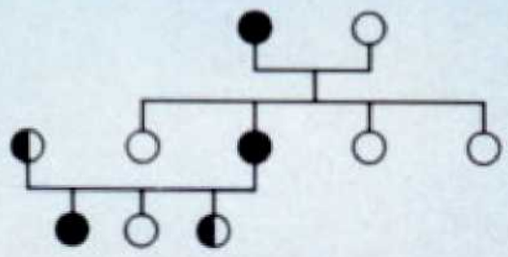
The medical therapy of allergic bronchial asthma generally produces a favorable response and the long-term prognosis is good. However, recurrences in adult life may be observed in a number of patients.

Intrinsic asthma usually develops in adults after the age of 35. Because allergic factors do not play an apparent role in etiology, and because infection is a causative factor in many patients, this heterogeneous form of bronchial

Extrinsic Allergic Asthma: Clinical Features

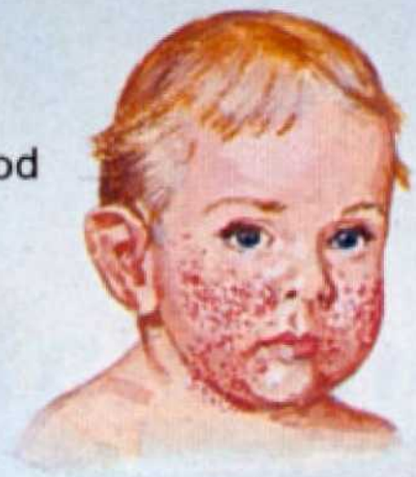
Young patient: child or teenager

Family history usually positive



History of eczema in childhood

"Allergic shiner" may be present

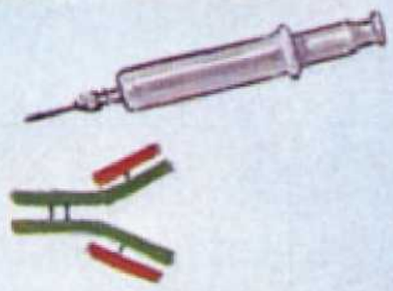


Attacks related to specific antigens

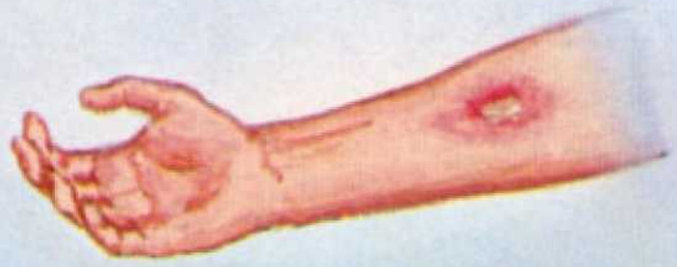
Pollens Foods Drugs Dusts Danders

Favorable response to hyposensitization

IgE associated



Skin tests are usually positive



Attacks are acute but usually self-limiting; prognosis favorable; condition is often outgrown but may become chronic; death rare

Features common to

Respiratory distress

Dyspnea, wheezing

Flushing, cyanosis

Cough

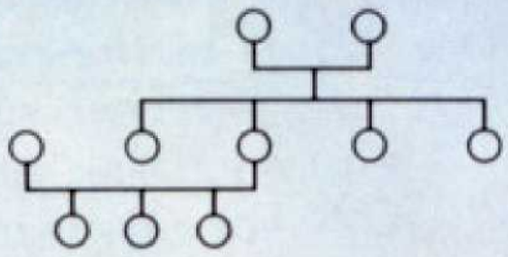
Flaring of alae

Use of accessory respiratory muscles

Intrinsic Asthma: Clinical Features

Adult patient: age 35 or over

Family history usually negative



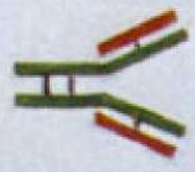
Attacks related to infections, exercise, etc.

Skin tests are usually negative

No history of eczema in childhood

Unfavorable response to hyposensitization

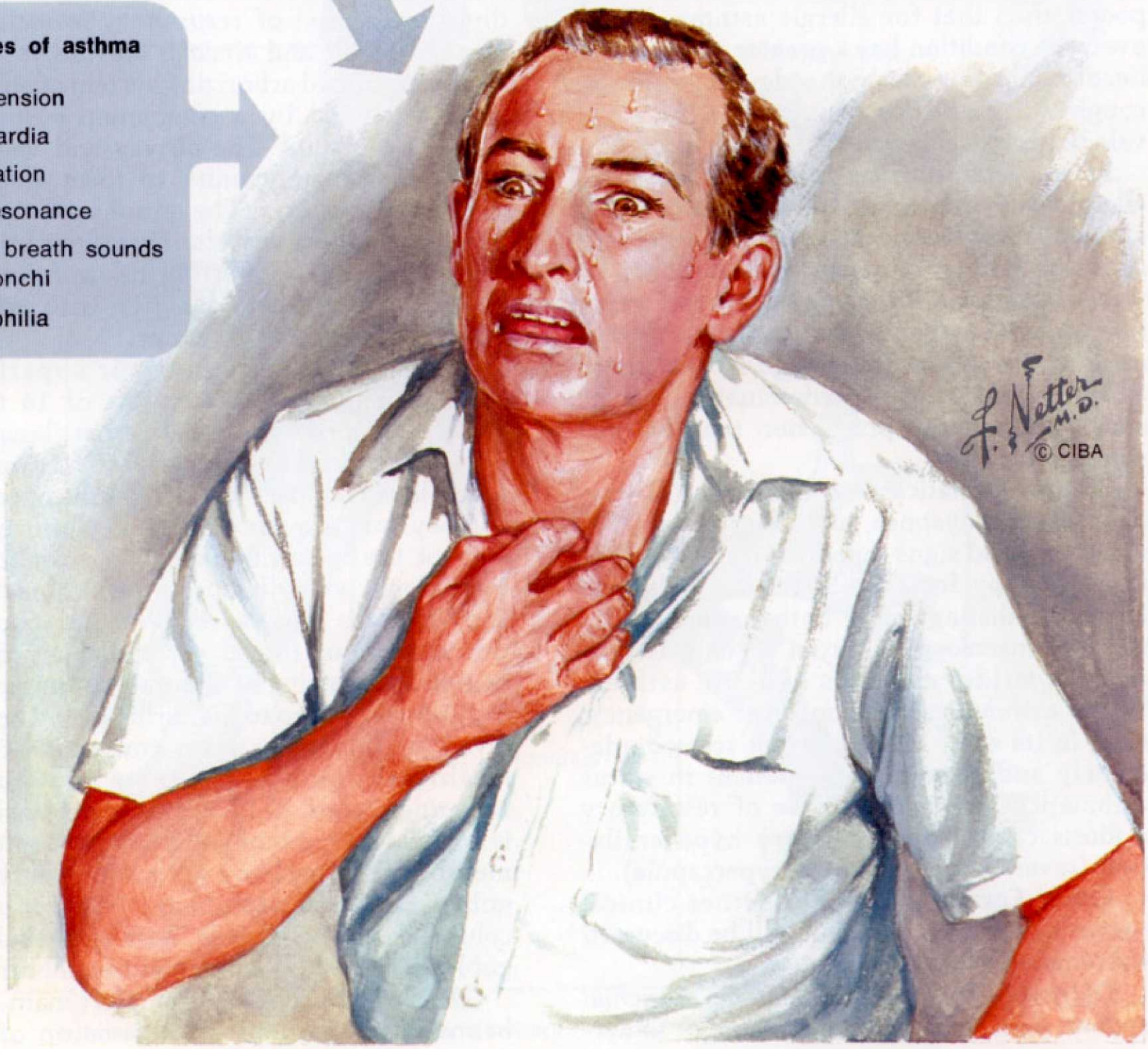
IgE not associated



Attacks are more fulminant and severe; prognosis poorer; condition may become chronic; death may occur

both types of asthma

- Apprehension
- Tachycardia
- Perspiration
- Hyperresonance
- Distant breath sounds and rhonchi
- Eosinophilia



asthma is also called *idiopathic* or *infective* asthma (Plate 2). Occasionally, however, there is a history of atopy (*i.e.*, various allergic manifestations).

Generally, the episodes of intrinsic asthma are indistinguishable from those of allergic asthma, although sputum production and cough may be more severe in patients with infective asthma. In other words, unless a complete and accurate history is available, the clinician usually will not be able to differentiate between infective and allergic asthma if the patient is first seen during an acute episode. Obviously, factors such as the patient's age and the simultaneous presence of infection in the sinuses or bronchial tree will suggest infective asthma, but once the acute episode has subsided, allergic asthma must be excluded in all patients by history and appropriate testing.

Therapy for intrinsic asthma is not always curative, and the prognosis is generally poorer than that for allergic asthma. Moreover, the condition has a greater tendency to become chronic with the development of cough and production of sputum in the intervals between acute attacks.

Mixed asthma refers to a combination of allergic and infective asthma. In this type, allergic factors are significant, but acute episodes of asthma are frequently initiated by viral or bacterial infections of the respiratory tree. In some patients, the features of mixed asthma may gradually change so that those of the infective type predominate. Chronic cough and sputum production then become significant.

Status asthmaticus is a severe clinical state of wheezing, dyspnea, and other respiratory symptoms and signs that are refractory to the usual therapy for acute asthmatic episodes. It can be distinguished both pathologically and pharmacologically from chronic asthma and the milder episodes of acute asthma. Status asthmaticus is a medical emergency, even in its early phases. If not treated adequately and promptly, the patient in status asthmaticus may die because of respiratory acidosis caused by pulmonary hypoventilation (severe hypoxemia and hypercapnia).

Other Forms of Asthma. Other clinical variants of asthma exist but will be discussed subsequently (page 39).

Diagnosis and management of bronchial asthma must be based on a thorough understanding of the complex pathophysiology of this condition. Such an understanding must begin with an appreciation of the normal structure of the tracheobronchial tree and lungs, as well as a knowledge of the physiologic responses of the respiratory system to external and internal stimuli. In addition, because certain tissue responses which initiate the chain of events in asthma are largely antigenically determined, a review of immunology is also necessary.

Anatomy

The tracheobronchial tree, serving as a conduit for the passage of air to and from the alveolar-capillary complexes, consists of the trachea and the right and left main bronchi and their subdivisions (Plate 3). Each bronchus forms, by a series of up to 23 or 24 dichotomous divisions, the *lobar*, *segmental*, *subsegmental*, and *smaller-order bronchi* and, ultimately, the *bronchioles*. The terminal subdivisions consist of *respiratory bronchioles*, *alveolar ducts*, and *alveolar air sacs*.

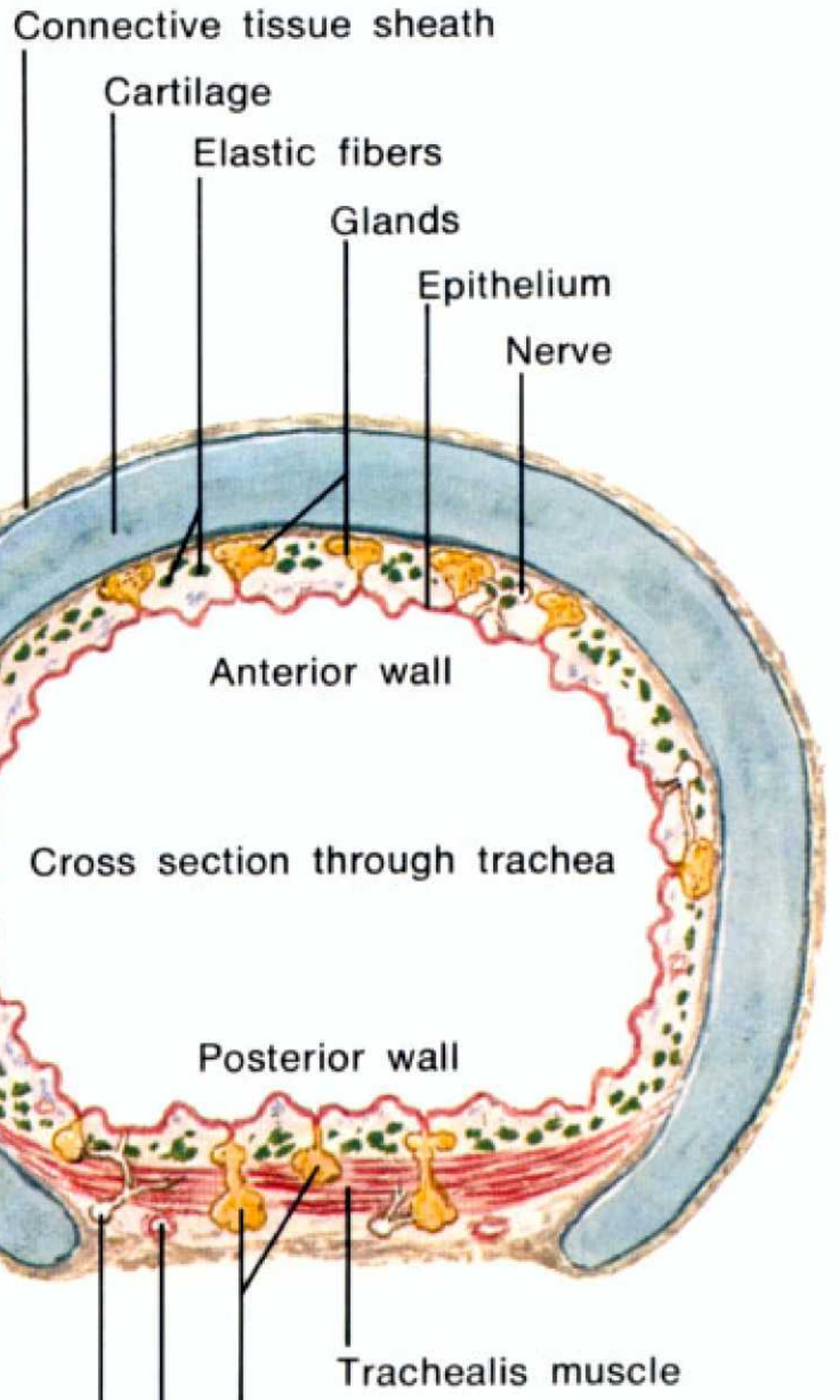
The described arborizing system of airways is accompanied by a companion system of vascular conduits. The airway and vascular systems ultimately unite to form *alveolar-capillary complexes*. The entire system of air passages, blood vessels, alveolar-capillary complexes, and supporting tissue forms the lungs, whose primary function is to provide an interface for gas exchange.

The Trachea. The outer or superficial portion of the trachea consists of 16 to 20 crescent-shaped, highly elastic, cartilaginous, partial rings. These rings help form the anterolateral aspect of the trachea, ensure patency, and provide rigidity. Posteriorly, the ends of the crescent-shaped rings are joined by an elastic, smooth muscle membrane called the *trachealis muscle*. Active contraction of this muscle, or forced expiration or cough, causes a narrowing of the tracheal lumen.

Internal or deep to the cartilage and muscle layers of the trachea is a connective tissue meshwork containing nerves and mucus-secreting glands. This connective tissue layer is covered on the luminal aspect by a mucous membrane consisting of mucus-secreting goblet cells and pseudostratified, ciliated, columnar, epithelial cells. Both epithelial and goblet cells rest on a basement membrane.

The Bronchi. The right and left main stem bronchi are formed by a division of the

Structure of the Trachea and Major Bronchi



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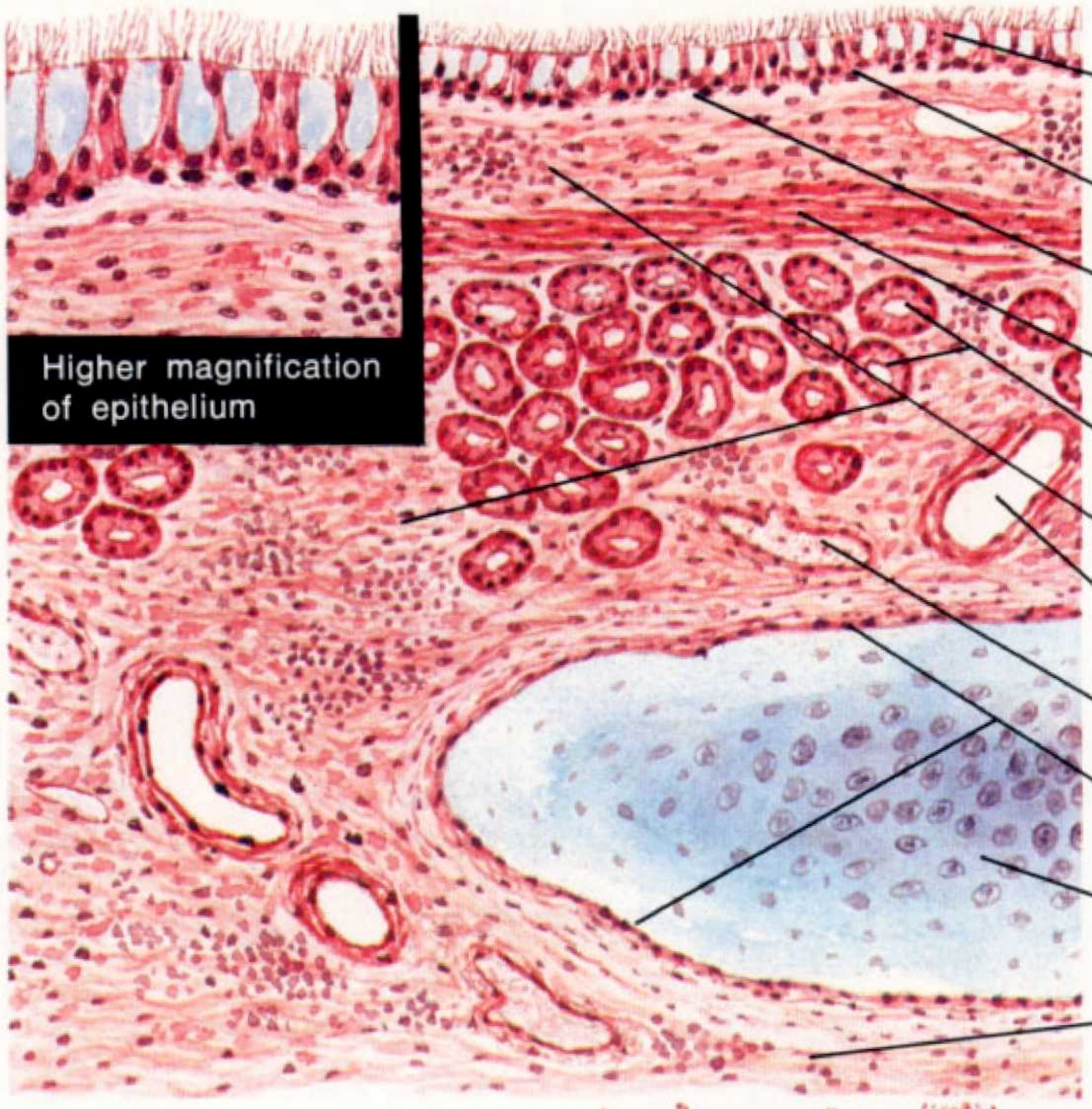
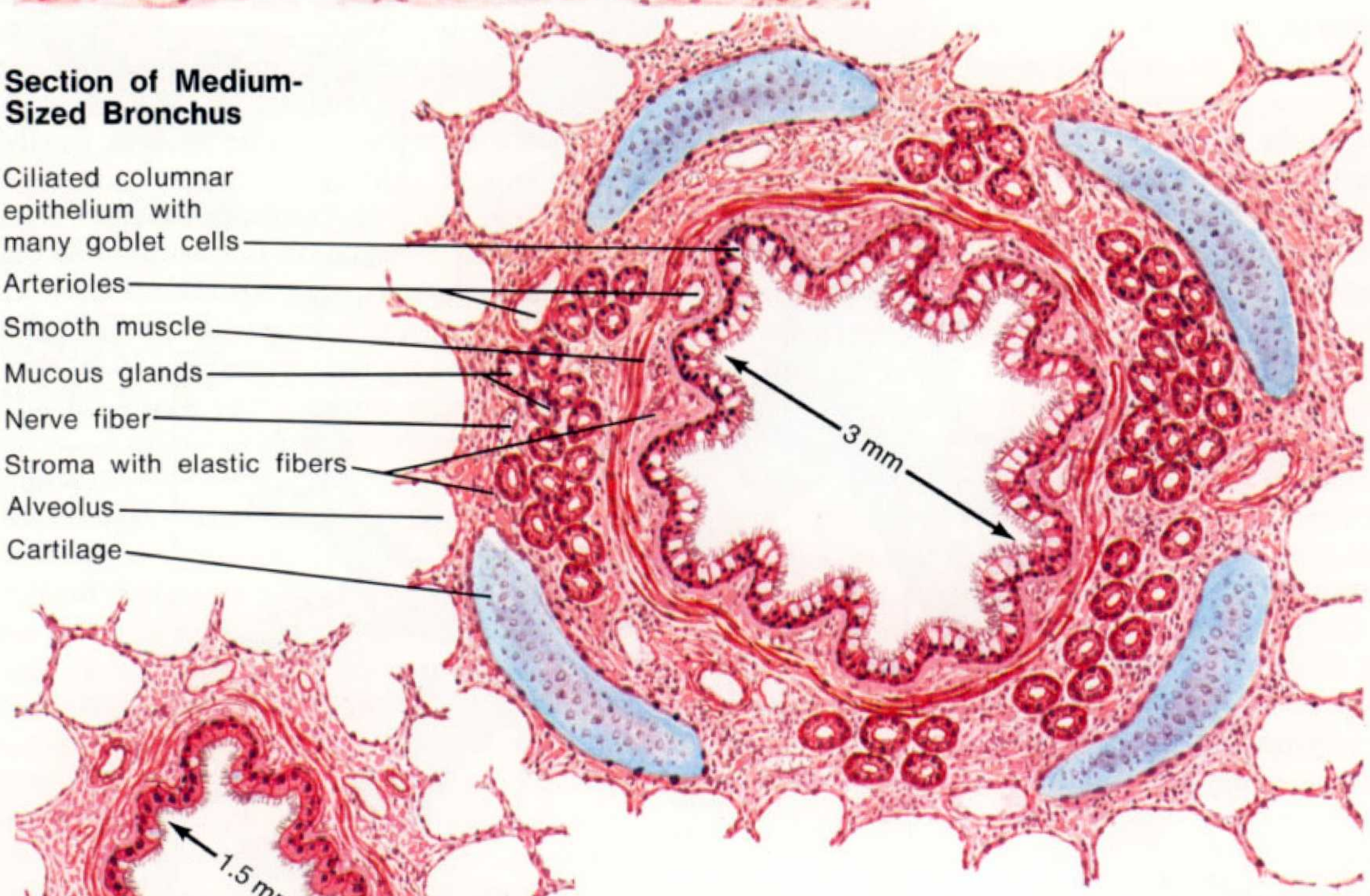
Section of Large Bronchus



Section of Medium-Sized Bronchus



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Section of Bronchiole

Ciliated, cuboidal epithelium with a few goblet cells; smooth muscle ring with nerve fibers and blood vessels; stroma contains many elastic fibers. Cartilage plates and glands absent

trachea. They divide into second-generation *lobar bronchi* (0.7 cm average diameter) which correspond to each of the lobes of the lungs (Plate 3). With the next division, the *segmental bronchi* (0.5 cm average diameter) are formed. The fourth-generation and the last bronchi to be named are the *subsegmental bronchi* (medium sized or fourth order), from which fifth- to tenth-order small bronchi arise (decreasing in diameter from 0.4 to 0.1 cm).

As in the trachea, cartilage and smooth muscle bands partially encircle the larger bronchi. In the larger airways, the horseshoe-shaped cartilage helps maintain patency. As the bronchi subdivide, however, the cartilage is first in the form of irregular plates and then, in the smaller airways, in the form of minute rods. At the level of the bronchioles, cartilage is absent (Plate 4).

Internal to the cartilaginous layer of each bronchus is a network of elastic collagenous, reticular, and smooth muscle fibers. Nutrient capillaries, lymphatics, and nerves are interwoven throughout this connective tissue and muscle layer which also contains mucous glands, blood elements (including lymphocytes and polymorphonuclear leukocytes), and many tissue mast cells with histamine granules.

As in the trachea, the inner surface of the bronchial tree is lined with an epithelium that rests on a basement membrane. This epithelium is composed of ciliated columnar cells and goblet cells. The goblet cells are more numerous in the main bronchi than in the trachea, but they decrease in number in the smaller bronchi.

The bronchioles (eleventh order and beyond; 0.15 to 0.1 cm in diameter) have walls composed, in part, of elastic tissue running longitudinally and an overlying layer of smooth muscle bundles (Plate 5). The larger bronchioles bifurcate into *terminal bronchioles* (0.05 cm in diameter) which in turn divide into *respiratory bronchioles* (0.025 cm in diameter) which give rise to *alveolar ducts*. The terminal bronchioles are the last of the conducting airways. Beyond them the airways are membranous and are also involved in gas exchange.

There is a progressive modification of structure throughout the tracheobronchial tree, not only of cartilage, which is entirely absent in the bronchioles, but also of other tissue elements. The epithelium of the tracheobronchial tree gradually decreases in height, until in the bronchioles it is cuboidal (low simple columnar). In the bronchi, the epithelial cells are ciliated but become nonciliated in the respiratory bronchioles. Peripherally, goblet cells and mucous glands become sparser, following the pattern of distribution of cartilage. A thin continuous film of mucus secreted by the goblet cells and mucous glands lies on the surface of the ciliated cells (page 17).

Smooth muscle constitutes an important structural component of the tracheobronchial tree. In the trachea and major bronchi, the smooth muscle lies posteriorly between the ends of the horseshoe-shaped rings of cartilage. In the small bronchi and bronchioles (beyond the fifth order), it is arranged in a double helical or spiral pattern and is increased in mass relative to the size of the lumen. The muscle forms an interlacing network and extends to the respiratory bronchioles as small spiral strands. Even in the alveolar ducts, isolated muscle fibers may be found (Plate 5).

The stroma of the bronchioles also contains an abundance of elastic fibers which are continuous with those of the adjacent lung alveoli. Because of this network of elastic tissue, the bronchioles are largely supported by the inflated, elastic alveoli in which they are imbedded (Plate 5).

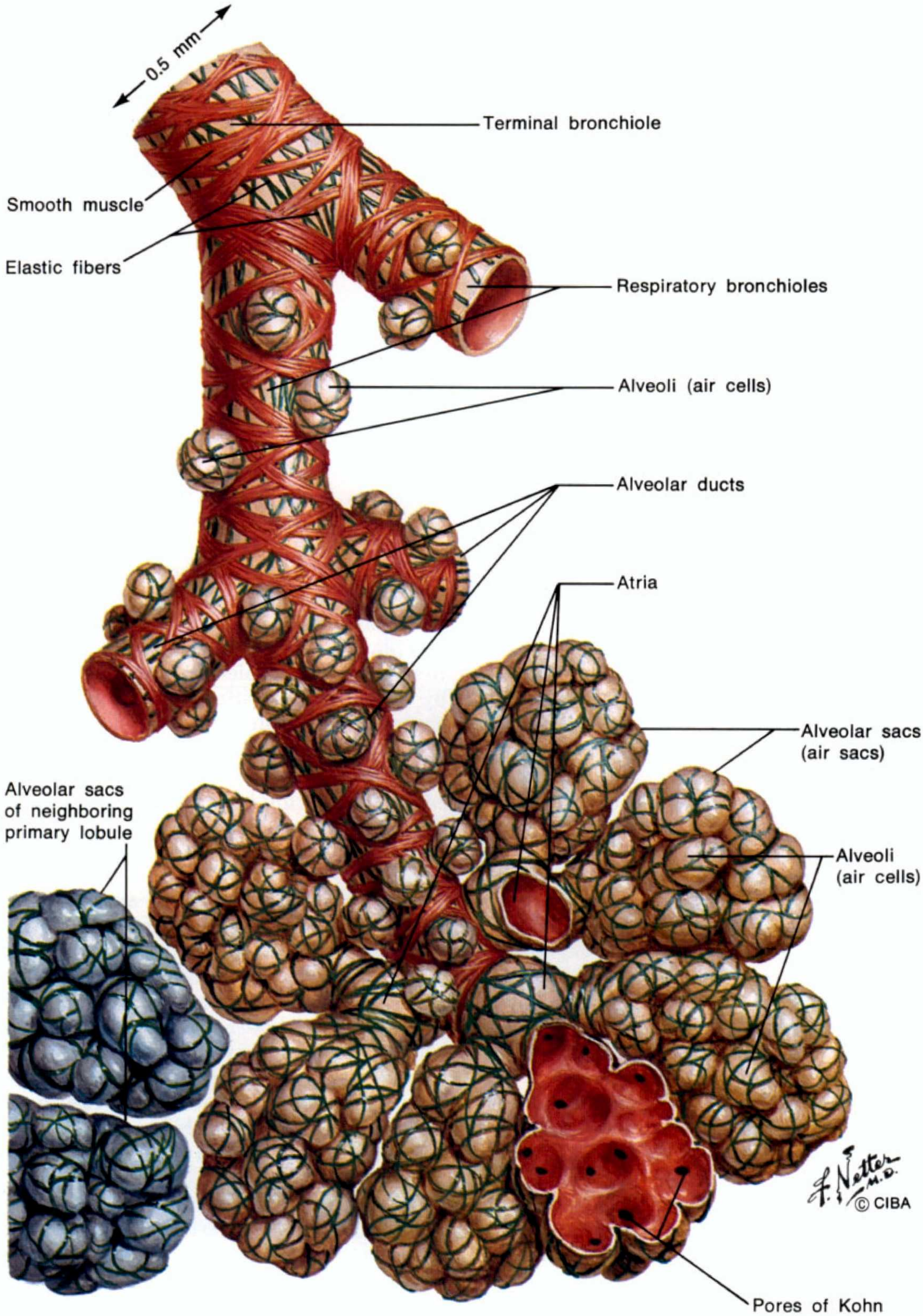
The Alveolar Ducts and Alveoli. The alveolar ducts, which are the extensions of the *respiratory bronchioles*, may have several branches. In the thin walls of these ducts are interlacing, helical bands of smooth muscle (Plate 5).

The alveoli are arranged as clusters of thin-walled outpocketings from the alveolar ducts. In addition, small outpocketings from the thin-walled respiratory bronchioles also occur; these structures are also alveoli which are identical to those arising from the alveolar ducts. In man, approximately 300×10^6 alveoli comprise between 55 and 60% of total lung volume. Each outpocketing or alveolus is sometimes called an *air cell*, and a cluster of air cells may be known as an *alveolar sac*.

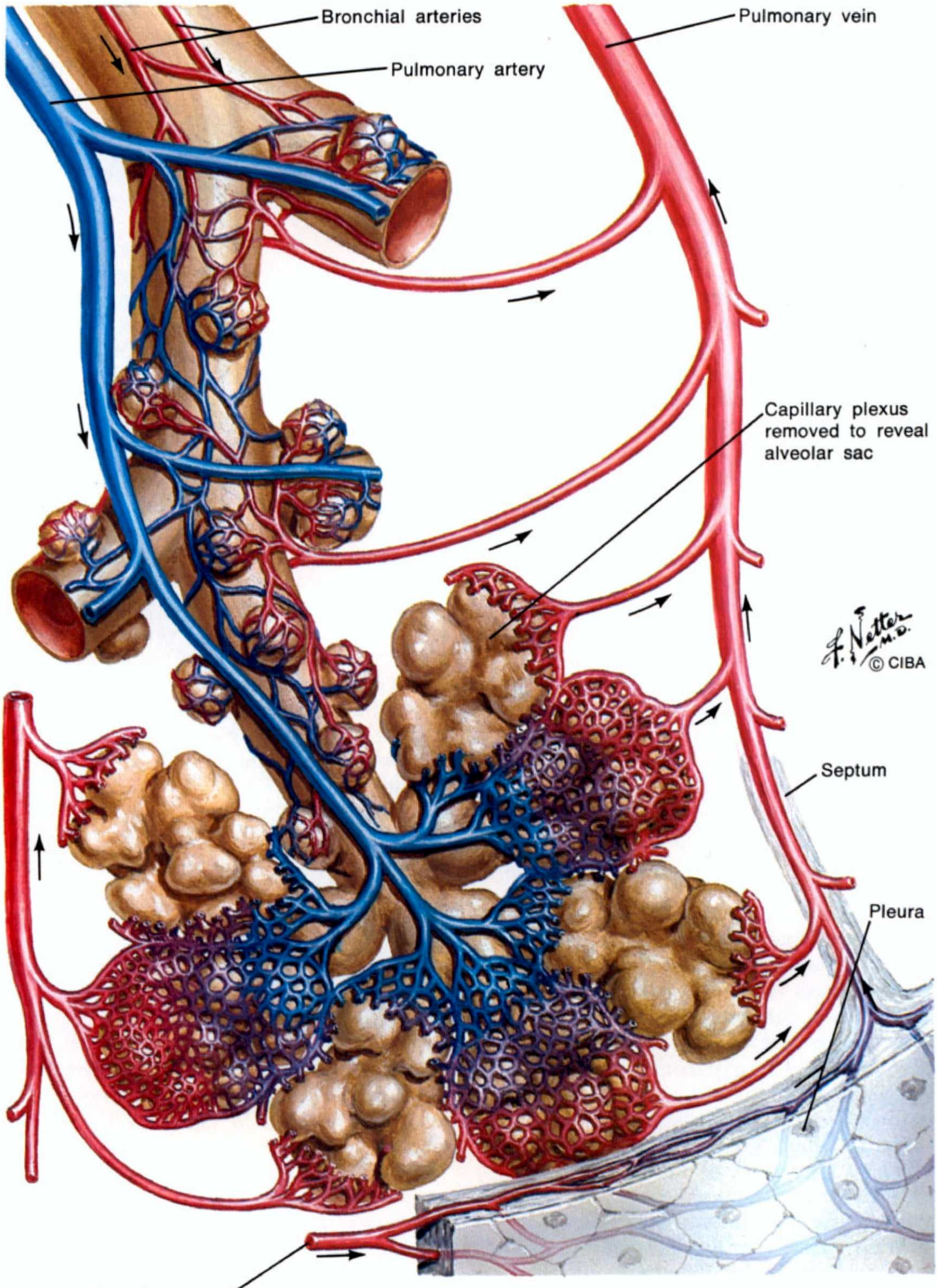
The alveolar wall, or *alveolar-capillary membrane*, is the interface for transfer of gases between the air and the blood. In the adult, the estimated alveolar surface area is 80 m^2 and the pulmonary capillary surface is

Plate 5

Structure of Terminal Air Spaces



Intrapulmonary Blood Circulation



of similar size. Also, the surface of the alveolar wall is a site for biosynthesis and secretion of surfactant material (a phospholipid bound to protein) and is involved with phagocytosis (page 19).

The structure of the thin (0.2 to 2.5 μ thickness) alveolar-capillary membrane favors passive transfer of gas. The epithelial lining of the alveolus and the endothelial lining of the capillary are in close proximity, with a thin interstitial matrix of supporting elastic, reticular, and collagenous fibers separating the two cell layers.

The fibers of the interstitial matrix permit stretch, prevent overexpansion, and contribute to the elastic recoil properties of the lung. Thus the alveolar diameter normally remains between 200 and 300 μ. Within the alveolar walls, small interalveolar openings, the *pores of Kohn*, are thought to permit air drift between adjacent alveoli.

Pulmonary Lobules. Within the lung there are *primary lobules* or *acini*. Each acinus represents the unit of lung structure served by a single terminal bronchiole, and each terminal bronchiole usually gives rise to about three orders of respiratory bronchioles before the alveolar ducts are formed. Thus, in Plate 5 only a portion of a primary lobule is shown.

The *secondary lobule* (of Miller) is composed of between five and 10 acini and is 1 to 2 cm in diameter. Such a pyramidal structure is surrounded by a thin fibrous septum. A portion of this septum is shown in Plate 6.

The Alveolar-Capillary Plexus. Accompanying the tracheobronchial tree are branches of the *pulmonary arteries* which carry deoxygenated blood from the right ventricle of the heart. Ultimately, each branch of the pulmonary artery that follows a respiratory bronchiole gives rise to a number of capillary plexuses. These plexuses surround the alveolar sacs (Plate 6), so that an effective interface between blood and air is formed. The blood leaving these alveolar-capillary plexuses is oxygenated and drains into a system of *pulmonary veins*; these veins enter the left atrium of the heart.

Bronchial Blood Vessels. The lung is also supplied by a network of *bronchial arteries* which contain oxygenated blood and which accompany the tracheobronchial tree. These are nutrient arteries to the airways as far as the terminal bronchioles. Blood draining from the capillary beds formed by the bronchial arteries may drain into the pulmonary system or into *bronchial veins*. (In Plate 6, the bronchial veins are not shown.)

Pathologic Changes in Asthma

In asthma, the normal airway undergoes a number of pathologic changes which are responsible for the airway obstruction and the resulting clinical picture of wheezing, dyspnea, and respiratory distress characteristic of asthma (page 3). These pathologic changes seem to occur because of the heightened reactivity of the airways to numerous stimuli. In general, the pathologic responses apparently are the same regardless of the type of stimulus. Therefore, the general kinds of stimuli which can cause asthmatic episodes will be described before the gross and microscopic findings are presented.

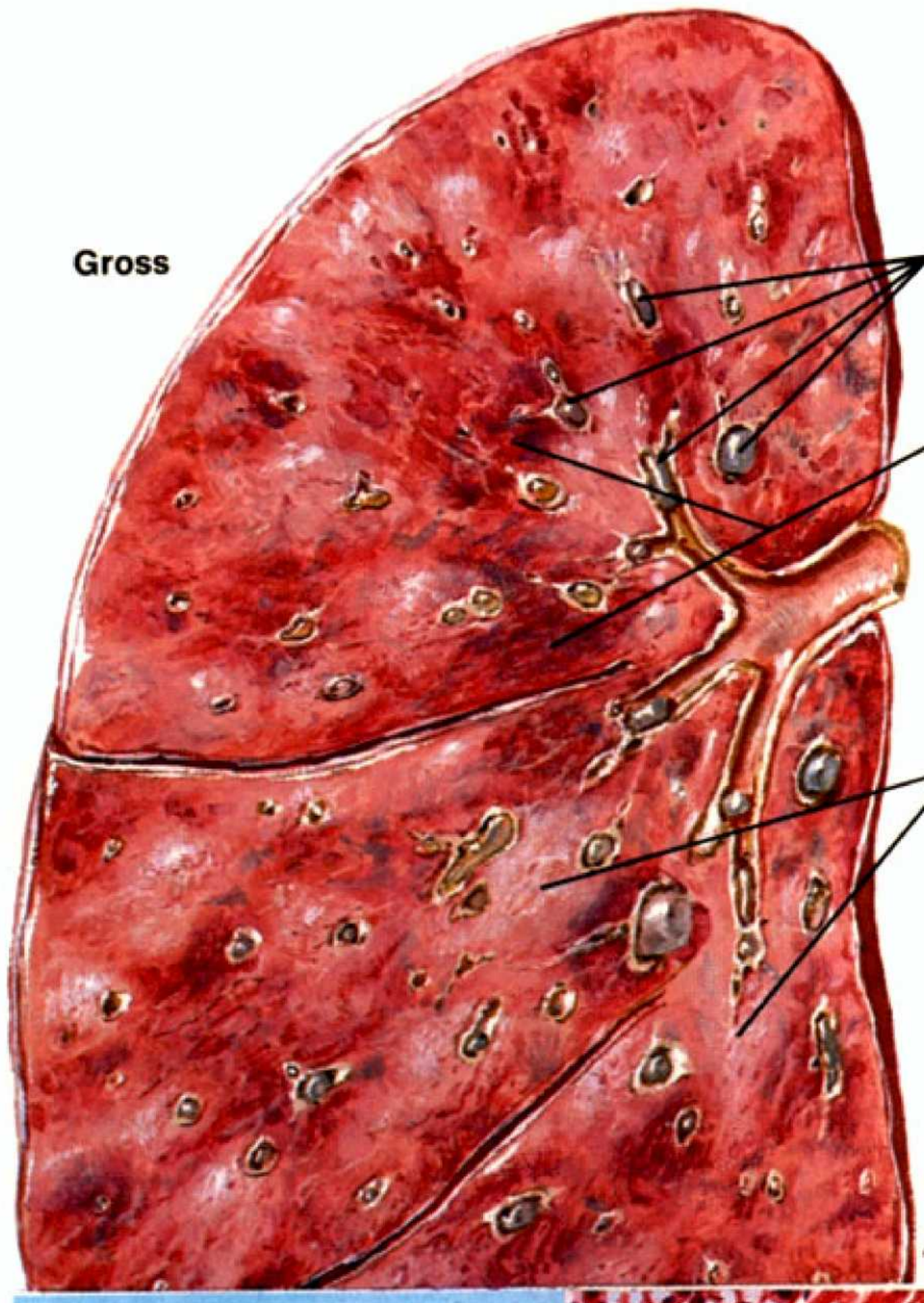
Allergic Stimuli. In patients with allergic asthma, the acute asthmatic episodes may be precipitated by inhaled or ingested *allergens*. Airborne allergens such as house dusts, feathers, animal danders, material used in furniture stuffing, fungal spores, and a variety of plant pollens are the types of substances that may be inhaled and may provoke an asthmatic episode. Foods likely to be allergenic are cow's milk, fish, eggs, various nuts, chocolate, shellfish, and tomatoes. However, as a cause of allergy, foods are less culpable than inhaled allergens. In some patients, an additive or even synergistic effect may exist between various allergens. (The nature of the allergic response will be discussed subsequently, page 20.)

Toxic and Irritative Stimuli. Many substances in the inhaled air may evoke or aggravate an asthmatic attack. Obvious examples are air pollutants including automobile exhaust, industrial fumes, and volatile substances such as paint or gasoline. Aspirates from regurgitated stomach contents in patients with hiatal hernia and inhaled anesthetic agents are less obvious examples of toxic and irritative stimuli. Other inhalants such as tobacco smoke and house dusts may act through a combined irritative-allergic mechanism.

Infection. Although infection (viral, bacterial, or fungal) is often the precipitating stimulus in infective asthma, it can also be a significant factor in allergic asthma. Thus, a bacterial sinusitis or common cold may trigger an asthmatic episode, or infection may

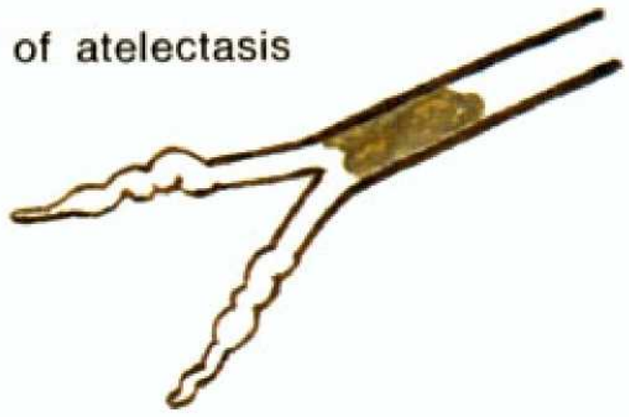
Pathology of Status Asthmaticus

Gross

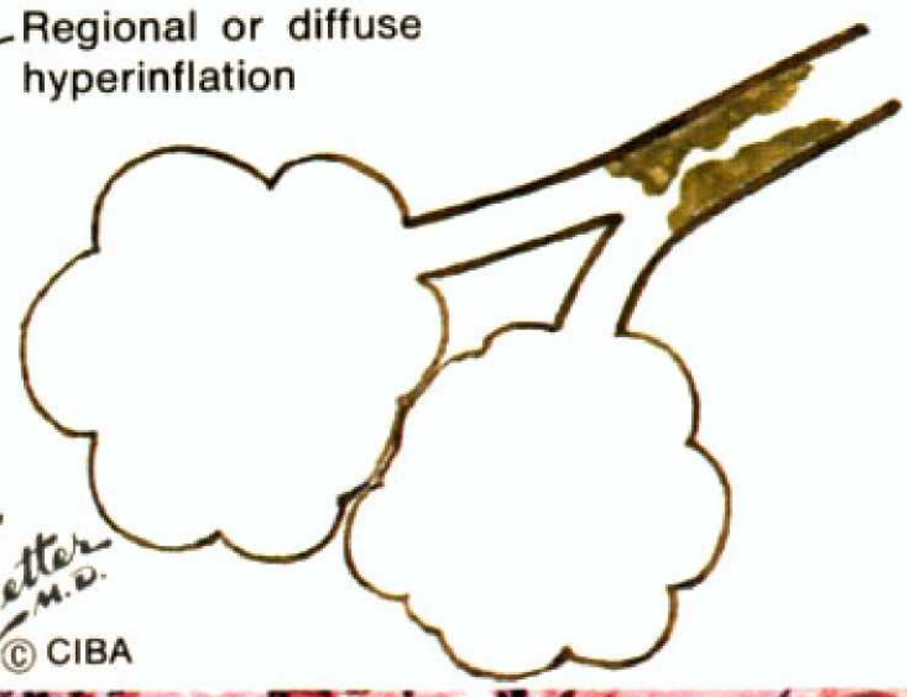


Tenacious, viscid mucous plugs in airways

Foci of atelectasis



Regional or diffuse hyperinflation



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Microscopic

Mucous plug

- PAS-positive matrix
- Polymorphonuclear neutrophils
- Eosinophils
- Charcot-Leyden crystals
- Curschmann's spirals
- Cluster of epithelial cells (creola body)
- Bacteria and/or viruses

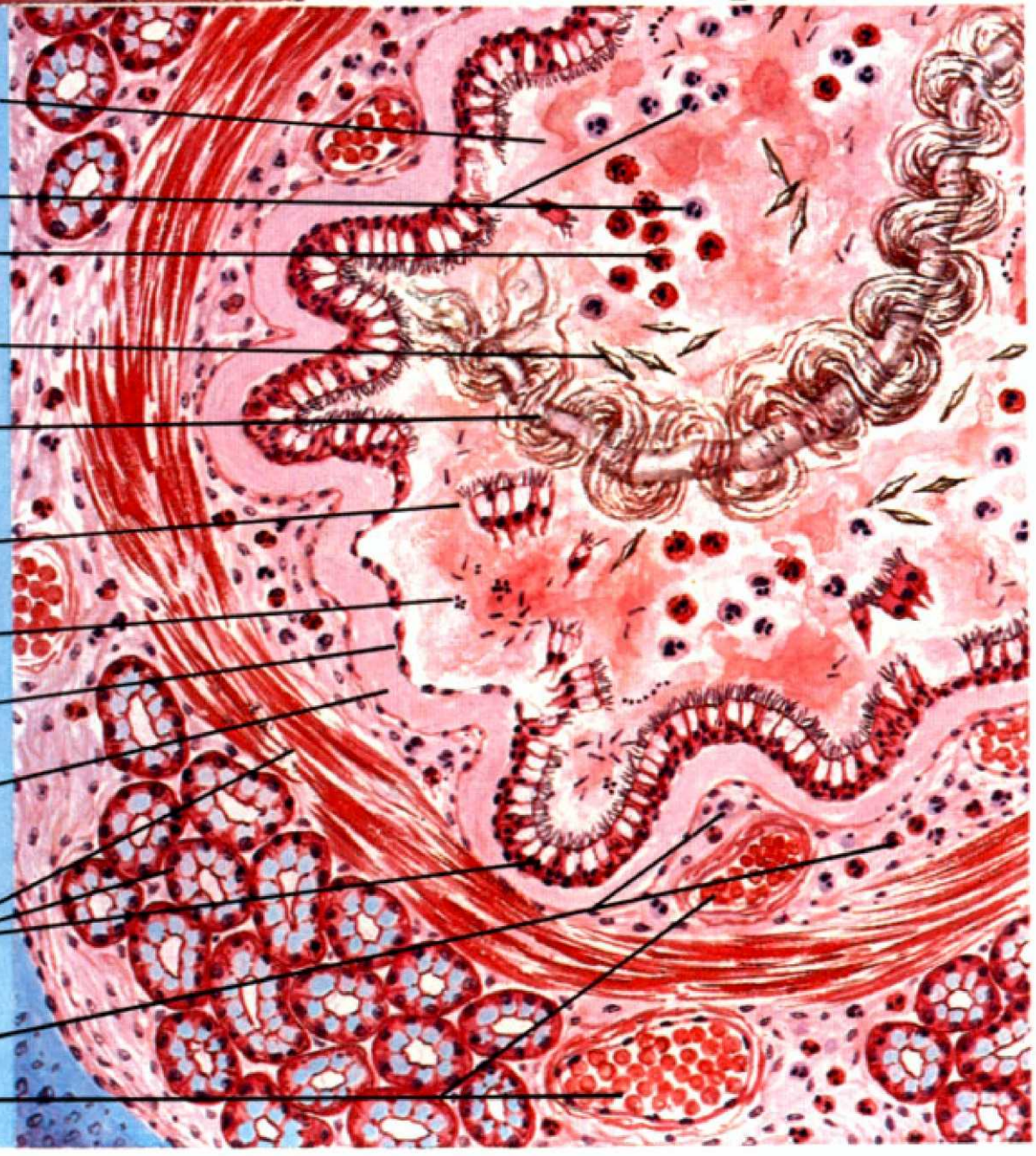
Epithelial denudation

Hyaline thickening of basement membrane

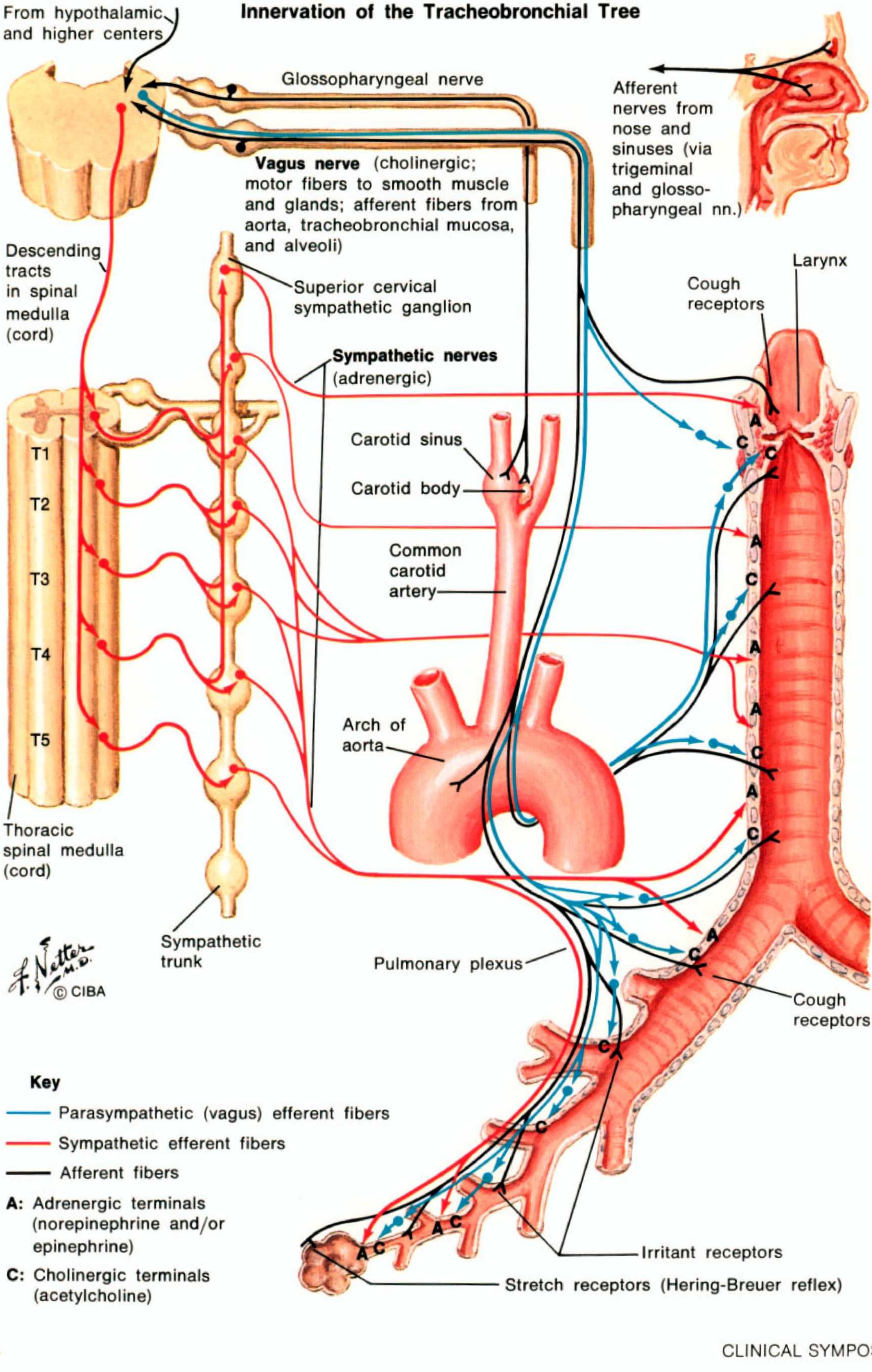
Hypertrophy of smooth muscle, mucous glands, and goblet cells

Inflammatory exudate with eosinophils and edema

Engorged blood vessels



Innervation of the Tracheobronchial Tree



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Key

- Parasympathetic (vagus) efferent fibers
- Sympathetic efferent fibers
- Afferent fibers

A: Adrenergic terminals (norepinephrine and/or epinephrine)

C: Cholinergic terminals (acetylcholine)

complicate an attack that began on a purely allergic basis.

Medications. Drugs may initiate acute asthma either by pharmacologic action (such as β-adrenergic blockade) or by evoking an allergic response as with penicillin and vaccines. In patients with aspirin sensitivity, symptoms may occur within 20 minutes after ingestion. (A triad of clinical findings commonly found consists of nasal polyposis, asthma, and aspirin use.)

Contributing Factors. Psychologic and physical stress may contribute to the occurrence of an asthmatic episode in susceptible individuals. Similarly, trigger mechanisms such as breathing cold air, rapid changes in temperature or humidity, physical exertion, or even laughing may cause an acute episode of bronchospasm and respiratory distress.

Gross and Microscopic Changes. The major pathologic features of bronchial asthma are limited largely to those observed in acute, severe asthmatic episodes *(status asthmaticus)*. However, it may be inferred that lesser degrees of the characteristic findings occur during milder attacks.

In status asthmaticus (Plate 7), the bronchi and bronchioles exhibit mucosal and submucosal edema, thickening of the basement membrane, a profuse leukocyte infiltration (particularly of eosinophils), intraluminal mucous plugs, and smooth muscle contraction (bronchospasm). Grossly, the lungs are overdistended, often with regional parenchymal zones of hyperinflation alternating with areas of atelectasis caused by thick, tenacious, intraluminal mucous plugs in bronchi and bronchioles.

Especially if dehydration is clinically evident, the mucous plugs are viscous and adhere to the bronchial wall, narrowing the lumen. Also, the reduction in luminal diameter is compounded by infolding of the epithelial surface of the bronchiole because of contraction of the hypertrophied smooth muscle. Thus, resistances to airflow are increased (Plate 17 on page 33).

The mucous plugs contain a PAS-positive matrix, polymorphonuclear neutrophils, eosinophils, and Charcot-Leyden crystals, which are degenerative crystalloids of eosinophils. Also characteristic are tiny whorls arising as casts within the smaller airways, the so-called Curschmann's spirals. Large areas of the epithelial surface may be denuded. These detached fragments may be seen in the lumen or sputum as clusters of ciliated cells (Creola bodies).

Mucous gland and goblet cell hypertrophy may be present, but is not as severe as that seen in patients with chronic bronchitis. The basement membrane is frequently thick and hyalinized. Partial atrophy of cartilage can occur. Tissue mast cells are sparse, but their histologic detection may be hindered by degranulation.

It should be emphasized that the alveolar destructive changes found in patients with pulmonary emphysema are generally absent. Furthermore, an asthmatic attack generally does not cause permanent pathologic changes.

The described, severe, pathologic changes of status asthmaticus and the lesser degrees of these changes which occur during acute asthmatic episodes of either allergic or infective asthma raise two important questions concerning the management of patients who have asthma. The first question is, *Why do these changes occur?* And the second is, *What effects do these changes have on respiratory function and blood gas physiology?* Fortunately, the second question, which is directly related to the management of the acute episode of asthma, can be answered with a high degree of certainty and will be discussed under the topic of pathophysiology (page 29). The first question concerns the etiology and pathogenesis of asthma and relates to both prevention and long-term management. The pathogenesis of asthma is complex and several hypotheses are attractive.

Before considering the various theories of the pathogenesis of asthma, it is necessary, *first*, to review the innervation of the tracheobronchial tree (because nerve reflexes appear to play a role in the occurrence of the acute asthmatic episode) and, *secondly*, to consider the normal responses of the tracheobronchial tree to inhaled allergens, pollutants, and irritants.

Innervation of the Tracheobronchial Tree

The tracheobronchial tree and lungs are innervated by the autonomic nervous system. Three types of pathways are involved: *autonomic afferent, parasympathetic efferent,* and *sympathetic efferent*. Each of these three types of fibers will be discussed in detail. In this discussion, however, the neurochemical

control of respiration will not be considered.

Autonomic Afferent Fibers. Afferent fibers from *stretch receptors* in the alveoli as well as fibers from *irritant receptors* in the bronchioles and bronchi travel via the pulmonary plexus to the vagus nerve (Plate 8). Similarly, fibers from other irritant receptors in the trachea and from *cough receptors* in the larynx reach the central nervous system via the vagus nerve. *Chemoreceptors* in the carotid and aortic bodies and *pressor receptors* in the carotid sinus and aortic arch also give rise to afferent autonomic fibers. The fibers from the carotid sinus and carotid body travel via the glossopharyngeal nerve, whereas those from the aortic body and the aortic arch travel via the vagus nerve. Other receptors in the nose and sinuses give rise to afferent fibers which form parts of the trigeminal and glossopharyngeal nerves.

Parasympathetic Efferent Fibers. All parasympathetic efferent fibers to the tracheobronchial tree are contained in the vagus nerve and pulmonary plexuses. These fibers carry motor impulses to the smooth muscle and glands of the tracheobronchial tree. The impulses are cholinergically mediated and produce bronchial smooth muscle contraction, glandular secretion, and vasodilatation (Plates 8 and 9).

Sympathetic Efferent Fibers. Postganglionic sympathetic fibers from the sympathetic trunk enter the thorax by passing directly from the thoracic ganglia. All these fibers are *adrenergic* and reach the lungs by the pulmonary plexuses (Plate 8). Sympathetic stimulation relaxes the bronchial smooth muscle, inhibits glandular secretion, and causes vasoconstriction (Plate 9).

As will be discussed in detail later (page 26), adrenergic receptor responses can be differentiated pharmacologically into α and β types.

Normal Responses of the Tracheobronchial Tree

The asthmatic individual and the nonasthmatic both breathe air of the same composition and quality. So-called clean air may contain as many as 3 million particles of foreign matter per cubic foot. As a result, pollens, dusts, animal danders, bacteria, viruses, fungi, and various pollutants are substances to which all people are exposed. A number of anatomic and physiologic responses defend against this continual barrage of foreign particles; in the nonasthmatic individual these responses usually do not impair pulmonary function but do ensure that the air which reaches the alveoli is warm, moist, and free of foreign matter.

Particle Size. Foreign particles in the air may be deposited at various sites throughout the air passages. The distribution and site of deposition is determined by a number of factors such as the size of the inhaled particle, the relative density of the particle, the volume and velocity of each breath, and the turbulences created in the airflow because of either branching of the passages or obstruction. In turn, the physiologic responses of the respiratory tract are influenced by the site of deposition.

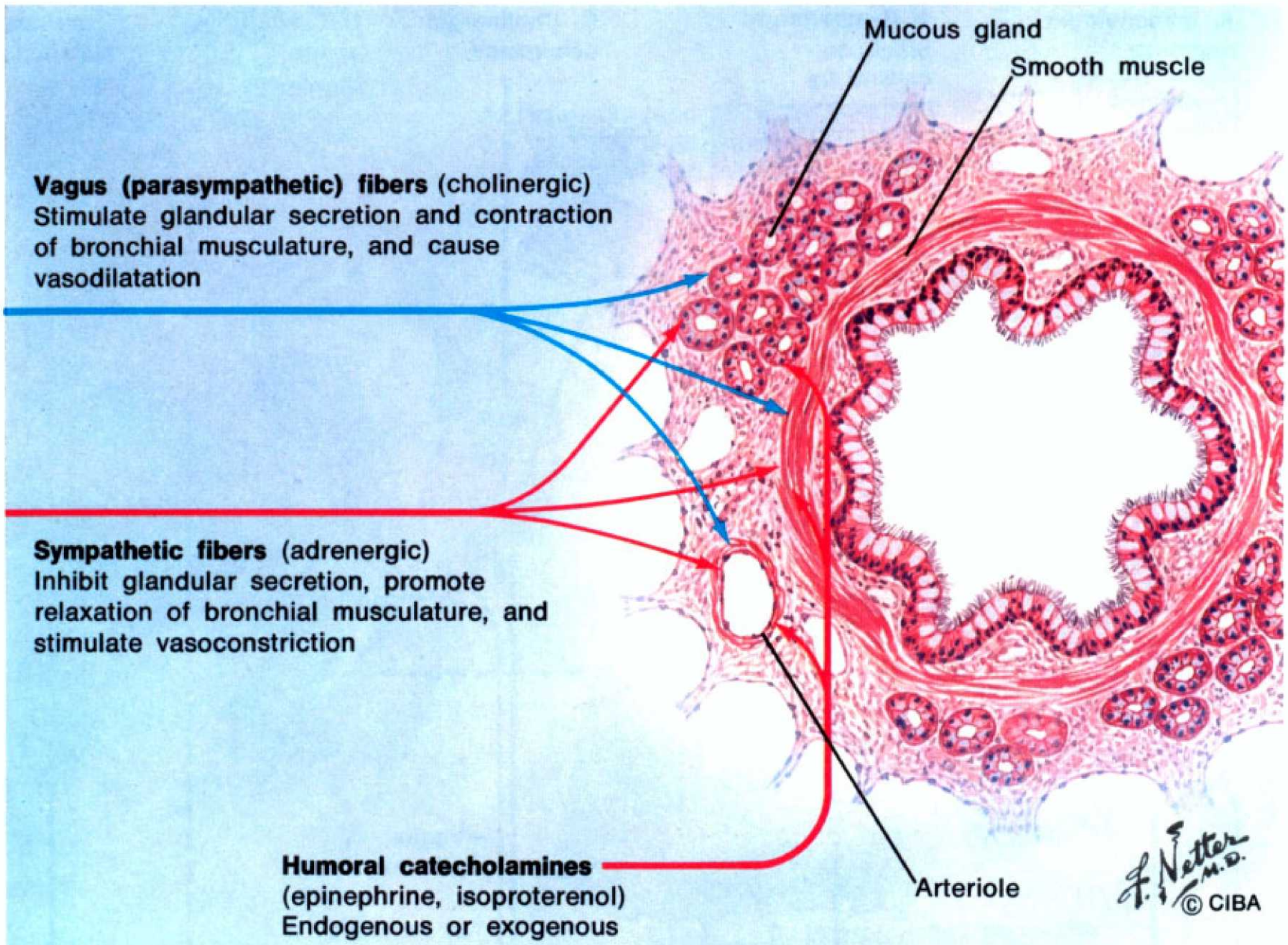
The deposition of particles may take place in one of two ways. If particles collide against the wall of the airway, usually at the bifurcations of the upper or first 12 generations of bronchi, they may impact by inertia (*inertial impaction*). On the other hand, in the lower or peripheral airways, particles tend to settle out by gravity (*gravitational sedimentation*). In the presence of airway obstruction, particles are more likely to be deposited in the upper (central) airways (page 34).

Particles greater than 10 μ, such as pollens or dust, are impacted in the nasal mucosa or upper pharynx; those between 0.3 and 2 μ reach the alveoli and may be expired or may impact there. Particles between 2 and 10 μ will be deposited at various sites in the bronchi or bronchioles. Water droplets in the inspired air, including therapeutic aerosols, and particulate matter contained within water droplets may similarly be deposited.

Protective Function of the Nose. The nose and nasopharynx function to protect the tracheobronchial tree and alveoli by *mechanically* filtering out larger particles and by adjusting the temperature and humidity of the inspired air. Because of the large mucosal surface area of the nose, pharynx, and upper trachea and the rich blood supply to these mucosal surfaces, temperature and humidity are adjusted to physiologic levels even under extreme environmental conditions.

The mouth and pharynx can also perform the described air-conditioning functions. However, the tracheobronchial tree, whose blood supply is relatively much less than that of the mouth, nose, and pharynx, is unable

Neurohumoral Control of Bronchial Musculature, Glands, and Vessels



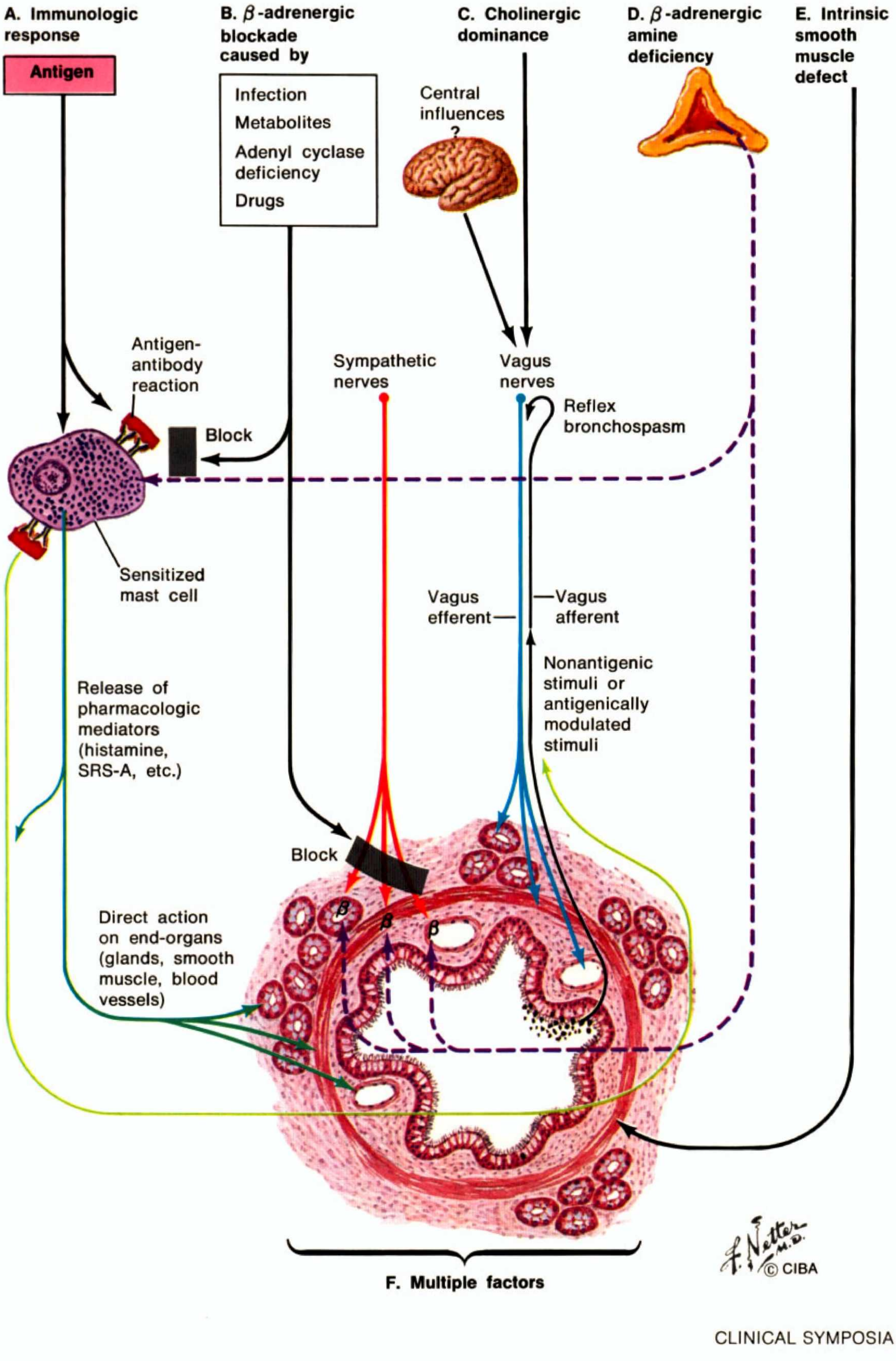
to make more than minor adjustments to temperature and humidity. This anatomic difference has practical, clinical significance. Patients breathing through an endotracheal tube or through a tracheostomy opening so that the nose, mouth, and pharynx are bypassed should receive warm, moist air or oxygen to prevent damage and drying of the mucosa of the tracheobronchial tree.

Cleansing Mechanism of the Tracheobronchial Tree. Foreign particles which settle from inspired air within the tracheobronchial tree become trapped in a thin blanket of mucus. This sticky, mucous layer, secreted by the surface goblet cells of the epithelium and by the submucosal glands, is a two-layered gel/sol film. The superficial gel layer traps particles and even dissolved gases. The cilia of the columnar epithelium project into the deeper sol layer of mucus and both support the mucous layer and propel it to the subglottic space. From here the mucus is expelled by coughing. This *physical* cleansing function of the mucous layer is aided by *local detoxification* involving proteolytic enzymes, antibodies (immunoglobulins), bacteriostatic or virucidal substances (*e.g.*, lysozymes, properdin, interferon, lactoferrin), and *cell defenses* such as polymorphonuclear leukocytes and macrophages. (For a description of the protective mechanisms in the alveoli see page 19.)

The exact chemical composition and physical properties of the mucus of the tracheobronchial tree are just beginning to be clarified. Mucus contains several types of high molecular weight *mucins*. Typically, mucin has a protein core and attached polysaccharide chains of sialic acid, with or without hexosamine and fucose. Such glycoprotein materials are able to bind large amounts of salt and water and thus can exist in a gel/sol phase. Differences in the viscosity of mucus may be partially a result of molecular coiling; thick mucus has tightly coiled molecules of mucin.

Plate 10

Postulated Mechanisms of Airway Hyperreactivity Causing Asthma



Many factors influence the production and characteristics of mucus. For instance, the activity of the mucous glands is stimulated by cholinergic action, as well as by pharmacologic mediators such as histamine. Thus, an increase in secretions may be caused by vagal stimulation as well as by chemical and mechanical irritants. Mucus will become more viscid if water is lost through evaporation, such as when air of low humidity is breathed. Also, if there is inflammation, transudation of fluid from the serum will influence the composition and action of mucus.

Cleansing of the Alveoli. Despite the mechanisms which remove most of the foreign matter from the inhaled air, some foreign particles, including bacteria, reach the respiratory bronchioles, alveolar ducts, and alveoli. As noted previously, particles between 0.3 and 2 μ in diameter can be deposited in the alveoli.

Particles deposited in the alveoli and nonciliated airways are cleared by macrophage phagocytosis and lymphatic drainage. Large mononuclear macrophages containing lysozymes and other enzymes surround and engulf the inhaled particles. These *alveolar macrophages*, displaying ameboid action, migrate to the terminal bronchioles and become imbedded in the mucous layer. They are then propelled by the cilia out of the tracheobronchial tree. Obviously, this process is slower than the ciliary mechanism of the upper airways.

Other defense mechanisms exist within the alveoli. Covering the alveolar cells is a thin layer of fluid that moves toward the bronchioles and the protective mucous blanket, possibly by surface tension. This layer helps cleanse the alveoli of particles. Some particles will remain within the alveoli and penetrate the alveolar walls to lodge in the interstitial tissue spaces. Here phagocytosis by tissue histiocytes may take place. However, other particles are never removed and may invoke either an inflammatory reaction such as pulmonary fibrosis or an allergic reaction such as allergic alveolitis.

Pathogenesis of Asthma

Various reasons have been postulated for the heightened airway reactivity which is characteristic of asthma. These theories generally consider the hyperreactivity to be an exaggeration of the normal defenses of the respiratory tract, *or* to result from abnormal tissue reactions in the bronchioles (which may be immunologically induced), *or* to represent an imbalance of the normally balanced responses.

Because of the diversity of stimuli known to produce asthma, no single current theory satisfactorily explains all types and cases. In all probability, the clinical picture of bronchospasm, dyspnea, wheezing, and respiratory distress, currently known as asthma, may be, in terms of etiology, several diseases. In Plate 10 several possible mechanisms of airway hyperreactivity are summarized. However, it is important to realize that the various mechanisms are interrelated even though in individual patients one mechanism may be dominant.

Action of the Bronchial Smooth Muscle

Normally, the physiologic tone of the smooth muscle of the bronchial airway is balanced by vagal (cholinergic) and sympathetic (β-adrenergic) influences. Vagal stimulation causes smooth muscle contraction and airway constriction, whereas sympathetic nerve stimulation or circulating catecholamines produce the opposite effects. In man, the role of α-adrenergic receptor stimulation in influencing bronchial smooth muscle tone currently remains unresolved.

Bronchial smooth muscle plays a primary role in the narrowing of the airways which is a *normal* reaction to foreign stimuli. (It should be noted, though, that airway diameter is also influenced by intra- and peribronchial pressures.) Because of the narrowing of the airway, the volume of air inspired and expired with each respiratory cycle (the tidal volume, page 29) is decreased. At the same time, the total surface area of the mucous membrane has not changed. As a result, the ratio of surface area of mucous membrane to volume of air inspired is probably increased. Thus, this normal reflex bronchial constriction is apparently a mechanism designed to protect the alveoli from harmful stimuli. In the asthmatic individual, however, the bronchial constriction is abnormally severe and produces impairment of respiratory function.

In the central, larger airways, the rigid cartilaginous rings act to moderate the constrictive forces of the smooth muscle; in small bronchi and bronchioles, the cartilage has

been replaced by membranous tissues, and the smooth muscle is arranged as double helical or spiral bundles (Plate 5 and page 9). Contraction of the smooth muscle causes narrowing and shortening of the airway, particularly in the small bronchi and bronchioles. Even the small, spiral strands of muscle in the respiratory bronchioles and the isolated fibers in the alveolar ducts appear to react to various stimuli. The *site* of the asthmatic reaction can therefore vary depending upon the anatomic location of the airway smooth muscle which is stimulated.

Bronchial constriction is partly an autonomic reflex. The *afferent* fibers of the arc arise from receptors in the tracheobronchial tree and travel to the central nervous system via the vagus nerve; at times, afferent fibers from the nose and sinuses may also be involved. The *efferent* motor fibers of the reflex arc return to the lung, also via the vagus nerve, to terminate on the bronchial smooth muscle.

Initiation of the reflex may begin with stimulation of irritant receptors by foreign particles, gases (such as sulphur dioxide, ether, and phosgene), pollens, or the chemical mediators of hypersensitivity reactions (page 24). Similarly, bronchial airway narrowing may be reflexly produced by strenuous exercise, paroxysms of cough, or inhalation of cold air. Airway caliber can also be altered by regional factors such as changes in oxygen or carbon dioxide tension which may occur with pulmonary embolus or asthma. In addition, it is probable that central nervous system activity, including stimuli arising in higher centers, can contribute to bronchomotor tone and may actually cause bronchial constriction.

Recently, the role of vagally mediated cholinergic influences in the causation of asthma has received renewed emphasis. According to the theory of *cholinergic dominance* (Plate 10), in the asthmatic patient responses to various stimuli are exaggerated in comparison to normal. In other words, the asthmatic patient reacts more severely to lesser degrees of exposure to both antigenic and nonantigenic stimuli. In addition, cholinergically mediated reflexes may be interrelated with the release of mediators (page 29), or may be incited by, and thus aggravate, the tissue responses to antigen-antibody reactions (Plate 11 and page 24).

Pharmacologically, bronchial constriction produced by autonomic reflex pathways can be blocked by atropine. Other substances which influence bronchial smooth muscle tone include acetylcholine, epinephrine, histamine, prostaglandins, and slow reacting substances of anaphylaxis (SRS-A). The role of these chemical compounds in causation and treatment of the obstructive processes in asthma will be discussed on pages 24 and 25.

Immunology

The many stimuli which provoke asthmatic episodes may do so by eliciting immune sequences, by being directly toxic or irritative, or by a combination of mechanisms. Contributing factors, such as physical or psychologic stress, rapid changes in environmental temperature, or infection of the ears or sinuses may be operative as well. In addition, bronchial infection may also complicate immunologically induced asthma.

Despite the potentially vast number of substances in the environment capable of inciting an asthmatic reaction, those which are *antigenic* are more significant because they evoke the immune response. However, before discussing this immune response, it is necessary to define several concepts.

An antigen is any substance foreign to the host that is capable of activating an immune response by stimulating the development of a specific antibody. Most antigens are naturally occurring vegetable or animal materials. They are usually proteins of medium molecular weight—3000 to 40,000. However, carbohydrates, lipids, cells, or particulate matter may also be antigenic.

Any protein molecule, because of its particular chemical-spatial configuration, may exert multiple, distinct antigenicity. Factors such as size, shape, chemical composition, ionization, and reactive sites influence such antigenicity and determine if it is also specific.

The ragweed pollen responsible for seasonal ragweed hay fever is a prototype antigen. This pollen, which is 20 to 60 μ in diameter, consists of an inner core of soluble proteins and an outer lipid-polysaccharide coating. If ragweed pollen is deposited on the respiratory mucosa, lysozymes from the mucosa digest the outer coating, releasing water-soluble proteins. These proteins or pollen fragments are thought to be antigenic with specific sensitizing properties. Additionally, other antigens may be small enough to

reach the lower airways where they would exert specific antigenicity.

A hapten is a specific, protein-free substance which can form a complex with a carrier protein. The hapten is not antigenic but when coupled with the carrier protein it may elicit the immune response. Penicillin is an example of a hapten.

An allergen is an antigen which can elicit allergic symptoms. Obviously, for any particular individual, every antigen is not necessarily an allergen. The reason why an atopic individual (one who has a hereditary predisposition to be allergic) reacts to one antigen and not to another is unknown. Moreover, the reaction of an atopic individual to a particular antigen may vary from time to time, depending on a number of factors. In other words, for any individual patient, allergen sensitivity, like the clinical course of asthma, is variable and unpredictable. Thus, in the clinical evaluation of any patient, the interaction of immunologic factors, infection, nonsensitizing irritants, and physical and emotional stress must be considered.

Nonspecific and Specific Defense Mechanisms. The immunologic mechanisms which result in an asthmatic episode are triggered when a patient is exposed to foreign substances. The body attempts to protect or rid itself of these offending materials by a number of mechanisms including cellular and humoral defenses. Several of these defense mechanisms are immunologically nonspecific and have been described previously (page 16). For convenience, they are summarized here:

1. *Physical barriers:* nasal turbinates and mucous membrane, the mucociliary blanket of the tracheobronchial tree, and the sneeze and cough mechanisms;
2. *Phagocytic cells:* leukocytes, histiocytes, and alveolar macrophages;
3. *Chemical substances:* lysozymes, proteolytic enzymes, and lactoferrin.

In addition, general factors such as satisfactory nutritional state and adequate degree of hydration assist the defense mechanisms of the body. Extremes of age, however, are often associated with lowered resistance of the body to foreign substances.

Complementing the immunologically nonspecific mechanisms are specific mechanisms involving mucosally secreted immunoglobulins. Secretory immunoglobulin A (IgA) is produced by the plasma cells of the bronchial submucosa. A glycoprotein (transport piece), produced in the bronchial epithelial cells, transports the IgA from the submucosa to the mucosal surface. Here IgA acts as the major antibody to foreign antigens trapped in the secretions of the tracheobronchial tree.

The Basic Immune Sequence. Generally, these defense activities of the tracheobronchial tree are successful. Occasionally though,

Table I

IMMUNE REACTIONS
(Primarily Pulmonary)

Type of Immune Reaction	Time of Reaction	Examples of Antigen	Antibody or Cell	Clinical Examples
I Immediate hypersensitivity	15 to 30 minutes	Pollens, danders, foods	IgE	Extrinsic asthma, anaphylaxis, hay fever
II Cytotoxic response	—	Cell membrane, basement membrane	IgG, IgM (± complement)	Hemolytic anemia, Goodpasture's syndrome
III Antigen-antibody complexes (Arthus phenomenon)	6 to 8 hours	Moldy hay (thermophilic actinomycetes), other organic dusts	IgG (+ complement)	Allergic alveolitis (farmer's lung)
IV Delayed hypersensitivity (cell-mediated hypersensitivity)	48 hours	Tuberculoprotein, poison ivy extract	Sensitized lymphocytes, monocytes	Tuberculosis, contact dermatitis

Table II

IMMUNOGLOBULINS

Type of Immunoglobulin	Normal Serum Concentration mg% (average)	Molecular Weight (x 10^3)	Percent of Total Globulins	Role
IgG	1200	150	80	Infections, Type III hypersensitivity
IgA	275	180	5 to 10	Local or mucosal reactions and infections
IgD	5	150	—	Unknown
IgM	120	900	5 to 10	Possible role in agglutinating particulate antigens
IgE	0.03	200	—	Type I hypersensitivity

depending on either the host or the nature of the antigen, the defense process may become "inappropriate" and pathologic sequelae develop.

In immune diseases, the initial encounter of an antigen leads to *secondary*, specific immune mechanisms whose purpose is to sequester or eliminate antigens. Specific antibodies including immunoglobulins E, M, G, D, and A (IgE, IgM, IgG, IgD, and IgA) are produced. Also, lymphocytes become sensitized for cell-mediated immunologic responses.

By the processes of localization, phagocytosis, and destruction, the antigen is usually eliminated. When this basic immune response is successful, it terminates with only minor consequences to the host. However, if the antigen persists because of its nature or because of genetic defects in the patient (atopy), a *tertiary* response occurs which produces disease. Four types of such immunologically induced diseases of man are recognized and are classified as Types I, II, III, and IV immune reactions (Table I).

Antibody Structure. The basic structure of the antibody molecule consists of two heavy (molecular weight about 50,000) and two light (molecular weight 20,000) polypeptide chains which are linked in a Y-shaped configuration by covalent disulfide bonds (Plate 11). For each of the five immunoglobulin classes (IgG, IgA, IgM, IgD, and IgE) the heavy chains are distinctive.

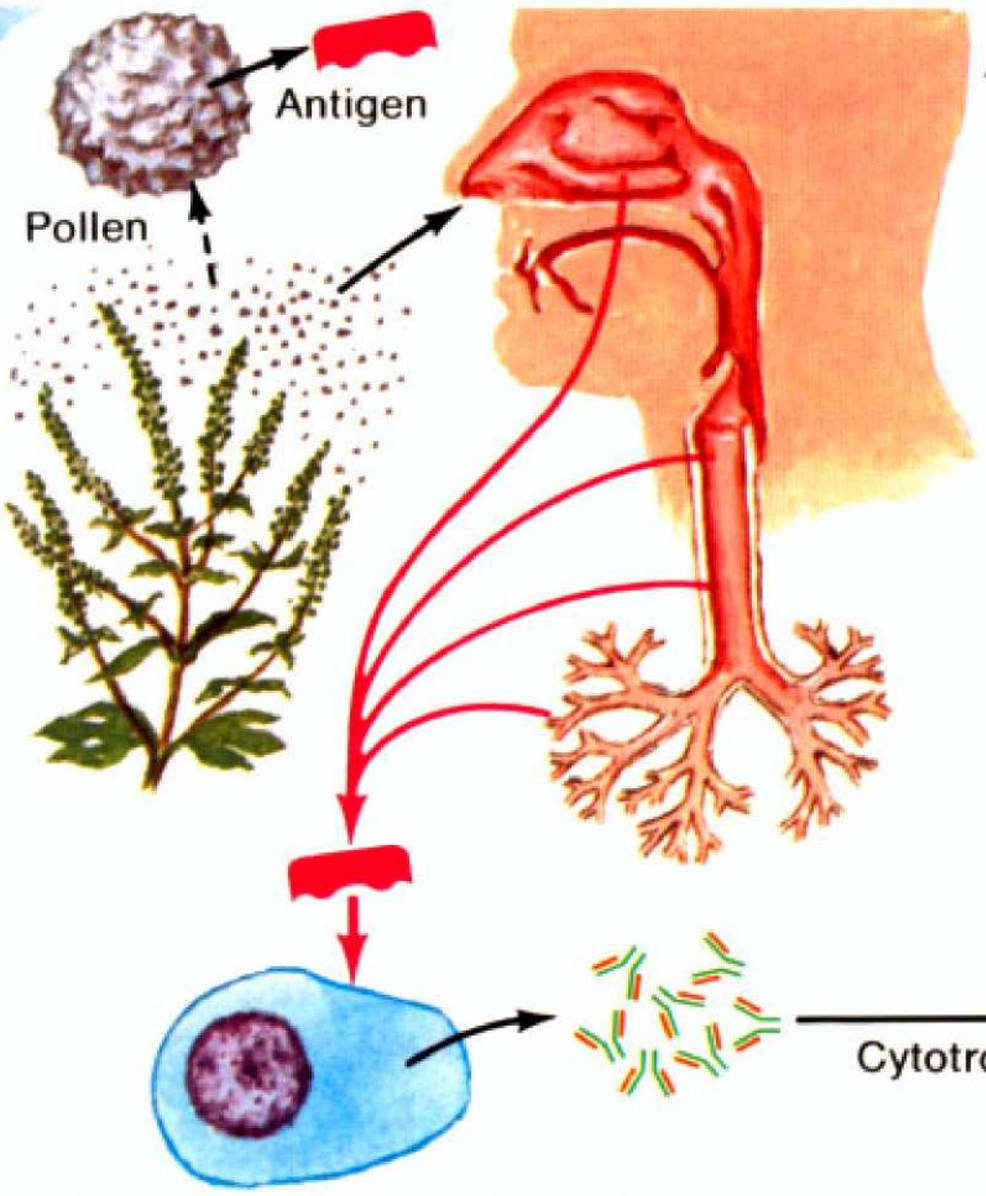
When the antibody is enzymatically degraded, three fragments result: one F_c (crystallizable) unit and two F_{ab} (antigen-binding) units. In the intact antibody, the F_c fragment binds the antibody to the surface of a cell, such as the mast cell (Plate 11); the F_{ab} fragment binds with antigen receptor sites.

The highest concentration of IgG is found in serum. IgG binds to, and enhances the phagocytosis of, bacteria; it also neutralizes bacterial toxins and binds complement. By transplacental transfer, IgG imparts humoral immune protection in the first six months of life. IgA is present in both serum and external secretions such as saliva and sputum; it plays a role in the defense mechanisms of the external surfaces of the body, including the mucous membranes. IgM is effective in both agglutinating and cytolytic reactions, whereas IgE has an important function in allergic disorders, including asthma. The characteristics of the various immunoglobulins are given in Table II.

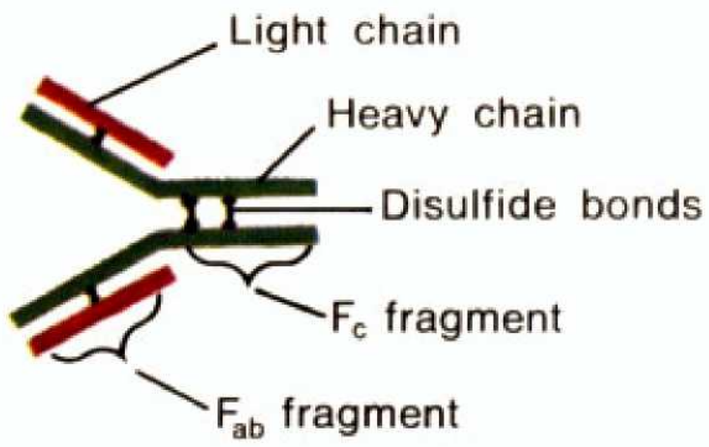
Immediate Hypersensitivity (Type I) Immune Reaction. Allergic bronchial asthma (extrinsic asthma) and other allergic diseases such as hay fever and anaphylaxis are examples of immediate hypersensitivity (Type I) immune reactions. Such allergic reactions take place in respective target organs such as the lungs, gastrointestinal tract, or skin. These immune processes leading to a hypersensitivity reaction represent the disease state referred to clinically as allergy.

Mechanism of Type 1 (Immediate) Hypersensitivity

Sensitization

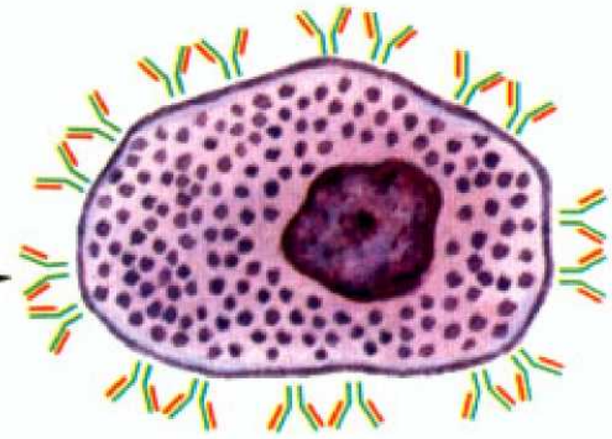


A. Genetically atopic patient exposed to specific antigen (ragweed pollen illustrated)



B. Plasma cells in lymphoid tissue of respiratory mucosa release immune globulin E (IgE)

Cytotropism



C. Mast cells and basophils sensitized by attachment of IgE to cell membrane

F. Netter M.D.
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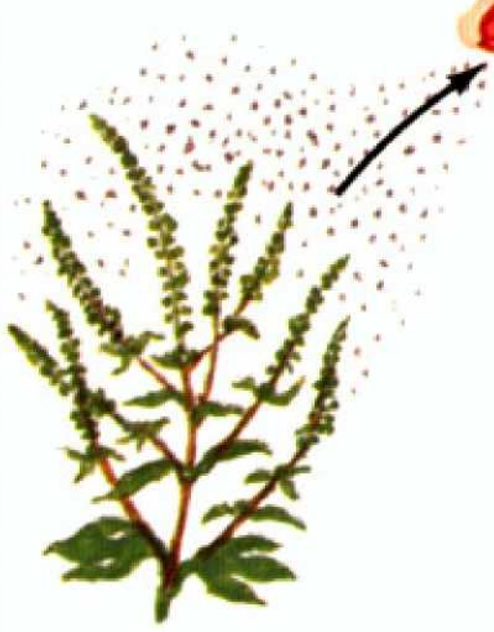
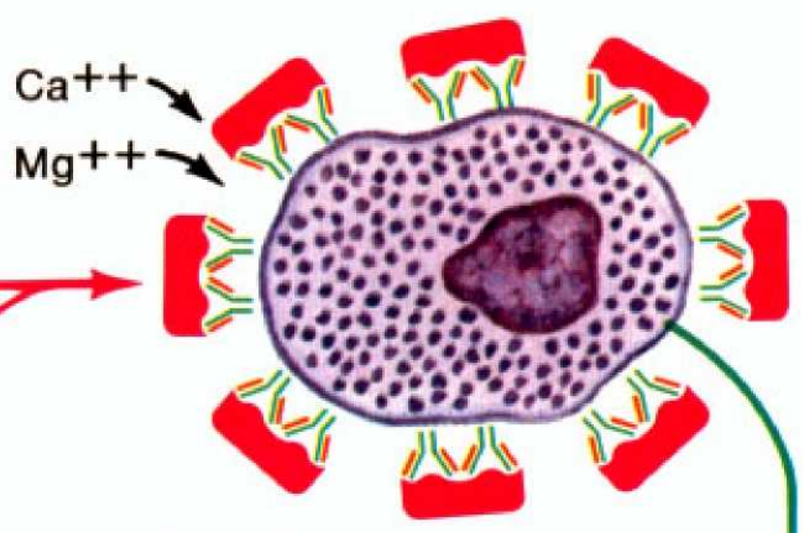
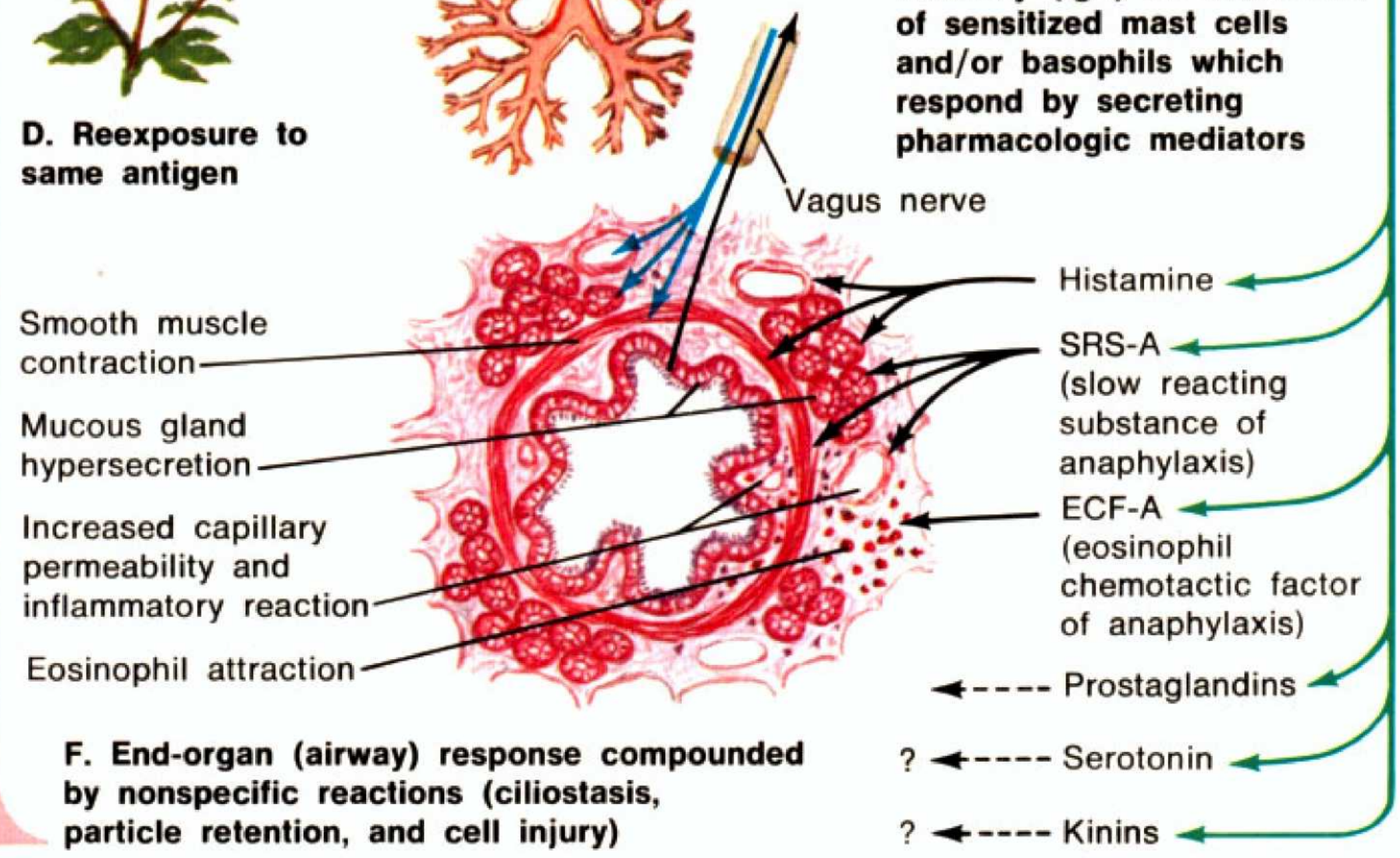
Allergic reaction



D. Reexposure to same antigen



E. Antigen reacts with antibody (IgE) on membrane of sensitized mast cells and/or basophils which respond by secreting pharmacologic mediators



F. End-organ (airway) response compounded by nonspecific reactions (ciliostasis, particle retention, and cell injury)

Immediate hypersensitivity reactions can result in a simple acute inflammatory response (urticaria) or can cause complex reactions that may be systemic (anaphylaxis) or predominantly bronchial smooth muscular (asthma). The immune *sequence* consists of the *sensitization* phase followed by a *challenge* reaction, which produces the clinical syndrome of allergy (Plate 11).

In the *sensitization* phase, a genetically atopic patient is exposed to antigen (*e.g.*, ragweed pollen). Lysozymes from the respiratory mucosa digest the outer lipid-polysaccharide coating of the pollen, releasing water-soluble proteins (molecular weight about 36,000). As these proteins are absorbed, plasma cells within the lymphoid tissues of the upper or lower respiratory mucosa respond by forming a specific cytotropic antibody of the IgE class (reagin). These IgE molecules attach to the surfaces of the mast cells or other cells such as basophils. (The affinity of the IgE molecules for certain cells is known as *homocytotropism [cytotropism]* and is species specific.)

Following a latent interval of variable duration (days to months), a reexposure of the patient to the specific antigen may result in a *challenge* (allergic) *reaction*. In the presence of certain cations such as calcium and magnesium, IgE-sensitized cells in contact with the specific antigen secrete pharmacologically active substances including histamine, slow-reacting substance of anaphylaxis (SRS-A), various kinins, eosinophil chemotactic factor (ECF), serotonin, and probably prostaglandins. Bronchial smooth muscle, blood vessels, and mucous glands respond to these substances. Muscular contraction, vasoconstriction, and hypersecretion of mucus occur together with an inflammatory response of increased capillary permeability and cellular infiltration.

The described immunologically induced, specific reactions, together with the nonspecific defenses, produce the clinical symptoms of bronchial asthma. Also, because of the inflammatory response, the cilia of the mucosal cells fail to function normally (*ciliostasis*). Particle retention results and may reflexly cause additional bronchoconstriction. Cell necrosis also aggravates the picture and may facilitate increased permeability of the tissues to the inciting antigen. Continued sensitization and reaction then occur.

Immunoglobulin E, the antibody mediator of the immediate hypersensitivity (Type I) reaction, is a γ-1-glycoprotein with a sediment coefficient of 8S and a molecular weight of 200,000. This immunoglobulin is synthesized by plasma cells in the mucosa of the nose, respiratory tract, and gastrointestinal tract, and in lymphoid tissues. It is found in various tissues, body fluids, and in nasal and bronchial secretions of allergic individuals. The presence of IgE in respiratory tract secretions may be the result of local secretion or may represent passive exudation from serum.

The serum concentrations of IgE are normally low, between 100 and 700 nanograms/ml (average, 300 nanograms/ml, or 0.03 mg %); IgE has a half-life of about two days, indicating active formation. Levels of IgE are increased in patients with parasitic infestations, allergic aspergillosis, seasonal rhinitis, eczema, food sensitivities, and in particular, during severe extrinsic bronchial asthma. However, such increased serum concentration is not necessarily a specific indicator of the extent or the severity of allergy.

The unique property of human IgE is that it possesses antigenic determinants which lead to *specific tissue binding*. This property is absent in other human immunoglobulins. Historically, the demonstration of the affinity of IgE for skin by direct skin tests lead to the term *skin-sensitizing antibody*. However, lung tissue can also be actively sensitized. Sera of allergic individuals which contain this skin-sensitizing antibody are responsible for the classic studies of passive transfer by Prausnitz and Küstner. As noted in Plate 1, extrinsic bronchial asthma is characterized by the presence of elevated levels of IgE.

Role of Mediators. As described previously, the challenge reaction of the immune sequence is characterized by the secretory release of pharmacologic mediators either from mast cells located in the respiratory mucosa or from circulating basophils. Complement is probably not directly involved in this challenge reaction, and cytolysis does not result. The release of mediators from mast cells is influenced or controlled by the intracellular concentration of cyclic AMP (page 27). The level of cyclic AMP is, in turn, influenced by a number of factors, including catecholamines.

The most thoroughly studied mediator is *histamine*, a vasoactive amine widely distributed in body tissues, particularly the lung.

Histamine is concentrated as granules within tissue mast cells and especially in those mast cells located in proximity to capillary endothelial cells in the bronchial submucosa. Histamine is also present in circulating basophils and neutrophils. The respiratory mucosa and perivascular sites are particularly rich in mast cells and thus have the propensity for allergic reactions following challenge by airborne allergens.

The release of histamine causes increased capillary permeability and vasodilatation with resulting edema and infiltration by inflammatory cells. Also, there is contraction of airway smooth muscle and increased secretion from mucous glands. Parenthetically, aerosol administration of histamine to asthmatic patients usually produces typical bronchospasm, whereas in normal subjects only minor effects occur.

In vitro, histamine release can be demonstrated following exposure of leukocytes or lung tissue of allergic individuals to appropriate antigens. This experimental evidence incriminates histamine action in the immune response. *In vivo* observations, however, including only minor clinical response to antihistamine drugs, have raised questions about the significance of histamine in human asthma.

The *slow-reacting substance of anaphylaxis* (SRS-A) is an acidic, thermostable (at alkaline pH) substance with definable solubility characteristics. SRS-A appears to be a major mediator in producing bronchial muscle contraction. However, pharmacologically significant features of the actions of SRS-A are a delay in maximal effect on the bronchial muscle and a more prolonged action than histamine. Moreover, its actions are uninfluenced by antihistamine drugs.

In addition to histamine and SRS-A, the *kinin system* may be operative in producing the inflammatory response and smooth muscle contraction of bronchial asthma. However, the exact role of kinins is unclear. *Bradykinin* is considered to be the most important mediator of the kinin group. It is a potent nonapeptide that causes bronchoconstriction in both animals and man.

The roles of several other substances as mediators in bronchial asthma require clarification. *Acetylcholine* is not a direct mediator in the airways but, as a neurotransmitter, is involved in the vagally mediated reflexes which represent a significant component of the asthmatic reaction (pages 20 and 24). *Anaphylatoxin,* a derivative of the complement system, appears to have no significant role in bronchial asthma. A substance known as the *eosinophil chemotactic factor of anaphylaxis (ECF-A)* may be produced in lungs challenged with specific antigen. It has been implicated in the attraction of eosinophils to the site of the allergic reaction. *Serotonin,* or *5-hydroxytryptamine (5-HT),* increases capillary permeability and constricts smooth muscle. However, the local lung concentrations of serotonin are negligible and aerosol challenges ineffective. (Prostaglandins will be discussed on page 29.)

The role of the *suprarenal-pituitary axis* in bronchial asthma is difficult to assess during acute attacks. Nevertheless, in individual patients, suprarenocortical function must be considered, primarily because of the important actions of the suprarenocorticosteroids. These actions include an antiinflammatory effect, decreased mucus secretion, lysozyme stabilization, inhibition of antibody formation, possible depletion of tissue histamine, and potentiation of bronchodilator agents.

Most asthmatic patients have normal suprarenal function even if they have taken corticosteroid medication on a short-term basis. As would be expected, continuous long-term therapy with corticosteroids may suppress the function of the suprarenal cortex. Asthmatic patients who are on long-term therapy are likely to have more severe asthmatic episodes including status asthmaticus, apparently because of suppressed suprarenocortical function (pages 57 and 68).

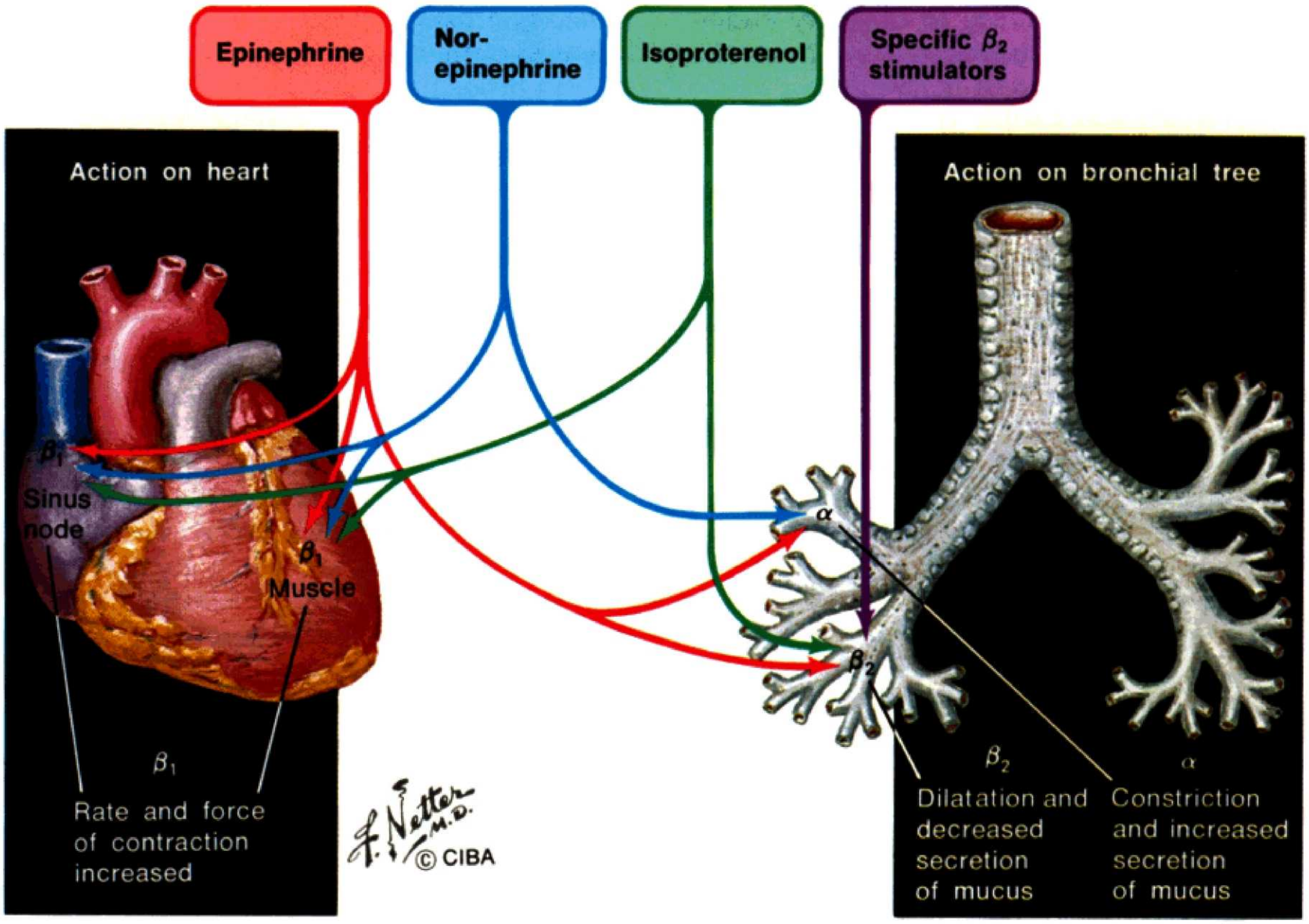
In some patients with severe asthma who are not taking steroid medication there is a limited response to ACTH. Similarly, the anticipated increase in urinary excretion of 11-hydroxycorticosteroids in response to stress does not occur. Therefore, these patients may be more vulnerable to stress and more susceptible to allergen challenge.

β-Adrenergic System

Immunologic mechanisms and the β-adrenergic system appear to play major roles in the defense processes of the body against foreign substances (Plate 10 and page 19). An understanding of both immunologic factors and dysfunction of the β-adrenergic system is thus necessary for an understanding of the

Plate 12

Catecholamine Action on α and β Receptors of Heart and Bronchial Tree



etiology and the pathogenesis of asthma and also provides the foundation for a rational approach to drug therapy.

Adrenergic Receptors. Pharmacologic studies indicate that there are two basic types of adrenergic receptors, α and β. The α receptors are located primarily in smooth muscle and exocrine glands. β receptors have been differentiated pharmacologically into β_1, located in the heart, and β_2 in the smooth muscle throughout the body, including bronchial and vascular smooth muscle.

Generally, α stimulation is excitatory. β stimulation may be inhibitory (relaxation of bronchial smooth muscle) or excitatory (increase in both heart rate and force of contraction). β stimulation also tends to mobilize energy by glycogenolysis and lipolysis.

Certain tissues contain both α and β receptors. The result of stimulation depends on the nature of the stimulating catecholamine and the relative proportion of the two types of receptors. For instance, in the lungs, β_2 stimulation causes bronchodilatation and possibly decreased secretion of mucus; α-adrenergic stimulation by pharmacologic agents causes bronchoconstriction.

Catecholamines are substances with a specific chemical configuration and sympathomimetic actions. The name is derived from the chemical similarity to catechol. The pharmacologic effects of individual catecholamine compounds depend, in part, on the relative degree of their stimulation of the α- and β-receptor sites.

In humans, three principal catecholamines are formed: *dopamine*, *norepinephrine*, and *epinephrine*. Although *dopamine* has some mild peripheral adrenergic effects, it is chiefly a neurotransmitter in the extrapyramidal nervous system and need not be considered further in this discussion. *Norepinephrine*, a metabolic precursor of epinephrine, is the principal neurotransmitter of the postganglionic sympathetic fibers. *Epinephrine* is the major hormone of the suprarenal medulla.

A number of synthetic catecholamines have been developed. Of these, *isoproterenol*, because of beneficial pharmacologic actions, is most frequently used in the treatment of

asthma. The effects of various catecholamines and of pure β_2 stimulators are shown in Plate 12.

β-Adrenergic Blockade in Bronchial Smooth Muscle. In the normal individual, airway tone and patency represent a balance between bronchorelaxation induced by β-adrenergic stimuli and bronchoconstriction caused by vagal impulses and possibly by α-adrenergic stimuli. One theory of the causation of asthma holds that partial blockade of the β-adrenergic system results in relatively unopposed, cholinergically induced bronchoconstriction. The effects of this blockade become obvious in an allergic reaction when mediators, including histamine, are released and stimulate bronchial muscle contraction. Bronchospasm and other features of the asthmatic reaction result. Because the β-adrenergic abnormality can also involve receptor sites throughout the body, this theory provides an explanation for other atopic diseases such as eczema or allergic rhinitis.

β blockade occurs because of a malfunction or deficiency of the enzyme *adenyl cyclase* within smooth muscle cells, glands, blood vessels of the lungs, and tissue mast cells. In the cell plasma membrane of the muscle, adenyl cyclase is located at the β-receptor site, or this enzyme may be the actual receptor (Plate 13). In the presence of magnesium ions, β-adrenergic stimulation activates adenyl cyclase which catalyzes the synthesis on the membrane of cyclic adenosine monophosphate (cyclic 3′,5′-AMP or cyclic AMP) from adenosine triphosphate (ATP). Cyclic AMP then diffuses into the cell where it has a number of functions. Its most important function, insofar as the bronchial smooth muscle cell is concerned, is the activation of mechanisms which prevent contraction or induce relaxation of the muscle.

By its production of cyclic AMP, the enzyme adenyl cyclase regulates, at cellular level, the interaction between circulating hormones or drugs and intracellular events. The circulating hormone has been called the first messenger and cyclic AMP, the second messenger.

A deficiency of adenyl cyclase may be acquired as the result of infection or by the action of certain metabolites. The deficiency may also be genetically inherited. As a result, the normal β-adrenergic responses to various stimuli would be inadequate and bronchoconstriction would occur. Alternatively, the β-adrenergic responses initially could be adequate, but the ability of adenyl cyclase to catalyze the production of cyclic AMP may become limited with time. In this circumstance, excessive or prolonged bronchoconstrictive stimulation (as described previously) would eventually overcome the counterbalancing bronchorelaxing effects of β-adrenergic stimulation. Another way in which β-adrenergic blockade may occur is through the action of adrenergic blocking agents such as propranolol.

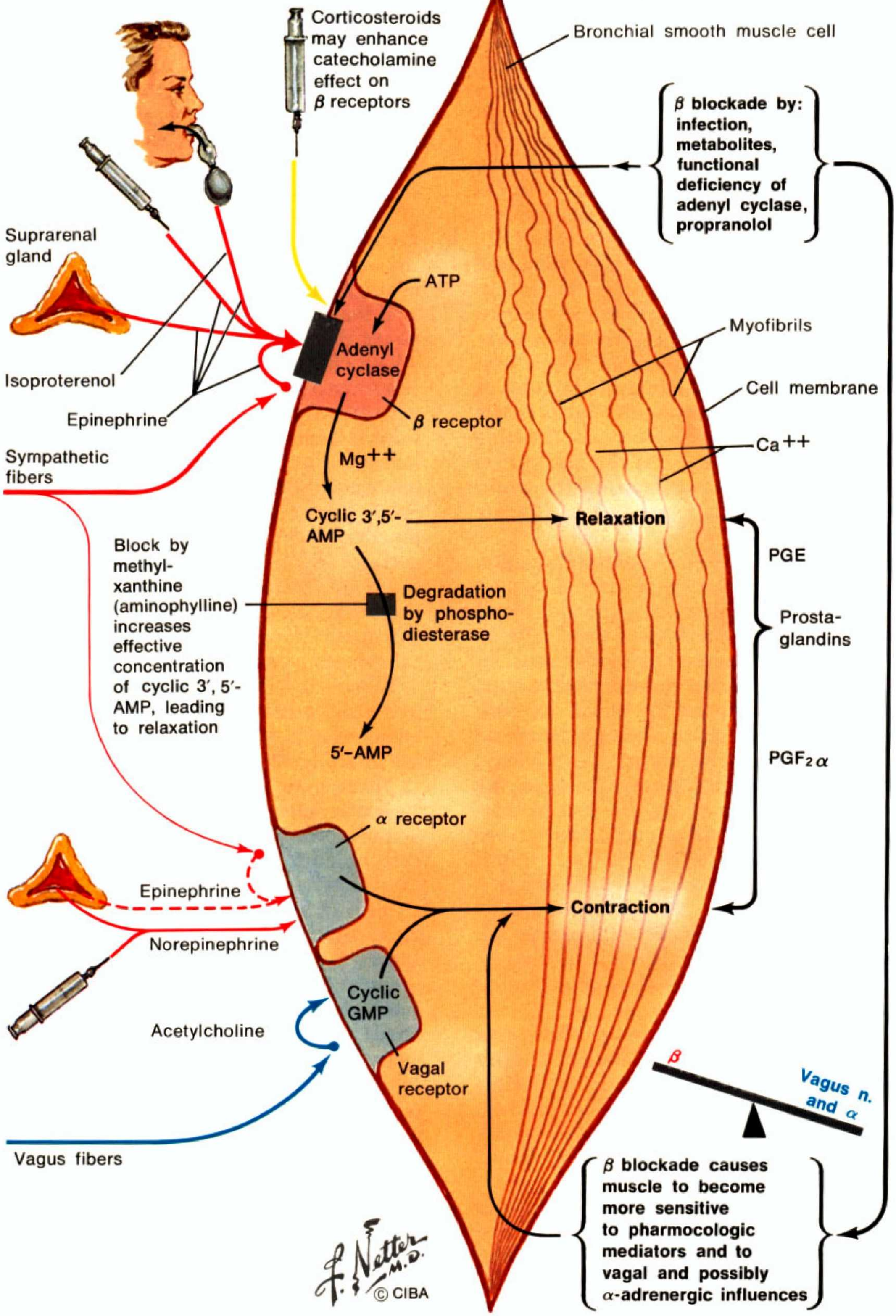
β Blockade in Tissue Mast Cells. In recent years mechanisms have been defined by which chemical mediators are released from tissue mast cells as the result of immunologic activity. Cyclic AMP has been found to inhibit immunologically induced release of histamine and other mediators. Thus, adequate concentrations of cyclic AMP (as would result from β-adrenergic stimulation in conjunction with sufficient amounts of adenyl cyclase) will inhibit mediator release; inadequate concentrations of cyclic AMP, as with β blockade or adenyl cyclase deficiency, will enhance mediator release and lead to the clinical symptoms of asthma.

Obviously, the *dual* effects of β-adrenergic blockade (bronchoconstriction and enhancement of chemical mediator release) are interrelated in the asthmatic reaction.

Therapeutic Implications. As noted, adenyl cyclase is activated by the binding of catecholamines to the β-receptor site. This action of catecholamines is apparently enhanced by corticosteroids. Conversely, a β-blocking agent such as propranolol prevents the binding of catecholamines and may cause bronchospasm. Thus, for an asthmatic patient, the *therapeutic* effect of the administration of a catecholamine, such as epinephrine or isoproterenol, or of a corticosteroid is a *biochemical* increase in the smooth muscle cell and mast cell concentrations of cyclic AMP. As a result, relaxation of the bronchial muscles and inhibition of chemical mediator release occur.

Cyclic AMP is degraded to 5′-AMP by the enzyme phosphodiesterase (Plate 13). This action is competitively inhibited by certain drugs such as methylxanthine (aminophylline). The administration of drugs of this type to an asthmatic patient will thus raise the smooth muscle cell concentration of cyclic

Theory of Catecholamine Effects and β-Adrenergic Blockade



AMP and produce bronchorelaxation. In addition, corticosteroids may inhibit the enzyme phosphodiesterase.

Additional Factors Influencing Mediator Release

Enhancement of mediator release is known to occur following experimental cholinergic stimulation. Thus, it is postulated that pharmacologic agents with distinct cholinergic actions probably can act by enhancing mediator release. This enhancement apparently occurs without directly affecting cyclic AMP. Instead, the cholinergic effect is believed to be mediated through the action of cyclic guanosine 3′,5′-monophosphate (cyclic GMP).

Vagally mediated reflex stimulation, as described on page 20, may result from impulses generated in irritant receptors by various antigenic and nonantigenic stimuli. Furthermore, the immune sequence that occurs in response to inhaled antigens may also be vagally mediated.

α-adrenergic stimulation, as with norepinephrine or phenylephrine, reduces the cellular level of cyclic AMP and enhances the release of chemical mediators. This effect is distinct from the effects of cholinergic stimulation and is not blocked by atropine. However, the role of α-adrenergic stimulation in bronchial asthma is currently unresolved.

Inhibition of mediator release may result from any action or stimulus which increases tissue concentration of cyclic AMP. Thus, in addition to the various β-adrenergic agents, including the newer, selective, β_2 stimulators, substances such as cholera toxin and prostaglandin fractions may inhibit mediator release. The prostaglandin fractions E_1 and E_2 (PGE_1 and PGE_2) released from the lung following antigen challenge, have a bronchodilator action. Conversely, prostaglandin fraction $F_{2\alpha}$ ($PCF_{2\alpha}$) acts as a bronchoconstrictor.

Pathophysiologic Effects of Asthma

As discussed on page 12, the severe pathologic changes which occur in status asthmaticus and the similar though less severe changes in acute and chronic asthma must be considered within the context of pathophysiology as well as pathogenesis. The pathophysiologic effects of airway obstruction on respiratory function and hence on blood gases and pH occur regardless of the specific mechanisms producing the asthmatic episode. In status asthmaticus these changes in respiratory function, blood gases, and pH represent the greatest immediate danger, and their reversal must receive therapeutic priority.

In this section, the pathophysiologic effects of airway obstruction are presented in general terms. A detailed discussion of these concepts appears in the section dealing with the management of status asthmaticus (page 48).

Lung Volumes and Capacities. Normally, during the active process of inspiration, thoracic volume increases through the actions of the diaphragm and the other muscles of inspiration. As the chest volume increases, the intrapleural pressure, which is normally negative relative to atmospheric pressure (−2 mm Hg), decreases sufficiently (to about −6 mm Hg) to overcome the tension of the elastic tissue in the lungs. As a result, the lungs expand to fill the increased chest volume. The pressure in the airways and alveoli thus becomes less than atmospheric pressure, and this pressure difference causes air to flow into the lungs. The movement of air through the airways is enhanced by the normally low airway resistance.

In contrast to inspiration, expiration during quiet breathing is *normally* passive and does not require the expenditure of muscular energy. As the muscles of inspiration relax, energy which has been stored because of the stretching of the elastic tissue in the lungs is released (elastic recoil). This elastic recoil property forces air out of the lungs and allows the thorax to return to the normal resting state.

The characteristics of the breathing capacities of the lungs may be measured by spirometry. This simple method provides the most objective measurements of the various lung capacities and volumes (Plates 14 and 15). A limitation of spirometry, however, is that the residual volume (RV) and, therefore, the functional residual capacity (FRC) and the total lung capacity (TLC) cannot be measured directly. The residual volume must be assessed by indirect methods such as body plethysmography and the helium-dilution or the nitrogen-washout techniques. However, in the assessment of the asthmatic patient, particularly during the acute attack, these more complex techniques are generally impractical.

As measured by spirometry, many of the lung capacities and volumes, including the

Spirometry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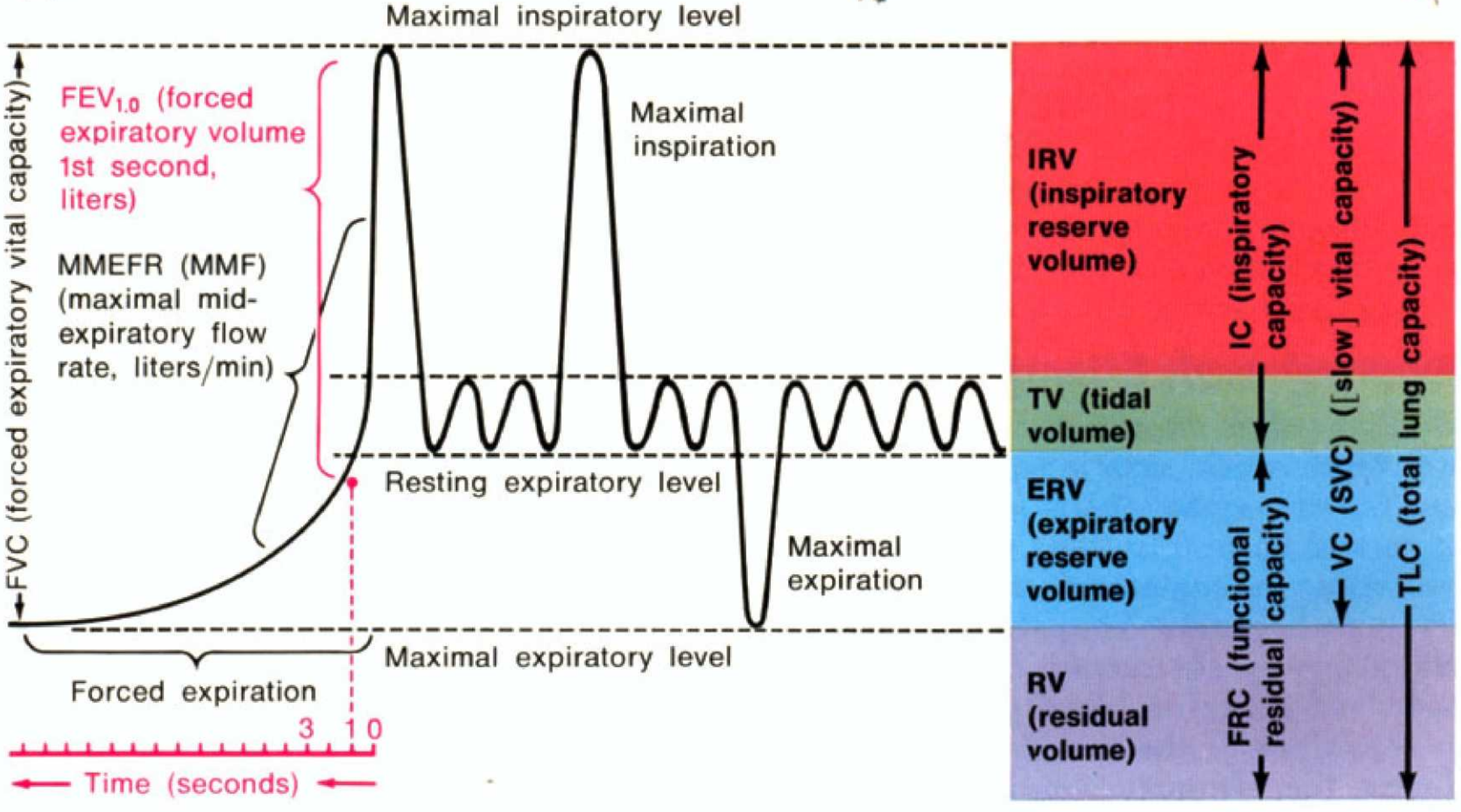
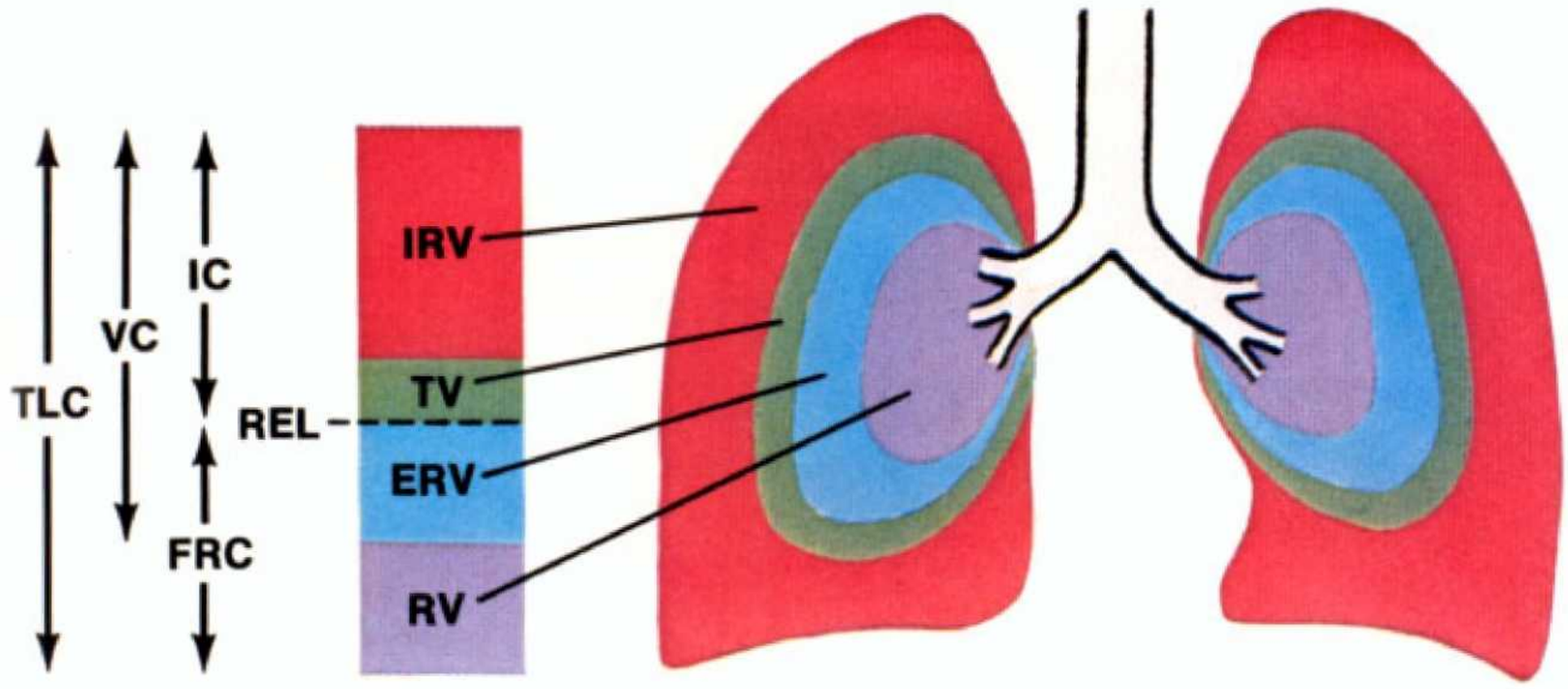

Maximal inspiratory level
FVC (forced expiratory vital capacity)
FEV1.0 (forced expiratory volume 1st second, liters)
MMEFR (MMF) (maximal mid-expiratory flow rate, liters/min)
Maximal inspiration
Resting expiratory level
Maximal expiration
Maximal expiratory level
Forced expiration
3
1
0
Time (seconds)
IRV (inspiratory reserve volume)
TV (tidal volume)
ERV (expiratory reserve volume)
RV (residual volume)
IC (inspiratory capacity)
FRC (functional residual capacity)
VC (SVC) ([slow] vital capacity)
TLC (total lung capacity)

Normal Lung Capacities and Volumes



Residual volume (RV) is approximately 25% of total lung capacity (TLC); vital capacity (VC) is about 75% of TLC; resting expiratory level (REL) is just below midpoint of TLC

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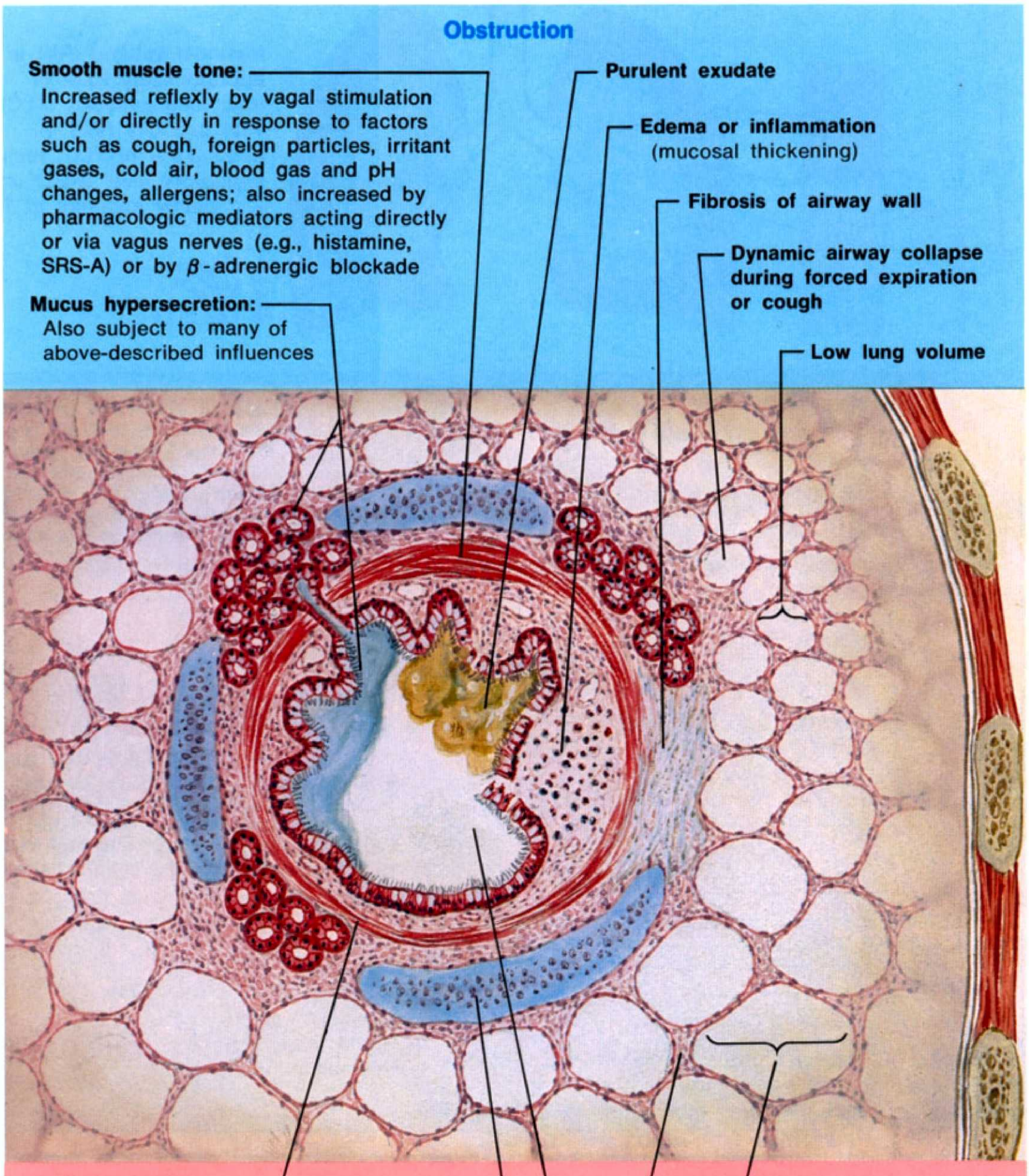
REL Resting Expiratory Level is the end-point of expiration during conditions of rest

Lung capacities		Lung volumes	
FRC	Functional Residual Capacity is the volume of air remaining in the lungs at the Resting Expiratory Level (REL)	TV	Tidal Volume is the volume of air inspired during *any* respiratory cycle
IC	Inspiratory Capacity is the maximum volume of air which can be inspired beginning at the Resting Expiratory Level (REL)	IRV	Inspiratory Reserve Volume is the maximum additional volume of air which may be inspired after the tidal volume has been inspired
VC	Vital Capacity is the maximum amount of air which may be expired after a maximum inspiration	ERV	Expiratory Reserve Volume is the maximum additional volume of air which may be expired after the tidal volume has been expired
TLC	Total Lung Capacity is the sum of all four Lung Volumes	RV	Residual Volume is the volume of air remaining in the lungs after maximum expiration

slow vital capacity, are not time-related observations. However, because of the continuous metabolic needs of the body, respiration and, therefore, ventilation (the amount of air inspired and expired) must be considered within the context of time. In the asthmatic patient, impaired airflow may cause impaired ventilation so that time-related measurements are of primary importance in the assessment of the extent of airway obstruction (Plate 14). Such time-related measurements are the forced expiratory vital capacity (determined by forced rapid expiration) and its mathematically calculated subdivisions: the forced expiratory volume in the first second ($FEV_{1.0}$, expressed in liters) and the maximal midexpiratory flow rate (MMEFR or MMF, expressed in liters per minute).

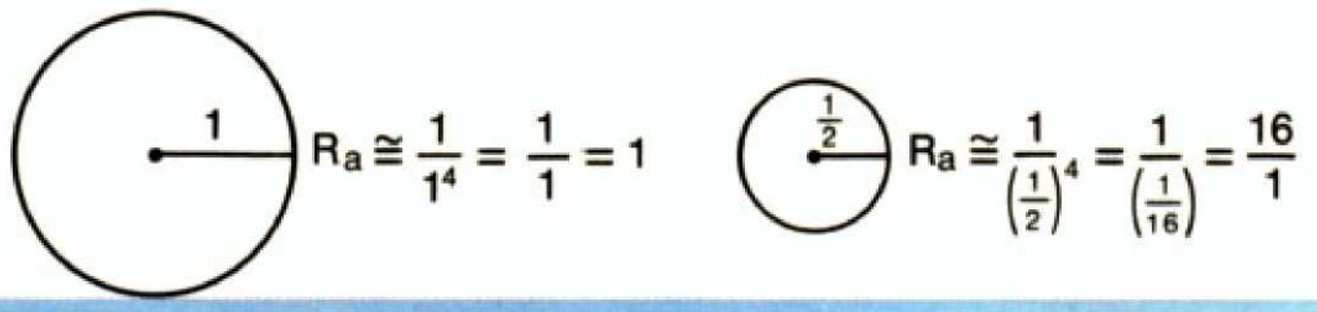
Ventilatory Function in Asthma. In asthma, the prime event from the clinical viewpoint is obstruction to airflow which is most marked in expiration. As discussed in the section on

Multifactorial Influences on Airway Caliber



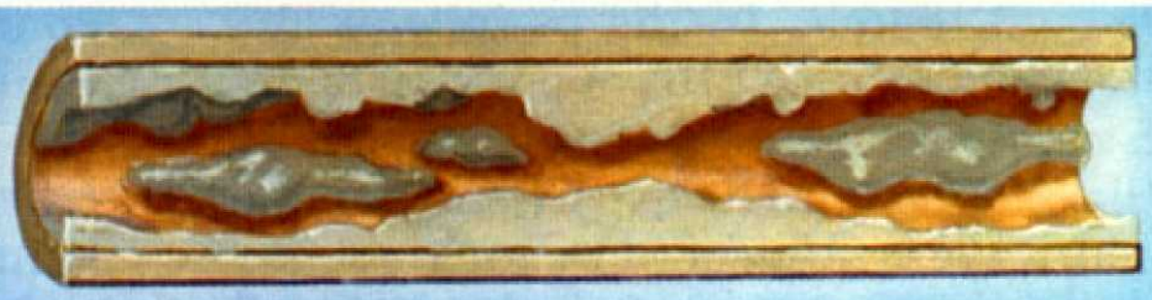
Factors Decreasing Airflow

Airflow resistance (R_a) varies inversely to the fourth power of radius; halving radius increases resistance sixteenfold (Poiseuille's approximation)

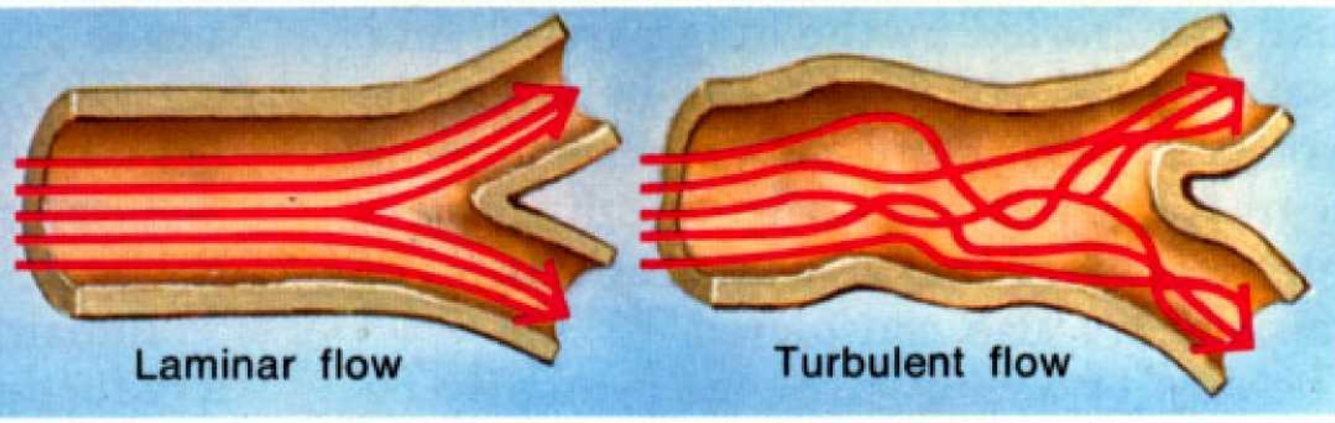


A. Bronchospasm with hypertrophy of airway smooth muscle with/without edema and inflammatory swelling of bronchial walls increase resistance

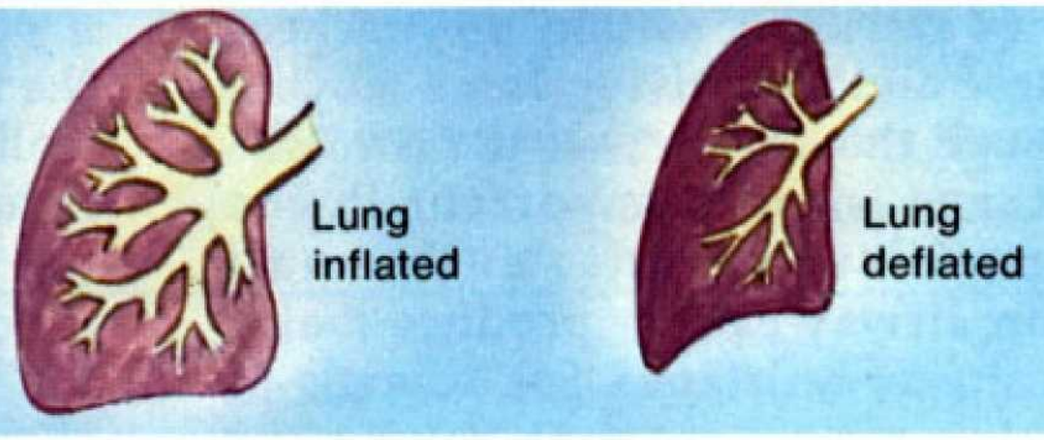
B. Intraluminal secretions (mucus and/or pus) increase resistance



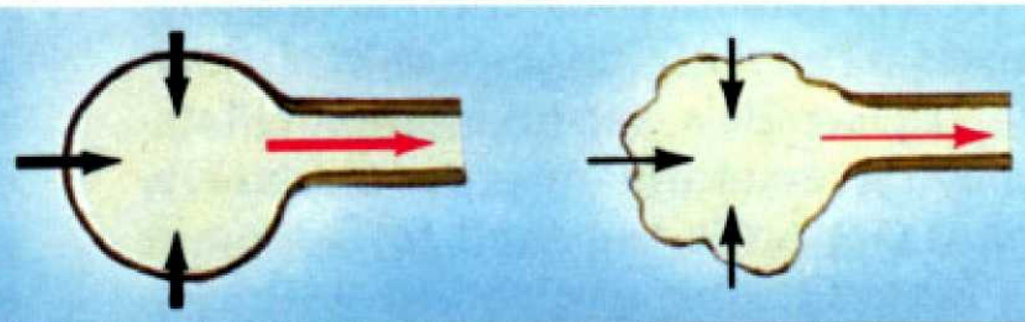
C. Turbulent airflow caused by branching and irregularity of bronchial walls or high velocity of airflow increases resistance



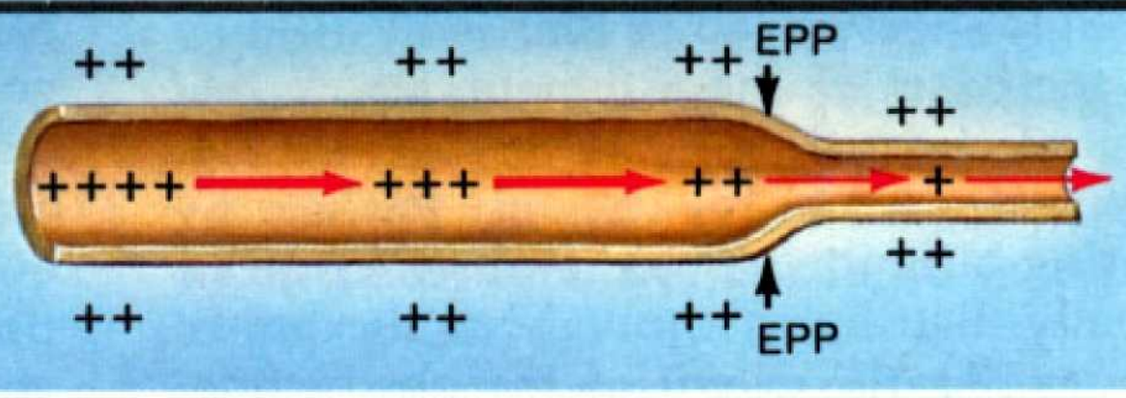
D. Low lung volume reduces airway diameter causing increased resistance



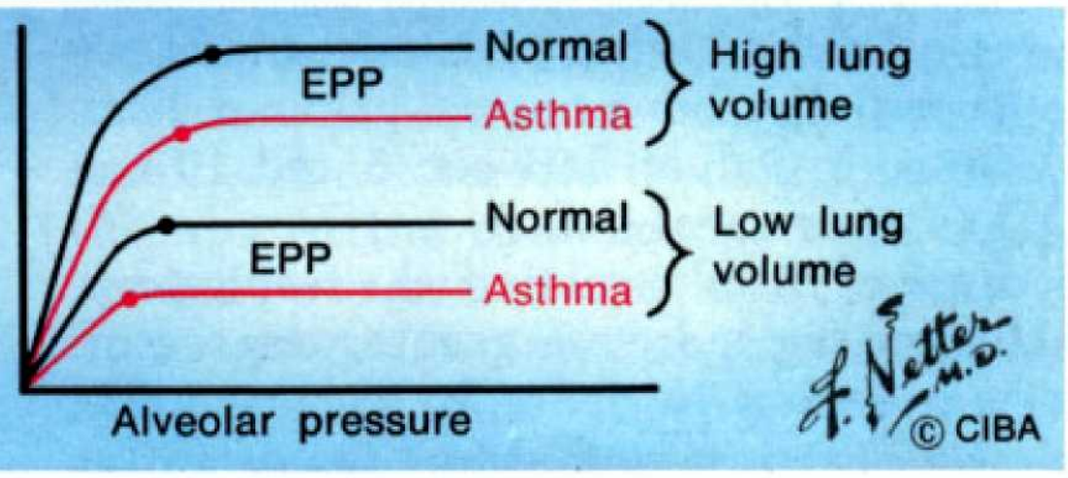
E. Decreased elastic recoil of parenchyma reduces driving pressure



F. Airway collapse at EPP (equal pressure point where intraluminal pressure equals or is less than extraluminal) increases resistance; greater expiratory effort will not increase flow



G. Forced expiratory effort increases alveolar driving pressure and increases airflow to point of airway collapse (EPP); in asthma EPP occurs at lower alveolar driving pressure



pathology, various combinations of bronchospasm, inflammation, edema, and mucus hypersecretion cause narrowing and plugging of the bronchial and bronchiolar lumina. In addition, peribronchial factors such as low lung volume and airway collapse during forced expiration may compound the airway obstruction (Plate 16). Opposing these obstructive processes are a number of factors that help maintain patency of the airway (Plate 16).

The rigid cartilaginous rings of the larger or central airways help maintain patency by resisting the constrictive forces of the bronchial smooth muscle. In the peripheral airways, however, there is little opposition to the smooth muscle action because of the paucity of cartilage. In addition, the patency of the smaller airways is influenced by lung volume because these airways are imbedded in and partially supported by the lung parenchyma. These *morphologic* differences between the central and peripheral airways assume an even greater significance when the differences in total cross sectional area and resistances of the airway are also considered.

The rate of airflow depends primarily on the degree of resistance within the tracheobronchial tree and the driving force moving the air through the airways. Of the two, airway resistance is more important in the asthmatic patient because even small decreases in airway caliber produce major changes in airway resistance. For example, if all other factors remain constant, halving the radius causes a sixteenfold increase in airflow resistance (Poiseuille's approximation, Plate 17). If airway resistance increases, active muscle contraction is required to force air from the lungs during expiration within a reasonably short period of time.

At the onset of the asthmatic attack the amount of obstruction is variable, depending upon the severity of the response to the precipitating stimuli. Also, the obstruction is unequally distributed throughout the bronchial tree. As the extent of the obstruction progresses, direct airflow resistance increases proportionately from a normal value of 2 cm H_2O/L/sec to values between 5 and 10 cm H_2O/L/sec, or even greater.

Because of the obstruction, the respiratory muscles must produce a greater degree of chest expansion in order to increase the inspiratory driving force. More importantly, the elastic recoil of the lungs is insufficient for *passive* expiration. As a result, the respiratory muscles must now play an active role in expiration. If obstruction is severe, air trapping will occur.

The airway obstruction also impairs both the distribution of gases to alveoli (page 37) and ventilation (the volume of air breathed in any unit of time, usually expressed in liters per minute). Impaired ventilation results in tachypnea (increased respiratory rate) and thus a *shortened* respiratory cycle, even though the inciting event (obstruction) tends to cause a *lengthened* respiratory cycle. The conflicting demands cannot be reconciled while the asthmatic attack continues.

The severity of the obstruction can be reflected in the spirometric measurements of volume and airflow. (Even symptom-free asthmatic patients exhibit minor abnormalities in pulmonary function.) The vital capacity (VC), forced expiratory vital capacity (FVC), inspiratory reserve volume (IRV), and inspiratory capacity (IC) are reduced during the acute attack (Plate 19).

Impairment of ventilation is indicated by a reduction in $FEV_{1.0}$ expressed in liters or as a percentage of predicted value. Similarly, the ratio $[FEV_{1.0}/FVC] \times 100$, which is normally approximately 80% or greater, is also reduced, particularly if there is large or central airway obstruction. Paradoxically, this ratio can be near normal if both $FEV_{1.0}$ and FVC are reduced proportionately. Thus, the absolute values also must be considered.

The peripheral airways have a proportionately large total cross sectional area (Plate 18). For this reason, the resistance of the peripheral airways accounts for only 20% of the total airway resistance. Thus a large amount of obstruction in these smaller airways may go undetected if the physician relies only on clinical findings. Obstruction in these smaller airways may be detected by calculating the MMEFR (MMF). Alternatively, determination of closing capacity (*i.e.*, the lung volume at which the dependent airways close) will provide a more sensitive index of the patency of smaller airways.

Other measures that reflect expiratory obstruction are the peak expiratory flow rate (PEFR) and integrated flow of the first liter exhaled (MEFR). Similar flow measurements may be made to determine the degree of inspiratory obstruction.

Central Versus Peripheral Airflow Resistance

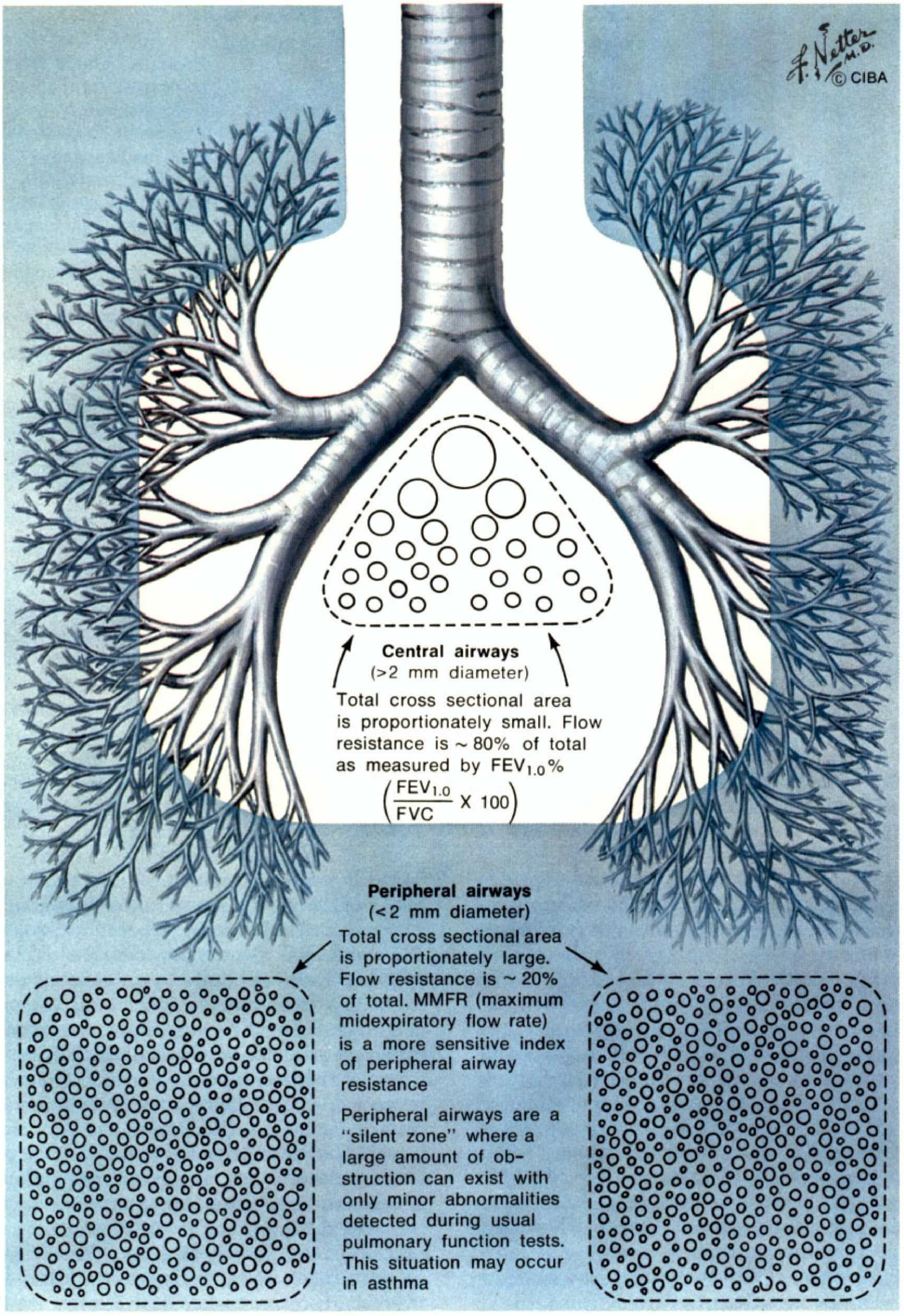
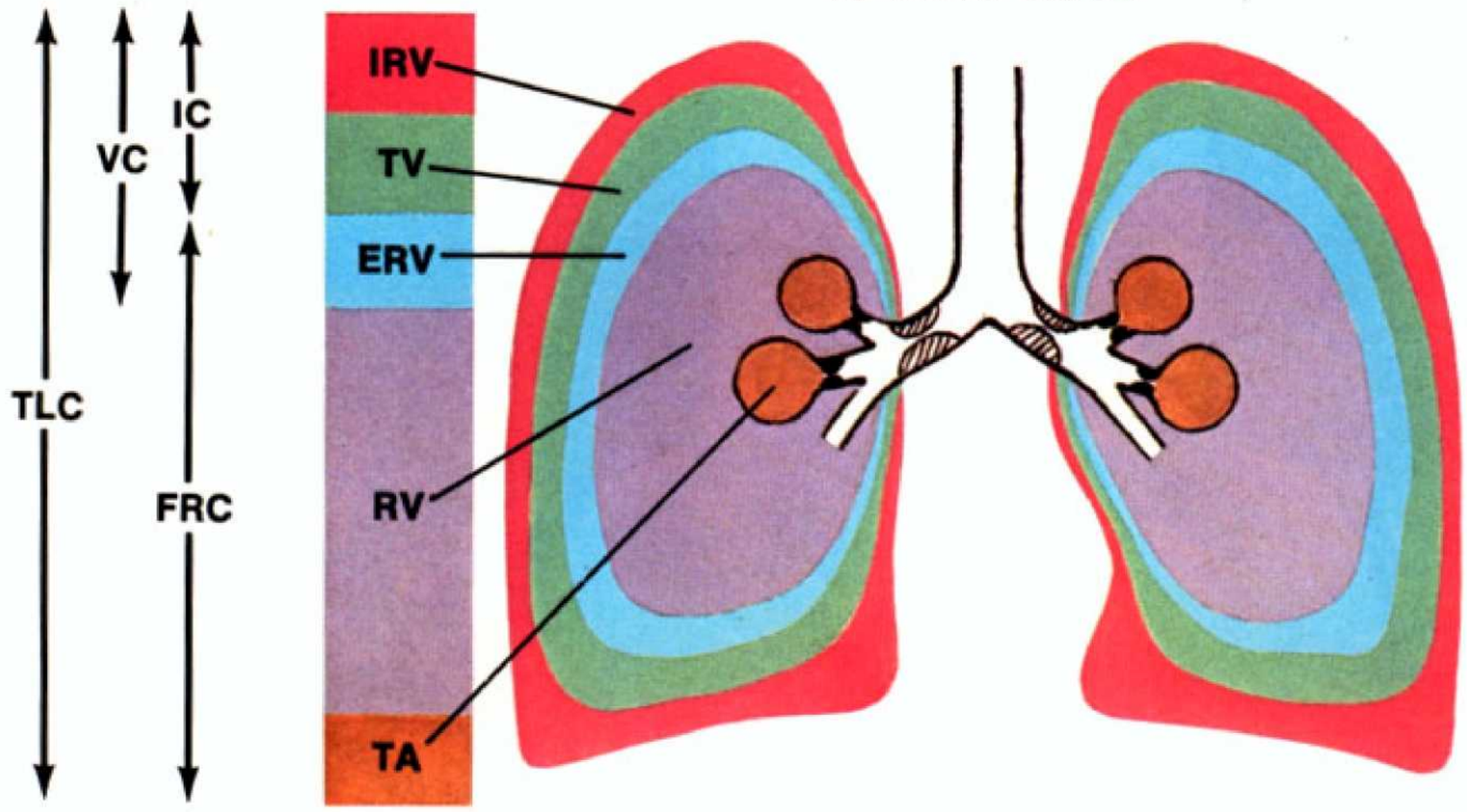


Plate 19

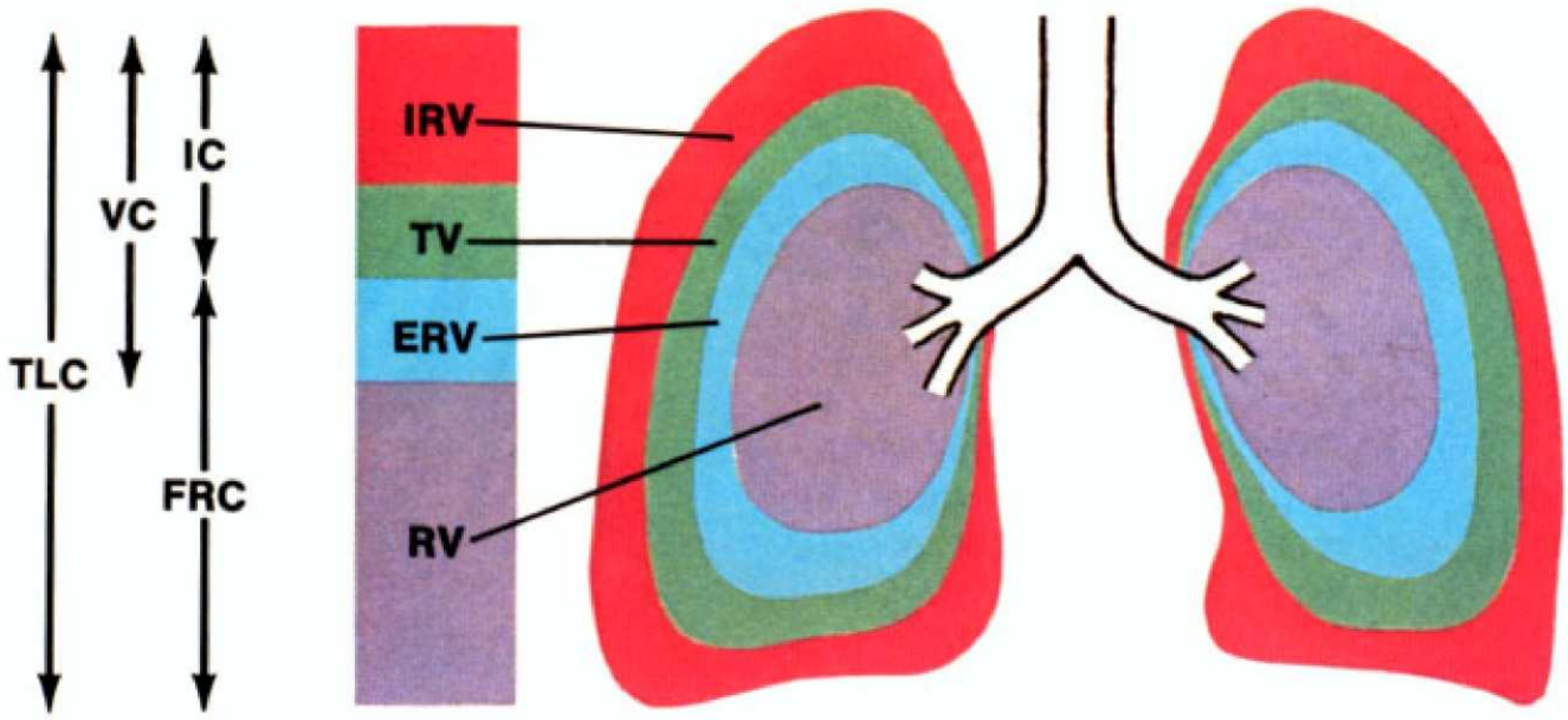
Lung Capacities and Volumes in Asthma

A. Acute attack



Residual volume (RV) increased; trapped air (TA); inspiratory reserve volume (IRV) decreased; total lung capacity (TLC) increased; expiratory reserve volume (ERV) decreased; vital capacity (VC) decreased both relatively and absolutely

B. After bronchodilatory therapy



Trapped air (TA) released; residual volume (RV) and total lung capacity (TLC) decreased (values close to preattack levels); inspiratory reserve volume (IRV) and vital capacity (VC) returned to near normal values

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The extent of reversibility of the obstruction can be estimated from the comparison of these parameters of ventilatory function before and after the administration of a bronchodilator (Plate 19). A 15 to 20% increase in ventilatory function can be considered evidence of a bronchoreversible process (Table III). A limited response to bronchodilators indicates either that factors other than bronchospasm are responsible for the obstruction or that the bronchospasm is refractory to bronchodilators. Similarly, serial determinations of FVC, $FEV_{1.0}$, or MMEFR help assess both the course of the asthmatic attack and the response to therapy. These and other spirometric measurements may also indicate whether the obstruction is central or peripheral (page 34).

With progressive obstruction, expiration becomes increasingly prolonged. Air becomes trapped thus increasing the residual volume (RV) and FRC. Because of increased RV and possibly as an inherent physiologic response, the patient breathes at higher lung volumes. The overall effect of this sequence of events is hyperinflation of alveoli which tends to increase further the diameter of the airways by exerting a greater lateral traction on the bronchiolar walls (Plates 16 and 17). Such hyperinflation of alveoli may also help preserve gas exchange. However, hyperinflation is disadvantageous because more energy is required during inspiration to overcome the tension of the already stretched elastic tissue of the lungs. Also, the increase in RV and trapped air compromises both the inspiratory

Table III

PULMONARY FUNCTIONS BEFORE AND AFTER AEROSOL BRONCHODILATOR THERAPY

	Before	After
FVC (liters) (% predicted in parentheses)	2.0 (50%)	3.5 (87%)
$FEV_{1.0}$ (liters)	0.8	2.5
$[FEV_{1.0}/FVC] \times 100$ (%)	40	71
Peak expiratory flow rate (L/min)	80	400
Maximum midexpiratory flow rate (L/min)	90	300
Maximum voluntary ventilation (L/min)	50	110
Direct airway resistance (cm H_2O/L/sec) (normal < 2.0)	8.5	3.1
Lung volumes (predicted L)		
RV 1.2	2.4	1.6
FRC 2.4	3.2	2.6
TLC 5.2	6.0	5.5
[RV/TLC] x 100 (normal $< 35\%$)	40	29
Diffusing capacity (ml/min/mm Hg) (normal $= 30$)	28	29

reserve capacity and vital capacity (Plate 19). Moreover, because inspiration is now occurring at higher lung volumes, the effectiveness of the cough is also reduced.

As the energy expended on breathing increases, fatigue ensues, and, as the effectiveness of respiration decreases, alveolar ventilation begins to fail. Progressive dyspnea, cyanosis, and tachypnea indicate the underlying pathophysiology.

Clinically, hyperinflation may be estimated by physical examination of the chest, by chest X-ray or, if possible, by standard gas-dilution techniques. Serial measurements of RV objectively assess the degree of pulmonary hyperinflation. *Pulsus paradoxus*, a useful clinical index of pulmonary overdistention, is usually present if the $FEV_{1.0}$ is less than 1.25 L.

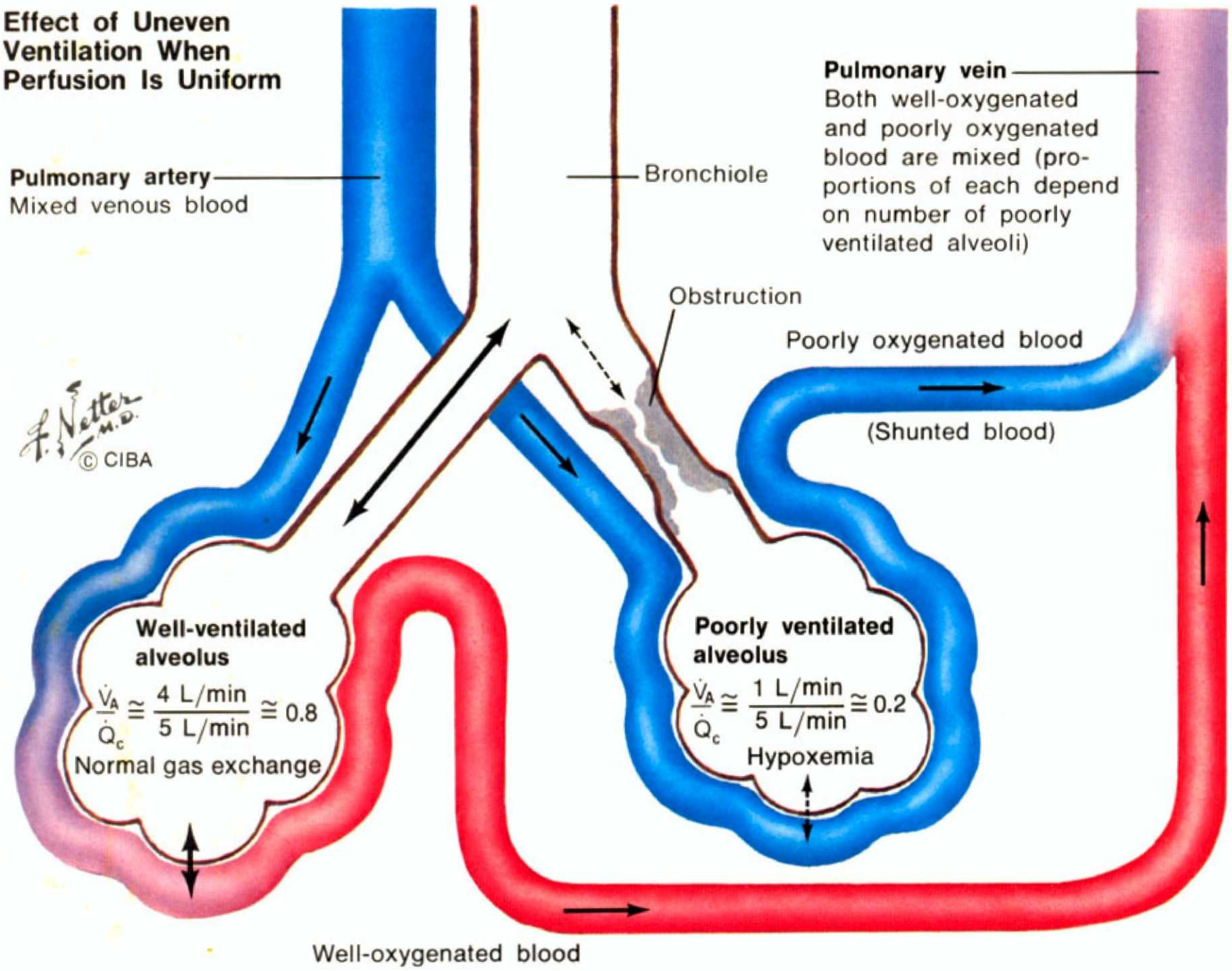
Impaired Gas Exchange. As a result of the uneven distribution of bronchial and bronchiolar obstruction in asthma, the distribution of inspired air to the terminal respiratory units is not uniform throughout the lungs. Alveoli which are hypoventilated because they are supplied by obstructed airways are interspersed with normal or hyperventilated alveoli; the severity of the asthma is directly related to the ratio of poorly ventilated to well-ventilated alveolar groups. Also, regional foci of reduced lung compliance which may be associated with atelectasis or pneumonia can interfere with alveolar ventilation.

Because pulmonary artery perfusion to the hypoventilated areas is relatively well preserved in comparison to the decrease in ventilation, so-called ventilation/perfusion ($\dot{V}_A/\dot{Q}_c$) disturbances occur (V = volume of gas, Q = volume of blood; a dot above the symbol indicates volume per unit of time; A = alveolar gas, c = pulmonary capillary). Mixed venous blood from the pulmonary arteries flowing through the capillaries of the poorly ventilated alveoli does not become saturated with oxygen. This poorly oxygenated blood mixes with blood from normally functioning alveolar-capillary units and returns to the left side of the heart and thus to the systemic circulation. Arterial hypoxemia (decrease in P_aO_2) results (P = pressure of gas a = arterial blood); this hypoxemia is the *primary* defect in gas exchange which occurs in asthma (Plate 20).

The net effect of the ventilation/perfusion disturbances on arterial oxygenation is determined by the number of poorly ventilated alveolar units compared to well-ventilated ones: As the *population* of alveolar units with a low $\dot{V}_A/\dot{Q}_c$ ratio increases, the degree of arterial hypoxemia also increases (low $\dot{V}_A/\dot{Q}_c$ ratio: ventilation reduced proportionately

Plate 20

Effect of Uneven Ventilation When Perfusion Is Uniform



more than perfusion; average normal $\dot{V}_A / \dot{Q}_c$ ratio for an entire lung is 0.8). The $\dot{V}_A / \dot{Q}_c$ disturbances are compounded if complete obstruction of some airways occurs. In this instance, actual right-to-left intrapulmonary shunting takes place in those terminal respiratory units where there is a total absence of ventilation.

Carbon dioxide elimination is usually not impaired while the number of alveolar-capillary units which are well ventilated and well perfused remains high relative to the number of units with $\dot{V}_A / \dot{Q}_c$ disturbances. As the degree of airway obstruction becomes more severe and more airways are involved, the number of hypoventilated alveoli increases. Simultaneously, appropriate increases in respiratory rate and depth (hyperventilation) occur, and, as a result, both the mechanical load and metabolic load of breathing are increased. This response eventually becomes limited; as the severity of obstruction increases, alveolar ventilation falls. Carbon dioxide retention now occurs together with increasing hypoxemia. This state is ventilatory failure (page 51).

Because the delivery of oxygen to body tissues is fundamental, the effect of the ventilation/perfusion disturbances must be viewed in context with the extent of oxyhemoglobin saturation, oxygen-hemoglobin affinity, red blood cell mass and hemoglobin concentration, and the compensatory mechanisms of cardiac output, systemic blood flow, and thoracic work.

Lung scan studies of perfusion in asthmatic patients reveal transient regional hypoperfusion which morphologically parallels the zones of hypoventilation. The hypoperfusion occurs because of regional pulmonary vascular reactivity; the hypoperfusion is migratory and fully resolves during remission of the asthmatic episode. However, blood flow changes do not occur at the same precise time

Table IV

CLINICAL CHARACTERISTICS OF EXTRINSIC (ATOPIC) AND INTRINSIC (NONATOPIC) ASTHMA

	Extrinsic, Atopic (Allergic)	Intrinsic, Nonatopic (Infective/Idiopathic)
Onset of symptoms	Usually during childhood	Usually in adults over age 35
Family history of atopy	Positive	Usually negative
History of infantile eczema	Positive	Negative
Identifiable allergy to inhaled and ingested substances	Positive	Negative
Passive transfer of IgE (skin-sensitizing) antibody	Positive	Negative
Reactions to skin test with inhalant allergens	Positive	Negative
Association with Type I, IgE reaction	Positive	Negative
Eosinophilia	Positive	Positive
In vitro release of histamine from washed leukocytes	Positive	Negative
Hyposensitization therapy	Favorable response	Equivocal
Typical attack	Acute and usually self-limiting	Often fulminant and severe
Relationship of acute attack to infection	May be present	Often present
Symptoms and physical findings	Identical for both types of asthma (see text)	
Aspirin sensitivity	Negative	Positive
Prognosis	Generally favorable	Less favorable
Death during acute attack	Rare	May occur

and are not of the same degree as the ventilatory changes. Also, pulmonary hypertension in asthma is not very severe or sustained, and chronic cor pulmonale, as seen with chronic bronchitis and emphysema, is absent. It should also be noted that diffusion limitations do not play a major role in the defects in gas exchange which occur in bronchial asthma.

Clinical Characteristics of Asthma

Generally, the most frequently used classification of asthma considers two main forms, extrinsic (allergic) and intrinsic (idiopathic or infective). Although these two forms were discussed on page 3, for convenience, their various clinical characteristics are summarized in Table IV (also see Plates 1 and 2).

These two principal forms of asthma have essentially similar pathologic and physiologic features. Patients with either form may have relatively symptom-free periods interrupted by paroxysms of acute airway obstruction which may progress to status asthmaticus (page 6).

The clinical course of asthma is variable so that patients often cannot be unequivocally classified as having the extrinsic or intrinsic type. For instance, *mixed asthma*, previously described on page 6, has features common to both forms of the disease. In addition, either type of asthma may become chronic, or infective bronchitis and even emphysema may coexist with the asthma and worsen the prognosis. Thus, a number of clinical subtypes of asthma exist:

1. *Chronic Asthmatic Bronchitis.* In patients with established chronic bronchitis, an asthmatic pattern may coexist but allergic factors are not necessarily definable. Primary therapy of the bronchitis can be supplemented by bronchodilator medication.

2. *Asthma, Aspirin Sensitivity, and Nasal Polyposis.* In this subtype, symptoms of asthma may occur within 20 minutes of

ingestion of aspirin. Nasal polyposis, however, is not always present. Most of the patients with aspirin sensitivity have the intrinsic form of asthma but with perennial symptoms. Coexisting eosinophilia can be severe. An estimated 10% of adult asthmatics have an intolerance to salicylates which does not appear to be immunologically induced. Bronchial sensitivity to indomethacin and other drugs may also develop.

3. *Exercise-Induced Asthma.* This variation of asthma is precipitated following moderate to severe exercise, particularly in atopic individuals. It frequently develops in younger patients within 10 minutes after exercise such as running. Bronchodilators or cromolyn sodium may be used prophylactically.

4. *Dual Type I and Type III Reactions.* As an example, sensitivity to the saprophytic mold *Aspergillus fumigatis* can induce a typical Type I asthma reaction (within 10 to 30 minutes of exposure), or a Type III reaction (2 to 6 hours after exposure), or both Type I and Type III reactions combined (Table I).

Patients who have a dual reaction will develop an acute episode of wheezing and dyspnea with a fall in $FEV_{1.0}$ within 10 to 15 minutes of exposure to the allergen. These findings may subside but are followed by a response 2 to 6 hours later. This second reaction develops more slowly than the first and is characterized by progressively severe airway obstruction, dyspnea, and, in some patients, pulmonary inflammatory infiltrates. Late (Type III) bronchial reactions can also occur in nonatopic patients who are sometimes classified, somewhat incongruously, as extrinsic, nonatopic asthmatics. Both immediate and late skin sensitivity may be found in association with the presence of reaginic IgE and precipitating IgG antibodies, suggesting that the pathogenesis is a consequence of immune processes involving these two immunoglobulins. Dual reactions can also occur in response to other substances, including platinum salts. Cromolyn sodium may inhibit the sequence.

5. *Chronic Asthma.* Chronic asthma may be caused by a number of precipitating factors and is characterized by symptoms of airway obstruction which occur on a more or less continuous basis.

Symptoms and Clinical Findings. Patients with bronchial asthma may experience symptoms and signs which range from discrete, acute episodes of shortness of breath, wheezing, and cough followed by remission to more or less continuous, chronic symptoms which wax and wane in severity. For any patient, symptoms may be mild, moderate, or severe at any given time. The asthmatic attack can be a terrifying experience, especially for patients who are aware of its potentially malignant progression.

The symptoms of an asthmatic episode may develop gradually or suddenly and may be preceded by a precipitating episode of allergic rhinitis or upper respiratory tract infection. A sensation of chest tightness and the feeling that it is more difficult to breathe in than out are frequent complaints of many patients. Expiratory and often inspiratory wheezing is audible and is associated with variable degrees of dyspnea.

Cough is often present and may be productive of sputum (Plate 22 and page 43). The sputum tends to be clear and mucoid. If the complications of infection and/or stasis occur, it may be green, gray, or yellow. The color of the sputum is the result of cellular necrosis and the products of the inflammatory response including large numbers of degenerated polymorphonuclear leukocytes (neutrophils and eosinophils). The inability to raise secretions is *ominous* and indicates widespread bronchiolar plugging with tenacious sputum.

Physical examination is vital for the evaluation of both the pulmonary and systemic effects of the asthmatic attack. Ordinarily, the patient prefers to sit upright and visibly uses the accessory respiratory muscles to augment the work of breathing. Anxiety and apprehension generally vary with the intensity of the insult. Tachypnea may be the result of fear, airway obstruction, or changes in blood and tissue gas tensions or pH. Hypertension and tachycardia reflect increased catecholamine output, although a pulse rate greater than 130/minute may indicate significant degrees of hypoxemia. Pulsus paradoxus is a helpful finding indicating significant pulmonary hyperinflation and usually occurs when $FEV_{1.0}$ is 1.25 L or less. If hypoxemia is severe, cyanosis may be noted. Flushing or perspiration of the face and upper torso and monosyllabic speech also signal the gravity of the attack. If severe hypoxemia and/or hypercapnia with respiratory acidosis supervene, the patient may be fatigued, confused, and

agitated, or show neuromuscular abnormalities such as asterixis and papilledema.

Chest examination will reveal a hyperresonant percussion note, a low-lying diaphragm, and other evidence of hyperinflation. Breath sounds can be coarse and loud with vesicular features but are often quite distant. Expiration is prolonged. Because of secretions, musical coarse rhonchi may be heard superimposed on this background of generalized inspiratory and expiratory wheezing. Focal areas of rales and evidence of consolidation should suggest atelectasis or pneumonia. The pitch of the wheezing tends to rise with progressive obstruction. If there is low-grade obstruction, wheezing may be slight or even absent but can be accentuated by rapid, deep breathing. However, if the degree of obstruction is great and airflow is severely reduced, the chest may become *paradoxically silent:* This is an *ominous* finding. Often a silent chest is inadvertently induced by the administration of hypnotics, tranquilizers, or sedative drugs which depress respiration. At the point where airflow is so decreased that the chest becomes silent, cough becomes ineffective despite repetitive, hacking maneuvers, and ventilatory failure may be present (page 51).

Complicating or coexisting diseases such as pneumonitis, pleurisy, atelectasis, heart failure, pulmonary emboli, or pneumothorax can contribute characteristic physical findings in addition to those produced by the asthma. Unfortunately, cardiac auscultation is frequently limited by the adventitious noise within the chest and by the increase in residual air. However, tachycardia and accentuated pulmonic second sound (S_2P) are often discernible. Laryngeal stridor or obstruction caused by tracheal masses (*e.g.*, tumors) generally should not be confused with diffuse airway obstruction. In elderly patients, heart failure should be easily diagnosed by the findings of typical prominent neck veins, rales at both lung bases, cyanosis, cardiac gallop rhythm, and peripheral edema. Clubbing of the fingers is unusual in asthmatic patients and its presence should alert the physician to the possible coexistence of suppurative, neoplastic, or other hypoxemic disease processes.

Physical examination may detect other complicating diseases. Careful examination of the ears, nose, sinuses, skin, and abdomen is essential and may disclose complicating or precipitating diseases such as sinusitis, nasal polyps, or hiatal hernia with aspiration.

Differential Diagnosis

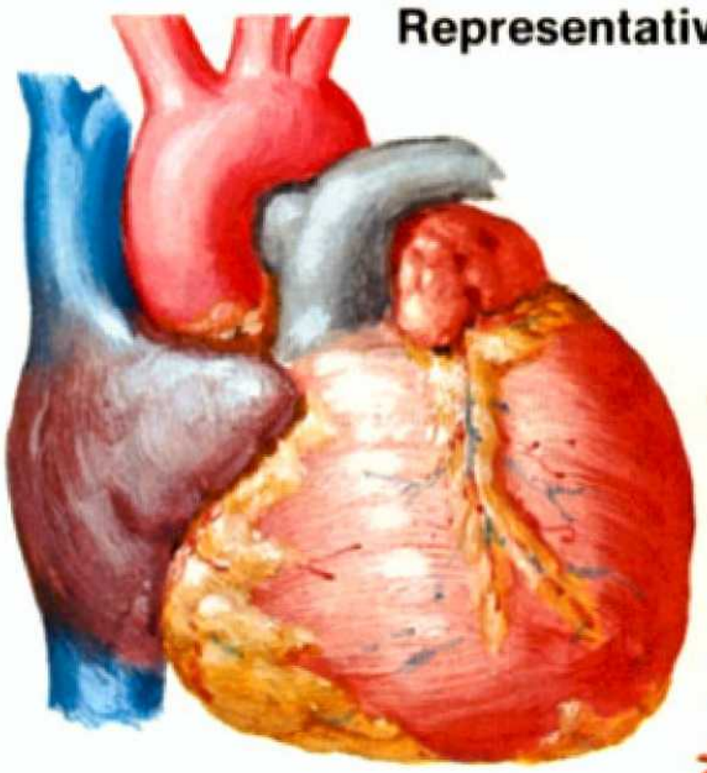
The erroneous concept that wheezing is synonymous with asthma is still prevalent. Accordingly, the cliche, "All that wheezes is not asthma" serves as a reminder that wheezing (and/or dyspnea) is not pathognomonic of bronchial asthma. For the patient who is wheezing, a combination of history, physical examination, and laboratory findings should suffice to establish a diagnosis. Diseases that must be considered in this differential evaluation are shown in Plate 21. Included in the category of pulmonary diseases, in addition to those conditions illustrated, are pneumoconiosis and periarteritis nodosa involving the lungs. In addition, wheezing episodes have been recently described following exposure to cotton fibers or inhalation of toluene diisocyanate in plastics manufacturing. Another type of pneumoconiosis that may follow an asthmatic pattern is baker's asthma from wheat flour sensitivity. In these specific cases, a history of the occupational exposure and reaction following exposure to the antigen will aid in diagnosis.

Laboratory Findings

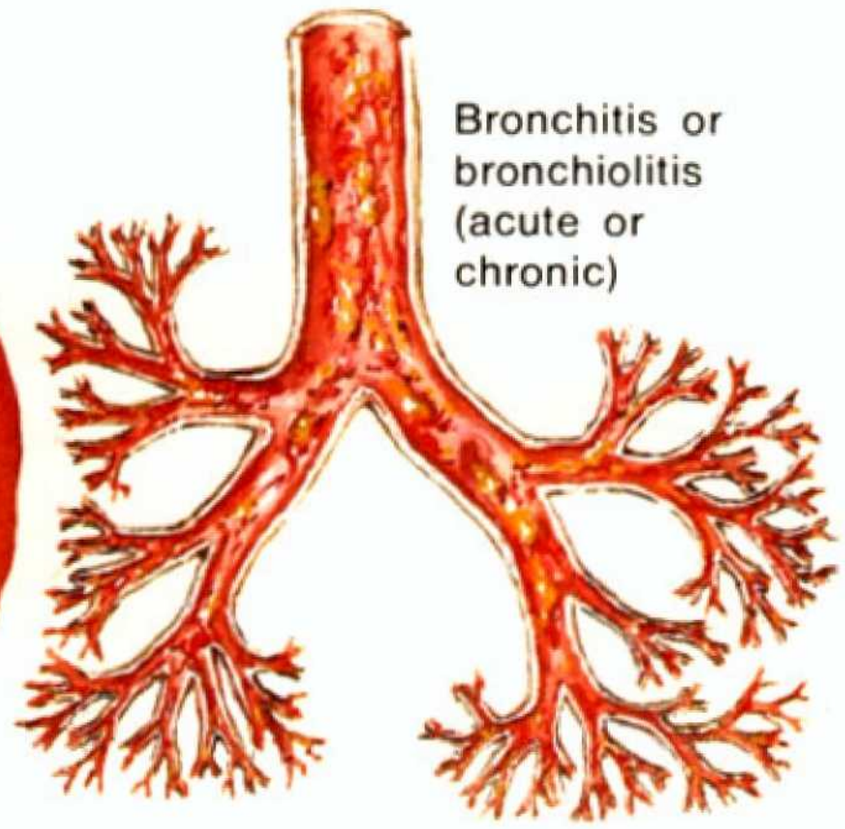
Specific therapy of the acute asthmatic episode is aided by the information obtained from various laboratory and diagnostic tests. The purpose of such diagnostic investigation is to evaluate pulmonary function (page 29), to assess the relative roles of infection and allergy, and to determine if complicating conditions coexist. In the following discussion, blood gas and pH studies are not included because they will be presented in the section on the management of status asthmaticus (page 48). Similarly, allergic skin testing will be discussed in conjunction with long-term management (page 69).

Radiography. The primary value of radiography is to exclude other diseases from consideration, as well as to determine if pneumonia, atelectasis, pneumothorax, or bronchiectasis exist. In a mild asthmatic attack, the chest X-ray will show no specific abnormal findings. If severe obstruction is present, however, a characteristic reversible hyperlucency of the lung is evident with widening of costal interspaces, depressed

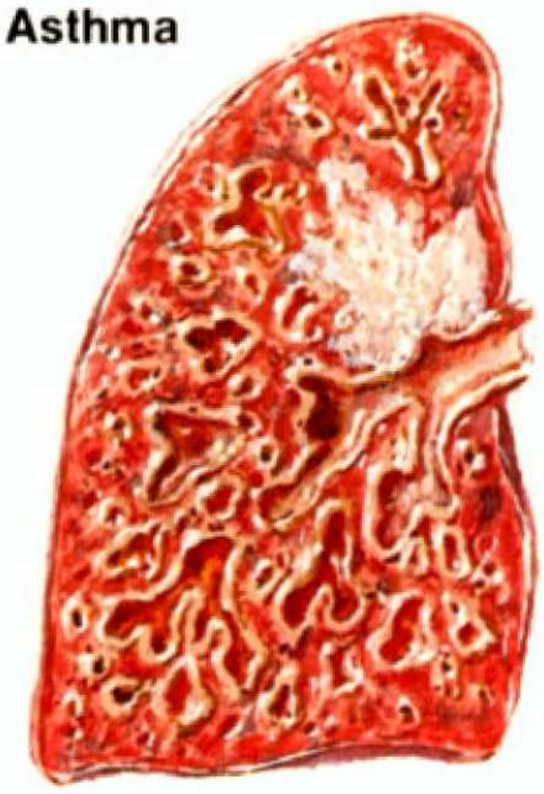
Representative Differential Diagnosis of Bronchial Asthma



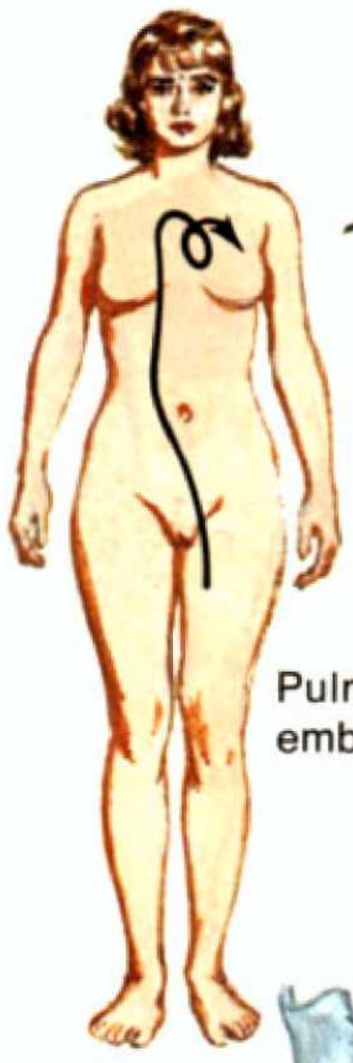
Congestive heart failure (cardiac asthma)



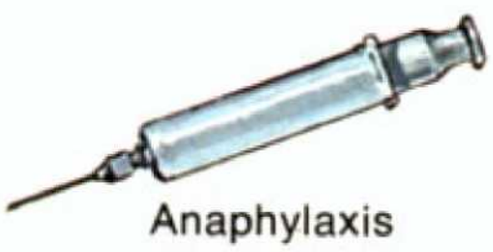
Bronchitis or bronchiolitis (acute or chronic)



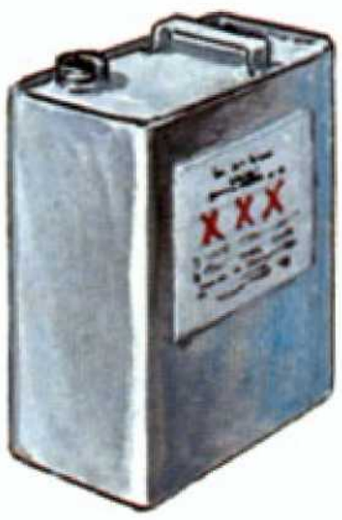
Bronchiectasis or other pulmonary disease (infective, neoplastic, or granulomatous)



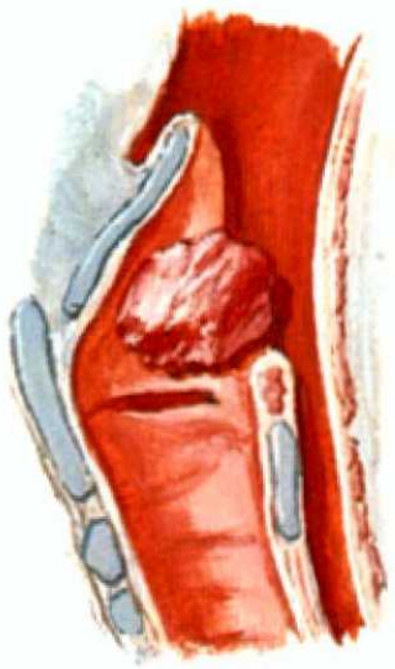
Pulmonary embolism



Anaphylaxis

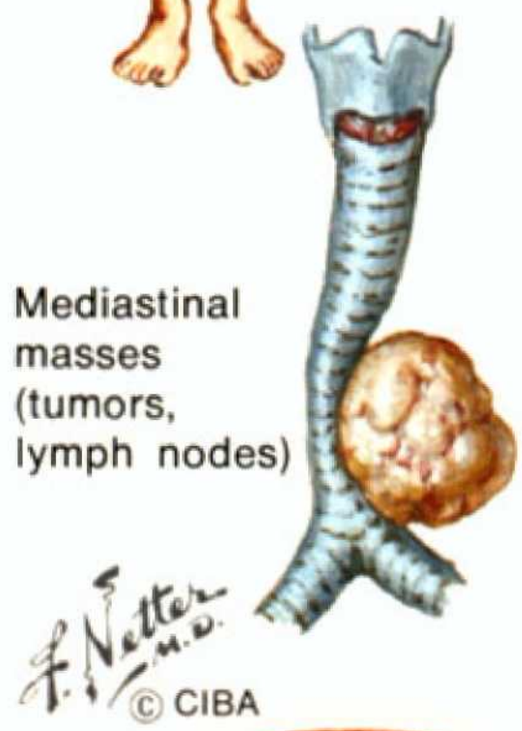


Irritant inhalants (industrial or home)

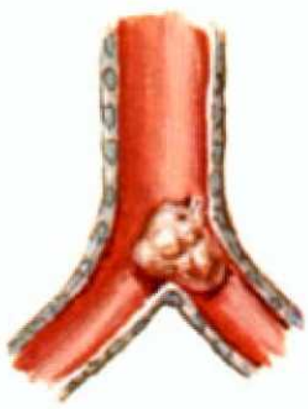


Aspiration (food or foreign body)

Farmer's lung (allergic alveolitis with dual asthmatic reaction)



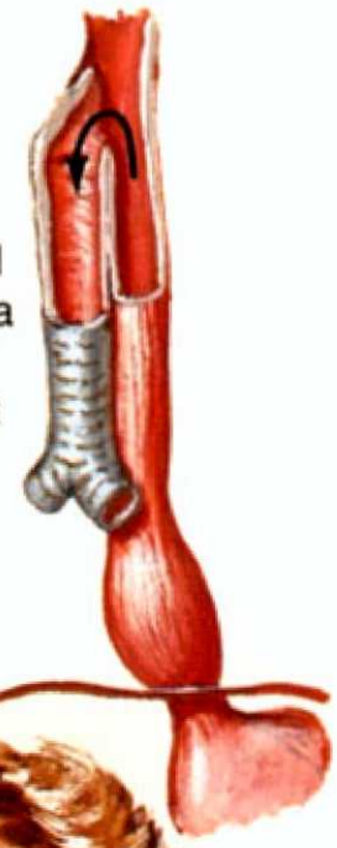
Mediastinal masses (tumors, lymph nodes)



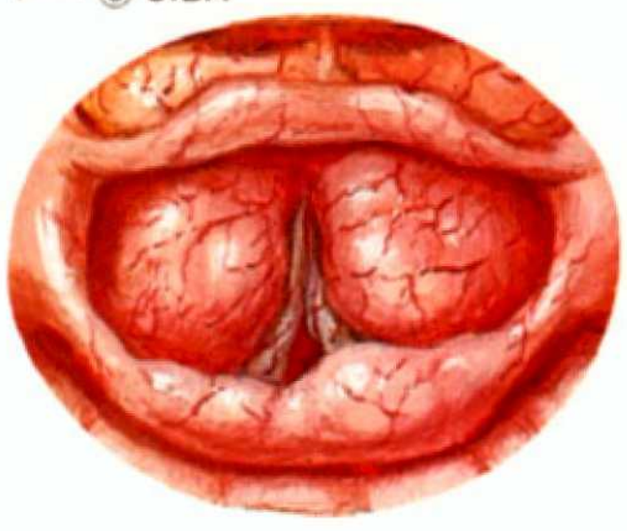
Tracheobronchial tumors

Congenital constrictive vascular rings

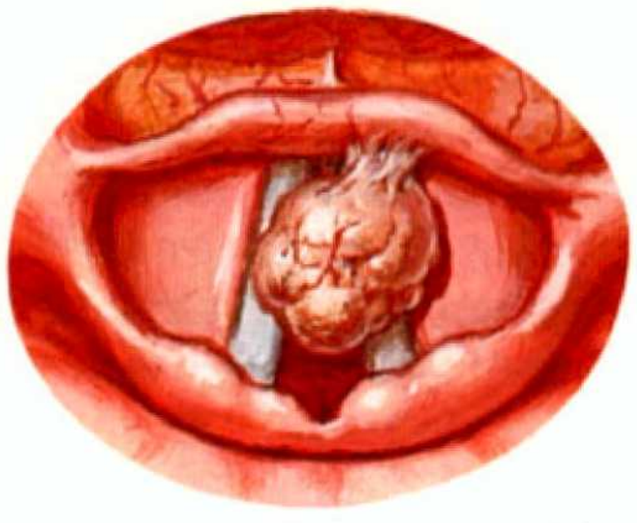
Aortic aneurysm



Hiatal hernia with reflux



Laryngeal edema (croup)



Laryngeal tumor or cyst (may be ball-valve type)

Anxiety hyperventilation

F. Netter M.D.

diaphragm, and the presence of increased air retrosternally. In contrast to chronic obstructive pulmonary emphysema where the vascular branching is attenuated and distorted, the vascular markings in asthma are generally undisturbed as judged by the caliber and distribution of major vessels. Occasionally, however, the main pulmonary artery segments are prominent. The heart size remains normal or small relative to the thoracic size, unless cardiac disease coexists.

Focal atelectasis, a complication of asthma, is caused by impaction or inspissation of mucus and may be seen on chest X-ray. In children, even a complete collapse of a pulmonary lobe may be observed. Atelectatic shadows may be transient and sporadic as mucus impaction shifts from one lung zone to another. When sputum is appropriately liquefied and the asthmatic attack is brought under control, these atelectatic patterns will no longer be found.

This pattern of fleeting and recurrent areas of atelectasis may also be observed in patients who have bronchial hypersensitivity associated with *Aspergillus fumigatus* (page 40). The characteristic radiographic feature is the occurrence of transient, ill-defined, pneumonic, or bandlike shadows which are located centrally or in the upper lobes and which are caused by inspissated mucous plugs containing the fungus. Patients with this type of bronchial hypersensitivity have eosinophilia and may show dermal reactivity or serum precipitins to the fungus. *Aspergillus fumigatus* may also be seen in smears or cultures of the sputum. The association of fleeting opacities, eosinophilia, and *Aspergillus fumigatus* in the sputum should suggest the diagnosis, although these opacities may also be caused by other disorders such as parasitic disease.

Radiography is also useful in evaluating coexisting disease of the paranasal sinuses, adenoidal masses, or nasal polyps. Other complications which may be documented by radiography include pneumothorax, pneumomediastinum, and rarely, pneumopericardium. Chest fluoroscopy may be helpful in assessing dynamic air trapping during expiration. An upper G.I. series is indicated in patients thought to have hiatal hernia with recurrent aspiration leading to asthma. However, these procedures are generally deferred until the acute episode has subsided. Lung scans or angiography may be required if pulmonary emboli are suspected of mimicking an asthmatic pattern.

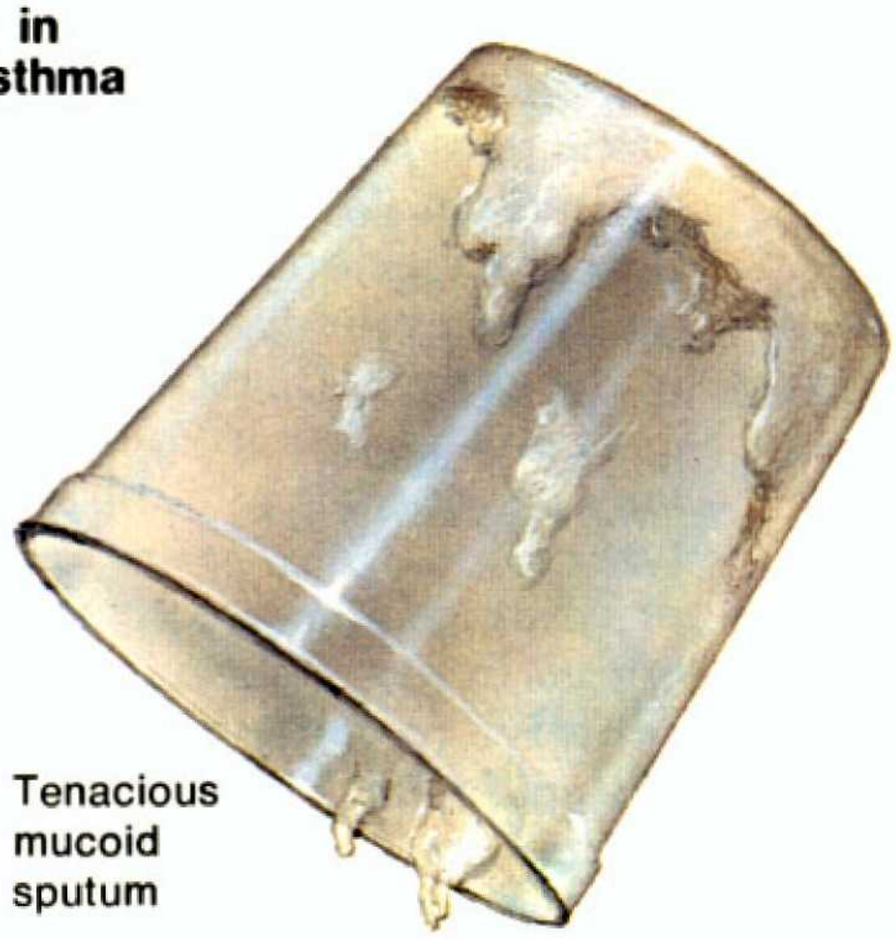
Sputum. Gross and microscopic examination of expectorated sputum is valuable as a means of evaluating the pathology occurring in the airways (Plate 22).

In any given case of asthma, the sputum may be mucoid, frankly purulent, or a mixture of both. *Mucoid sputum* is an opalescent or white gelatinous substance which is generated in purely allergic insults. It is quite adhesive to contiguous structures, such as the epithelial lining of the airways, and is internally viscous because of the presence of mucopolysaccharide and mucoprotein fibers. These physical properties also appear to relate to water content; the more water that mucoid sputum contains, the less viscous and less adhesive it is. Recognition of such sputum is based on its color, thickness, and adherence to the patient's tongue or to the walls of the sputum jar. Clinically these properties of mucoid sputum promote stasis and impaction of secretions within the bronchi and bronchioles, leading to critical obstruction and possibly secondary infection. This type of sputum is very difficult to expectorate.

Purulent sputum may be yellow, gray, or green. Like mucoid sputum, it is thick or viscous but this property is the result of desoxyribonucleic acid fibers arising from necrotic debris of inflammatory cells, bacteria, or parenchymal cells. When infection is present, large volumes of purulent sputum may be produced, but the color of the sputum is not related to a specific bacterial pathogen.

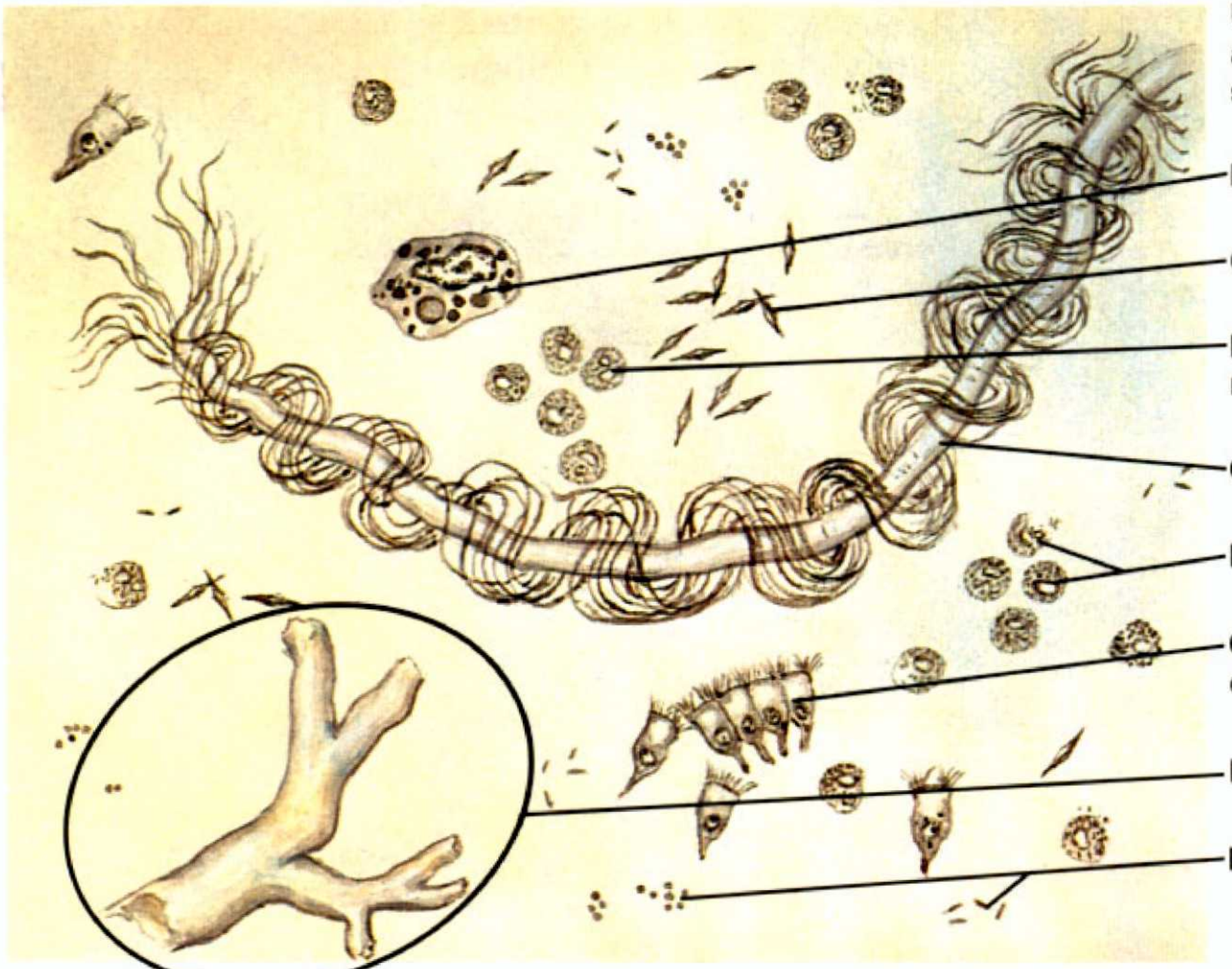
The sputum should be examined microscopically; it may be stained with aqueous crystal violet or viewed as a wet preparation under a cover slip. Thin spiral bronchiolar casts, measuring several centimeters in length, are strongly indicative of asthma. These are called Curschmann's spirals and may often be detected grossly. Ciliated columnar bronchial epithelial cells are frequently found in sputum smears. This type of cell may be recognized by the presence of cilia and by the ovoid, basally displaced nucleus, granular cytoplasm, and tapered base or tail which represents the attachment of the cell to the basement membrane. Another cell that is easily recognized by its granular cytoplasm and, in wet preparations, its brownian movement, is the polymorphonuclear neutrophil

The Sputum in Bronchial Asthma

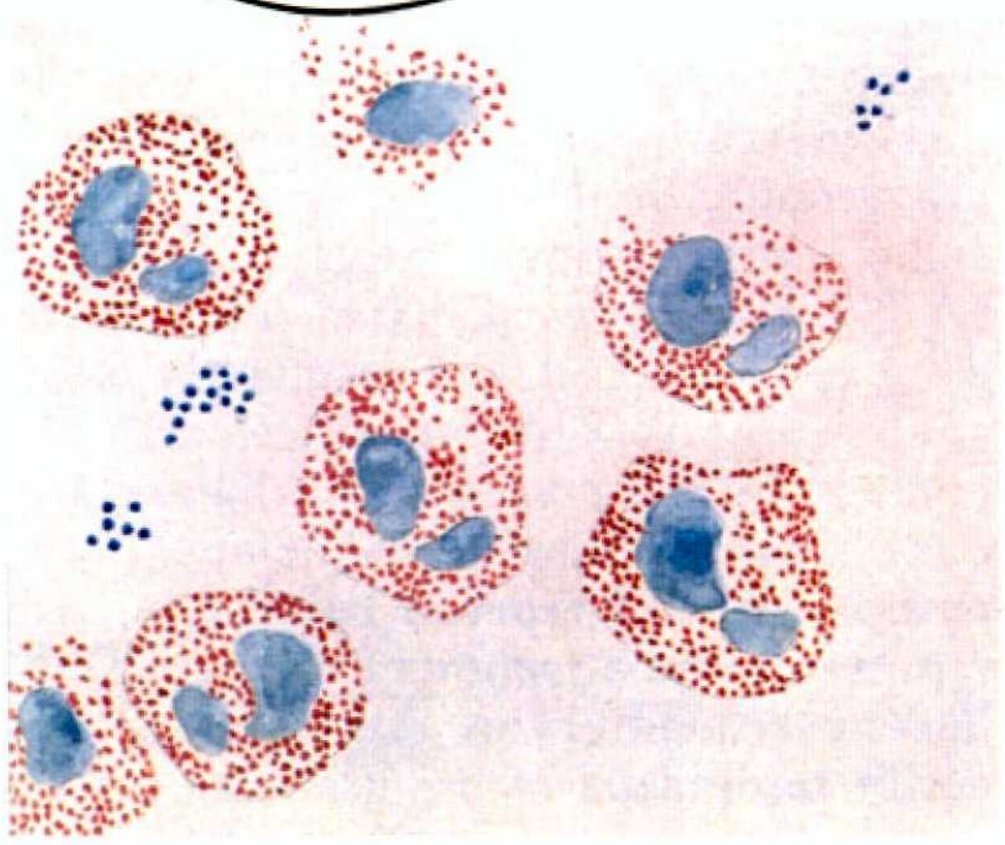


Tenacious mucoid sputum

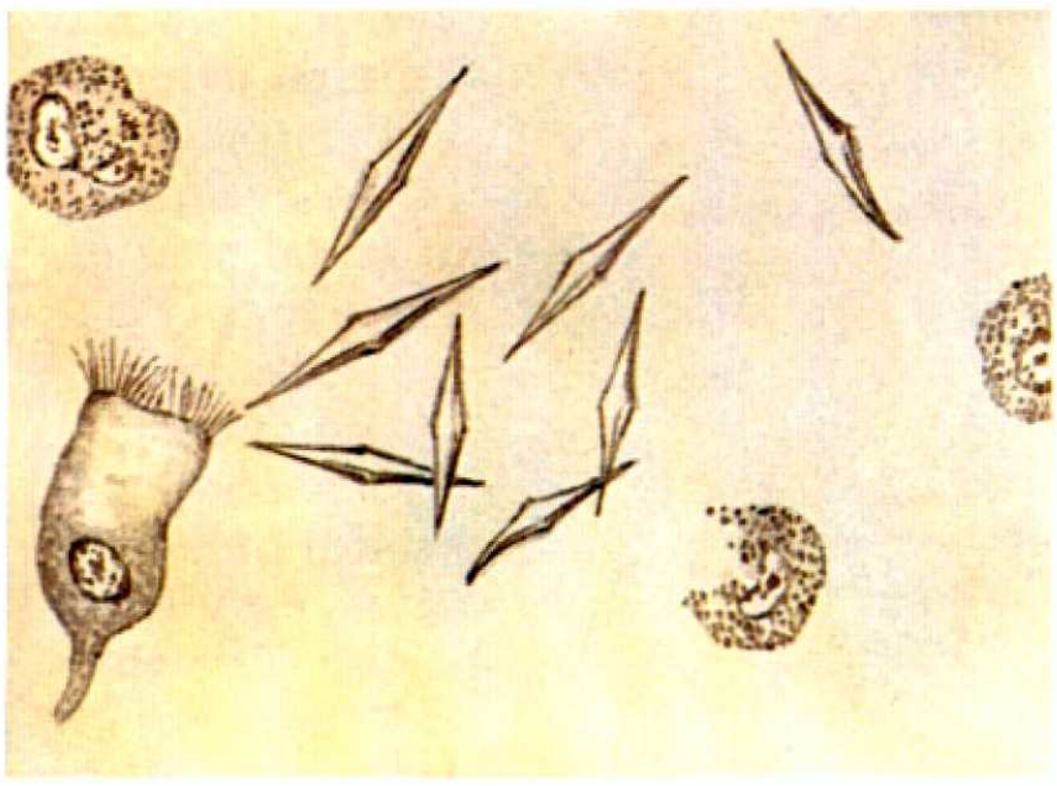
Purulent sputum



Unstained smear of asthmatic sputum; schematic (low power)



Eosinophils and staphylococci in stained smear



Charcot-Leyden crystals, eosinophils, and an epithelial cell under high power

leukocyte (PMN). This cell measures 10 to 15 μ in diameter. In a purely infectious exacerbation of bronchial asthma, the polymorphonuclear neutrophil leukocyte is the predominant cell.

In allergic bronchial asthma, a plethora of eosinophils are stimulated and may comprise from 10 to 90% of the cell population in the sputum. Eosinophils are structurally similar to polymorphonuclear neutrophils except that the cytoplasmic granules are larger, more uniform, and highly refractile. This refractile property can be detected by focusing up and down with the microscope. Large numbers of crystalloid degenerations of eosinophils can also be identified in the sputum smear. These colorless fragments (20 to 40 μ in length), called Charcot-Leyden crystals, are elongated and octahedral in shape. Creola bodies, seen in wet preparations, are clumps of bronchial epithelial cells with moving cilia. They are very characteristic findings in the sputum of patients with severe bronchial asthma.

Macrophages are large cells (10 to 40 μ in diameter) and have numerous inclusion bodies. Adequate numbers (>10 to 15% of the cell population) reflect appropriate cellular defenses.

Brown plugs or casts in the sputum may be caused by allergic aspergillosis and should prompt a search for fungi. Finally, a gram stain is important because it can guide initial antimicrobial therapy pending the results of specific bacterial cultures and sensitivities.

The amount of sputum raised often indicates the effectiveness of secretion mobilization. Early in status asthmaticus the sputum is often sparse and, as will be discussed later, this sparsity indicates the need for mobilization of secretions. One significant finding indicating lysis of an asthmatic attack is the appearance of increased quantities of sputum. Supportive measures are mandatory to assist an ineffective cough, promote sputum clearance, and prevent exhaustion.

Nasal smears can be analyzed in the same way as sputum. This examination may be particularly helpful in diagnosing allergic rhinitis if eosinophil counts of 10% or greater are found.

Blood Tests. Because of stress, dehydration, or infection, leukocytosis may occur. However, an increase (>15,000/mm^3) in the polymorphonuclear neutrophil leukocytes, including band forms, indicates superimposed infection. Basophilia is variable. A low blood eosinophil count may be seen in the early stages of the asthmatic episode or if infection is present. A differential count of greater than 5% usually suggests an allergic asthmatic reaction. Total eosinophil counts are more quantitative and are of greater clinical significance. They can be used serially to judge the efficacy of treatment, particularly corticosteroid therapy. Values higher than the normal count of 250/mm^3 (often in the range of 800 to 1000/mm^3) provide a rough indication of the severity of the allergic reaction. However, eosinophil counts greater than 4000/mm^3 are more likely to be associated with parasitic infection. Conversely, the absence of eosinophils does not exclude asthma from the diagnosis. If during therapy with corticosteroids the eosinophil count does not drop, it may be indicative of steroid-resistant bronchial asthma.

Usually, blood chemistries are normal unless secondary complications develop. For example, vomiting, diarrhea, or severe dehydration may cause electrolyte changes. Also, in patients who are taking diuretics or steroids, blood electrolyte changes may occur; a complicating hypochloremic/hypokalemic alkalosis can contribute to ventilatory depression. If pulmonary emboli, heart failure, or collagen disorders are masquerading as bronchial asthma, appropriate blood tests may be of diagnostic value. Also, a nonspecific increase of hepatic transaminase enzymes may be caused by hypoxia. If recurrent infections are believed to be the basis for the asthmatic episodes, immunoglobulin concentrations should be determined.

Electrocardiogram. A tachycardia greater than 120/minute may indicate serious hypoxemia ($P_aO_2 < 40$ mm Hg). Usually a sinus tachycardia occurs during an asthmatic attack and reverts to regular sinus rhythm with remission. Occasionally, during a very severe asthmatic episode, pulmonary hypertension may cause reversible right ventricular strain with axis shift, right bundle branch block, and prominent right atrial P waves. Differentiation from pulmonary hypertension caused by embolization can be difficult.

In elderly patients, the stress of the asthmatic episode can precipitate arrhythmias or myocardial ischemia. Arrhythmias can also be produced by the administration of cardiac-stimulating drugs, such as epinephrine or

isoproterenol, particularly in the hypoxemic individual with coexisting coronary artery disease, valvular disorders, or various cardiomyopathies.

Principles of Management

Although prompt treatment of acute asthmatic episodes is imperative, *prevention* of the symptoms and signs of asthma is fundamental to any program of therapy. The patient must be thoroughly evaluated in an effort to determine all possible causative and contributing factors, because long-term management (page 63) depends on the elimination or control of such inciting influences.

The acute attack requires specific drug therapy. Most acute attacks respond to treatment and hospitalization is not required. However, any episode may progress to life-threatening status asthmaticus. Thus, it is better to treat an episode in its earlier stages before more desperate, heroic measures are required.

Treatment of the Acute Episode

The patient with an acute asthmatic paroxysm requires prompt therapy using specific drugs. Aqueous epinephrine 1:1000 is preferred for its rapid action. Formulations of epinephrine that provide more prolonged relief also have slower absorption, while aerosol preparations are less effective.

Aqueous epinephrine, in doses of 0.1 ml for children and up to 0.3 ml for adults, should be given subcutaneously, and this dose may be repeated at 30- to 60-minute intervals as needed if the response is adequate. In children, the dose may also be based on body weight (0.01 ml/kg); in both children and adults, doses are sometimes repeated as often as every 15 minutes. Simultaneously, oxygen should be administered if indicated by the degree of respiratory distress (Plate 23).

In the hypertensive, hyperthyroid, or cardiac patient, epinephrine must be used with caution. Also, intravenous epinephrine is not recommended for any patient.

The initial response to epinephrine administered subcutaneously may be inadequate or the patient may become refractory to the drug while the acute episode progresses. (This refractoriness has been ascribed in part to coexisting respiratory acidosis which is reversible by the intravenous administration of bicarbonate, page 63). If the patient does not respond to subcutaneous epinephrine, repeated injections of this drug are of no value and may be detrimental because of side effects. In this event, aminophylline, which is longer acting and which has an additive effect with sympathomimetic drugs, can be administered intravenously in doses of 250 to 500 mg. This drug must be injected *very slowly* over a period of 10 to 15 minutes, because too rapid administration can cause serious hypotension and even death.

Although individual variations in response must be considered, the bronchodilating effect of aminophylline is generally related to its serum concentration, with effective levels ranging from 10 to 20 μg/ml. These serum levels can usually be achieved with an initial intravenous adult dose of 5 to 6 mg/kg followed by a maintenance dose of 0.9 mg/kg/hr. Total daily dose should not exceed 2 grams. In children, the initial dose of aminophylline is 7 mg/kg, injected intravenously over a 15-minute period. If maintenance therapy is required in children, 4 mg/kg may be given every 6 hours by intravenous infusion.

In both adults and children, the clinical response or evidence of toxicity may dictate a lower maximum dose. If nausea, vomiting, nervousness, insomnia, or diarrhea supervene, the dosage should be reduced rather than discontinued. Overdosing can be associated with convulsions, coma, cardiac irregularities, or fatalities.

Because of the side effects of epinephrine which include hypertension, hypoxemia, palpitations, anxiety, tremors, tachycardia, and even arrhythmias, aminophylline is preferred for older patients. This preference for aminophylline is particularly important for patients who have "cardiac asthma" or wheezing from causes other than bronchial asthma. Aminophylline given orally or by rectal solution or suppository is usually not effective for the acute episode.

If the asthmatic attack does not respond to the previously described therapy, corticosteroids may be given. However, corticosteroid peak action does not usually occur until several hours after intravenous or intramuscular administration. Prednisone or an equivalent glucocorticosteroid (Table VI on page 57) should be administered intravenously in an initial adult dose of 40 to 80 mg. Between 200 and 400 mg of prednisone may be given during the first day of therapy. Patient response

Management of Acute Asthmatic Attack

1. Give aqueous epinephrine 1:1000 subcutaneously, 0.1 ml for children, 0.3 ml for adults; if initial response is adequate, repeat at 30 to 60 minute intervals as needed; oxygen as indicated; in hypertensive, hyperthyroid, and cardiac patients use epinephrine with extreme caution (aminophylline and oxygen preferable)

2. If response to epinephrine is inadequate or if patient becomes refractory, give aminophylline intravenously in dose of 250 to 500 mg very slowly over 10 minutes; administer oxygen

3. If necessary, corticosteroids, which act more slowly, also can be given (prednisone 40 to 80 mg intravenously, 200 to 400 mg first day)

4. Hospitalization is indicated if patient fails to respond to drugs

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Table V

SIGNS AND SYMPTOMS OF HYPOXIA AND RESPIRATORY ACIDOSIS

Hypoxia	Hypercapnia (or decreased pH)
Insomnia, changes in judgment, euphoria	Confusion, somnolence, coma
Restlessness, confusion, anxiety	Headache, papilledema, miosis
Coma	Muscle twitching, asterixis
Tachycardia, arrhythmias	Hypertension (later hypotension)
Central cyanosis, diaphoresis	Diaphoresis
Hypertension or hypotension	Cardiac failure
Cardiac or renal failure	

may indicate larger or smaller doses. (Dosage for children is given on page 57.)

Vitally important supportive measures in the treatment of the acute episode include initiating appropriate antimicrobial therapy if infection is present, establishing adequate hydration, and administering oxygen. In addition, expectorants, oral ephedrine, and isoproterenol by inhalation may also be given providing the patient is carefully observed. However, if the patient fails to respond to the previously described therapy with epinephrine and aminophylline, hospitalization is indicated.

Management of Status Asthmaticus

Status asthmaticus is an emergency situation with respiratory distress which is refractory to conventional therapy for the acute attack, and which taxes the resources of both patient and physician. Because of the intensive nursing care and continuous monitoring that are required for patients in status asthmaticus, hospitalization in an intensive medical or respiratory care unit is recommended.

Frequently, multiple factors are responsible for the extreme degree of airway obstruction found in patients with severe asthma. Because the obstruction carries the risk of respiratory failure, every effort must be made to identify and correct the underlying causes.

Changes in Blood Gases and pH. As a consequence of the advanced degree of airway obstruction which leads to serious $\dot{V}_A / \dot{Q}_c$ disturbances (page 37), certain changes in arterial oxygen and carbon dioxide tensions and pH occur. In fact, dangerous levels of hypoxemia may develop with alarming rapidity in patients with severe asthma and, at least initially, without retention of carbon dioxide. This phenomenon may lead to sudden death.

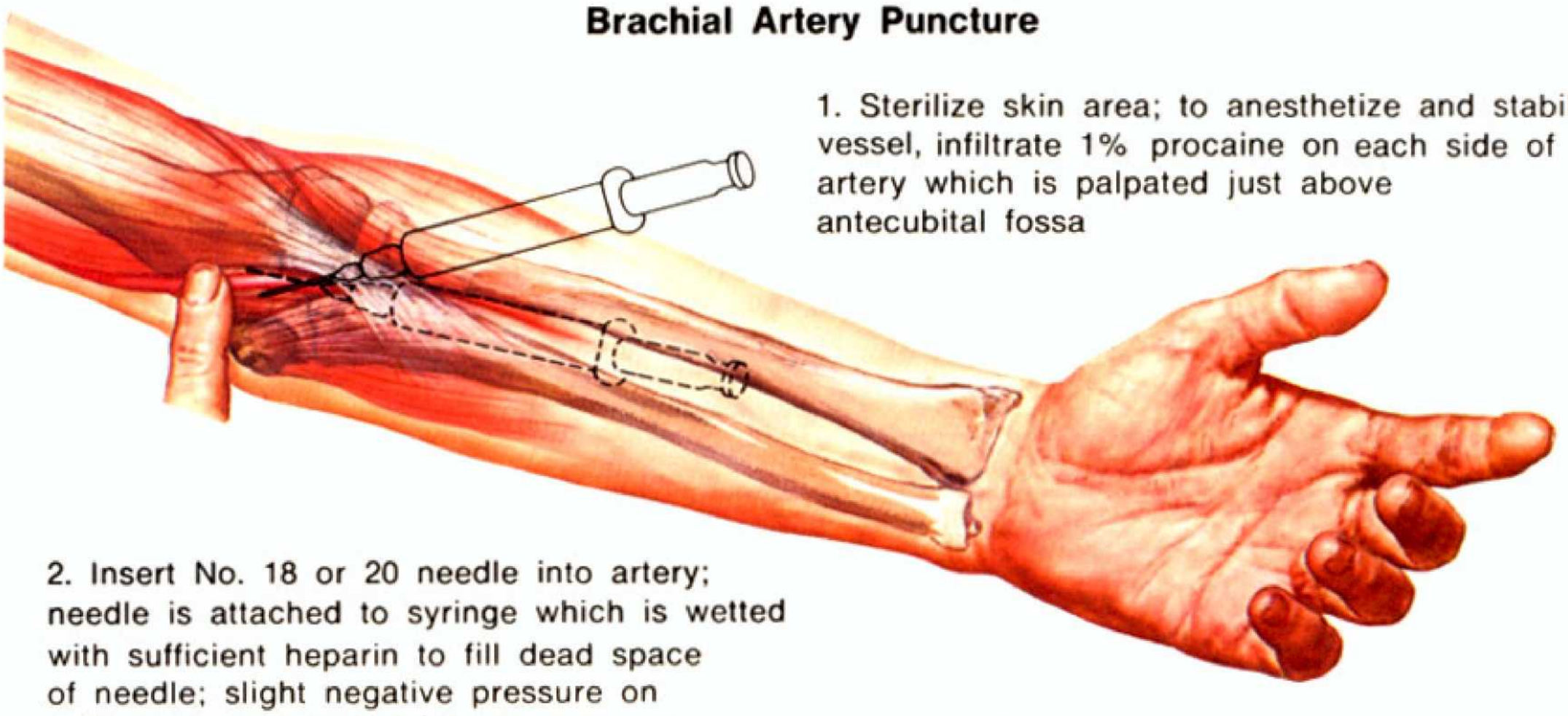
The changes in blood gases and pH cannot be quantitated by simple clinical observation but certain nonspecific signs and symptoms may be suggestive (Table V). Furthermore, a correlation between blood gas profiles and FVC and $FEV_{1.0}$ does not necessarily occur. (Usually, though, P_aO_2 tends to fall as FVC and $FEV_{1.0}$ decrease, and if the FVC is less than 1 L, hypercapnia is frequently present.) The considerable variation in these nonquantitative correlations, plus the need for precise documentation of the biochemical state, *mandates* obtaining blood gas and pH measurements. These determinations must be made repeatedly in order to evaluate serially the changes in gas exchange, and particularly the response to therapy.

The most convenient procedure for obtaining arterial blood is the brachial or radial artery puncture. The correct technique is shown in Plate 24. The illustrated precautions are necessary to prevent serious erroneous determinations of blood oxygen and carbon dioxide. As a reference for the interpretation of the blood gas and pH results, the concentration of oxygen being breathed should be noted as the blood is withdrawn.

Based on the arterial blood gas and pH data, the clinical profile of the patient with asthma may be classified as follows:

Phase I. P_aO_2 is normal ($\geq$85 mm Hg) or mildly reduced (75 to 84 mm Hg); oxyhemoglobin saturation (S_aO_2) is preserved ($\geq$94%); P_aCO_2 is normal (40 mm Hg) or mildly reduced; pH is normal (7.40) or slightly alkalotic (>7.42). These findings are typical for the asymptomatic patient or during a very minor attack. A modest impairment of pulmonary function may also be noted with

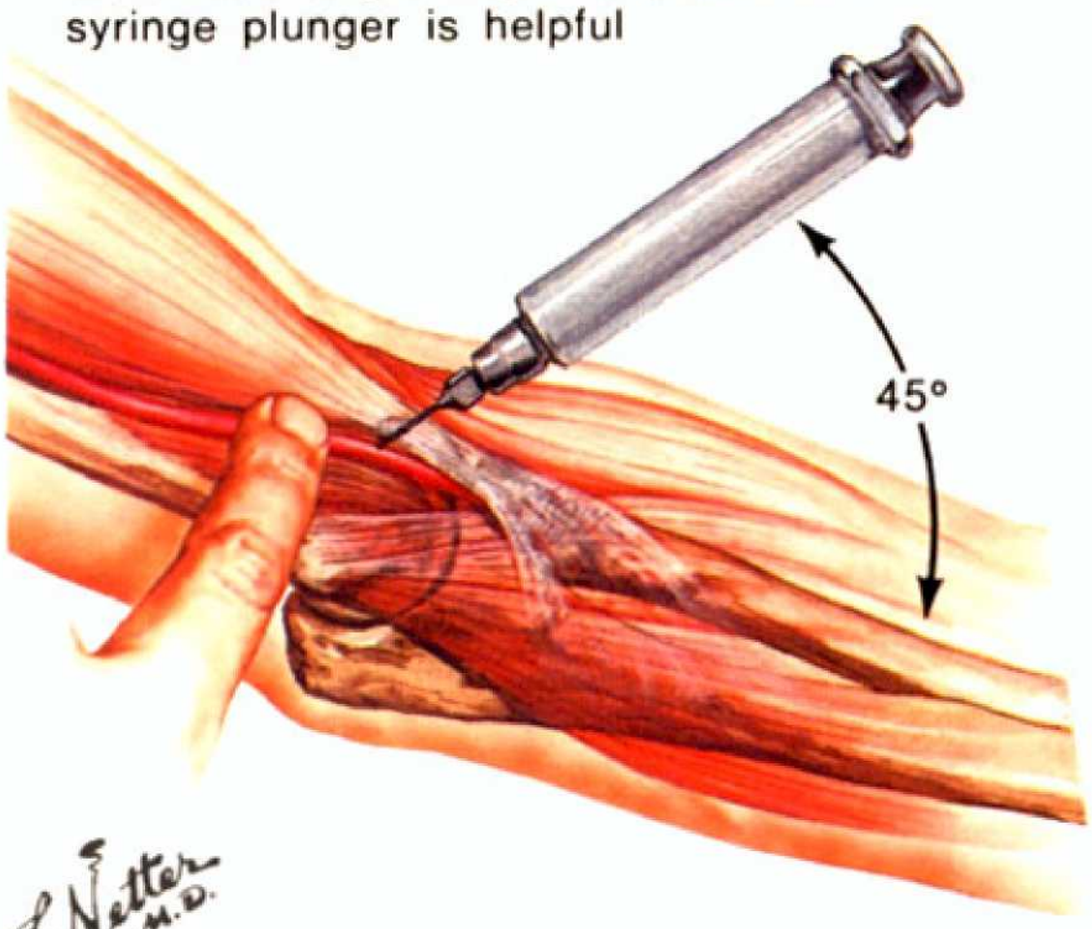
Brachial Artery Puncture

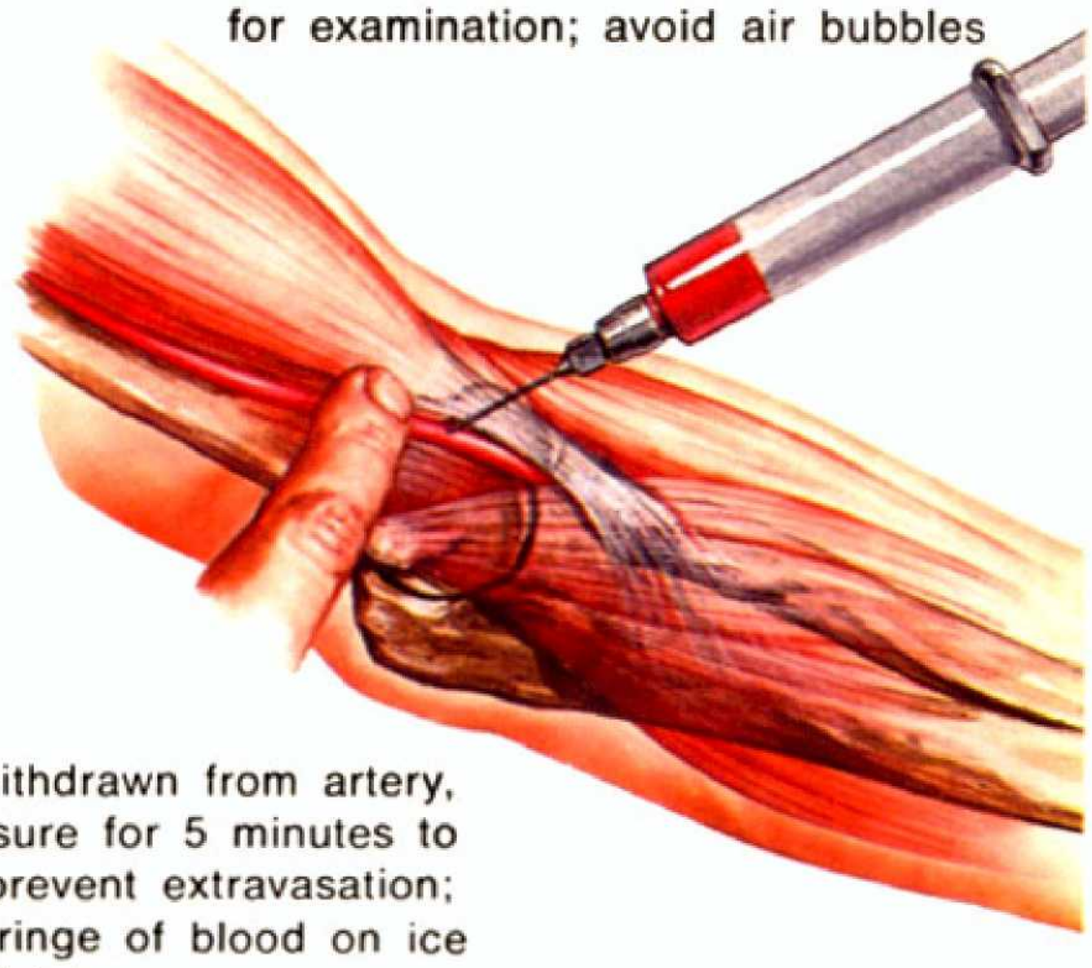


1. Sterilize skin area; to anesthetize and stabilize vessel, infiltrate 1% procaine on each side of artery which is palpated just above antecubital fossa

2. Insert No. 18 or 20 needle into artery; needle is attached to syringe which is wetted with sufficient heparin to fill dead space of needle; slight negative pressure on syringe plunger is helpful

3. If blood does not appear, slowly withdraw needle, manipulating until pulsatile blood is seen; once blood appears, hold syringe steady and slowly withdraw enough blood for examination; avoid air bubbles





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4. As needle is withdrawn from artery, apply digital pressure for 5 minutes to puncture site to prevent extravasation; cap and place syringe of blood on ice and assay immediately

spirometry, especially in expiratory flow rates.

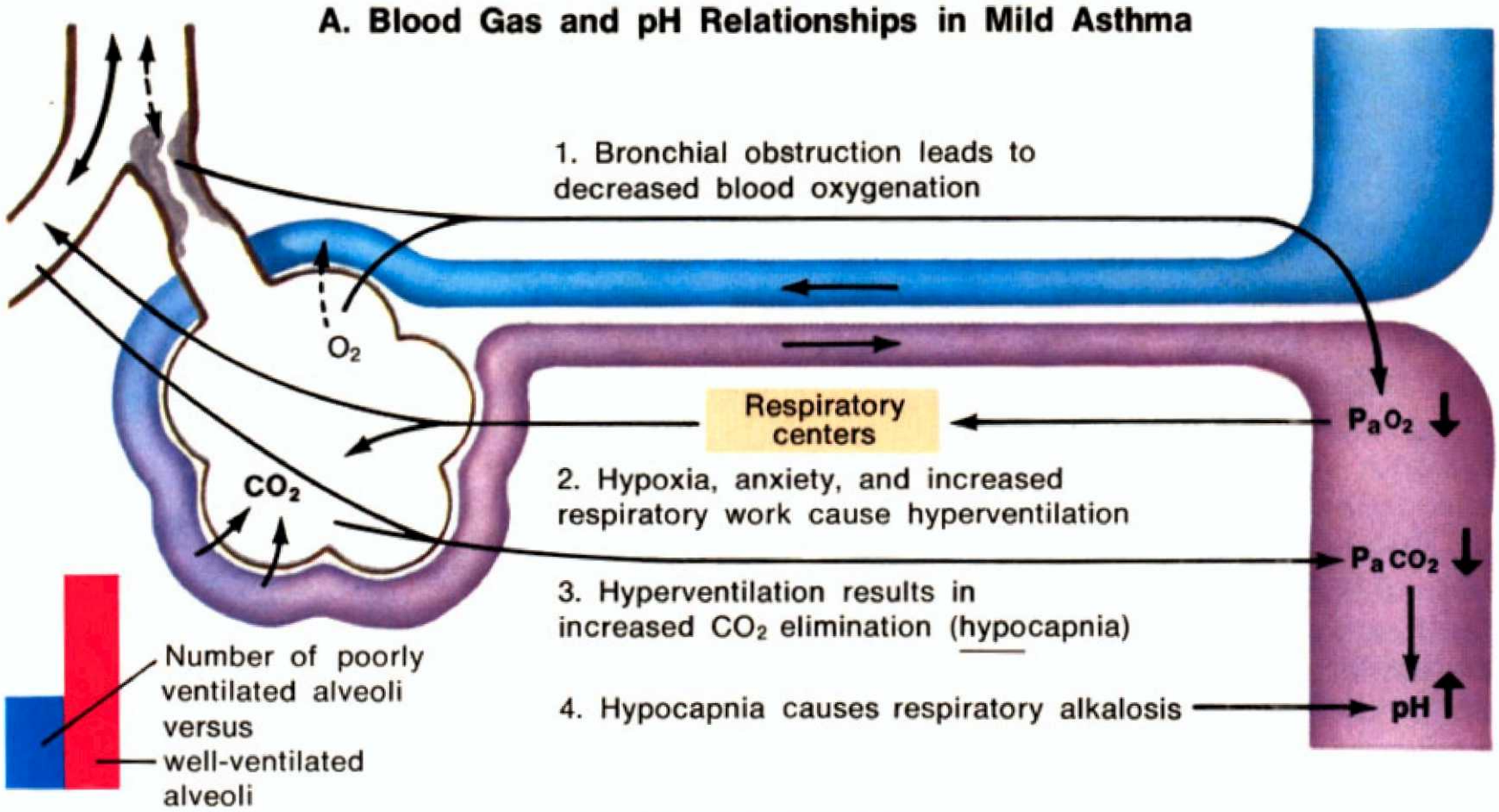
Phase II. In the early stages, hypoxemia and hypocapnia ($P_a CO_2 < 35$ mm Hg) are noted (Plate 25, A); respiratory alkalosis which may be compensated for to a variable degree also exists. This profile may be found in patients in a moderately severe chronic state of asthma or during a moderately severe acute attack. Pulmonary function is also impaired. Often this degree of obstruction will respond to therapy with bronchodilator medication.

With more severe obstruction, P_aO_2 decreases to a range of 55 to 70 mm Hg, S_aO_2 is between 85 and 90%, and $P_a CO_2$ is less than 30 mm Hg; respiratory alkalosis (pH >7.50) is apparent. This profile is associated with the acute, moderately severe episode or early phases of status asthmaticus. Spirometry shows significantly impaired flow and volume indices, and the response to bronchodilator drugs is variable.

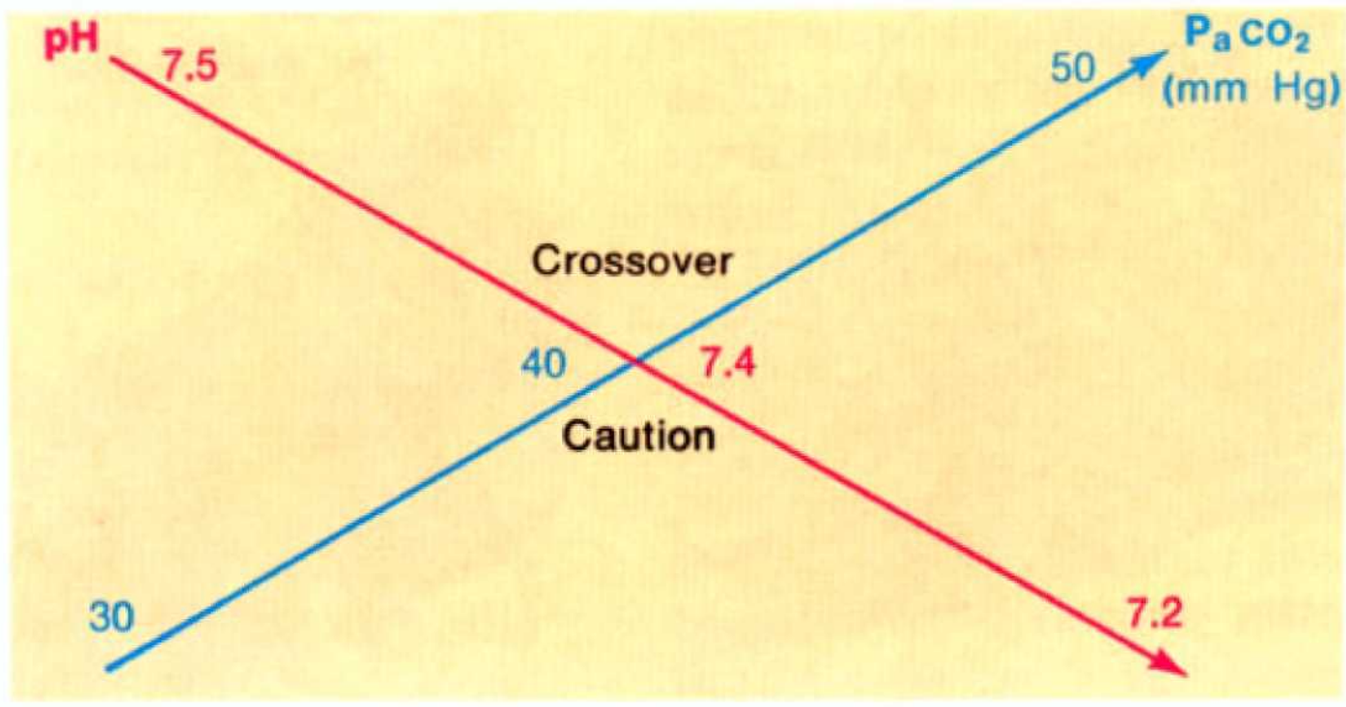
Phase III. In this crossover phase (Plate 25, B), hypoxemia is significant unless the patient is receiving supplemental oxygen; P_aCO_2 is *paradoxically* in the normal range, as is pH. Spirometry is grossly abnormal. (The significance of Phase III is discussed on page 51.)

Phase IV. Hypoventilation is associated with severe hypoxemia ($P_aO_2 < 55$ mm Hg,

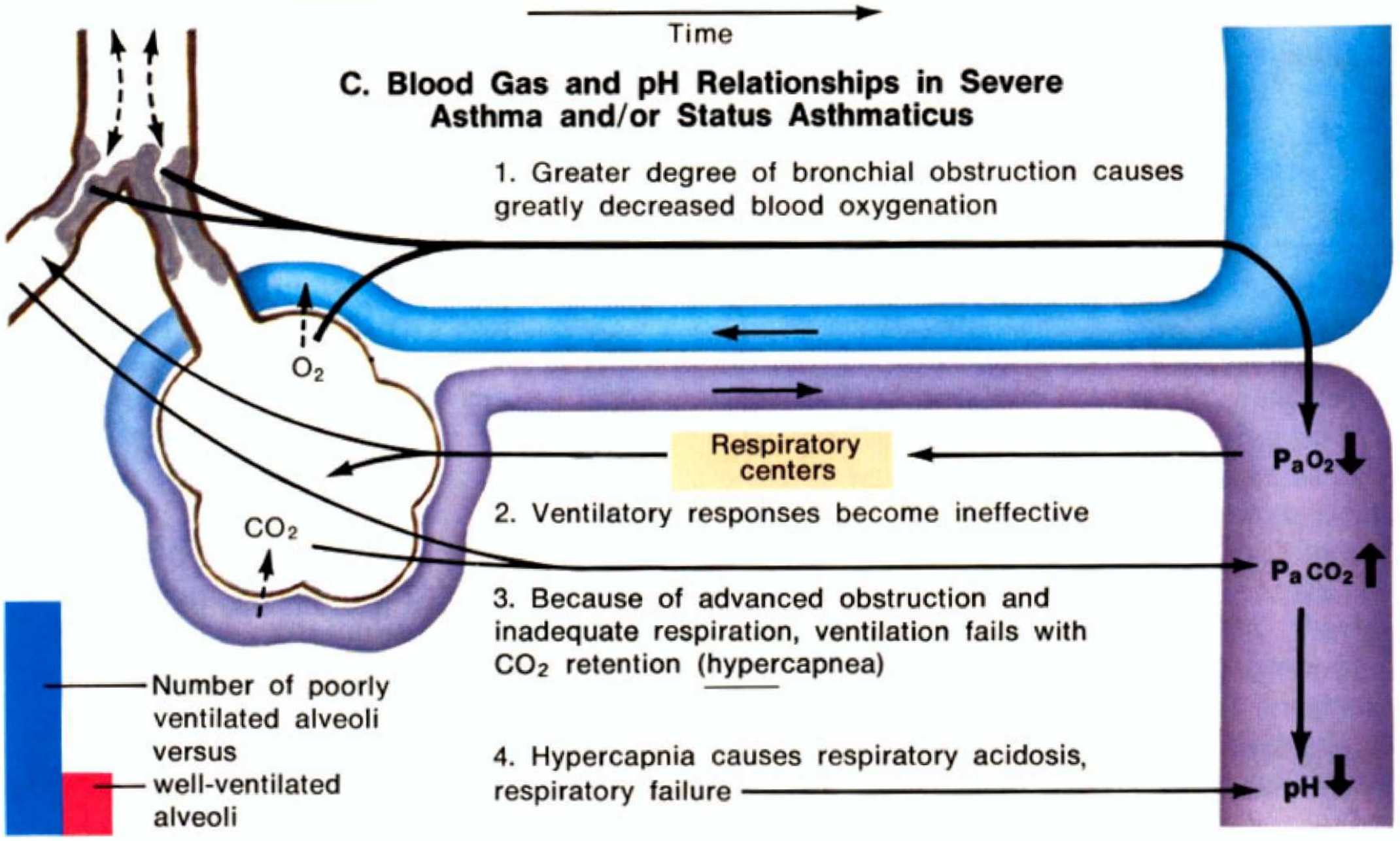
A. Blood Gas and pH Relationships in Mild Asthma



B. Crossover Phase



C. Blood Gas and pH Relationships in Severe Asthma and/or Status Asthmaticus



S_aO_2 <85%), hypercapnia (P_aCO_2 >45 mm Hg), and respiratory acidosis (pH <7.35). This profile is typically found during the more advanced stages of status asthmaticus (Plate 25, C). Response to bronchodilator medication during this phase is limited or absent.

In Phase I, the asymptomatic patient may exhibit mild hypoxemia because of minor gas-distribution abnormalities and $\dot{V}_A / \dot{Q}_c$ ratio disturbances. Patients with low-grade chronic asthma also fit into this category, even though arterial oxygen tension may be lower (in the range of 60 to 70 mm Hg) than that usually associated with Phase I. The patient with an acute, self-limiting asthmatic paroxysm, properly classified in Phase I, may transiently develop more severe hypoxemia. Although such attacks usually respond to bronchodilator therapy, the administration of oxygen during such periods is advisable.

In the initial phases of status asthmaticus, a Phase II profile may be observed, with a direct correlation existing between the severity of the airway obstructive process and the degree of arterial hypoxemia. During this stage of the attack, patients inevitably will manifest alveolar hyperventilation, which is distinct from, and should not be confused with, an increased respiratory rate (tachypnea). In fact, both hyperventilation and tachypnea may be present.

Alveolar hyperventilation is considered to exist when there is a reduction in the arterial carbon dioxide level (hypocapnia). Assuming that the rate of carbon dioxide production ($\dot{V}CO_2$) is constant, net alveolar ventilation ($\dot{V}_A$) is roughly *inversely* proportional to arterial carbon dioxide tension (P_aCO_2). Clinically, the net adequacy of alveolar ventilation is therefore judged by P_aCO_2 : If P_aCO_2 is 40 mm Hg, alveolar ventilation is normal; P_aCO_2 >40 mm Hg reflects net alveolar hypoventilation; and P_aCO_2 <40 mm Hg reflects net alveolar hyperventilation.

Hyperventilation may be induced by a variety of stimuli such as reflexes initiated by the intrapulmonary stretch receptors, hypoxia, increased respiratory work and metabolic demands, anxiety, and fear. This increased alveolar ventilation may lead to hypocapnia and acute (or chronic) respiratory alkalosis. Although such compensatory or augmented ventilation will effectively eliminate carbon dioxide from alveolar-capillary units with normal $\dot{V}_A / \dot{Q}_c$ ratios, it cannot contribute significantly to raising arterial oxygen tension: Alveolar-capillary units with normal ventilation (normal $\dot{V}_A / \dot{Q}_c$ ratios) are already operating maximally at the plateau of the S-shaped oxygen dissociation curve, whereas units with impaired ventilation (low $\dot{V}_A / \dot{Q}_c$ ratios) cannot effectively contribute to increasing oxygen tension. The degree of the resultant arterial hypoxemia is determined by the ratio of poorly ventilated alveolar-capillary units to well-ventilated ones and is thus directly proportional to the amount of obstruction.

During the later stages of Phase II, arterial carbon dioxide tension from 35 mm Hg to a low of 20 or even 15 mm Hg is encountered, with the lower levels often indicating a more serious attack. At this phase, the patient in severe status asthmaticus may have the following profile: P_aO_2 of 50 mm Hg, P_aCO_2 of 20 mm Hg, pH of 7.55, and S_aO_2 of 75 to 80% (Plate 25, A).

As the airway narrowing progresses, impairing gas exchange in increasing numbers of alveolar-capillary units, respiratory work is stressed beyond the patient's capacities. Both minute and effective alveolar ventilation fail, leading to alveolar *hypoventilation* (Plate 25, C). This is Phase IV which is characterized by advanced hypoxemia, hypercapnia (in contrast to the hypocapnia of the later stages of Phase II), and acute respiratory acidosis (in contrast to the respiratory alkalosis of the later stages of Phase II). These ominous events can occur either slowly or precipitously. If the pH changes occur rapidly, the buffering actions of the body are usually limited.

Patients with severe asthma who exhibit a Phase IV profile generally require support of respiration by artificial ventilation (page 59), because this serious clinical and biochemical state is associated with a high mortality rate. Treatment must correct respiratory failure and its functional consequences. Serial blood gas and pH determinations are mandatory.

Progression from early, effective hyperventilation (Phase II) to alveolar hypoventilation (Phase IV) includes a transitional or *crossover* period when relatively normal arterial carbon dioxide tension and pH are found (Plate 25, B). During this critical and diagnostically important period, oxygen tensions may be reduced. However, if the patient is receiving supplemental oxygen, oxyhemoglobin

saturation paradoxically will be preserved. As arterial carbon dioxide tension and pH shift from hypocapnia and respiratory alkalosis to hypercapnia and respiratory acidosis, the transitional, crossover period of normal blood gas and pH values must be recognized by the physician as indicating the possible onset of Phase IV. Treatment must be appropriately modified or intensified. Clearly, this admonition is not applicable for those patients who have normal arterial carbon dioxide tension and pH because they are improving clinically.

In many patients, progressive alveolar hypoventilation is iatrogenically produced or aggravated because of uncontrolled oxygen administration or because sedative or tranquilizing drugs depress respiration (page 57).

Because the primary reason for the arterial blood gas and pH changes in status asthmaticus is bronchial and bronchiolar obstruction, establishing and maintaining a patent airway is fundamental. As discussed previously, the principal causes of the obstruction are bronchospasm, inflammation, and the presence of secretions.

Mobilizing Secretions and Clearing the Airway. Bronchial and bronchiolar secretions may be the result of a bacterial or viral infection or may be immunologically induced. Infection can initiate status asthmaticus through a direct inflammatory process or by an allergic mechanism. In addition, secondary infection may aggravate or perpetuate an established attack. Because the exact causative organism is often not immediately identifiable, a gram stain of a representative sputum specimen plus the information obtained from the history can guide the initial selection of an antibiotic. Subsequent therapy may be based on the results of sputum cultures and bacterial sensitivity. A thorough search for ear and/or paranasal sinus infection should also be made because such extrapulmonary foci of infection may have triggered the onset of status asthmaticus.

In conjunction with the control of allergy and infection, rapid mobilization of secretions and cellular debris will help terminate the asthmatic episode. As shown in Plate 26, multiple approaches must be used to clear the airway.

1. *Adequate Hydration.* Patients in status asthmaticus are often dehydrated because of poor fluid intake, imperceptible water loss (from fever and/or tachypnea and hyperpnea), and, in children, posttussive vomiting. As a result, secretions become inspissated and thickened. Low humidity in the inspired air or in therapeutic oxygen further aggravates the drying process and favors stasis. Dehydration with hypovolemia has been implicated as a cause of death in status asthmaticus. Therefore, adequate amounts of fluids must be given orally or intravenously. For an average 70-kg adult, 3 to 4 liters/day is generally satisfactory. Concurrently, the inspired air or oxygen should be humidified using nebulizer-humidifier units which may be warmed to increase the humidity. Ultrasonic nebulizers are often poorly tolerated but may be used intermittently.

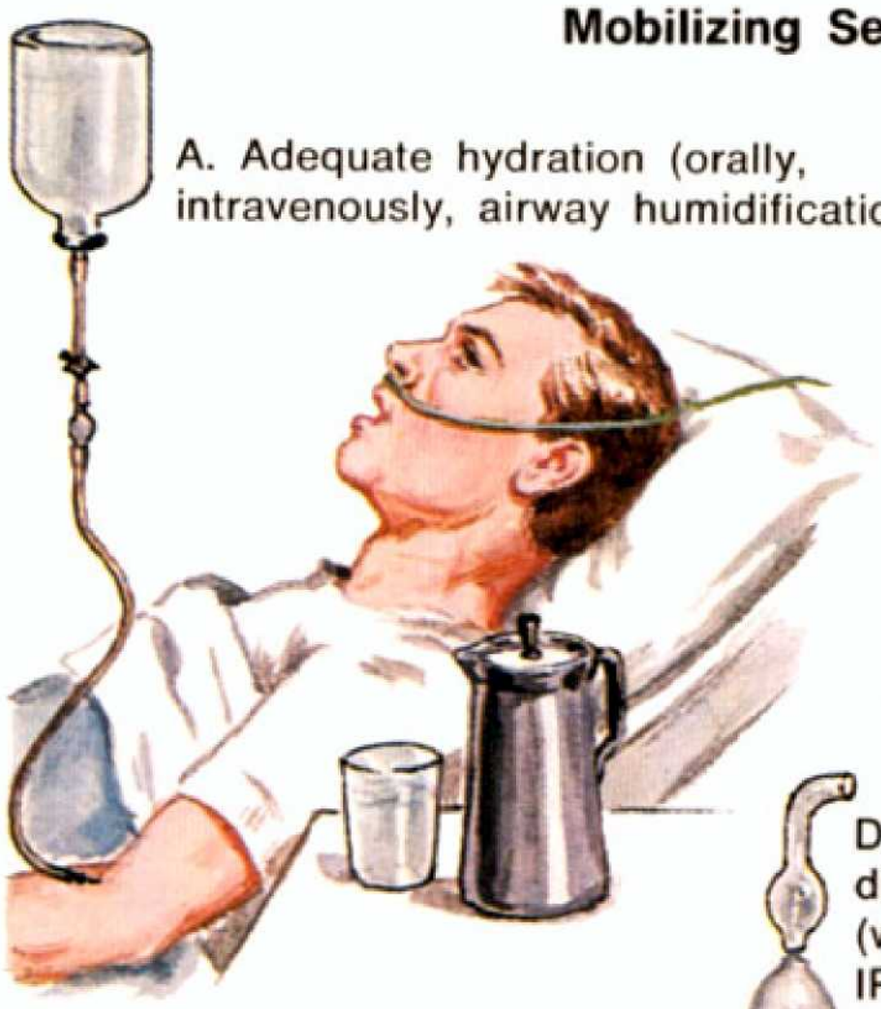
2. *Expectorant and Mucolytic Drugs.* Although adequate hydration and humidification appear to be most effective for loosening secretions, expectorant drugs may also be used. Orally administered potassium iodide solution or intravenous sodium iodide are probably of value, although allergic and other adverse reactions, such as pruritis and fever, may occur. Ammonium chloride or glyceryl guaiacolate and other oral expectorants are often used, but firm evidence of their efficacy is lacking.

Mucolytic drugs may be administered by nebulization or endotracheal instillation. For mucoid and purulent secretions, N-acetylcysteine is utilized; for purulent secretions that contain desoxyribonucleic acid fibers (from necrotic bacteria and inflammatory cells), pancreatic dornase can be used for enzymatic liquefaction. Administration of N-acetylcysteine frequently causes bronchospasm in bronchoreactive patients, and must be used *cautiously*. The dose, by nebulizer, is 3 to 5 ml of 5 to 10% N-acetylcysteine mixed with 0.5 ml of 1:200 isoproterenol. This drug can also be instilled and then suctioned during bronchoscopy. Dornase therapy will occasionally produce bronchospasm. The dose of dornase is 50,000 units in saline *q.i.d.* by aerosol or by direct instillation.

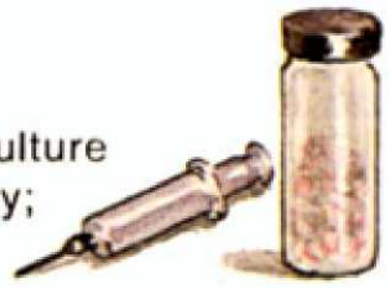
3. *Removal of Secretions.* When secretions are loosened, they must be removed by coughing, suctioning, or bronchoscopy and lavage. In patients who have an effective and productive cough, frequent changes in body position, gentle percussion over the thorax, and encouragement to cough will facilitate raising the secretions. Cough suppression is generally not recommended because it

Mobilizing Secretions and Clearing Airway

A. Adequate hydration (orally, intravenously, airway humidification)

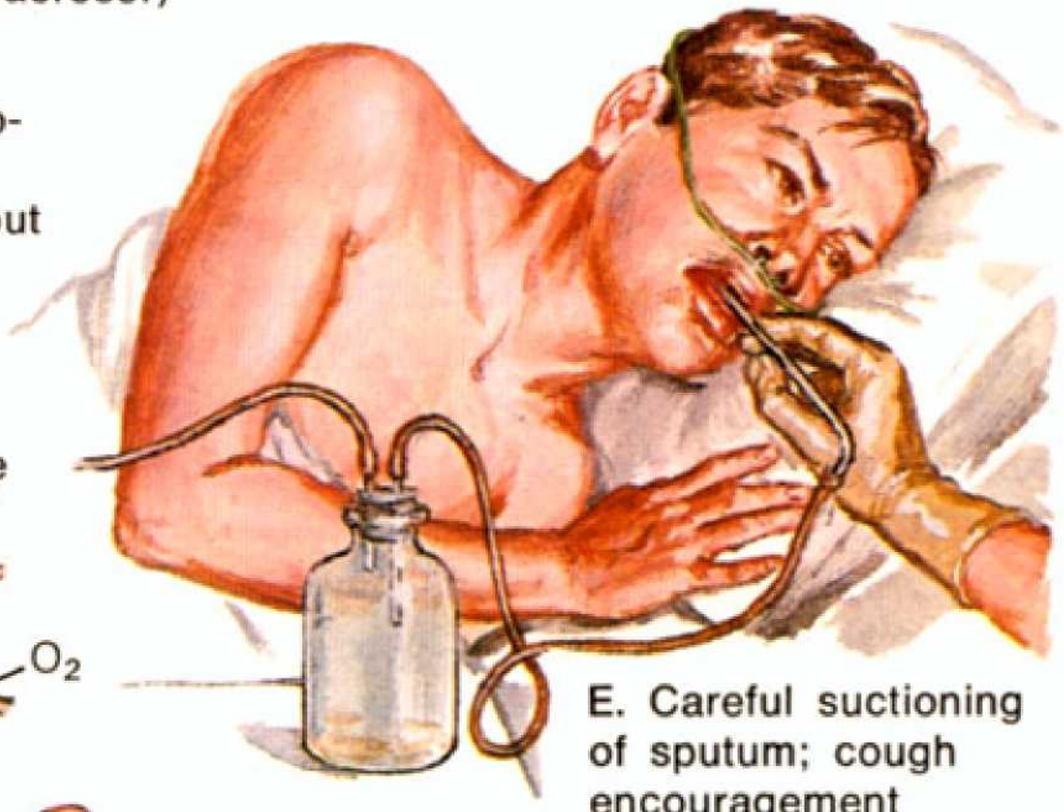


B. Expectorant and mucolytic drugs (orally, intravenously, or by aerosol)



C. Sputum culture and sensitivity; preliminary antibiotics pending results

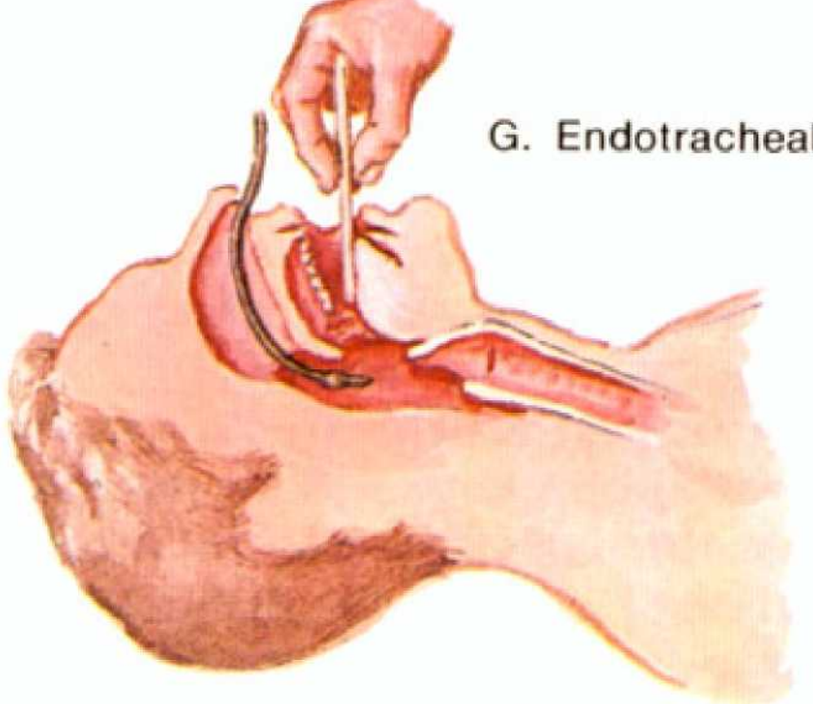
D. Broncho-dilators (with/without IPPB)



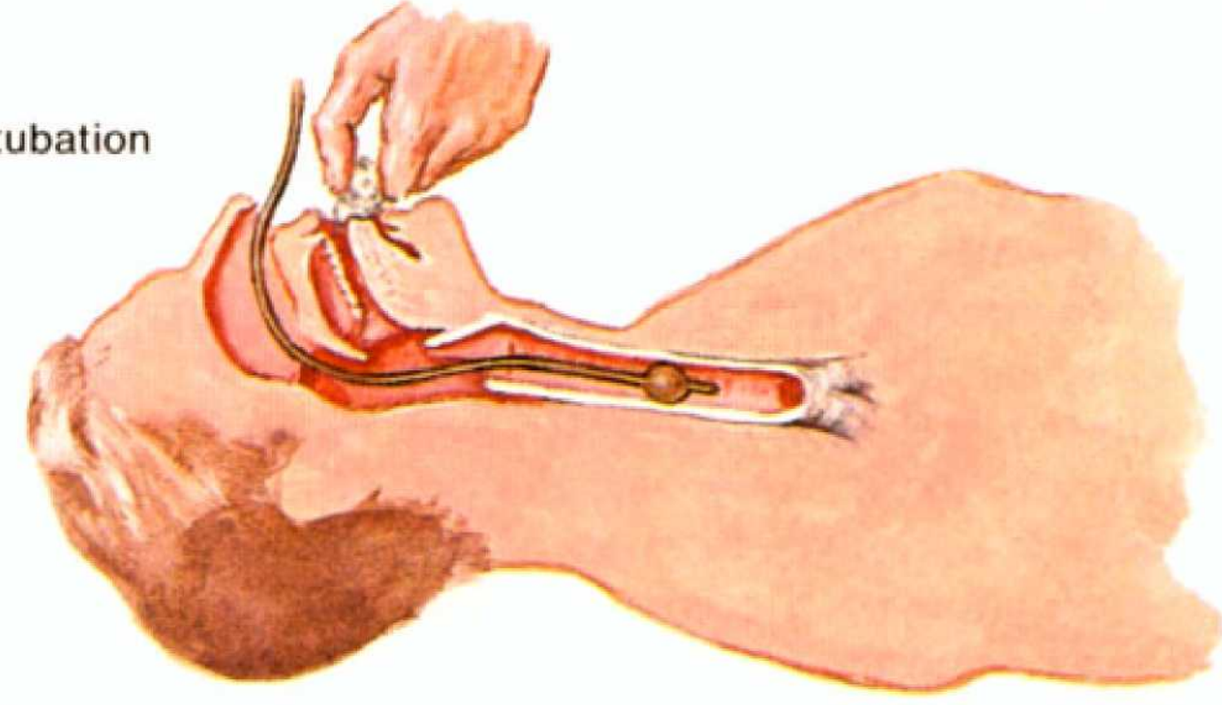
E. Careful suctioning of sputum; cough encouragement

F. Bronchoscopy for aspiration and lavage

G. Endotracheal intubation



Catheter introduced; position in pharynx checked with aid of tongue depressor and light



Tongue pulled forward; patient takes deep breath, and tube quickly advanced into trachea; balloon tip expanded; mechanical ventilation may then be applied

involves the risk of both depression of respiration and inspissation of secretions. However, because coughing paroxysms may further aggravate bronchospasm, cough may be *cautiously* suppressed on rare occasions.

Suctioning is necessary in any patient who has an ineffective cough, who is obtunded, or in whom an endotracheal tube has been inserted. Secretions should be suctioned at regularly timed intervals. Hypoxemia must be avoided during the procedure by supplying the patient with supplemental oxygen and by using appropriate suctioning techniques. Traumatic movements which may damage the airway mucosa must be avoided.

Bronchoscopy and lavage may be required for patients who cannot raise their secretions and in whom suctioning has not been successful (*e.g.*, when a lobar atelectasis results from a mucous plug). For patients who are severely obtunded and/or who have *severe* degrees of obstruction, removal of secretions by bronchoscopy can provide dramatic improvement. The secretions should be liquefied by the introduction of isotonic saline or a mucolytic agent through the bronchoscope with immediate suctioning (Plate 26).

If airway obstruction is severe, endotracheal intubation may be necessary to establish a patent airway. An endotracheal tube provides a direct route for removing secretions and supplying oxygen, and facilitates artificial ventilation. For patient comfort, a nasotracheal tube is preferable to an orotracheal one. Complications created by the presence of a tube in the trachea are generally avoidable and include pressure necrosis of the larynx or trachea with secondary infection and possibly stenosis. (A tube with a low-pressure cuff will reduce the likelihood of mucosal injury.) Care must be taken to ensure that the tube is not inserted so deeply that it is placed into one of the major bronchi. Careful nursing is required and accretion of secretions in the tube must be avoided.

Tracheostomy is usually not required and, in fact, is best avoided in patients with bronchial asthma. It is rarely indicated even on an emergency basis. If, however, the procedure does become necessary because of upper airway obstruction or the complications associated with prolonged use of an endotracheal tube, tracheostomy should be performed in the operating room with an endotracheal tube in place.

Relief of Bronchospasm. In the management of asthma, medications which reverse bronchospasm are fundamental. As discussed previously (Plate 13 and page 27), the bronchodilators in clinical use fall into two main categories: drugs such as catecholamines which act on the β-adrenergic receptors, and agents which inhibit the enzyme phosphodiesterase. Both types of drugs increase tissue concentrations of cyclic AMP.

1. *Catecholamines.* Epinephrine has both α- and β-adrenergic effects, but its β action predominates. Use of this drug in the acute episode of asthma has been described previously (page 46).

Isoproterenol, a rapidly acting and potent β-adrenergic stimulator, is usually administered as an aerosol. The dose is 0.25 to 0.5 ml of 1:200 solution mixed with 2 ml of saline and delivered by a conventional nebulizer or intermittent positive pressure breathing (IPPB) unit on, for example, a *q.6.h.* schedule (Plate 27). In children, intravenous isoproterenol appears to be effective. As with epinephrine, isoproterenol must be used with caution and excessive dosage avoided. In fact, tachycardia and many otherwise unexplained arrhythmias may be attributable to overdosing. Constant review of the medication record is thus essential while managing patients with status asthmaticus.

Although the therapeutic value of epinephrine and isoproterenol in relieving airway obstruction and reducing the mechanical work of respiration is indisputable, three deleterious events are possible: the patient may become refractory to treatment; an increase in airway obstruction may occur; a fall in arterial oxygen tension may be seen.

Refractoriness in patients who are receiving epinephrine may be related to the presence of coexisting respiratory acidosis. Correction of the respiratory acidosis by the administration of sodium bicarbonate and by the use of other supportive measures which reduce arterial carbon dioxide often resolves the problem (pages 59 and 63).

An increase in airway obstruction has been reported with isoproterenol. This unexpected bronchoconstrictive effect may be related to the formation of a metabolite with a β-blocking action and can be responsible for deterioration of the patient's condition and persistence of symptoms. Improvement will occur when isoproterenol is discontinued.

Inhalant Bronchodilator Therapy

A. Hand-squeezed nebulizer; use 0.25 to 0.5 ml 1:200 isoproterenol in 2 to 5 ml saline and allow no more than two inhalations every six hours

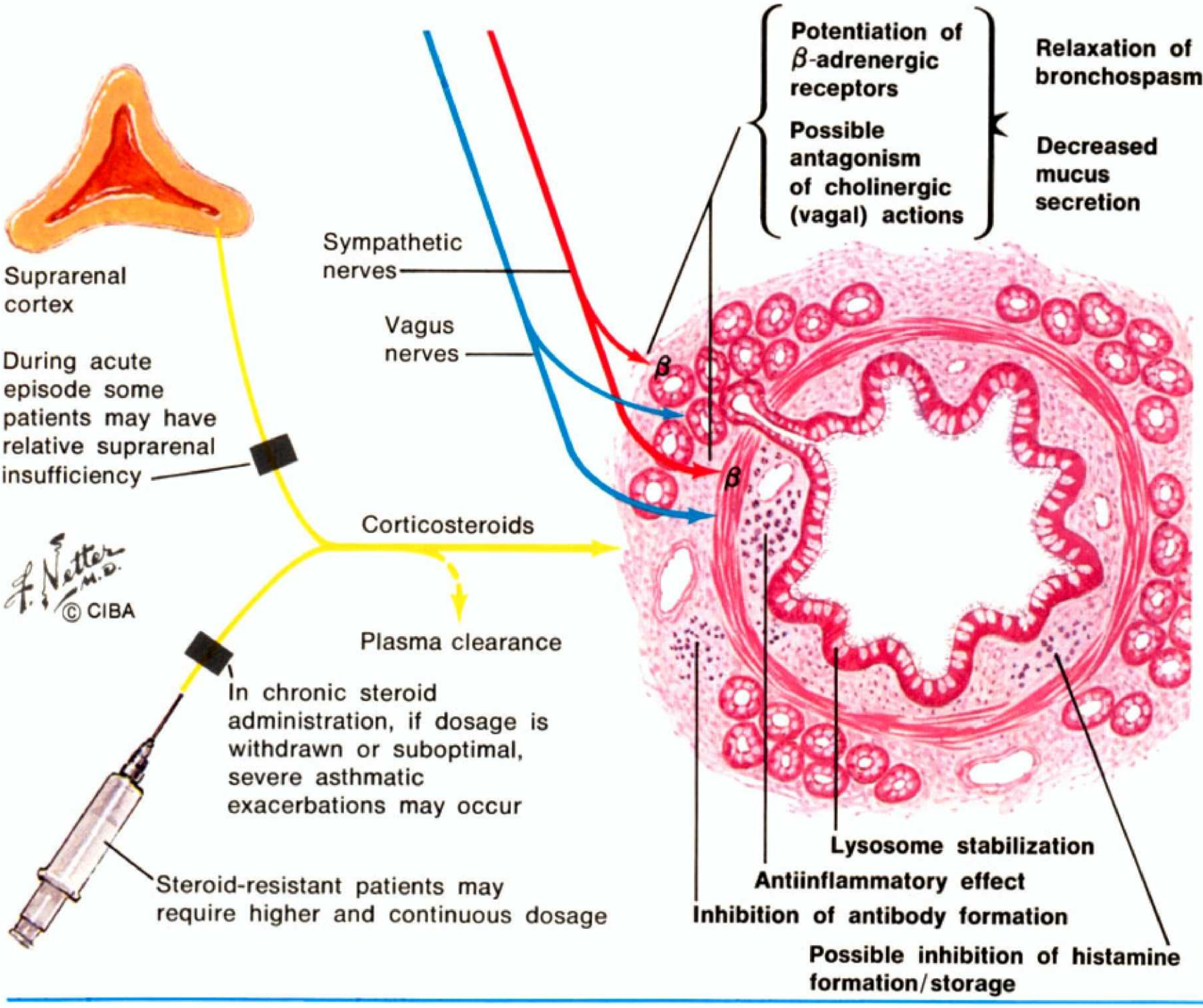
Bulb squeezed synchronously with deep inhalation; hold breath

B. Gas-propelled nebulizer; beware of cardiotoxic effect

Caution:
Do not overdose

C. Intermittent positive pressure breathing (IPPB) apparatus with nebulizer

Corticosteroid Actions in Bronchial Asthma



A paradoxical fall in arterial oxygen tension may be observed in some patients receiving isoproterenol despite a decrease in airway obstruction with resultant improvement in ventilation. Stimulation of β_1 receptors in the heart together with dilatation of the pulmonary vascular bed leads to an augmented pulmonary blood flow. This increased blood flow involves alveolar-capillary units which are still poorly ventilated and thus intensifies the $\dot{V}_A / \dot{Q}_c$ disturbances. In a hospital, any decrease in arterial oxygen tension is easily corrected by oxygen therapy.

2. *Methylxanthines.* Aminophylline (theophylline ethylenediamine) is the most useful and potent xanthine preparation. As noted previously (Plate 13 and page 27), it acts by inhibiting phosphodiesterase and thus increasing cellular concentrations of cyclic AMP. Following administration of aminophylline, vital capacity increases and airway resistance decreases. These effects last for several hours. Because the cardiovascular side effects of aminophylline are less than those of catecholamines, the drug is particularly useful in hypertensive, hyperthyroid, or cardiac patients. Aminophylline doses have been described previously (page 46).

3. *Suprarenal Corticosteroids.* As a result of their multiple actions (Plate 28), corticosteroids may provide significant relief of asthmatic symptoms which are uncontrollable by other therapy. Pharmacologically, these drugs may enhance the effects of catecholamines on β-adrenergic receptors and may also inhibit the enzyme phosphodiesterase. In status asthmaticus, corticosteroids must be viewed as lifesaving. Early administration is advisable, particularly for critically ill patients, or for those who have been on corticosteroid therapy prior to the current episode of status asthmaticus.

Generally, high doses are preferred. Prednisone, 40 to 80 mg intravenously (or an equivalent preparation, Table VI), should be given initially, with daily doses varying from 300 to 400 mg. If necessary, even higher daily doses may be required. In children, the dose of prednisone is 2 mg/kg/24 hours for status asthmaticus. Dosages should be sustained until clinical improvement warrants a reduction. Corticosteroids should not be withdrawn suddenly; instead, doses should be gradually tapered. This precaution is particularly important for children because suprarenal suppression may occur more rapidly than in adults.

Although the exact corticosteroid dose is difficult to define, an amount which will give a minimum plasma level of 1.5 μg/ml of 11-hydroxycorticosteroid appears to be sufficient to reduce edema and inflammation and to stabilize mast cells. Another useful working guide to judge the biologic effectiveness of corticosteroid medication is a fall in the eosinophil count to 100/mm^3 or less. Thus, doses may be titrated to produce and sustain eosinopenia. ACTH is not recommended for patients in status asthmaticus because, presumably, the suprarenal cortex is already maximally stimulated.

Undesirable side effects of corticosteroid medication are not usually seen during short-term therapy for status asthmaticus. However, chronic therapy may cause suprarenal suppression, edema, hypertension, aggravation of diabetes mellitus, exacerbation or spread of infection, osteoporosis, myopathy, aseptic necrosis of the femoral or humoral heads, subcapsular cataracts, peptic ulceration with bleeding, psychosis, pseudotumor cerebri, and hypokalemic alkalosis. To prevent some of these adverse effects, potassium should be given, sodium should be restricted to less than 1 gm/day, serum electrolytes and blood sugar should be monitored, and antacids may be given. Only careful and continuous follow-up of the patient will minimize the possibility of adverse reactions.

Table VI

EQUIVALENT DOSES OF CORTICOSTEROIDS

	Equivalent Dose (mg)
Hydrocortisone	20
Prednisolone	5
Methylprednisolone	5
Prednisone	5
Methylprednisone	4
Triamcinolone	4
Dexamethasone	0.75

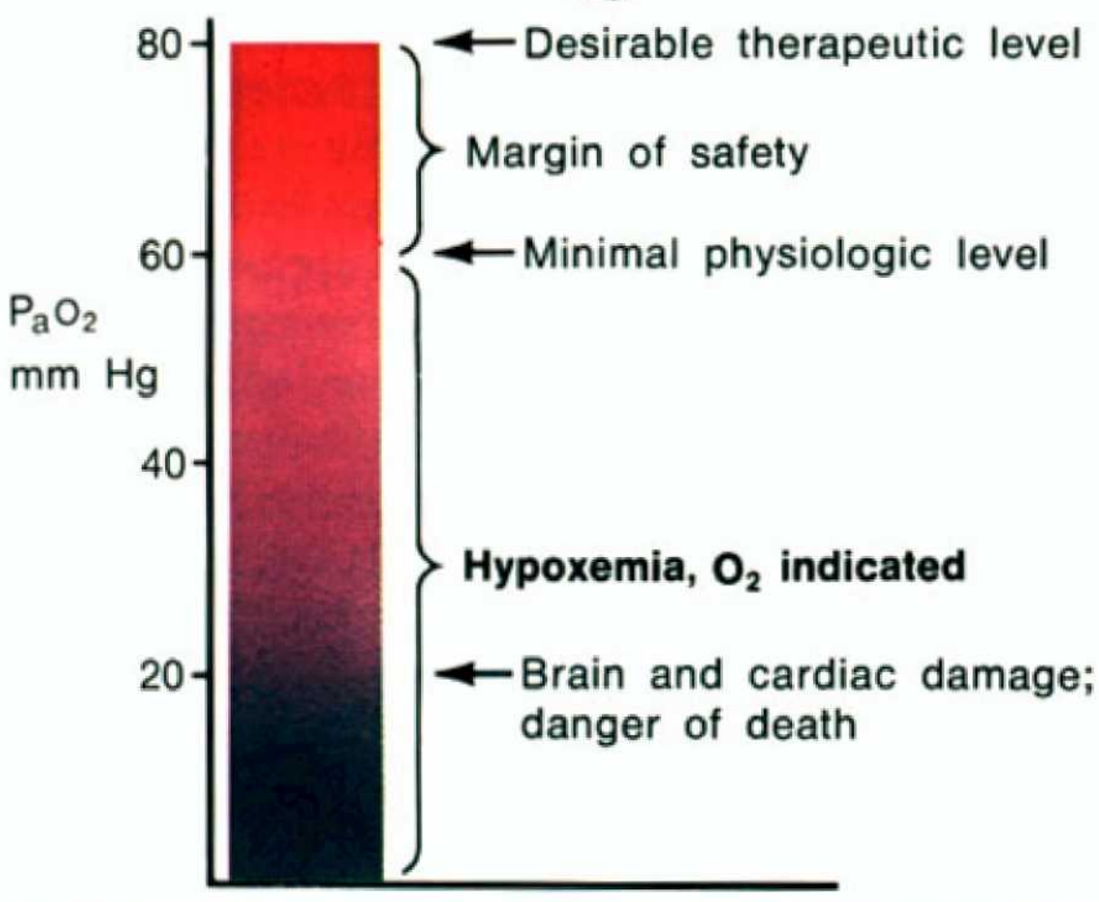
Medications of Limited Value. In the treatment of status asthmaticus, a number of medications are sometimes used for theoretical or empirical reasons but are not necessarily effective. For instance, antihistamines, which might be expected to be of value because they act by competitive antagonism of histamine, are of no apparent value. In fact, because these agents can cause drying of the mucous secretions, they should generally not be used. Similarly, because of the drying effect on mucous secretions of anticholinergic drugs, medications currently available, such as atropine, also should not be used in patients with status asthmaticus. This precaution exists in spite of the proven bronchodilator action of certain anticholinergic agents.

Sedatives should be used cautiously in the treatment of patients in status asthmaticus because they may be a contributing cause of death. Improper use usually results because anxiety is such a predominant finding in patients during an acute asthmatic episode. However, suppressing this anxiety will not correct the underlying airway obstruction with its attendant abnormalities in blood gases. In fact, the dangers of unrecognized respiratory suppression cannot be sufficiently emphasized. The sedated patient will be quieter and will exhibit less anxiety, less respiratory work, and less wheezing. These findings may be inadvertently misinterpreted as improvement in the patient's condition. If sedative or tranquilizing agents are considered to be necessary in selected instances, minimum dosages should be used, and monitoring of blood gases is mandatory. The use of sedatives is generally much less hazardous, though, when the patient is being managed on a respirator (page 61).

The same precautions which apply to the use of sedatives are also applicable to narcotic agents such as morphine and meperidine. The benefits of these drugs are outweighed by the

Monitoring of Blood Gas

P_aO_2, P_aCO_2, and pH read in blood gas analyzer



Beware of oxygen-induced hypoventilation. If not immediately correctable by adjustment of O_2 delivery, mechanical ventilation must be instituted

disadvantages of respiratory center depression or cough suppression.

Because of the potential for drug allergy or reaction, medications such as salicylates, penicillin, iodides, and indomethacin should be used cautiously.

Oxygen Therapy. The administration of oxygen is basic therapy for patients in status asthmaticus. Arterial oxygen tension (P_aO_2) below a range of 20 to 25 mm Hg for more than 2 to 4 minutes may cause irreversible damage to the brain, heart, and kidneys and, if allowed to persist, will lead to death. Lesser degrees of hypoxia can result in numerous physiologic and metabolic derangements including encephalopathy, pulmonary hypertension, cardiac failure, hepatic injury, or increased airway resistance.

P_aO_2 of 60 to 70 mm Hg and a concomitant hemoglobin saturation (S_aO_2) of 85 to 90% should be considered the minimum physiologic standards providing red blood cell mass, oxygen-hemoglobin affinity, cardiac output, and systemic blood flow are adequate. However, higher P_aO_2 (range of 80 to 100 mm Hg) is preferable (Plate 29). Such higher levels provide a margin of safety particularly when the patient is being suctioned or if bronchodilator drugs tend to lower P_aO_2 (page 56).

Appropriate concentrations of oxygen can be obtained by a variety of equipment (Plate 30). All such equipment can deliver an oxygen concentration in the inspired air in excess of 21% (Table VII).

The average range of P_aO_2 in status asthmaticus is from 50 to 70 mm Hg so that oxygen concentrations in the inspired air of between 30 and 50% are usually adequate. Many patients, however, may have P_aO_2 less than 50 mm Hg, and these patients would require higher inspired levels of supplemental oxygen. Regardless of the oxygen concentration in the inspired air, repeated proof of the adequacy of oxygen therapy must be obtained by serial arterial oxygen measurements: Hypoxemia can develop rapidly whenever a patient's P_aO_2 corresponds to values on the descending slope of the oxygen-hemoglobin dissociation curve.

Because oxygen delivered from a tank or wall outlet is absolutely dry, adequate humidification is crucial to minimize drying of

secretions and additional bronchial irritation.

Oxygen-induced hypoventilation may occur in a small number of asthmatic patients, perhaps more frequently in children. The mechanism is complicated and depends on the relative importance of P_aCO_2 and P_aO_2 in the regulation of respiration. In a few asthmatic patients, the chemoreceptors to carbon dioxide presumably become less sensitive; as a result, an elevated P_aCO_2 is no longer a stimulus for respiration. Instead, hypoxia becomes the dominant stimulus. Unfortunately, P_aO_2 must be quite low (<50 to 60 mm Hg) in order to stimulate increased ventilation. If oxygen is being given, so that P_aO_2 increases, the crucial stimulus for respiration is thereby removed. Thus hypoventilation persists in spite of hypoxemia and increasing carbon dioxide retention. Immediate reappraisal of the situation is required, and artificial mechanical ventilation may be necessary to ensure adequate oxygenation and carbon dioxide elimination. It should be emphasized, however, that oxygen must not be withheld because of the potential danger of inducing ventilatory depression. The goal of therapy must be to administer oxygen to produce a physiologic range of P_aO_2. Any oxygen-induced hypoventilation which may occur can subsequently be treated as a separate complication.

A potential for oxygen toxicity (epithelial damage, atelectasis) exists if oxygen is administered at concentrations in the inspired air of greater than 50 to 60% for several days. Little benefit is to be gained if P_aO_2 is greater than 100 mm Hg. Instead, the lowest inspired oxygen concentrations which provide a physiologic range of P_aO_2 are desirable. In addition, care must be taken if pressure-limited ventilators are used without mixing valves. Such equipment may deliver 90% oxygen when set at 40%. Occasionally, helium-oxygen mixtures (75% He) may be used and may possibly prevent the development of oxygen toxicity.

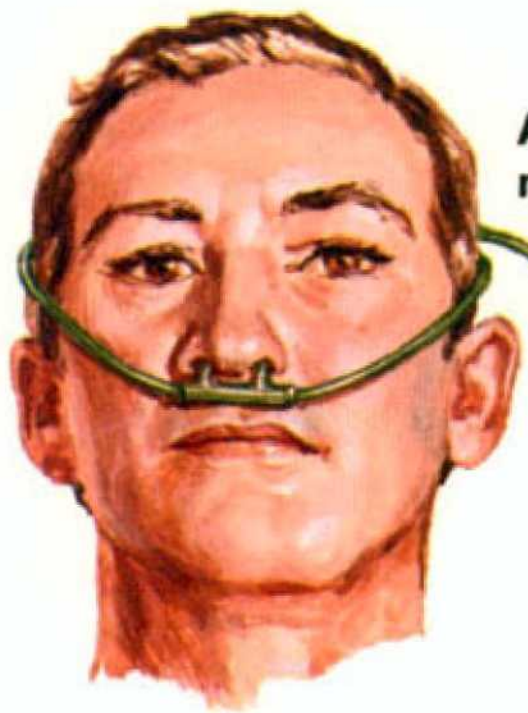
Mechanical Ventilation. Ventilatory failure is a dangerous and often lethal phase of status asthmaticus and may require use of mechanical ventilation. It can occur rapidly, especially in children whose smaller airways are easily obstructed by mucous plugs. A patient who is refractory to all other forms of therapy for the asthmatic episode and in whom P_aCO_2 is 50 mm Hg and pH is ≤7.20 may be considered to need ventilatory support. Alternatively, a patient in whom an uncontrollable rise in P_aCO_2 occurs at the rate of 5 to 10 mm Hg per hour would also need mechanical ventilation once P_aCO_2 reaches approximately 50 mm Hg. At times, the clinical status of the patient (such as the occurrence of oxygen-induced ventilatory depression, as described previously, or of apnea) may indicate ventilatory support before such biochemical values are attained (Plate 29). However, the decision to use mechanical ventilation should not be made in haste and desperation; it should be made as the result of continuous clinical and biochemical observations.

Table VII

OXYGEN ADMINISTRATION

Type of Equipment	O_2 Concentration (%)	Characteristics
Nasal cannula, prongs	22 to 35	Comfortable, low humidity
Venturi mask	24, 28, or 35	Accurate delivery, fixed concentrations at specified flow rates, occasionally uncomfortable, can be humidified
Mask without reservoir	35 to 65	Easy to use, slight discomfort
Mask with reservoir	40 to 100	Rebreathing of CO_2 unless fitted with one-way valves
Mask with nonbreathing reservoir	As desired	Adequate humidity possible
Face tent	30 to 55	Well tolerated, good humidity
Canopy tent	Variable, up to 50	Good humidity, but patient is inaccessible; more appropriate for children
Ventilator	To 100	Appropriate concentrations of O_2 can be regulated, humidity adequate

Methods of Oxygen Administration



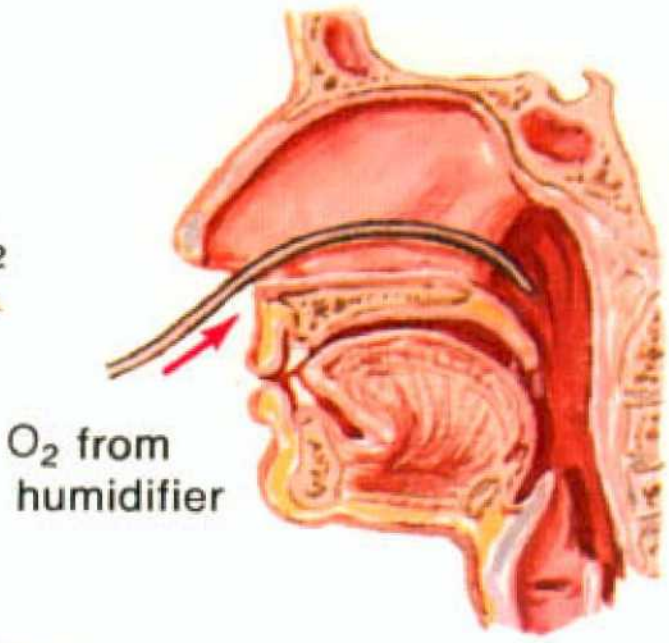
A. Cannula with nasal prongs

Flow-meter

O_2

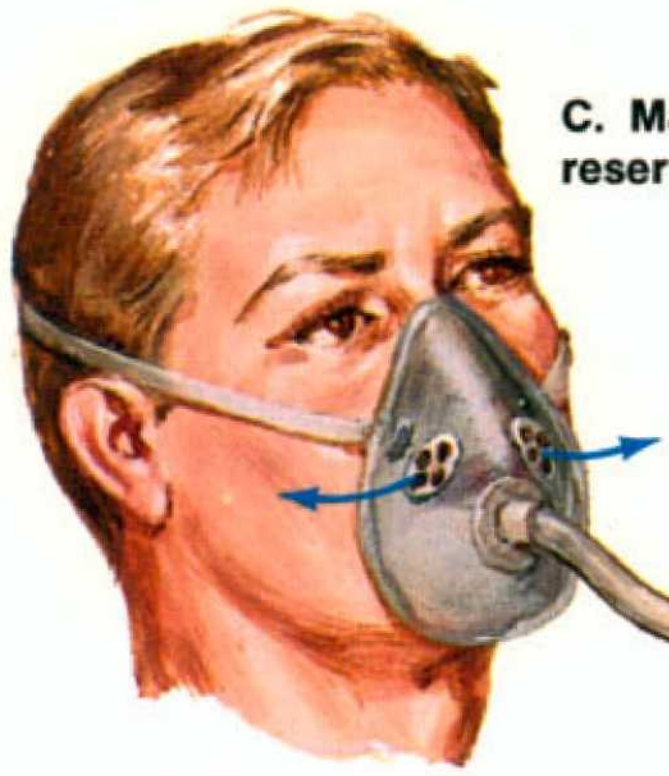
O_2

Humidifier



O_2 from humidifier

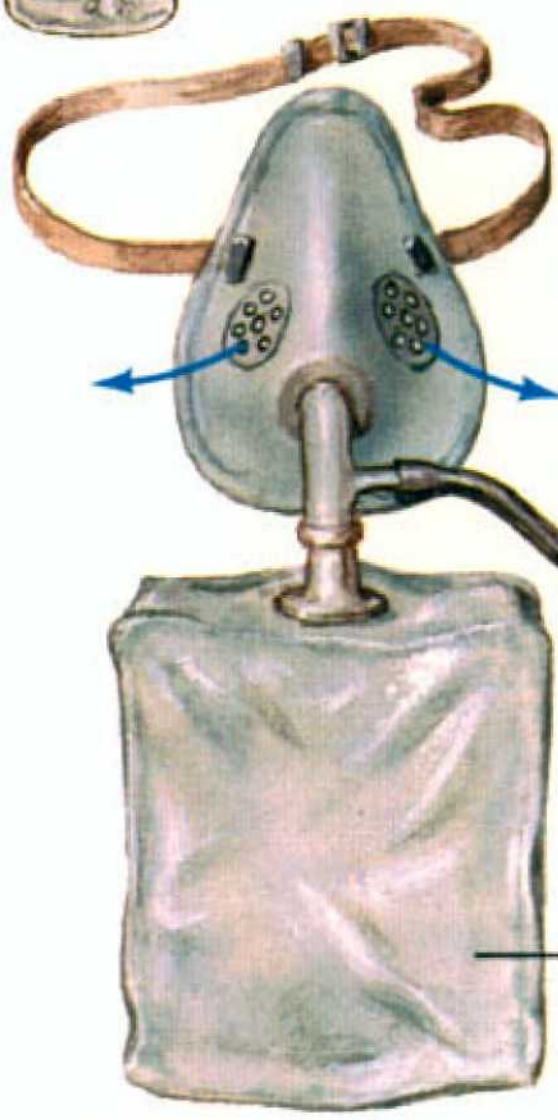
B. Nasal catheter



C. Mask without reservoir bag

Exhaled air and safety inlet

O_2 from humidifier

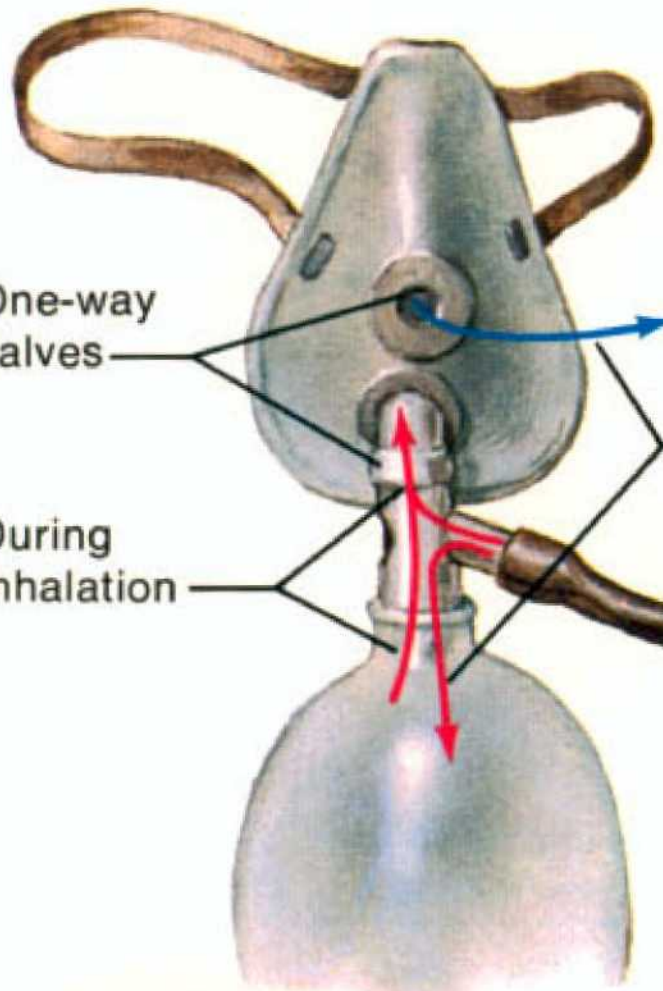


D. Mask with reservoir bag (partial rebreathing)

Exhaled air and safety inlet

O_2 from humidifier

Reservoir bag



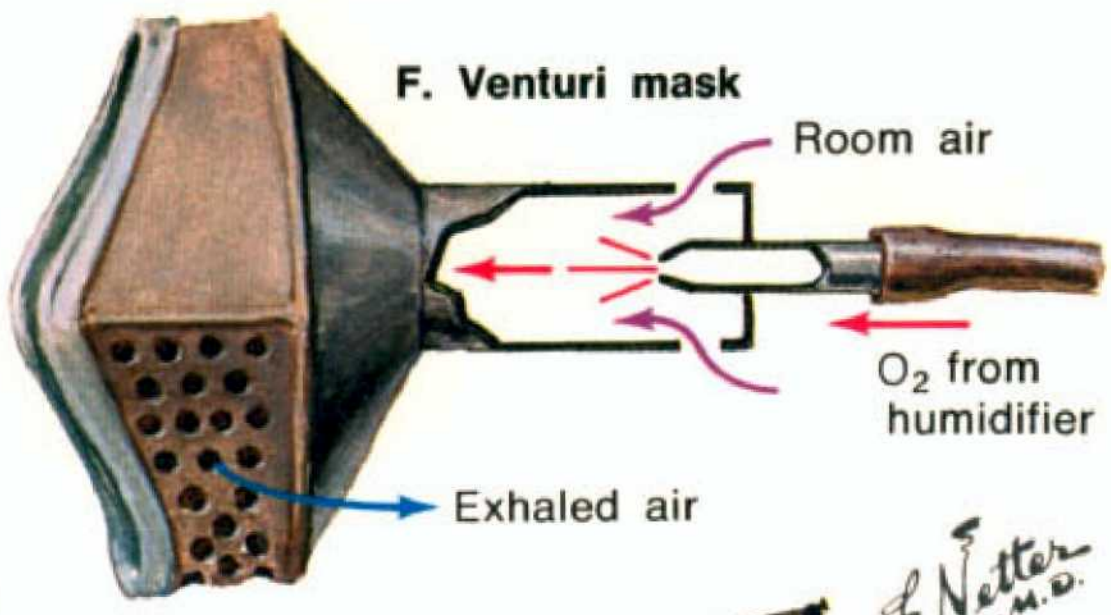
E. Mask with reservoir and one-way valves (nonrebreathing)

One-way valves

During inhalation

During exhalation

O_2 from humidifier

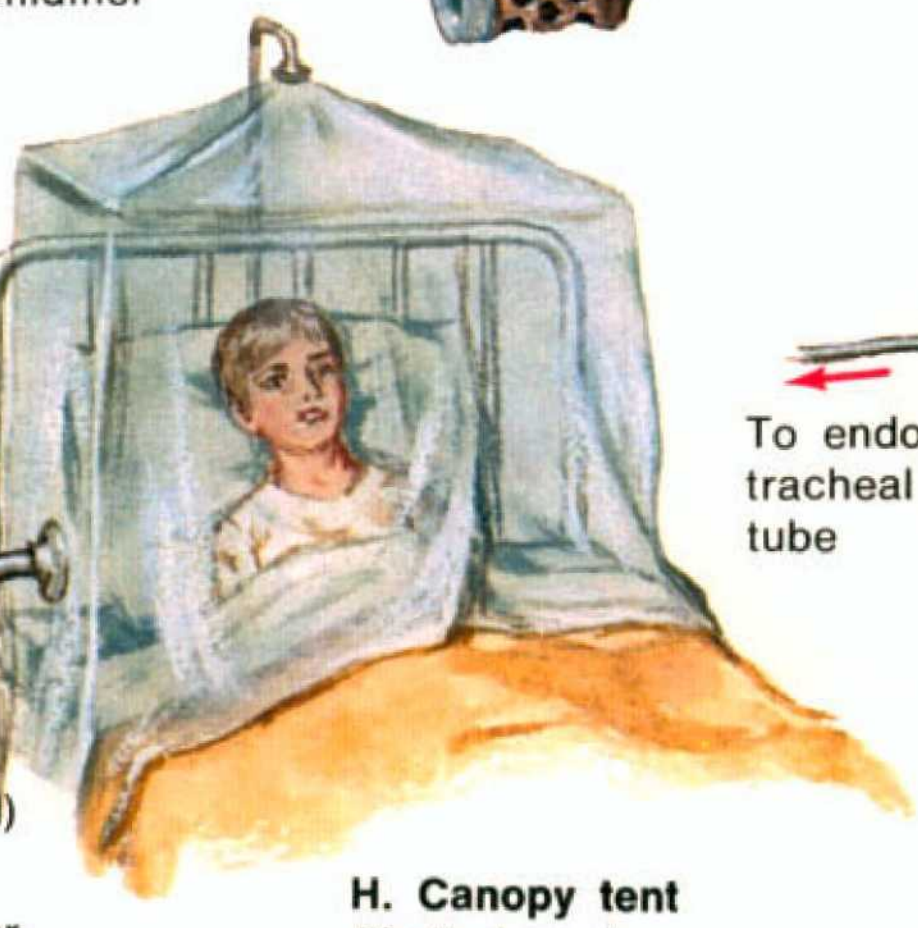


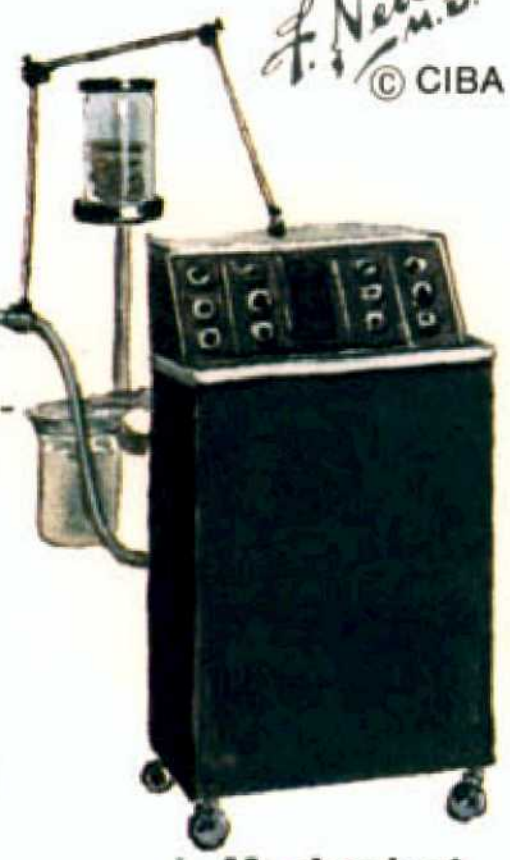
F. Venturi mask

Room air

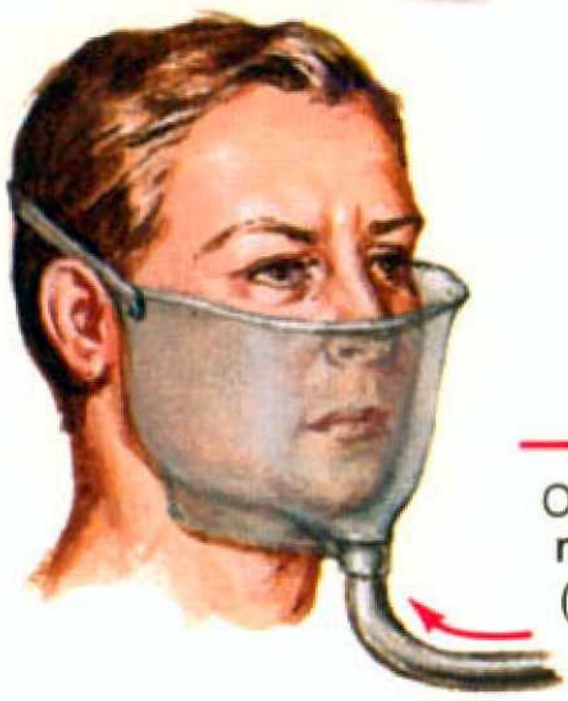
O_2 from humidifier

Exhaled air





To endo-tracheal tube



O_2-air mixture (humidified)

O_2 from humidifier

G. Face tent

H. Canopy tent (limited use)

I. Mechanical ventilator

The type of ventilation equipment used may provide either a *patient-assisted* ventilatory cycle or a *machine-controlled* cycle. With a patient-assisted cycle, the ventilator is activated by and coordinated with the patient's respiratory efforts; with a machine-controlled cycle, the work and timing of respiration are assumed by the ventilator.

In cooperative patients, some benefit may be obtained with conventional IPPB units used *intermittently* (*e.g.*, for 10 minutes every 2 to 4 hours) to deliver aerosol medication, especially bronchodilators, and/or to improve ventilation and alleviate thoracic work. However, *continuous* ventilation is mandatory when refractory patients are in respiratory failure.

Continuous patient-assisted ventilation can only be used if the patient is cooperative. If agitation, exhaustion, confusion, or tachypnea occur and arterial blood gases show progressive deterioration, *controlled* ventilatory support is necessary. Such controlled ventilation will reduce ineffective respiratory patterns and relieve excessive thoracic work until the underlying pathology of the asthmatic episode is resolved.

Volume-limited units provide more uniform ventilation and can generate high cycling pressures. Low inspiratory flow rates and large tidal volumes will limit turbulent airflow and provide a more homogeneous distribution of ventilation. To provide adequate gas emptying from obstructed lung segments, an inspiratory:expiratory time ratio of 1:2 or 1:3 is desirable. For example, a respiratory rate of 10 to 12 breaths per minute and a tidal volume of 800 to 1200 ml (15 to 25 ml/kg) may be used for an adult patient.

Many patients will satisfactorily synchronize with the respirator. Others, however, resist the action of the equipment, and morphine sulfate, sedatives, or even curarelike drugs must be used to coordinate the patient with the ventilator.

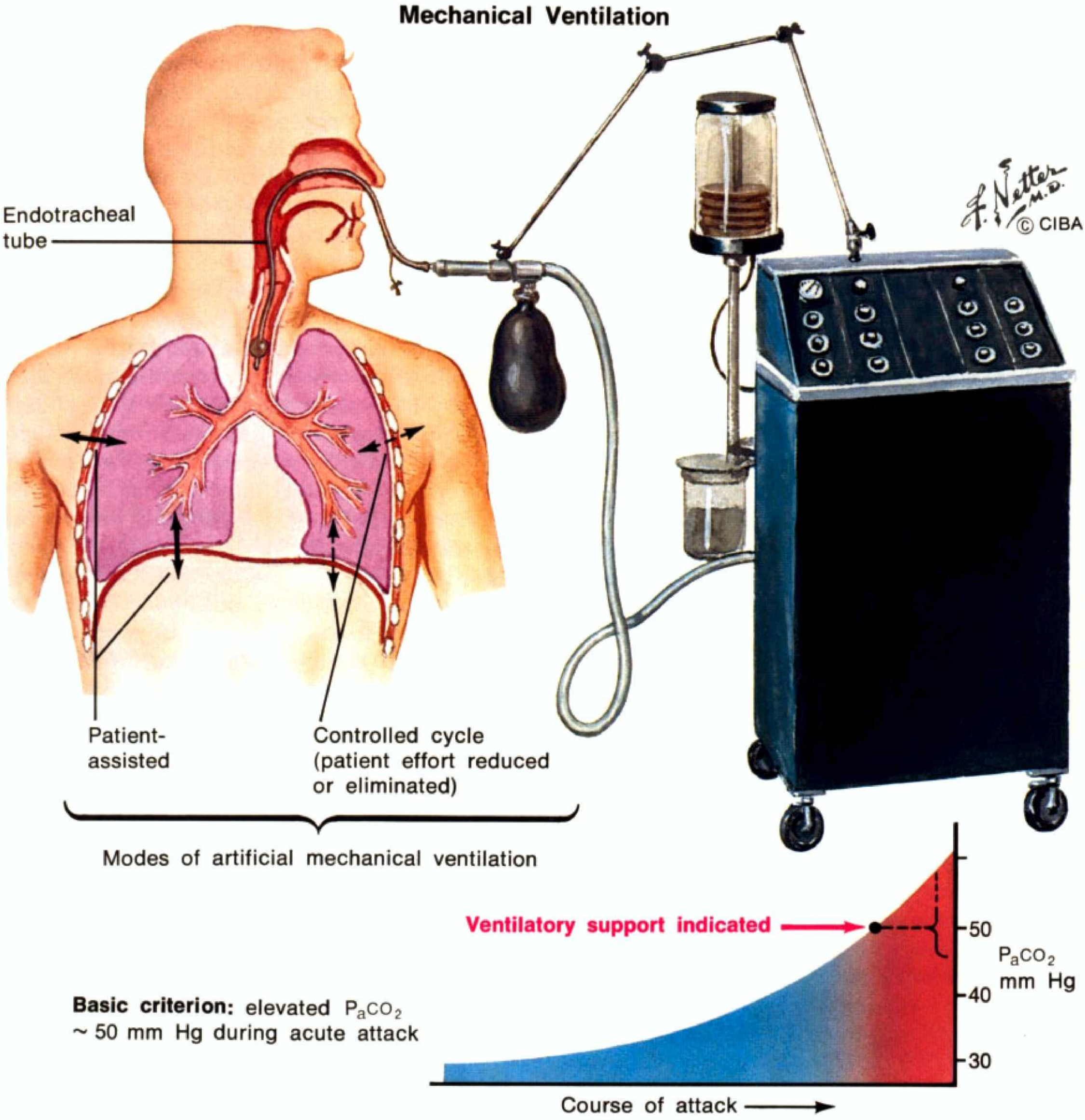
In order to achieve such respiratory suppression, doses of morphine should be titrated carefully. For an adult patient, 2 to 5 mg given intravenously is an adequate initial dose which may be followed by smaller doses administered periodically. Rarely will total doses of more than 30 mg of morphine be needed. Sedation may be achieved with titrated doses of either diazepam or barbiturates. In some instances, muscle paralysis may be induced with succinylcholine in a dose of 1 mg/kg intravenously. Recently, pancuronium bromide has been advocated as a nondepolarizing muscle relaxant for asthmatic patients.

A detailed discussion of the various problems associated with ventilatory support is outside the scope of this monograph, but a number of dangers must be emphasized. The use of drugs is accompanied by the possibility of adverse reactions. These side effects, which may include hypotension, prolonged respiratory depression, or reduced cardiac output, must be detected by careful monitoring. Other complications which may be anticipated during artificial ventilation include gastrointestinal bleeding, gastric dilatation, renal failure, endotracheal tube obstruction by secretions, laryngeal or tracheal injury or necrosis, atelectasis, arrhythmias, myocardial infarction, pneumothorax, pulmonary emboli, nosocomial infections and bacteremia, hypotension (caused by high mean pulmonary pressures impairing venous return), iatrogenic hyperventilation (which is ventilator induced and may be associated with hypocapnic seizures), iatrogenic hypoxemia or hyperoxemia, or accidental, incorrect placement of the endotracheal tube.

Continuous monitoring of the patient must accomplish three objectives: (1) determine the effectiveness of mechanical ventilation; (2) forestall the occurrence of drug side effects or the complications of ventilation by early detection; and (3) guide appropriate therapy of the underlying asthmatic episode.

Mechanical ventilator effectiveness must be assessed by serial determinations of arterial blood gases. In addition, physical examination must be repeated frequently to determine the general clinical status of the patient. The following specific parameters must also be checked repeatedly: vital signs, electrocardiogram, chest X-ray, sputum (volume, gross characteristics, and culture), serum electrolytes and osmolality, minute volume (respiratory rate multiplied by tidal volume, or $\dot{V}_E = f \times V_T$), effective lung compliance (tidal volume/peak ventilator pressure at point of zero flow, or $C_{eff} = V_T / P_{peak}$), body weight, total fluid intake and output, and, if indicated, central venous pressure.

The ratio of physiologic dead space to tidal volume (V_D / V_T) provides an index of $\dot{V}_A / \dot{Q}_c$ disturbances and can be serially monitored. This ratio is determined by simultaneously



measuring the partial pressure of carbon dioxide in expired air (P_ECO_2) and the arterial carbon dioxide tension (P_aCO_2), and applying the values to the Bohr equation modified for physiologic dead space:

$$\frac{V_D}{V_T} = \frac{[P_aCO_2 - P_ECO_2]}{P_aCO_2}$$

An increase of this ratio above a normal of 0.3 indicates the extent of wasted ventilation. (A pathologic increase in dead space will mean a relative reduction in alveolar ventilation unless minute volume has also increased proportionately.) Values of 0.5 to 0.6 or greater indicate that 50 to 60% of the tidal volume is distributed to space not participating in effective gas exchange. The ratio, V_D / V_T, if followed serially, can be used as an index for weaning the patient from the ventilator; if there is simultaneous clinical improvement, a value <0.5 indicates that weaning of the patient from the ventilator can begin.

Another indication of the patient's gas exchange status is the *oxygen gradient* which is the difference between the mean oxygen tension in alveolar air (P_AO_2) and that in the arterial blood (P_aO_2), and which is indicated by $_{A-a}DO_2$. Serial determinations of

this gradient provide a measure of the underlying $\dot{V}_A/\dot{Q}_c$ disturbances, and thus the patient's progress. For example, if arterial oxygen tension (P_aO_2) rises from a previous level of 60 mm Hg to 100 mm Hg, while, simultaneously, the minute volume and inspired oxygen concentration remain unchanged, oxygen transfer from alveolar air to arterial blood must have increased. Thus a decrease in $_{A-a}DO_2$ reflects an improvement in oxygen transfer. Such an improvement indicates reversal of the $\dot{V}_A/\dot{Q}_c$ disturbances and resolution of the obstructive process.

The alveolar oxygen tension (P_AO_2) cannot be measured directly. Therefore, in order to calculate $_{A-a}DO_2$, the alveolar oxygen tension (P_AO_2) is *estimated* from the alveolar air equation:

$$P_AO_2 \cong P_IO_2 - \frac{P_ACO_2}{RQ}$$

It can be assumed that P_ACO_2 is equivalent to P_aCO_2 and that the respiratory quotient (RQ) is 1. Thus the equation becomes:

$$P_AO_2 \cong P_IO_2 - P_aCO_2$$

To determine P_IO_2, the percent concentration of oxygen is multiplied by the barometric pressure minus an allowance for water vapor (47 mm Hg). The simplified equation becomes: $P_AO_2 \cong [\%\ O_2$ inspired air $\times$ (barometric pressure $-47)] - P_aCO_2$.

In practice, the P_aO_2, P_aCO_2, and concentration of oxygen in inspired air must be measured simultaneously. Once the P_AO_2 is estimated, the $_{A-a}$ oxygen difference is calculated by subtracting P_aO_2 from P_AO_2. The normal value when breathing ambient air is 10 to 15 mm Hg. Serial determinations of $_{A-a}DO_2$ can be used to determine the patient's progress.

Acid-Base Disorders in Status Asthmaticus. The mechanisms producing either *respiratory alkalosis* or *respiratory acidosis* have been discussed in detail (pages 48 to 51, and Plate 25). If respiratory alkalosis is induced by hyperventilation because of vigorous mechanical ventilation leading to acute falls in P_aCO_2, the patient may develop seizures, hypotension, and apnea, and even death may occur. These sequelae can be avoided by reducing the output of the ventilator to an appropriate minute volume.

For respiratory acidosis, the logical treatment is to improve alveolar ventilation. If, however, severe acidosis exists (pH <7.20), sodium bicarbonate may be given in an initial dose of 45 to 90 mEq, slowly injected intravenously pending improvement in ventilation. Alternatively, the total adult bicarbonate dose, in milliequivalents, may be calculated: The difference between the normal bicarbonate level (25 mEq/L) and the measured bicarbonate level is multiplied by one-half the body weight in kilograms. Initially, one-half to two-thirds of the total dose may be given; the pH is best titrated to approximately 7.30. If sodium restriction is necessary, tromethamine solution, which is sodium free, may be used instead. However, caution is necessary because this product may depress ventilation.

Metabolic acidosis may develop (particularly in infants and children) if cardiovascular collapse or severe hypoxemia occurs. Also, diarrhea or various other conditions which occur independently of asthma may cause metabolic acidosis. Therapy must be based on a correlation between clinical events and biochemical findings.

Metabolic alkalosis can result from chloride or potassium ion depletion caused by vomiting, nasogastric suction, diuretics, or chronic corticosteroid administration. Appropriate replacement therapy is required. Uncompensated metabolic alkalosis may contribute to hypoventilation which is otherwise unexplained. Use of nomograms can assist the physician in the interpretation of these acid-base disturbances.

Long-Term Management

The objectives of long-term management of any patient with asthma must be to prevent both the occurrence of asthmatic symptoms and the development of respiratory disability. If prevention is not possible, control of symptoms must be the goal. Obviously, if the patient is first seen in status asthmaticus or during a less severe acute attack, priority must be given to resolving this episode. Also, adequate investigation and a consideration of the differential diagnosis (Plate 21 and page 41) are essential.

As mentioned previously (page 12), many diverse stimuli can interact to produce asthma; therefore, multiple therapeutic approaches are essential for long-term management. These multiple approaches may be grouped under the following categories: general health

General Management Principles for the Asthmatic Patient

Good health measures

Nourishing nonallergenic diet

Liberal fluid intake

Adequate rest and sleep

Reasonable physical activity and exercise

General factors to be avoided

Overfatigue

Dampness

Volatile chemicals

Tobacco fumes

Extremes of temperature

Crowds and individuals with head or chest colds

Moldy basements

Occupational hazards

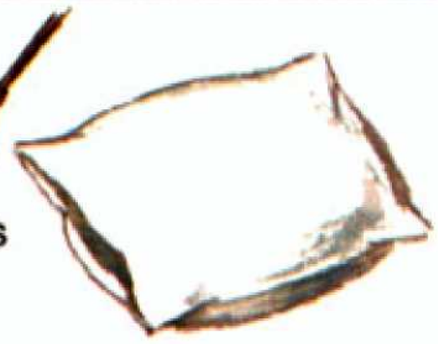
Environmental factors to be avoided

Pollens and all other offending allergens

Draperies

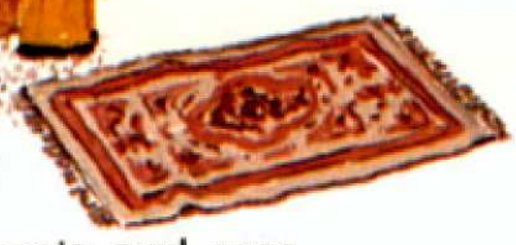
Stuffed toys

Dusts



Feather pillows

Provocative drugs

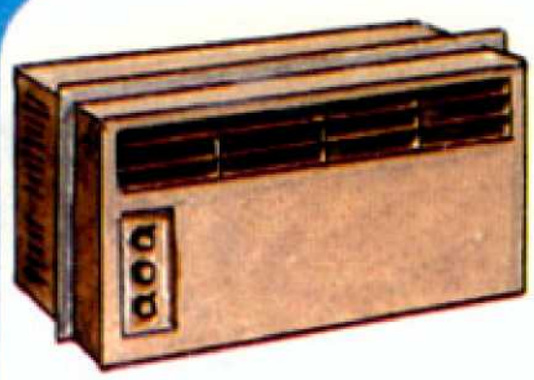


Carpets and rugs

Wool blankets

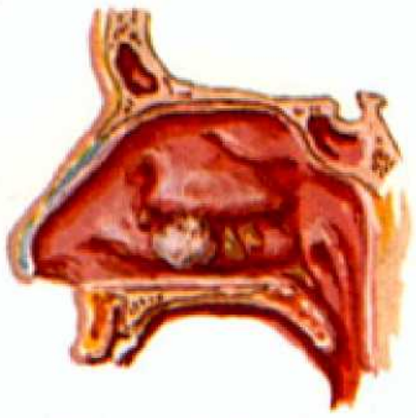
Pets

Mechanical or electronic aids

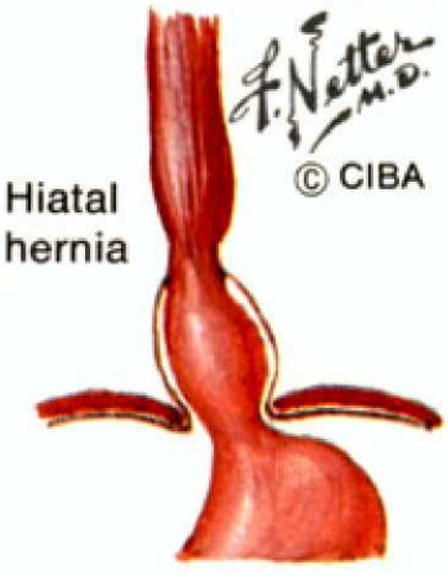


Air conditioners, humidifiers, filters, electronic air cleaners

Elimination or control of precipitating causes



Sinus infection, nasal polyps



Hiatal hernia

measures, environmental control, and avoidance therapy; psychologic management; medication; hyposensitization; and miscellaneous therapy.

General Health Measures, Environmental Control, and Avoidance Therapy. General health measures must become an integral part of the life style of any patient suffering from asthma. These measures include a nourishing, nonallergenic diet, liberal fluid intake, adequate rest and sleep, and a reasonable amount of physical activity and exercise (Plate 32). The patient must also be instructed to practice moderation in daily activities while avoiding exposure to those precipitating factors which play a role in the etiology of asthma. Thus, for example, the patient should avoid fatigue, dampness, inhalation of volatile chemicals, tobacco fumes, extremes of temperature, exposure to individuals with active respiratory infections, moldy basements, and various occupational hazards. Similarly, the patient's environment in the home, and particularly in the bedroom, should be such that most of the factors shown in Plate 32 are eliminated. If possible, pollens and other airborne allergens should be excluded by the use of air conditioners, window filters, and electronic air cleaners which act by electrostatic precipitation of airborne particles. Humidifiers are particularly important during the winter season when decreased humidity may cause irritation to mucous membranes. A relative humidity of 50% or greater is desirable.

Nose, sinus, and throat disorders such as infection or polyps must be vigorously treated if discovered in any asthmatic patient. Often the assistance of an otolaryngologist will be needed for diagnosis and treatment. Polypectomy is indicated if nasal polyps are causing nasal obstruction, are triggering asthmatic episodes, or are preventing adequate sinus drainage.

The avoidance of all precipitating factors is not usually possible (Plate 33). However, it is generally easier to avoid provocative drugs or foods than airborne inhalants. If only one allergen, such as dust or dog dander is the cause of the patient's asthma, avoidance therapy will be beneficial. Patients must also be instructed to limit the duration of exposure and the amount of activity during periods of high urban or occupational air pollution.

Psychologic Management. The psychologic and emotional environment of patients with asthma deserves special note (Plate 34). The physician must understand that asthma may place severe stress on the patient and the family. To help reduce this stress, the physician should develop rapport and open communication with the patient and family. Everyone concerned must be given adequate instruction about the general nature of asthma, the necessity of avoiding the common precipitating factors, and the need for good general health measures. Most importantly, the patient must realize the desirability of seeking medical attention whenever new or progressive symptoms are not controlled by the methods usually employed. An asthmatic attack can be aborted more easily than it can be treated.

A pleasant home environment and an understanding family are essential, particularly if the patient is a child. Because extrinsic asthma often abates as the child matures, an optimistic attitude should be fostered in children. Parental resentment or excessive protectiveness should be minimized. Counseling with the child's teachers may also be of benefit. If serious emotional disturbances exist, psychiatric evaluation and therapy are indicated. Socioeconomic problems may require the services of a social worker. Adults may need occupational counseling.

A word of caution is necessary concerning the role of apprehension and fear in asthma. These symptoms are seen in practically every patient during an acute asthmatic episode and at times may be perpetuating or even precipitating factors. However, in severe asthma or status asthmaticus, psychogenic factors must be considered secondary rather than primary causes; the physician must initially treat the bronchial and bronchiolar obstruction.

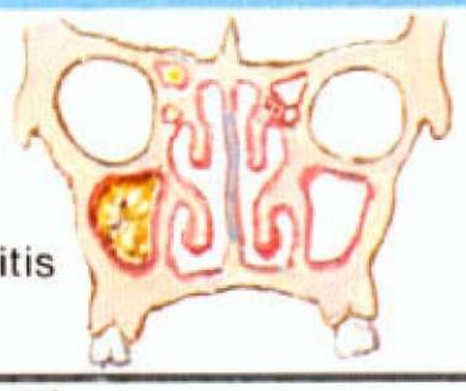
Medication. Asthma which is only mildly incapacitating is often easily controlled by the general measures described previously and simple drug therapy. Medications include bronchodilators administered orally or by aerosol, antihistamines, decongestants such as ephedrine, and expectorants if needed. Often daily use of medication will prevent attacks and lessen chronic symptoms.

Patients with moderate degrees of asthma respond well to maintenance therapy with aminophylline preparations which may be administered rectally or orally in a dose for

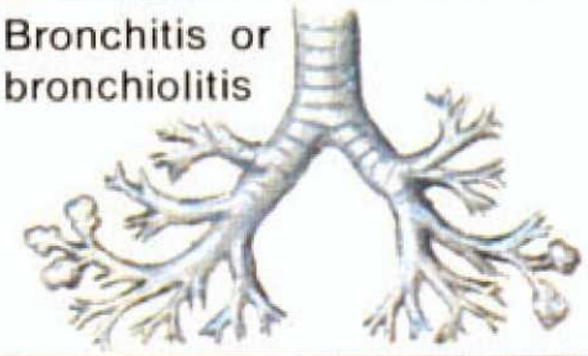
Common Precipitating Factors in Etiology of Bronchial Asthma

Infections

Common cold or other viral infections

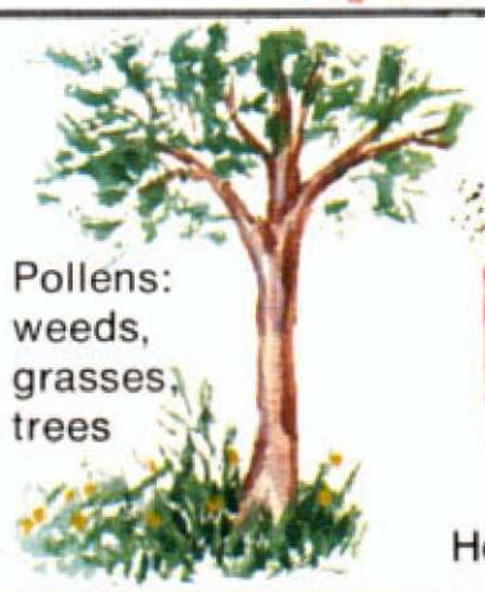


Sinusitis



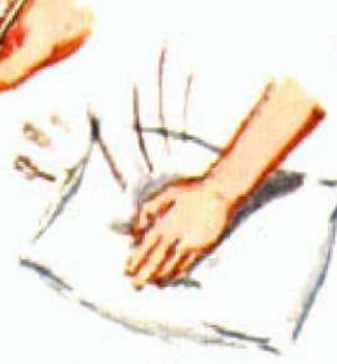
Bronchitis or bronchiolitis

Inhalant allergens



Pollens: weeds, grasses, trees

House dusts



Feathers

Animal danders

Furniture stuffing

Fungal spores

Irritant inhalants

Paint

Gasoline

Tobacco smoke

Industrial chemicals

Fumes

Cold air

Air pollutants

Food allergens

Milk

Eggs

Nuts

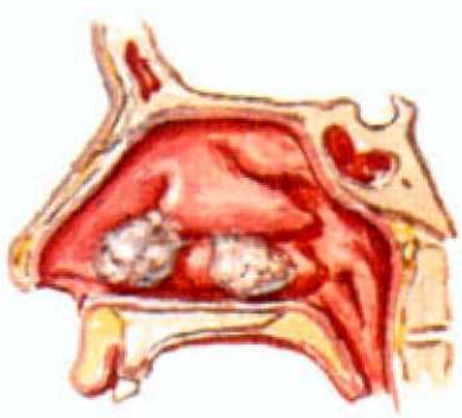
Chocolate

Fish

Shell-fish

Tomatoes, strawberries

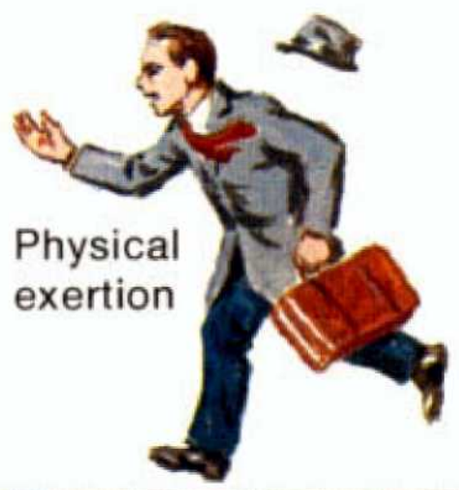
Trigger mechanisms



Nasal polyps

Laughter

Changes in temperature



Physical exertion

Psychologic stress

Drugs

Vaccines

Penicillin

Various drugs

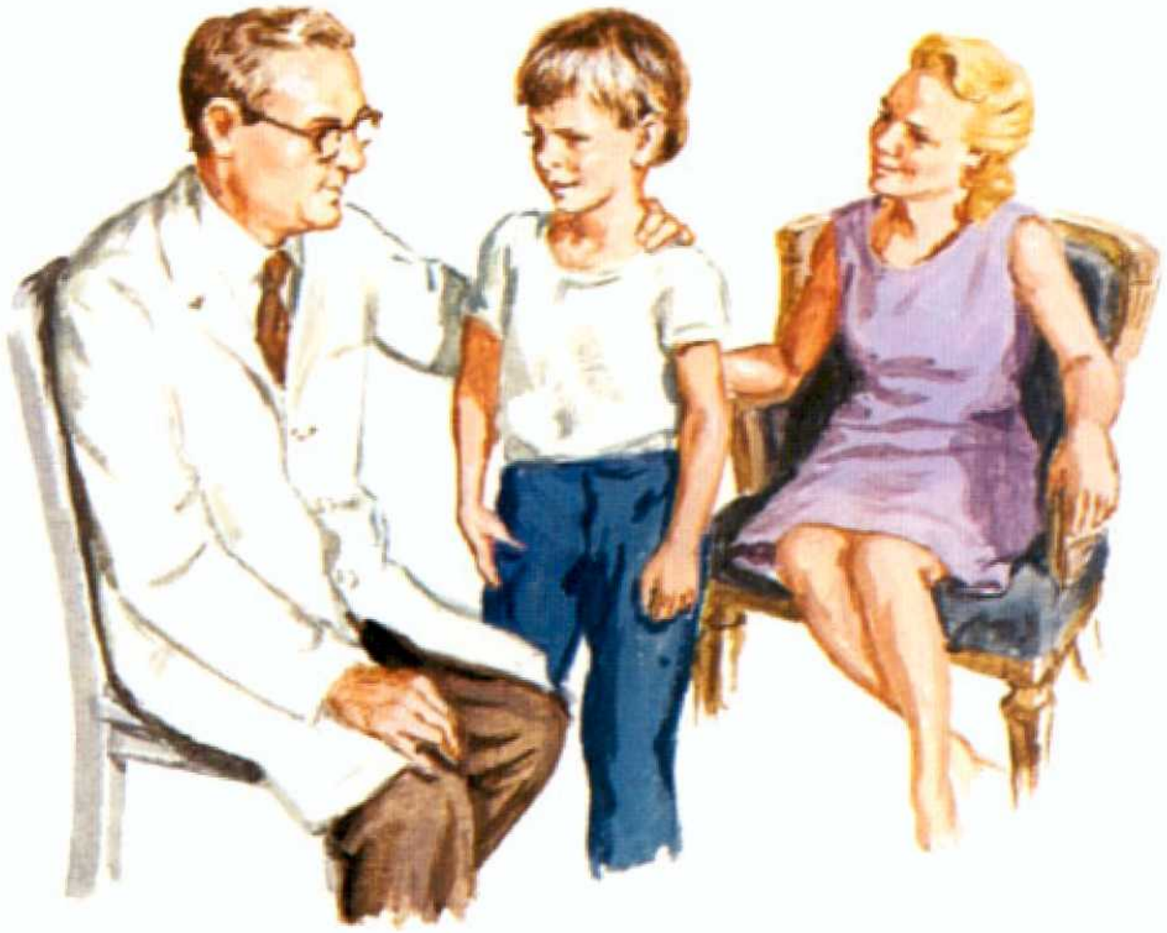
Aspirin

Anesthetic agents

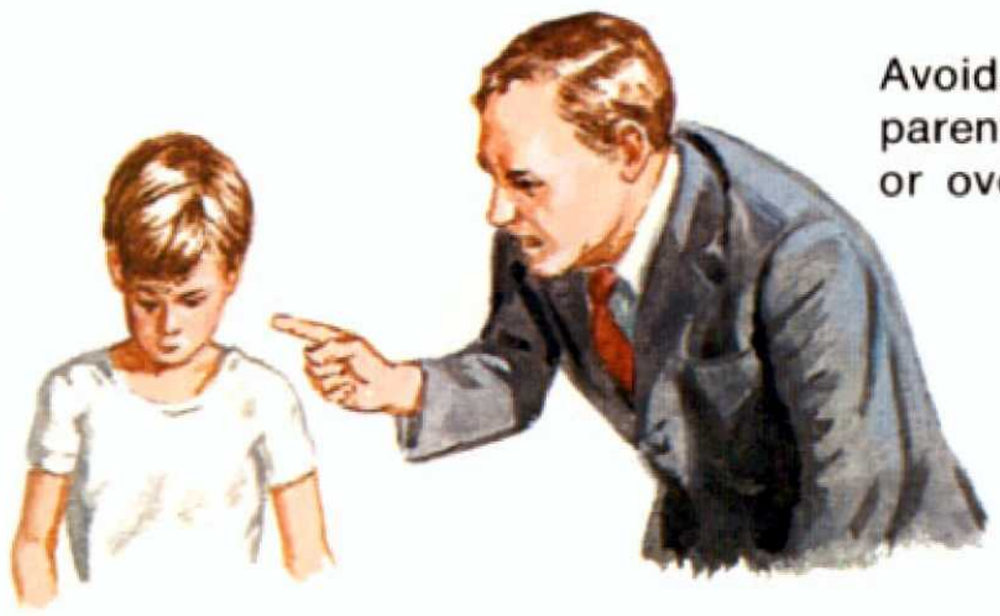
Plate 34

Psychologic and Emotional Factors in Management of Allergic Patient

Pleasant, understanding home environment



Regular observation by compassionate physician



Avoidance of
parental resentment
or overprotectiveness

F. Netter M.D.
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adults of 250 mg, 4 to 6 times daily, depending upon need. Higher doses may be used if necessary. In children, the usual dose is 10 to 12 mg/kg/24 hours, in three or four equal doses. Such therapy is the foundation of long-term ambulatory management.

Aerosol preparations which contain either epinephrine or isoproterenol should not be the primary forms of drug therapy and should never be dispensed without appropriate instruction about the correct method of use, the proper dose, and the danger of overdosing. A usual dose is two inhalations *t.i.d.* as necessary. One or two such inhalations is usually followed by prompt relief of a minor episode. If wheezing, chest tightness, or dyspnea are not controlled by such a dose, or if symptoms promptly return, the patient should immediately seek medical help.

One practice which is to be condemned and about which the patient should be warned is the almost continuous use of gas-propelled aerosol inhalators. A patient may become dependent on such inhalators and may take an inhalation every five minutes or so, even though there are no symptoms of bronchospasm. Such use is prompted by habit rather than by therapeutic need. Obviously, for such patients, the dangers of overdose are great and propellant-induced cardiotoxic effects are more likely to occur.

Sudden death can occur in status asthmaticus, and, in one survey done in Great Britain, was noted especially in children of 10 to 14 years of age. These deaths were attributed in large measure to the abuse of gas-propelled isoproterenol nebulizers. A direct cardiotoxic effect of the propellant may have been responsible, or the deaths may have resulted from overdosing which produced cardiac arrhythmias and/or a paradoxical fall in P_aO_2 (page 56). Parenthetically, most of these children

had severe, diffuse, secretional obstruction of their airways.

To prevent such complications and deaths, proper instruction of the patient in the correct use of nebulizers and in the avoidance of excessive dosage is imperative. Patients should be instructed to advise their physicians whenever increased use of nebulizers is associated with decreased response. Such lessening of beneficial effects may be an index of the progressive severity of asthma.

Ephedrine in an adult dose of 25 mg *t.i.d.* has a weaker bronchodilator action than either epinephrine or isoproterenol administered by aerosol. Ephedrine also has decongestant actions and may be used to relieve rhinitis. Sympathomimetic side effects of ephedrine, epinephrine, or isoproterenol may be counteracted by mild sedatives or tranquilizers.

At the first sign of an acute infection, antimicrobial therapy may be started even before the reports of initial bacterial cultures are available. Whenever possible, however, culture specimens should be obtained before therapy is begun. Tetracycline or erythromycin may be used as initial treatment, but other antimicrobials may be substituted later if indicated by the information obtained from culture and sensitivity reports. However, the various penicillins must be used cautiously because of the danger of drug allergy.

In some patients chronic or recurrent infection is a causative factor in asthma. Viral vaccines may be used prophylactically for many of these patients. However, the effectiveness of stock or autogenous bacterial vaccines remains disputed.

For ambulatory patients with severe degrees of asthma, corticosteroids are usually required. These drugs must always be used under close medical supervision. Corticosteroids should only be used on a long-term basis if the response to comprehensive conventional therapy has been marginal or has failed. In children, chronic administration of corticosteroids may suppress linear growth and must be avoided if at all possible.

To minimize side effects and especially to prevent suprarenal cortex suppression, alternate-day therapy is combined with potassium supplements, dietary sodium restriction, and antacids. The lowest effective dose must be used. Prednisone, 7.5 to 10 mg taken every other morning, or an equivalent product, will usually suffice. Acute asthmatic episodes are treated by increasing the dose and by instituting other appropriate therapy. (If the dosage of corticosteroid is suboptimal, or if the medication is suddenly withdrawn from steroid-dependent patients, status asthmaticus may be precipitated.) Once the acute attack is in remission, the dose must be gradually tapered to a maintenance level. As described previously, eosinophil counts can be used as a basis for adjusting the dose of corticosteroids. During periods of stress, such as surgery, the dose of corticosteroids should be temporarily increased. Patients who need more than 15 mg of prednisone per day should be considered steroid resistant and should receive large doses continuously. Such steroid resistance may result from accelerated plasma clearance.

A number of drugs are currently under evaluation for the treatment of asthma. Many of these are not appropriate for status asthmaticus but may be of benefit in long-term management and prevention of the acute attack. Cromolyn sodium acts by inhibiting release of bronchoconstricting mediators from the mast cell and thus cannot be classified as a bronchodilator. Its onset of action is delayed so that its use is limited to prophylaxis on an ambulatory basis. Cromolyn sodium is of most benefit to young patients with extrinsic asthma or exertional asthma. It is particularly useful in permitting reduction of maintenance doses of corticosteroids and is of no value for acute exacerbations.

Selective β_2-stimulating drugs would be expected to have fewer adverse cardiovascular effects because β_2 receptors are absent from the heart. Also, these drugs would not be expected to produce a paradoxical fall in P_aO_2 (page 56). Two such agents, terbutaline and albuterol have more prolonged action than isoproterenol.

The role of prostaglandins has been discussed previously (page 29 and Plate 13). An aerosol preparation of PGE_1 has been shown to reduce airway obstruction. Future studies will clarify the clinical role of prostaglandins.

Aerosol preparations of corticosteroids have recently been shown to be deposited in the airways where they can produce an adequate therapeutic response. This route may reduce the need for oral administration and thereby reduce systemic complications of corticosteroid therapy. However, it must be explained to the patient that aerosol preparations of corticosteroids do not have the same

pharmacologic actions as sympathomimetic bronchodilators.

Hyposensitization. For patients with extrinsic asthma, or with mixed asthma in whom allergy plays a significant role, a program of specific hyposensitization is an important part of long-term management. Such a program causes discomfort, is time-consuming, and is expensive. Obviously, it should only be undertaken if the asthma is sufficiently severe, and if general avoidance measures and drug therapy prove to be ineffective.

The first step in a program of hyposensitization is to obtain a detailed history. One of the purposes of this history is to help determine the avoidable antigens. These include salicylates, penicillin, household dusts, pet danders, or specific foods. Another function of the history is to help identify allergens which cannot be avoided and to which the patient should be hyposensitized. The determination of the antigens which must be included in a hyposensitization program will depend on the results of skin testing.

A large variety of antigens are available for skin testing, and a physician must use his clinical judgment in selecting those most likely to be allergenic for the particular patient. For instance, the occurrence of asthma during the last two weeks of August or first two weeks of September in a patient living in the northeastern United States suggests that ragweed pollen is probably causing symptoms.

A positive association between exposure to an airborne antigen and the onset of symptoms is more likely to correlate with a positive skin test reaction to the particular antigen. On the other hand, a similar association between ingestion of a food and the onset of symptoms is not as likely to be corroborated by the results of skin testing. Food allergies are better diagnosed by history and diet manipulation.

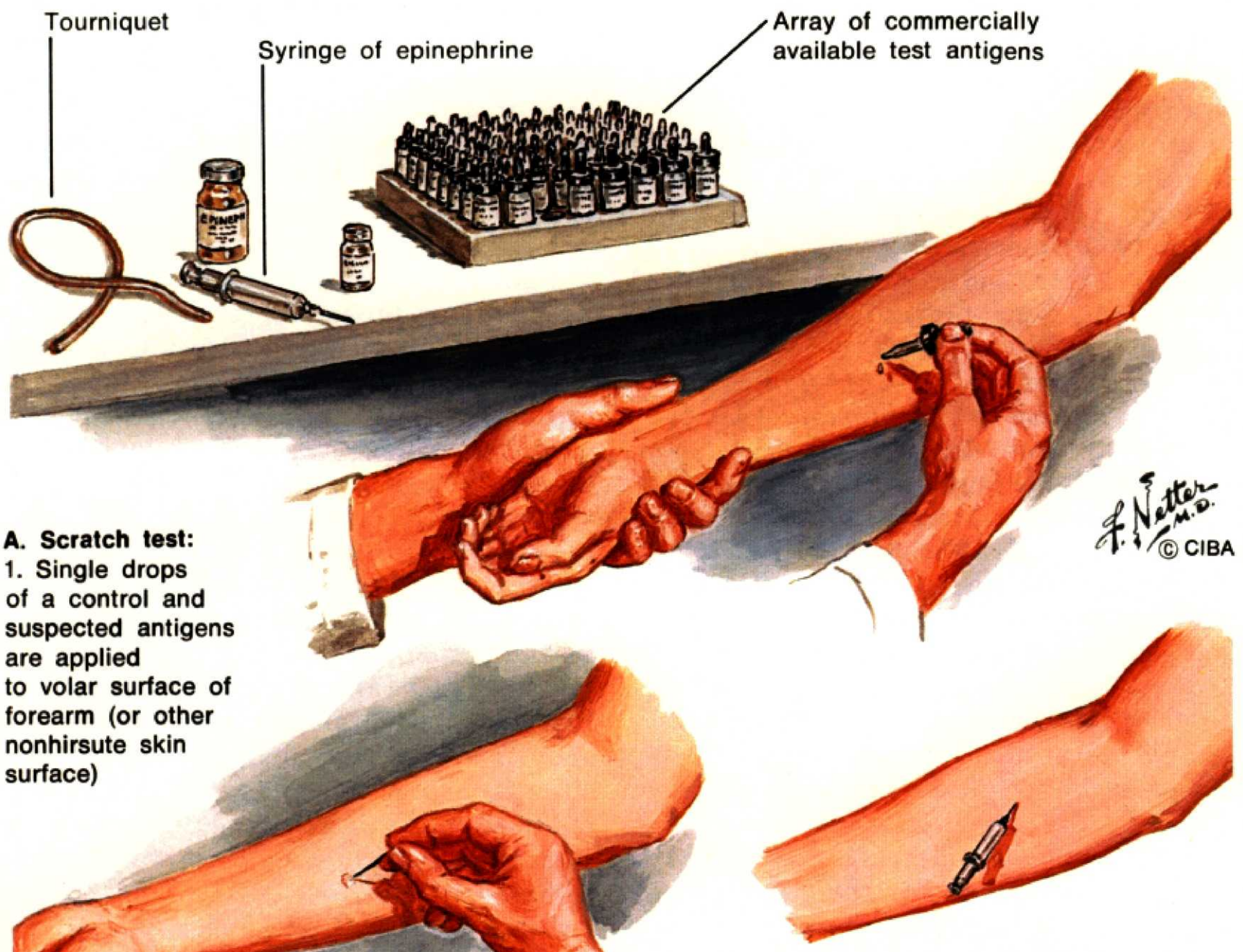
Preferably, skin tests are performed by a scratch (prick) technique (Plate 35) using commercial aqueous extracts of common antigens such as molds, pollens, fungi, house dusts, feathers, foods, or animal danders. Mixtures of unrelated antigens should not be used. A drop of sterile, aqueous antigen solution is placed on the volar surface of the forearm. A prick or scratch of the skin made through the drop with a sterile needle permits a small volume of antigen to penetrate the skin. If skin-sensitizing antibodies to the antigen are present, a wheal-and-flare reaction develops within 15 to 30 minutes; the control test with saline diluent should show little or no reaction. Various methods are used to grade response; a scale of 0 (negative) to 4+ is often used (Plate 35). A negative reaction does not necessarily exclude the antigen as a cause of allergic symptoms. For example, a skin test reaction to house dusts may be negative even though other evidence indicates the culpability of this antigen. Conversely, many individuals with an atopic family history have positive skin tests to various antigens but otherwise have no evidence of allergic disease.

Optimally, both the history and dermal reactivity will give corresponding results. However, some patients will have positive histories with negative or questionable skin tests. In other patients negative histories and positive skin tests indicate immunologic specificity which is clinically insignificant. Such equivocal results require a reevaluation of the situation. The following technical factors must be considered: potency or age of the antigen extract, whether correct antigen was used, technique of testing, presence of nonspecific skin irritants, concentration of selected antigen, and partial inhibition of reactivity by prior administration of sympathomimetics, antihistamines, or aminophylline. (Corticosteroids have no suppressant effect on skin test reactivity.)

If retesting is required because scratch test results were negative or weakly (equivocally) positive while history and clinical symptoms suggest allergic sensitivity, intradermal tests may be indicated. Intradermal tests are much more sensitive than scratch tests, but they are also more time-consuming. More importantly, intradermal tests are more likely to produce systemic reactions or acute asthmatic episodes. If the scratch test is negative, the intradermal test should be performed with a 1:1000 or 1:1500 concentration of antigen and a small bore (26-gauge) needle.

Alternatively, provocative challenges by bronchial inhalation of molds, fungi, or house dusts in conjunction with serial spirometry measurements may be used to determine allergenicity. Bronchial provocation is a more direct method of determining the causative role of a specific allergen. It may be especially

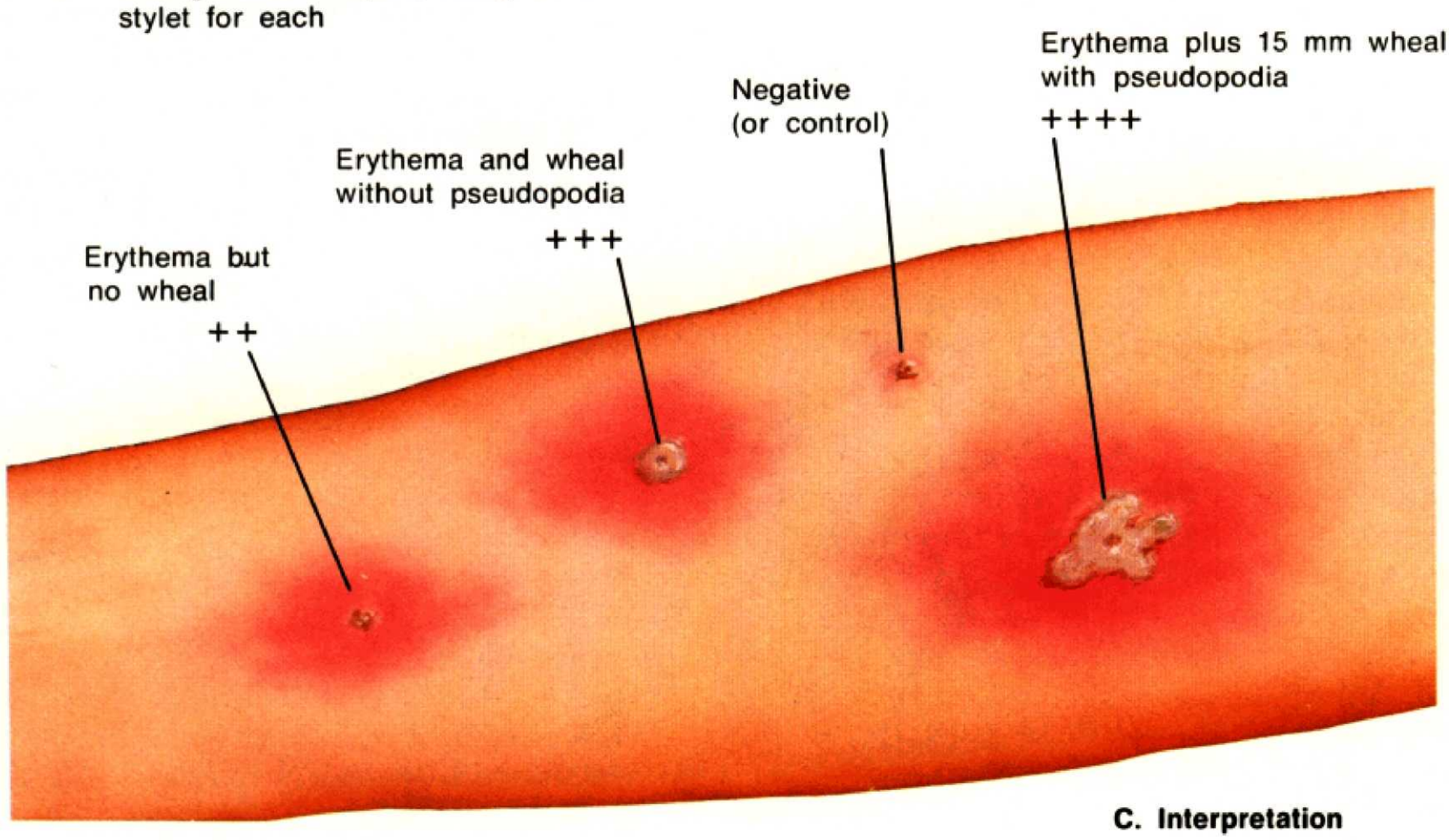
Skin Testing for Allergy



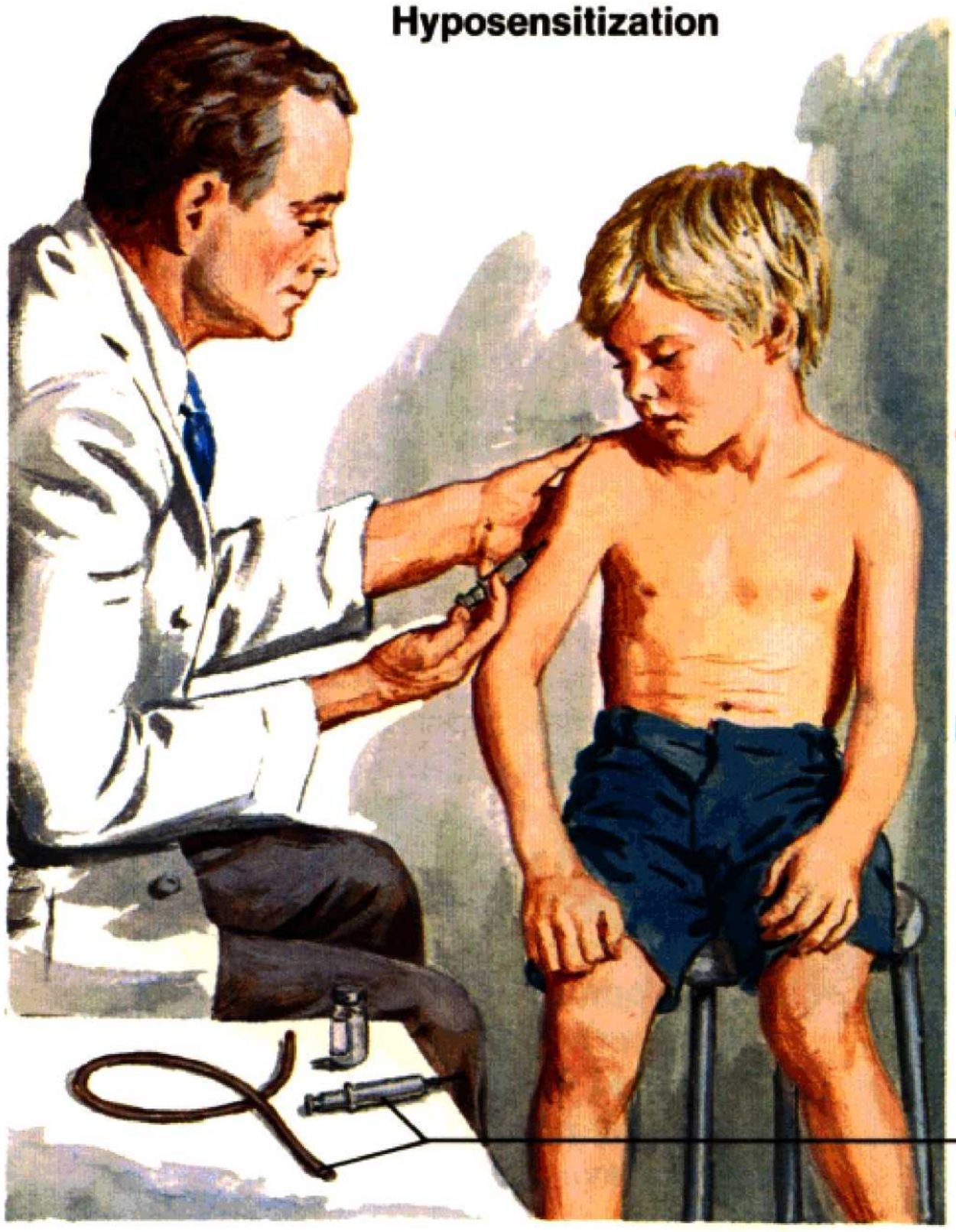
A. Scratch test:
1. Single drops of a control and suspected antigens are applied to volar surface of forearm (or other nonhirsute skin surface)

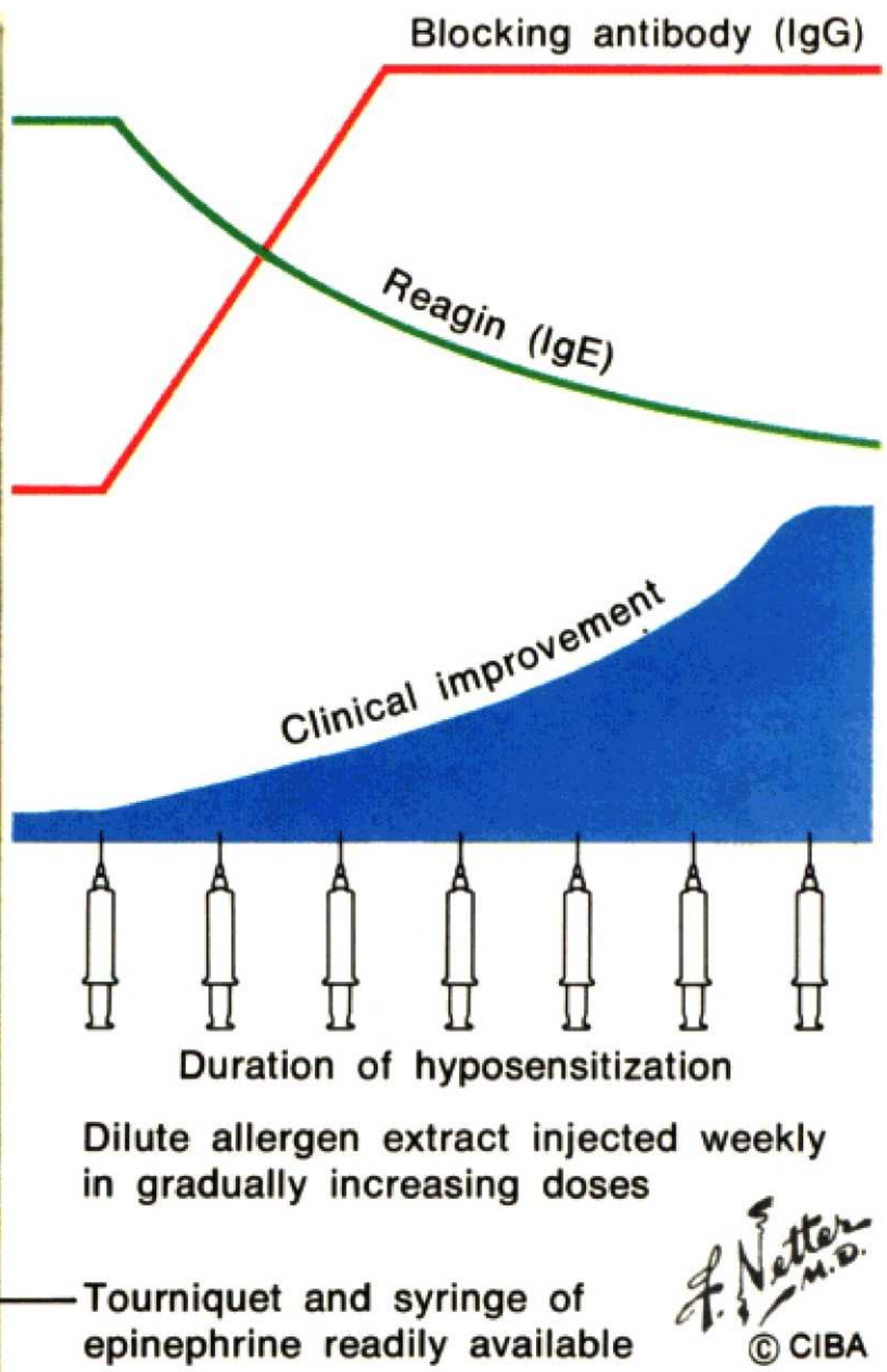
2. Small prick or scratch is made through each droplet, using clean stylet for each

B. Intradermal test: Method is more sensitive but is more liable to produce systemic reaction



C. Interpretation





valuable for evaluating a patient with a negative skin reaction but a strongly positive clinical history.

During any type of testing, a syringe of epinephrine and a tourniquet which can be applied proximal to the test site should be available in case of a systemic (anaphylactic) or asthmatic reaction. Also, intravenous fluids, emergency drugs (corticosteroids, aminophylline, and vasoconstrictive agents which can be administered parenterally), and the equipment necessary for establishing an airway should be readily accessible.

The results of skin testing, and, if necessary, of bronchial provocation testing, must be correlated with the clinical history. A decision is then made as to whether a program of hyposensitization will benefit the patient. Best responses to hyposensitization can be expected when pollens are the offending antigens. Less favorable responses may be anticipated when molds and dusts are implicated.

Hyposensitization must be done under the supervision of a physician. Injections of dilute extracts of antigen are given on a weekly basis in gradually increasing doses until maximum protection is achieved (Plate 36). Schedules of hyposensitization may be perennial, coseasonal, or preseasonal. Obviously, perennial therapy is continued all year, and coseasonal therapy is given only during the season when the particular antigen is prevalent. Preseasonal therapy is begun 2 to 3 months before the specific allergy season and is not discontinued until the season is over. The patient's responses must be reevaluated periodically, and, if these are less than expected, new sensitivity to other antigens must be considered.

Formation of a blocking antibody (IgG) is postulated to occur in response to the injections of antigen. The affinity of IgG for the antigen is greater than the affinity of IgE for the antigen. Thus, IgG combines with the antigen before IgE. A correlation between IgG titer and clinical improvement in hay fever victims appears to exist. Serum IgE levels in these patients are apparently decreased, and cellular release of histamine may also be reduced.

In controlled trials, up to 70% of patients with allergy to pollens have been shown to improve substantially with hyposensitization. The best responses may be expected in young asthmatics, but even adults should have the benefit of a therapeutic trial if clinically indicated.

Various other treatment schedules may be used and other antigen preparations are available. For example, alum-precipitated and oil-repository antigens may be used in some instances. Bacterial or fungal vaccines have been mentioned previously (page 68).

Miscellaneous Therapy. Some patients whose asthmatic symptoms are refractory will benefit by a move to another climate. Because no geographic area is devoid of airborne allergens, the response to such a move is highly variable. However, a move to a less humid or less industrialized area is more likely to prove beneficial. All factors must be considered. Optimally, a trial vacation or a period of residence in the prospective geographic area will facilitate making the decision.

Physical therapy is beneficial for certain patients. Such therapy includes breathing exercises to improve exercise tolerance and relaxation techniques to temper the distress of an acute attack. Postural drainage can also be used by those patients with copious secretions.

Surgical procedures are rarely indicated for asthma. The merits of glomectomy (carotid body removal) have not been scientifically substantiated. However, surgical correction of trigger foci such as hiatal hernia, focal bronchiectasis, nasal polyps, or sinusitis may be considered for selected patients.

Conclusions

Between 4000 and 7000 asthmatics die annually in the United States. However, the number of deaths among children is low in relation to the number of childhood asthmatics; of 6 to 8 million asthmatics in the United States, 1.5 million are children, yet less than 200 children die annually of causes related to asthma.

The greatest danger of death in asthma occurs during severe attacks or status asthmaticus. Prevention of such deaths requires intensive, individualized treatment based on the following *principles:*

1. The gravity of an acute attack must be recognized by patient, family, and physician so that appropriate treatment may be initiated immediately.

2. Treatment must be directed toward clearing the airway, mobilizing secretions, relieving bronchospasm, and preventing or correcting blood gas and pH disturbances.

3. Continuous clinical and physiologic observation of the patient is necessary to follow the progression of the attack, to judge the effectiveness of therapy, and to anticipate the development of complications.

Long-term management is based on the principle of *prevention*. This principle has a threefold application: preventing acute attacks, preventing (or ameliorating) chronic symptoms, and preventing the onset or progression of respiratory disability. Obviously, an individualized program of therapy must be developed for each patient. This program depends on the identification of the particular causes of the patient's asthmatic symptoms and demands an environment of open communication and trust among patient, physician, and family.

Young asthmatic patients can anticipate significant relief of symptoms by the time they reach puberty. Even in adults, asthmatic symptoms can be substantially alleviated by treatment. Bronchial asthma is reversible with proper management, and the onset or progression of permanent respiratory disability can be prevented.