Bronchial Asthma

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. Episodes of dyspnea and wheezing—symptoms of airway obstruction—are characteristic features of the disorder. In some patients, cough, with or without tenacious sputum, may occur. Asthmatic symptoms are results of obstructive bronchospasm, bronchial wall edema and inflammation, and hypersecretion by mucous glands, leading to hyperinflation, gas exchange defects and increased respiratory work. Asthmatic episodes may be continuous or paroxysmal with impaired respiratory function ranging from modest disability to life-threatening asphyxiation—status asthmaticus. A major feature of asthma is that it is *reversible* to some extent either spontaneously or through treatment.

Clinical Forms of Bronchial Asthma

Clinically, patients can exhibit several forms of asthma. The most common classification is based on etiologic factors but also takes account of both clinical variations and therapeutic implications.

Extrinsic Asthma. Also called *allergic asthma*, extrinsic asthma usually affects children and young adults (Plate 13). It is characterized by reversible paroxysms of bronchospasm with wheezing, dyspnea and other symptoms of respiratory distress following exposure to causative allergens. These episodes are usually of sudden onset and brief duration, and between them the patient may be relatively symptom free. A personal history of other allergic manifestations such as hay fever or eczema *(atopy)* is common, as is a family history of atopy. Dermal reactivity to offending allergens is significant, with immunoglobulin E (IgE) playing a role. Response to medical therapy is generally favorable and long-term prognosis is good. However, in adult life a number of patients experience recurrences.

Intrinsic Asthma. Intrinsic asthma usually develops in middle age (Plate 14). Immunologic factors have no apparent role in etiology, and respiratory tract infection is a frequent causative factor; this form is also called *idiopathic* or *infective* asthma. Occasionally there is a history of atopy.

Often in the initial presentation intrinsic asthma is clinically indistinguishable from allergic asthma, although sputum production (purulent) and cough may be more severe in patients with infective asthma. Obviously, factors such as age or infection in the sinuses or bronchial tree will favor intrinsic asthma, but once the acute espisode has subsided, the more precise form can then be determined by a complete and accurate history and laboratory data.

Therapy for intrinsic asthma is not always fully effective, and the prognosis is generally poorer than for the allergic variety. Moreover, intrinsic asthma has a greater tendency to become chronic, with continuous cough and sputum production.

Other Forms of Asthma. The clinical course of asthma is variable, so patients often cannot be unequivocally classified as having the extrinsic or intrinsic type.

Mixed asthma refers to a combination of variable allergic and infective factors, which can affect even one patient. In addition, a number of clinica subtypes of asthma exist:

Chronic Asthmatic Bronchitis. Asthma coexist with chronic bronchitis; allergic factors are nc necessarily identifiable. Therapy for bronchitis supplemented with bronchodilators.

Asthma, Aspirin Sensitivity and Nasal Polyposis Symptoms of asthma develop within 20 minute of ingestion of aspirin, with or without nasa polyposis. Most patients have intrinsic asthm with perennial symptoms. Coexistin eosinophilia can be severe. An estimated 10% adult asthmatics have an intolerance to salicylate

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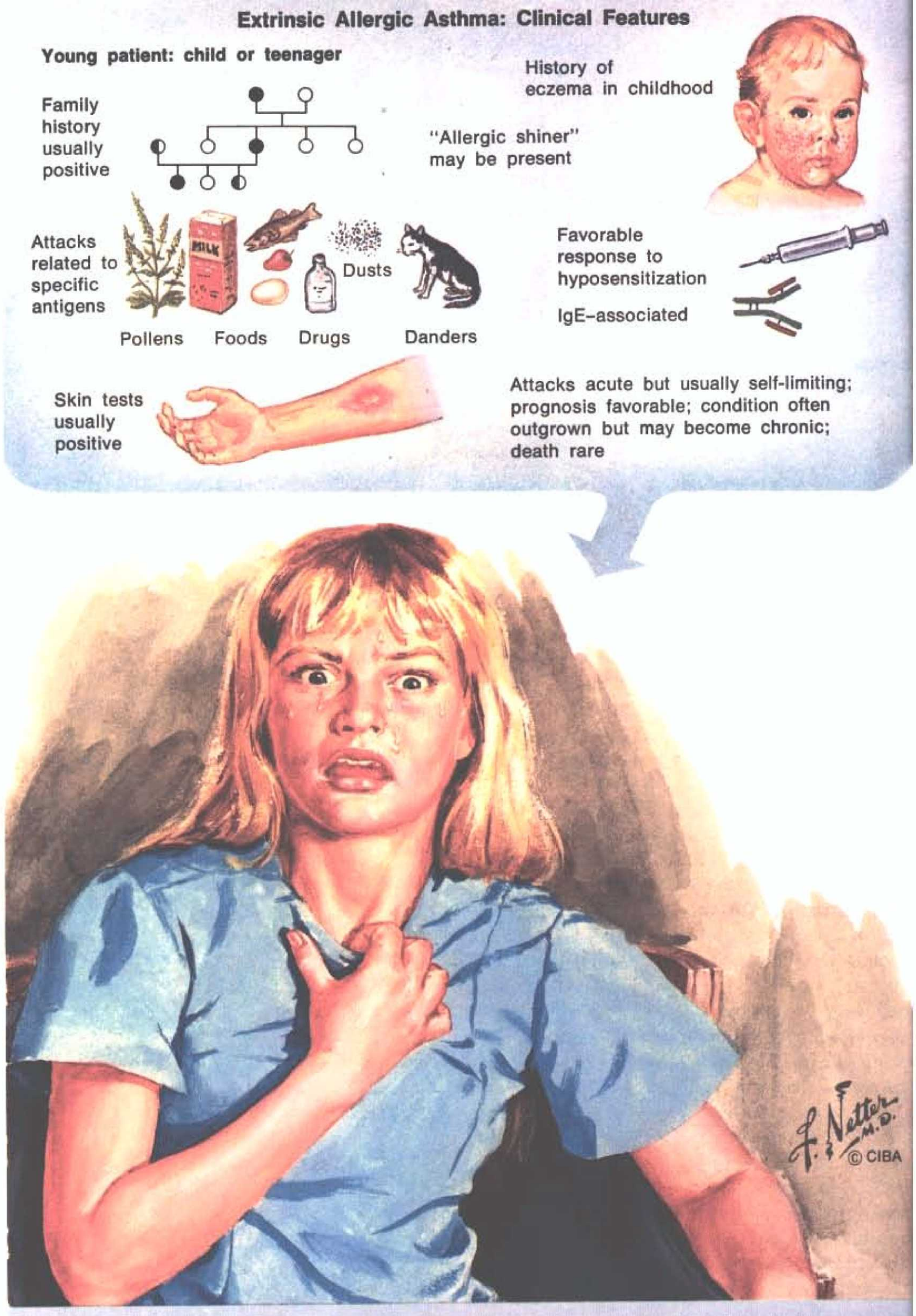


Features common to both extrinsic allergic and intrinsic asthma:
Respiratory distress, dyspnea, wheezing, flushing, cyanosis, cough, flaring of alae, use of accessory respiratory muscles, apprehension, tachycardia, perspiration, hyperresonance, distant breath sounds and rhonchi, eosinophilia

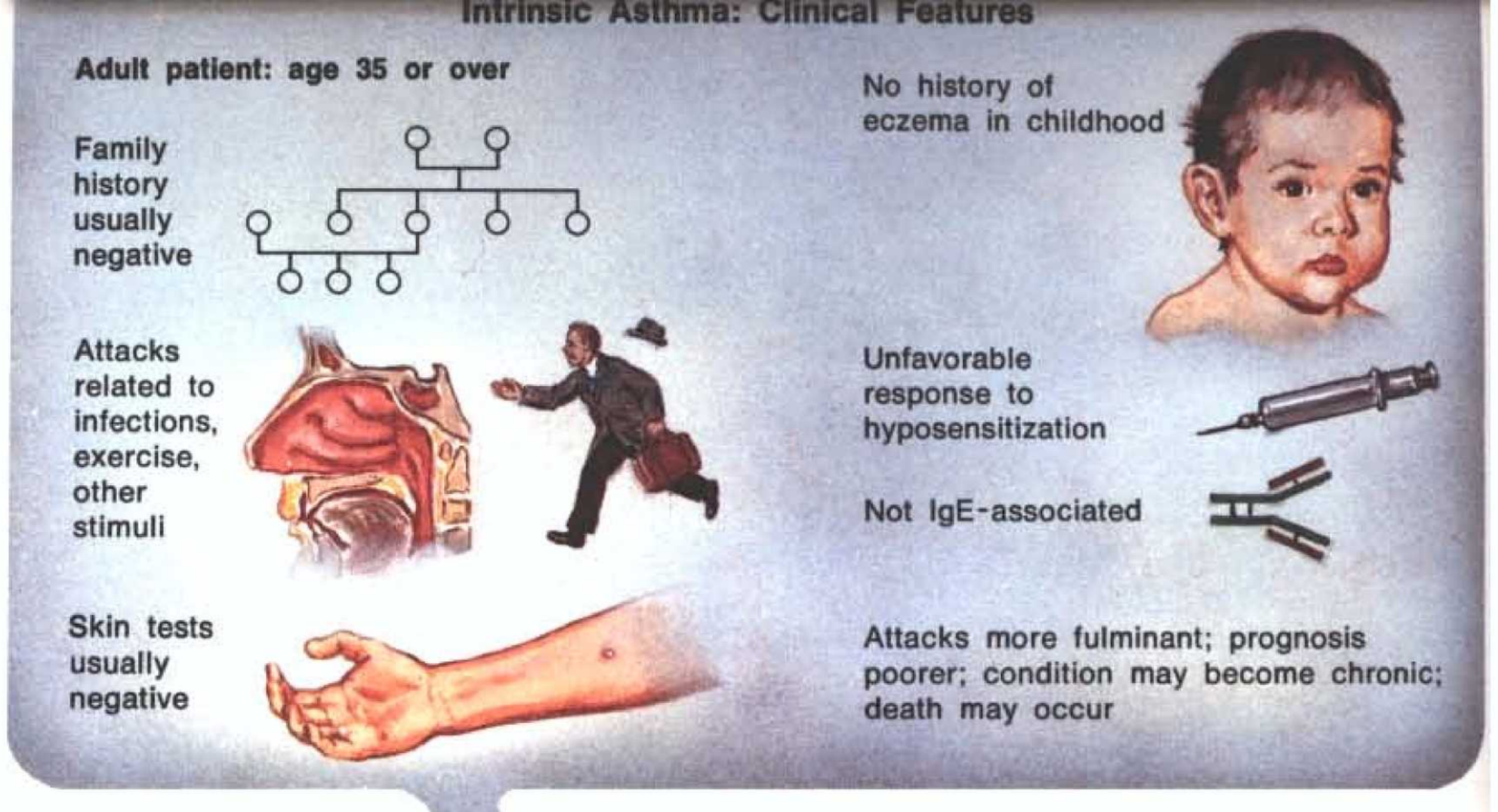
Bronchial Asthma
(Continued)

which does not appear to be immunologically induced. Bronchial sensitivity to indomethacin, yellow dye No. 5 (tartrazine) and other drugs may also be present.

Exercise-induced Asthma. This variant of asthma is precipitated following moderate to severe exercise, particularly in young atopic individuals, becoming maximal 10 minutes after the start of exercise such as running. Bronchodilators or cromolyn sodium may be used prophylactically; alternatively, physical activities should be restricted to those least likely to provoke symptoms.

Dual Type I and Type III Reactions. More than one immune mechanism can lead to asthma. For example, sensitivity to the saprophytic mold *Aspergillus fumigatus* can induce a typical Type I "immediate hypersensitivity" asthma reaction (within 10 to 30 minutes of exposure), or Type III "Arthus type" reaction (two to six hours after exposure), or both Type I and Type III reactions combined. Patients with a dual reaction will develop an acute episode of wheezing and dyspnea with a fall in FEV_1 within 10 to 15 minutes of exposure to the allergen. These findings may subside, to be followed by a relapse two to six hours later. The second reaction develops more slowly and is characterized by progressively severe airway obstruction, dyspnea and, in some patients, pulmonary inflammatory infiltrates. Late (Type III) bronchial reactions can also occur alone and even in nonatopic patients. Both immediate and late skin sensitivity may be found in association with reaginic IgE and precipitating IgG antibodies in the serum, suggesting that the pathogenesis is a consequence of immune processes involving these two immunoglobulins in addition to serum complement and polymorphonuclear cells. Dual reactions can also occur in response to other substances, including avian allergens, mites and wood dusts. Cromolyn sodium may inhibit the sequence. Therapy consists in avoidance of the cause. If this is not possible, corticosteroids may be used.

Status Asthmaticus. This is a severe clinical stage of asthma, refractory to the usual drug therapy for acute episodes, and distinguishable both pathologically and pharmacologically from milder episodes of acute asthma. It is a medical emergency, even in the early phases, since if not treated adequately and promptly, death may result from hypoxia and/or respiratory acidosis (see page 131).



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Respiratory distress, dyspnea, wheezing, flushing, cyanosis, cough, flaring of alae, use of accessory respiratory muscles, apprehension, tachycardia, perspiration, hyperresonance, distant breath sounds and rhonchi, eosinophilia

Pathogenesis of Asthma

Theories about asthma generally explain the hyperreactivity of the airways as an exaggeration of the normal defense response of the respiratory tract. This can result from abnormal tissue reactions in the airways, which may be immunologically induced, or from a biochemical or neurohumoral imbalance of other normally functioning responses. Because of the diverse stimuli known to produce asthma, no single current theory satisfactorily explains all types and cases (Plate 15).

Immediate Hypersensitivity (Type I) Reaction. Allergic bronchial asthma (extrinsic asthma) and other allergic diseases like hay fever and anaphylaxis are examples of immediate hypersensitivity (Type I) reactions (Plate 16). Such allergic reactions take place in specific target organs—the lungs, gastrointestinal tract or skin. These immune processes leading to a hypersensitivity reaction represent the disease state referred to clinically as "allergy."

Immediate hypersensitivity reactions can lead to a simple acute inflammatory response *(urticaria)*, or can cause complex reactions that may be systemic *(anaphylaxis)* or chiefly limited to bronchial smooth muscle *(asthma)*. The immune

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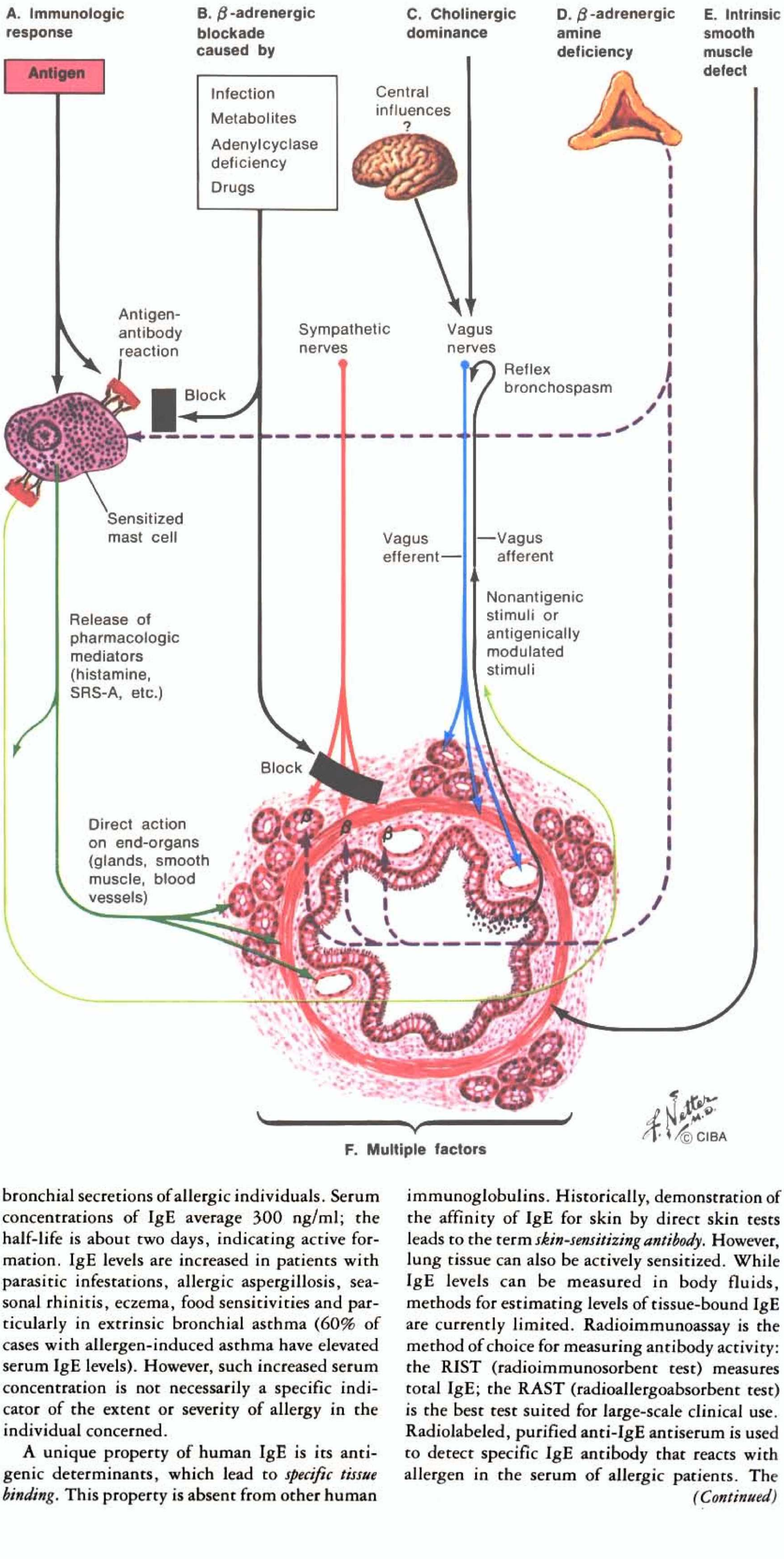
Postulated Mechanisms of Airway Hyperreactivity Causing Asthma



Bronchial Asthma
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sequence consists of the sensitization phase, followed by a challenge reaction which produces the clinical syndrome concerned.

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. 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).* The IgE molecules attach to the surfaces of the mast cells, or other cells such as basophils. (This affinity of the IgE molecules for certain cells is known as *homocytotropism* [cytotropism], and is species specific.) The mast cells containing IgE are distributed in the mucosa of the upper and lower respiratory tract and perivascular connective tissues of the lung.

After a variable latent interval (days to months), a reexposure of the patient to the specific antigen may result in a *challenge* (allergic) *reaction.* IgE-sensitized mast cells in contact with the specific antigen secrete preformed pharmacologically active substances including histamine, slow-reacting substance of anaphylaxis (SRS-A), various kinins, eosinophil chemotactic factor (ECF), serotonin and probably prostaglandins. Calcium and magnesium ions are required for the reaction to occur, and each antigen molecule has to bridge at least two of the IgE molecules bound to the surface of the cell. Muscle contraction, vasoconstriction and hypersecretion of mucus, together with an inflammatory response of increased capillary permeability and cellular infiltration with eosinophils then follow, producing 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 aggravates the picture and may facilitate increased permeability of the tissues to the inciting antigen. Continued sensitization and reaction may then occur.

Immunoglobulin E, the antibody mediator of the immediate hypersensitivity reaction, is a heat-labile gamma-l-glycoprotein with a molecular weight of 200,000. Synthesized by plasma cells in the mucosa of the nose, respiratory and gastrointestinal tracts, and lymphoid tissues, it is found in various tissues, in body fluids and in nasal and bronchial secretions of allergic individuals. Serum concentrations of IgE average 300 ng/ml; the half-life is about two days, indicating active formation. IgE levels are increased in patients with parasitic infestations, allergic aspergillosis, seasonal rhinitis, eczema, food sensitivities and particularly in extrinsic bronchial asthma (60% of cases with allergen-induced asthma have elevated serum IgE levels). However, such increased serum concentration is not necessarily a specific indicator of the extent or severity of allergy in the individual concerned.

A unique property of human IgE is its antigenic determinants, which lead to *specific tissue binding.* This property is absent from other human immunoglobulins. Historically, demonstration of the affinity of IgE for skin by direct skin tests leads to the term *skin-sensitizing antibody.* However, lung tissue can also be actively sensitized. While IgE levels can be measured in body fluids, methods for estimating levels of tissue-bound IgE are currently limited. Radioimmunoassay is the method of choice for measuring antibody activity: the RIST (radioimmunosorbent test) measures total IgE; the RAST (radioallergoabsorbent test) is the best test suited for large-scale clinical use. Radiolabeled, purified anti-IgE antiserum is used to detect specific IgE antibody that reacts with allergen in the serum of allergic patients. The

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Bronchial Asthma
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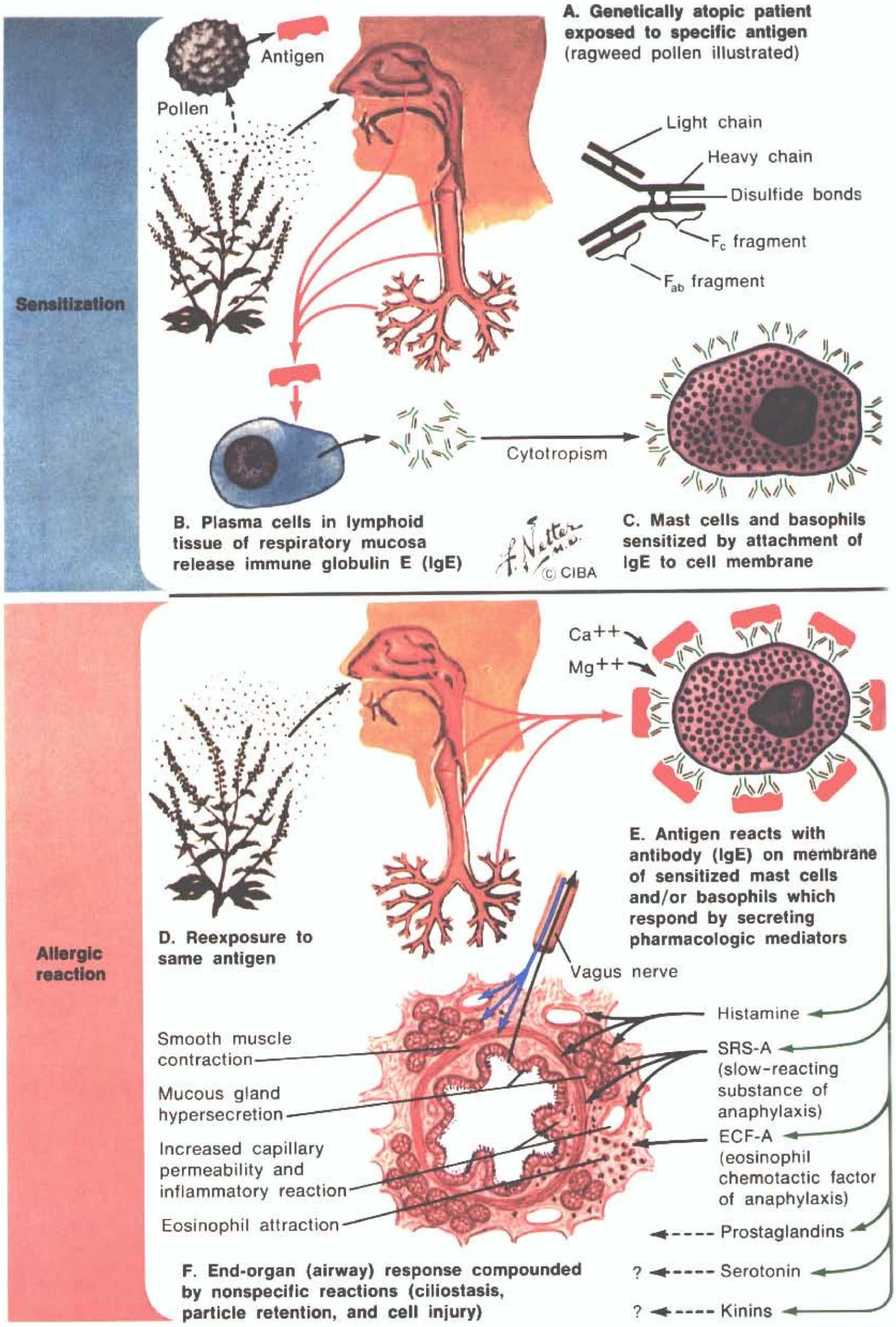

RAST seems to correlate with skin test reactivity and leukocyte histamine release.

While immunologic mechanisms may have a significant role in the causation of asthma, the regulation of the release and generation of mediators, as well as the expression of their effects, is under significant neurogenic controls. An understanding of the beta adrenergic system and cholinergic factors is necessary for a fuller appreciation of the etiology and pathogenesis of asthma. It also provides a foundation for a rational approach to therapy.

Adrenergic Receptors. The sympathetic nerves are poorly represented in the lung by direct innervation, except to the vasculature. However, *circulating catecholamines* probably have a marked influence in the lung. Pharmacologic studies indicate that there are two basic types of adrenergic receptors, alpha and beta. The alpha receptors are located primarily in smooth muscle and exocrine glands. Beta receptors have been differentiated pharmacologically into $beta_1$, located in the heart, and $beta_2$, located in smooth muscle throughout the body, including the bronchial and vascular smooth muscle (Plate 17; see also page 22).

Generally, alpha stimulation is excitatory. Beta stimulation may be either inhibitory (relaxation of bronchial smooth muscles) or excitatory (increase in both heart rate and force of contraction). Certain tissues contain both alpha and beta receptors. The results of stimulation depend on the nature of the stimulating catecholamine, and the relative proportion of the two types of receptors present. For instance, in the lungs, beta stimulation causes bronchodilatation and possibly decreased secretion of mucus; alpha stimulation causes bronchoconstriction.

In humans, three principal catecholamines are formed: dopamine, norepinephrine and epinephrine. *Dopamine* is chiefly a neurotransmitter in the extrapyramidal nervous system. *Norepinephrine*, a metabolic precursor of epinephrine, is the main neurotransmitter of the postganglionic sympathetic fibers. *Epinephrine* is the major hormone of the adrenal medulla. A number of synthetic catecholamines have been developed. Of these, *isoproterenol* (or its derivatives) is most often used in the treatment of asthma. The role of circulatory neurohormones in bronchial asthma is concerned with (1) inhibition of mast cell mediator release and (2) bronchial smooth muscle relaxation.

Beta Adrenergic Blockade. In the normal individual, airway tone and patency represent a balance between bronchorelaxation forces induced by beta adrenergic stimuli and bronchoconstrictive tendencies caused by vagal impulses (and possibly by alpha adrenergic stimuli), although other factors already cited can also have some influence (Plate 18).

Beta adrenergic stimulation activates *adenylcyclase*, an enzyme thought to be closely associated with but not necessarily identical to the beta receptor which is located in the cell membrane of the muscle or mast cell. This is produced by a circulating hormone or drug—the first messenger—linking with these selective receptors which are responsible for hormonal specificity in tissues. Adenylcyclase catalyzes the synthesis of cyclic adenosine monophosphate (cyclic 3′, 5′-AMP, or cAMP) from adenosine triphosphate (ATP). Cyclic AMP then diffuses into the cell where it has a number of functions. Its most important function for the bronchial smooth muscle cell is activation of mechanisms that prevent contraction or induce relaxation of the muscle. In the mast cell, cAMP serves to inhibit mediator release.

These receptors modulate the activity of adenylcyclase, which controls the level of cAMP activity and hence of the metabolic functions according to the enzyme profile of the cell. Functionally opposing biologic transmitters also

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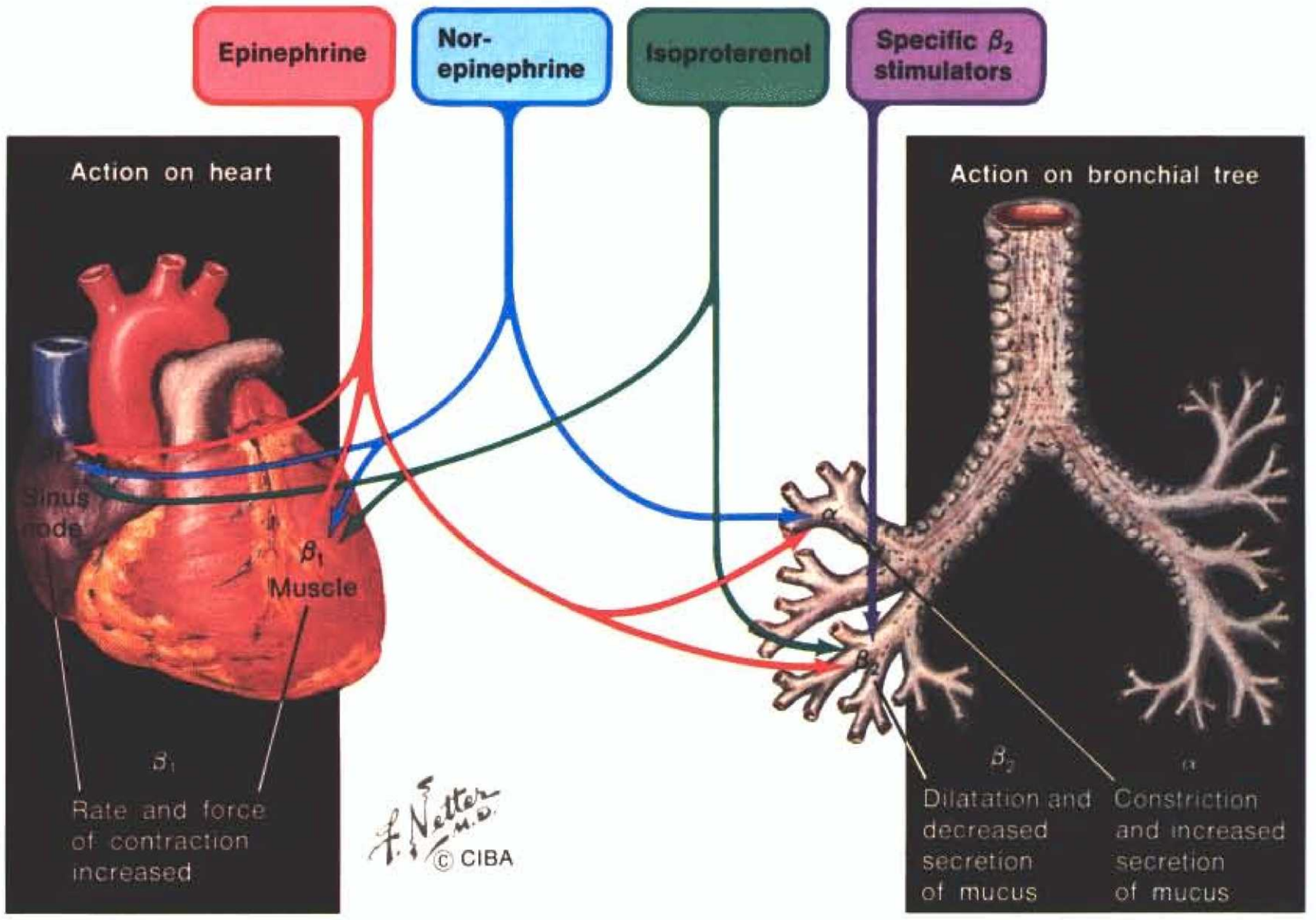
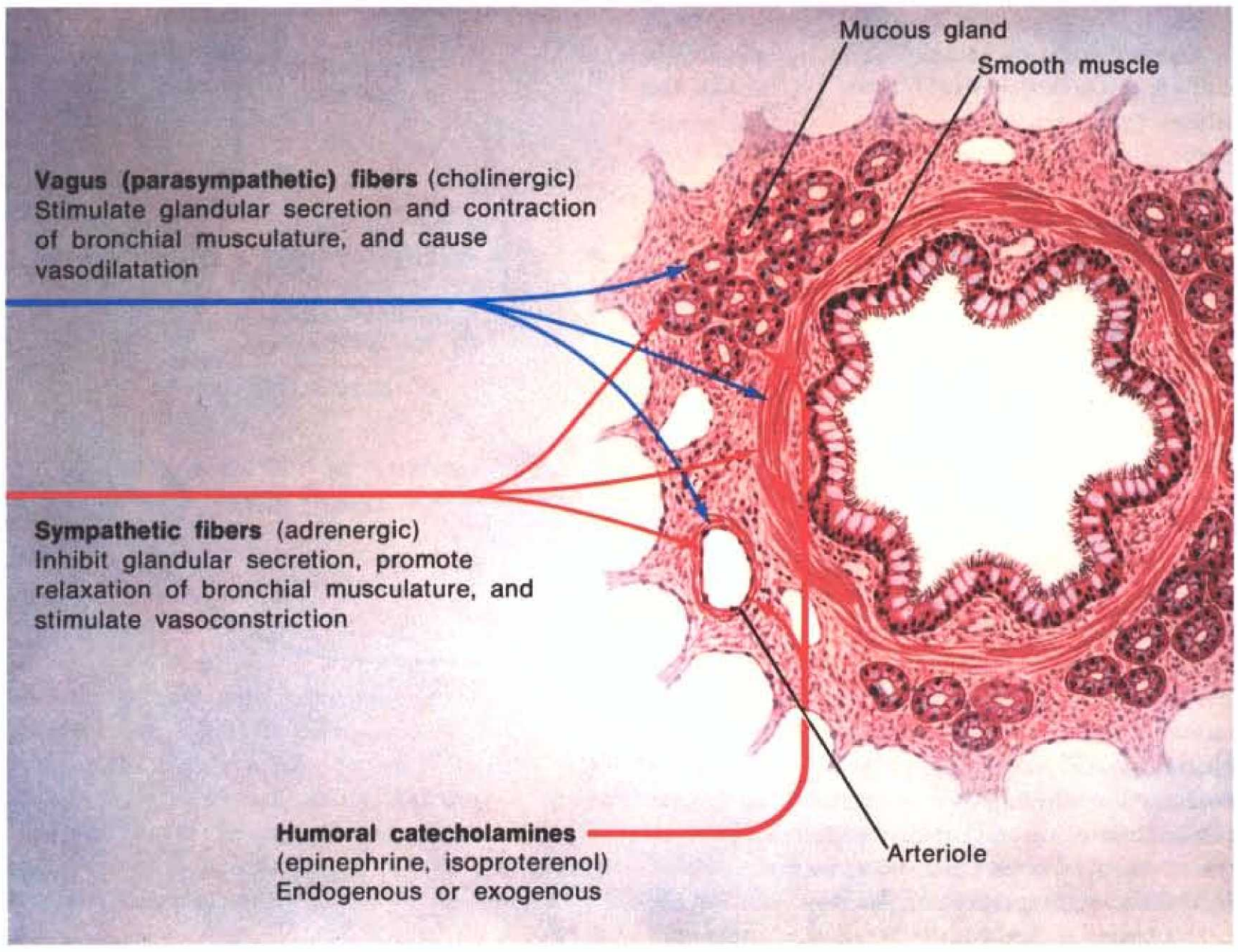
Catecholamine Action on α and β Receptors of Heart and Bronchial Tree



Neurohumoral Control of Bronchial Musculature, Glands, and Vessels



Bronchial Asthma
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stimulate specific cell membrane receptors and activate the nucleotide cyclic 3′, 5′, guanosine monophosphate (cGMP). Acetylcholine is a major cause of increased tissue cGMP.

Beta adrenergic blockade may occur because of a malfunction or deficiency of the adenylcyclase system within the smooth muscle cells of the airway, glands, blood vessels of the lungs and tissue mast cells.

Such deficiency may be acquired from infection or arise from certain metabolites, or it may be inherited. It causes normal beta adrenergic responses to various stimuli to become inadequate, and bronchoconstriction occurs by autonomic imbalance (or other similar influences). Alternatively, the same result could develop when beta adrenergic responses are initially adequate, but the ability of adenylcyclase to catalyze production of cAMP is limited. Hence, in the airway, excessive or prolonged tonic constrictive stimulation would eventually overcome the counterbalancing bronchorelaxing effects of beta adrenergic stimulation; in the mast cell these events would lead to mediator release. Beta adrenergic blockade may also be caused by adrenergic blocking agents, such as *propranolol*.

Role of the Vagus. As discussed above, bronchial constriction is partly an autonomic reflex. The afferent fibers of the arc arise from receptors in the tracheobronchial tree or, at times, in the nose and sinuses. 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 originates with stimulation of epithelial "irritant receptors." Concurrently, airway caliber can also be altered by regional changes in oxygen or carbon dioxide tension, which may occur with pulmonary embolus or asthma, or by a direct action on smooth muscle from chemical mediators of the allergic reaction released by mast cells. In addition, it is possible that central nervous system activity, including stimuli arising in higher centers, can contribute to bronchomotor tone and induce bronchial constriction.

Recently, the role of these vagally mediated cholinergic influences in causing asthma has received renewed emphasis. It is suggested that vagally mediated responses to various stimuli are exaggerated in the asthmatic patient compared with a normal person. In other words, the bronchi of the asthmatic patient react more severely to mild degrees of both antigenic and nonantigenic stimuli than do normal bronchi. An increased sensitivity of the irritant receptors is proposed as the mechanism of asthma in these cases. This effect might be partially due to increases in the amounts of cGMP released from mast cells following cholinergic discharge. Or it might have a neurogenic basis, provoking hyperresponse of the receptors or of the airway smooth muscle. Pharmacologically, bronchial constriction produced by this autonomic reflex pathway can be blocked by atropine or vagotomy whether induced by specific antigenic stimuli or nonspecific irritants.

Mediator Release and Activity. As described above, the challenge reaction of the immune sequence is characterized by the release of pharmacologic mediators from either mast cells located in the respiratory mucosa or circulating basophils. Complement is probably not generally involved in the challenge reaction, and cytolysis does not result. The secretory release of mediators from the mast cell is influenced by the intracellular cyclic nucleotides, cAMP and probably cGMP.

Increased cAMP levels *inhibit* mediator release from mast cells and also prevent the contraction or facilitate the relaxation of the smooth muscle of the airway (Plate 18). Increased cGMP occurs when the cholinergic receptor is stimulated by acetylcholine. Increased cGMP *augments* the release of mediator from mast cells. Thus, cyclic

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Bronchial Asthma
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nucleotides modulate both the release of mediators from sensitized mast cells and the patency of the airway by an action on the airway musculature. Therapeutic agents that stabilize the plasma membrane or modify the cAMP-cGMP balance can act to inhibit mediator release and hence can interrupt the immunologic asthmatic sequence.

Histamine is a vasoactive amine widely distributed in body tissues, particularly the lung, where it is concentrated as granules within tissue mast cells, especially those in proximity to capillary endothelium in the bronchial submucosa. It is also present in circulating basophils and neutrophils. However, the respiratory mucosa and perivascular sites are particularly rich in mast cells and are thus responsible for the propensity for allergic lung reactions following challenge by airborne allergens.

The release of histamine causes increased capillary permeability and vasodilatation, with resulting edema and infiltration by inflammatory cells (Plate 16). Contraction of airway smooth muscle and increased secretion from mucous glands also take place. Parenthetically, aerosol administration of histamine to asthmatic patients usually produces typical bronchospasm, whereas in normal subjects only minor effects occur at equivalent concentrations. *In vitro,* histamine release can be demonstrated in leukocytes or lung tissue of allergic individuals on exposure to appropriate antigens; blood histamine levels also rise in sensitive subjects after antigen inhalation. *In vivo* observations, however, including the minor clinical response to antihistamine drugs, suggest that histamine is not the sole mediator in human asthma. Histamine may have a dose-dependent action: low doses acting through vagal reflexes and higher concentrations directly stimulating both peripheral and central airway smooth muscle.

The *slow-reacting substance of anaphylaxis (SRS-A)* is an acidic, thermostable (at alkaline pH) substance which appears to be a major mediator. Its pharmacologically significant features are a delay in maximal effect on bronchial contraction, and a more prolonged action than histamine has. Moreover, its actions are uninfluenced by antihistamine drugs. Its role in man is unclear.

In addition, the "kinin system" may be operative in producing inflammatory responses and smooth muscle contraction, although its exact role is also unclear. *Bradykinin,* considered the most important mediator, is a potent nonapeptide yielding bronchoconstriction in animals and man.

The roles of several other substances may be noted. *Acetylcholine* is not a direct mediator, but as a neurotransmitter it is involved in the vagally mediated reflexes. *Anaphylatoxins,* C3a and C5a, derivatives of the complement system, have been described in a limited number of patients after antigen challenge. The *eosinophil chemotactic factor of anaphylaxis (ECF-A)* produced in lungs after challenge with antigen is implicated in attracting eosinophils to the allergic site. A *neutrophil chemotactic factor* has also been identified. *Serotonin* increases capillary permeability and constricts smooth muscle; however, its local lung concentrations are negligible, and aerosol challenges are ineffective. *Prostaglandins (PG),* metabolites of arachidonic acid, are released in the lung under a variety of stimuli, including antigen exposure. They exert contractile or relaxant effects on the smooth muscles of the airways and vasculature. PGE has a bronchodilator action, while PGF_{2a} and thromboxanes act as bronchoconstrictors. Their relatively high potency suggests that the ratio of tissue PGE/PGF_{2a} may be important in influencing tension responses in airway smooth muscle. Aerosol PGE has been shown to be an effective bronchodilator in some patients with asthma. Increased serum levels of PGF_{2a} have been found following allergen inhalation in other asthmatic patients. The full biologic and potential therapeutic roles for prostaglandins or other metabolites such as thromboxanes are yet to be established.

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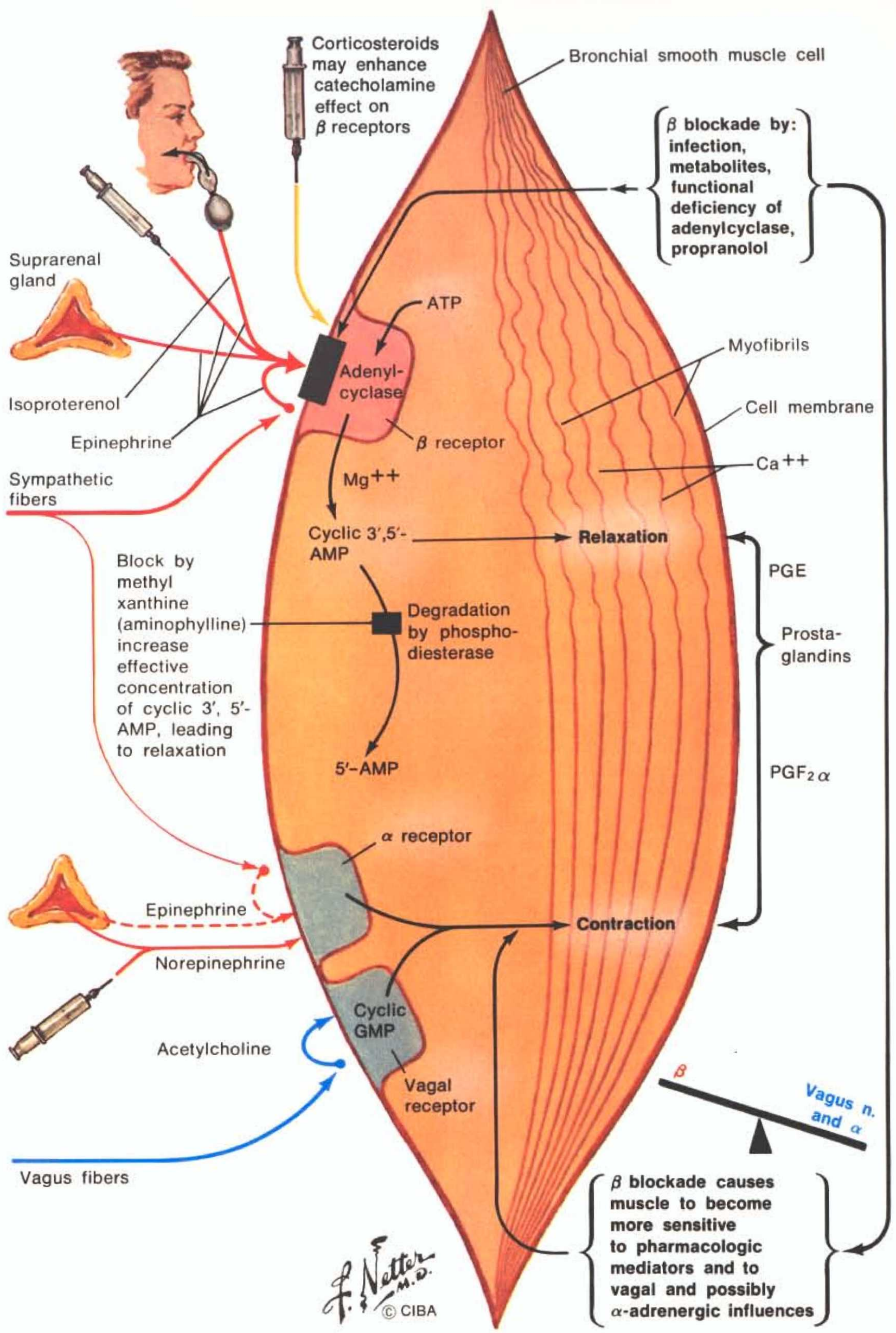

Bronchial Asthma
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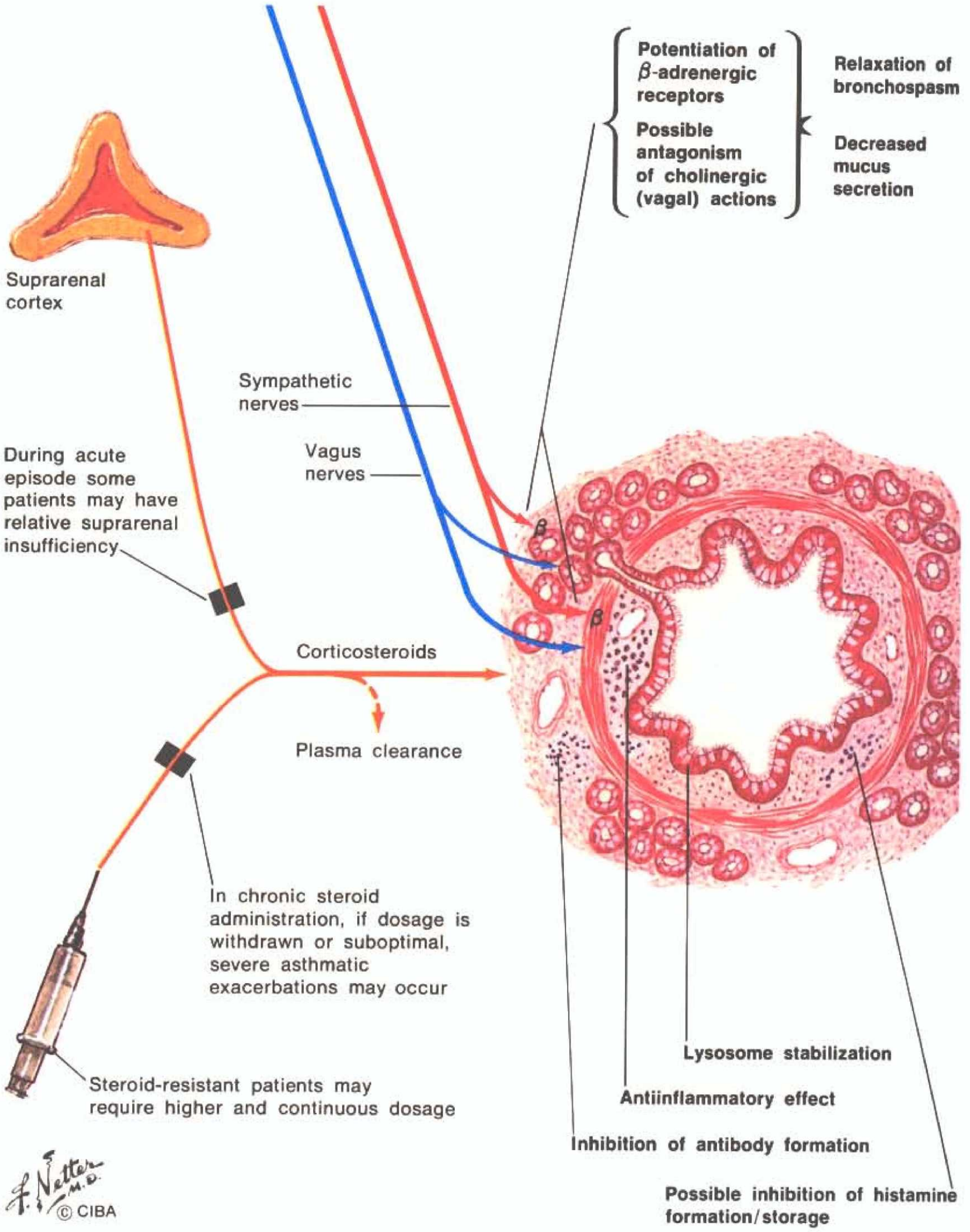
Complex biologic interactions between these mediators appear to exist. For example, histamine-stimulated contractions can be potentiated by SRS-A or prostaglandin intermediates; inhibition of mediator generation or release may be influenced by histamine or PGE by its action on cellular cyclic nucleotides.

Adrenal Corticosteroids. The role of the adrenal-pituitary axis in bronchial asthma is difficult to assess during acute attacks. Nevertheless, adrenocortical function must be considered, primarily because of the important actions of the adrenal corticosteroids. These include an anti-inflammatory effect, decreased mucus secretion, lysosome stabilization, inhibition of antibody formation, possible depletion of tissue histamine, and potentiation of bronchodilator agents (Plate 19). Most asthmatic patients including those who have taken corticosteroid medication on a *short-term* basis have normal adrenal function. As would be expected, continuous *long-term* therapy with corticosteroids may suppress the function of the adrenal cortex. Asthmatic patients on chronic corticosteroid therapy are likely to have more severe asthmatic episodes, including status asthmaticus, apparently because of suppressed adrenocortical function. In some patients with severe asthma not on such medication, there is also a limited response to ACTH. Similarly, the anticipated increase in urinary excretion of 11-hydroxy-corticosteroids in response to stress does not occur. Therefore, these patients may be more vulnerable to stress and more susceptible to allergic challenge.

Therapeutic Implications. Briefly, the activation of adenylcyclase by catecholamines (or sympathomimetic amines) provides a biochemical rationale for their clinical use. cAMP is degraded to 5′-AMP by the cytoplasmic enzyme phosphodiesterase. Hence, the increase in cAMP that results from methyl xanthine competitive inhibition of phosphodiesterase yields a synergistic action with the beta stimulant drugs. Corticosteroids have many effects and among them they are able to potentiate the action of adrenergic bronchodilators. Beta blocking agents—propranolol, for example—cause an expected worsening of asthma. Concurrently, cellular cGMP is influenced by vagal activity. Thus, for an asthmatic patient, drug action influences the biochemical and physiologic events in the mast cells and/or smooth muscle leading to inhibition of chemical mediator release and hence to muscle relaxation.

Finally, physical changes may be important factors in hyperresponsiveness. Patients with chronic asthma have increased airway smooth muscle, which might be a contributing factor. Also, a precontracted airway (by Poiseuille's law) might contract more easily, offering a lower threshold for further airway obstruction. Clearly, one or many factors could contribute to the hyperirritant process.



General Causes of Asthma

Common precipitating factors in asthma are illustrated in Plate 20.

Allergic Stimuli. In allergic asthma, acute episodes may be precipitated by inhaled or ingested *allergens*. Airborne allergens such as house dusts, feathers, animal danders, insect fragments, furniture stuffing, fungal spores and various plant pollens are substances that may be inhaled. Allergenic foods like cow's milk, fish, eggs, various nuts, chocolate, shellfish and tomatoes are less culpable as a cause of asthma. In some patients, various allergens may have an additive or even synergistic effect. Allergens causing sensitivity in a patient are unpredictable and variable; the response can change, and often decreases in severity from childhood to adult life.

Toxic and Irritative Stimuli. Many irritative factors in the inhaled air may evoke or aggravate an asthmatic attack. Obvious examples are tobacco smoke, air pollutants including automobile exhaust and industrial fumes, and volatile substances such as paint or gasoline. Chemicals such as TDI (toluene diisocyanate) and metals such as platinum or nickel can also provoke an attack.

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, bacterial sinusitis or a common cold may trigger an asthmatic episode, or infection may complicate an attack that began on a purely allergic basis. In man, experimental or naturally induced respiratory viral infections increase bronchoconstrictive responses to inhaled irritants or cholinomimetic drugs.

Medications. Drugs may initiate acute asthma either by pharmacologic action (beta adrenergic

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Bronchial Asthma
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blockade) or by an allergic response, as with penicillin and vaccines. In patients with aspirin sensitivity, symptoms may occur within 20 minutes after ingestion.

Other Causes and Contributing Factors. Psychological and physical stress may contribute to 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.

Pathologic Changes in Asthma

Gross and Microscopic Changes. The major pathologic features of bronchial asthma are generally limited to those observed in association with severe episodes (status asthmaticus). However, it may be inferred that lesser degrees of characteristic findings occur during attacks of a milder nature.

In status asthmaticus (Plate 21), the bronchi and bronchioles exhibit mucosal and submucosal edema, thickening of the basement membrane, a profuse leukocyte infiltration (particularly with eosinophils), intraluminal mucous plugs and smooth muscle hyperplasia and contraction. Grossly, the pale lungs are overdistended, often with regional parenchymal zones of hyperinflation alternating with areas of atelectasis caused by creamy, thick, tenacious, intraluminal mucous plugs. Especially if dehydration is clinically evident, the mucous plugs are viscous and adhere to the bronchial wall, narrowing the airway lumen. The process is compounded by enfolding of the epithelial surface from contraction of hyperplastic and possibly hypertrophied smooth muscle. Collectively, these actions cause the major increases in airflow resistance.

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

Submucosal gland hypertrophy is not as severe as in chronic bronchitis, yet a typical finding is goblet cell metaplasia, especially in the peripheral airways. 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. Limited immunoglobulin deposition is described.

It should be emphasized that the alveolar destructive changes which are found in patients with pulmonary emphysema are absent, as are severe permanent pathologic sequelae.

Pathophysiologic Effects of Asthma

The pathophysiologic effects of airway obstruction on respiratory function and hence on blood gases and pH values occur regardless of the specific mechanisms producing asthma. In status asthmaticus, severe gas exchange defects represent the greatest immediate danger, and their improvement demands therapeutic priority.

Spirometry and Ventilatory Function in Asthma. In asthma, the prime physiologic disturbance is obstruction to airflow, which is more marked in expiration. This obstruction is variable in severity and in its site of involvement and is, by definition, reversible to some degree. Various combinations of smooth muscle spasm, inflammation, edema and mucus hypersecretion produce this airflow impediment. In addition, low lung volumes with terminal airspace collapse may compound the airway obstruction. In the larger airways there are the rigid cartilaginous rings

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Bronchial Asthma
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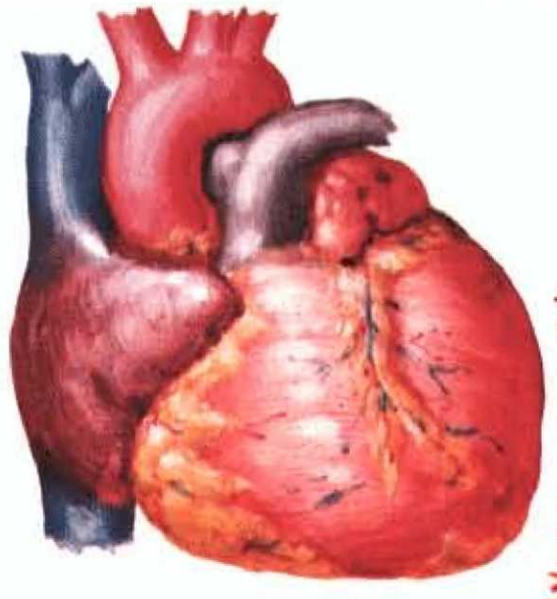
cough is impaired since the velocity of respiratory airflow is seriously reduced.

Clinically, hyperinflation is estimated by physical examination of the chest, by chest x-ray studies 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 (as is sternocleidomastoid muscle retraction), is usually present if the FEV_1 is less than 1.25 liters.

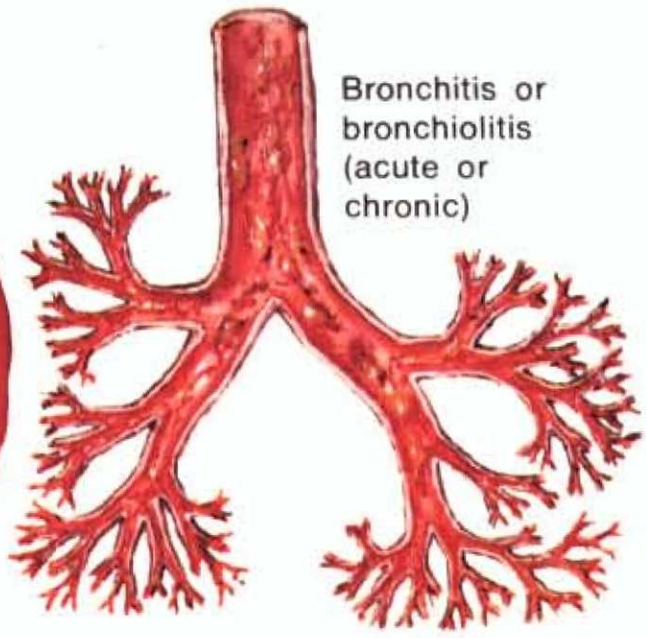
As a result of the nonhomogeneous airways obstruction in asthma, the distribution of inspired air to the terminal respiratory units is not uniform throughout the lungs. Alveoli which are hypoventilated because they are supplied by obstructed airways are interspersed with normal or hyperventilated alveoli; hence, the severity of asthma is directly related to the ratio of poorly ventilated to well-ventilated alveolar groups. Arterial hypoxemia, which is the primary defect in gas exchange in asthma, is due to this $\dot{V}_A/\dot{Q}_C$ nonhomogeneity. As the population of alveolar units with a low $\dot{V}_A/\dot{Q}_C$ ratio increases (because of advancing obstruction), the degree of arterial hypoxemia also intensifies. The $\dot{V}_A/\dot{Q}_C$ disturbance is compounded if some airways are completely obstructed. The right-to-left intrapulmonary shunt effect results in arterial hypoxemia.

Carbon dioxide elimination is not impaired when the number of alveolar-capillary units with normal $\dot{V}_A/\dot{Q}_C$ ratios remains large relative to the number of those with low $\dot{V}_A/\dot{Q}_C$ ratios. As airway obstruction progresses, there will be more and more hypoventilated alveoli. Simultaneously, appropriate increases in respiratory work, rate and depth occur. Such a response initially minimizes the increase in physiologic dead space but eventually becomes limited, and alveolar ventilation finally fails to support the metabolic needs of the body. Carbon dioxide retention now occurs together with increasing hypoxemia. This is a state of ventilatory failure, and commonly arises when the FEV_1 is less than 25% of that predicted.

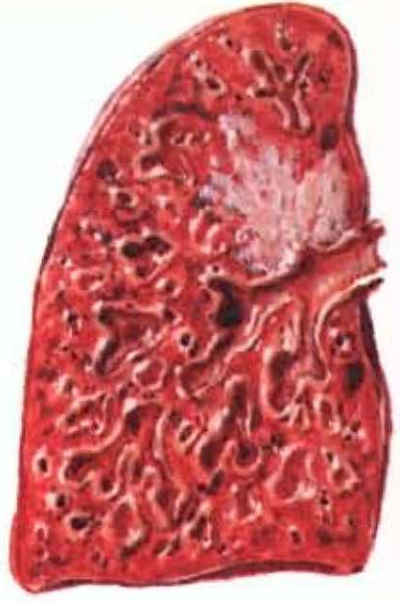
Perfusion lung scan studies in asthma reveal transient areas of regional hypoperfusion which morphologically parallel the zones of hypoventilation. The hypoperfusion occurs because of regional hyperinflation or pulmonary vascular reactivity; it is migratory and fully resolves with remission of the asthmatic episode. (It may be confused with pulmonary embolism.) The pulmonary hypertension in asthma is not very severe or sustained, and chronic cor pulmonale, as seen with chronic bronchitis and emphysema, is generally absent. Diffusion limitations do not play a major role in asthma.



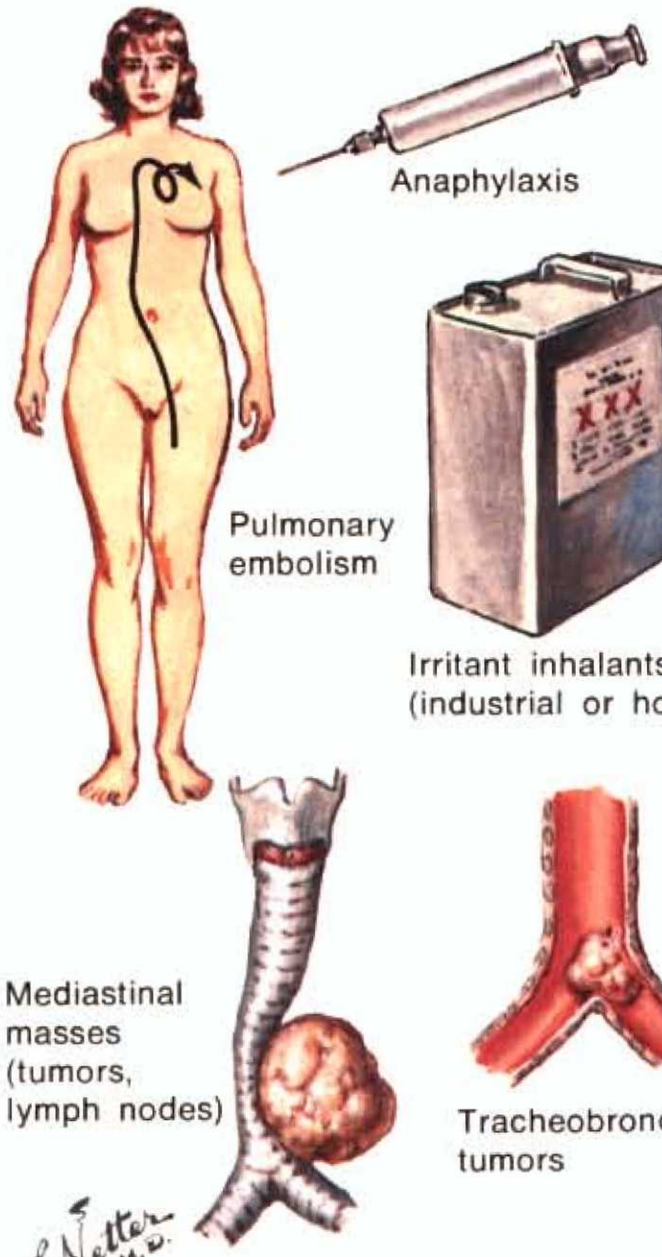
Congestive heart failure (cardiac asthma)



Bronchitis or bronchiolitis (acute or chronic)



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



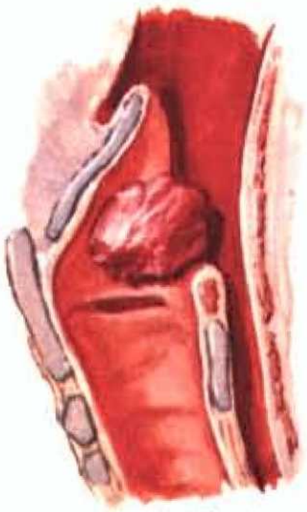
Mediastinal masses (tumors, lymph nodes)

Tracheobronchial tumors

Pulmonary embolism

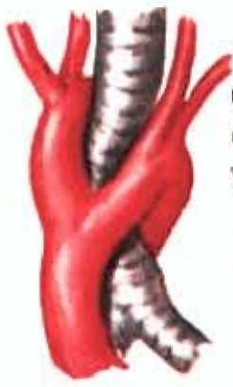
Anaphylaxis

Irritant inhalants (industrial or home)

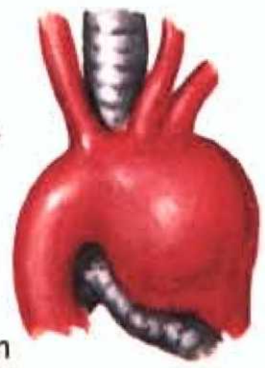


Aspiration (food or foreign body)

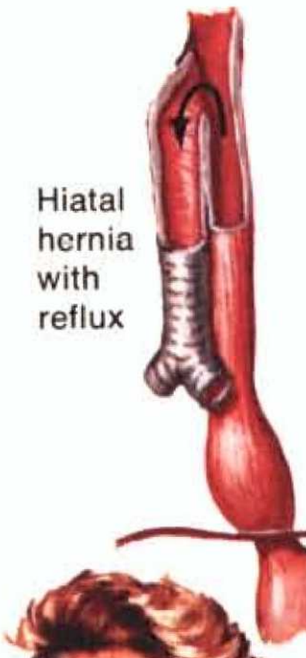
Farmer's lung (allergic alveolitis with dual asthmatic reaction)



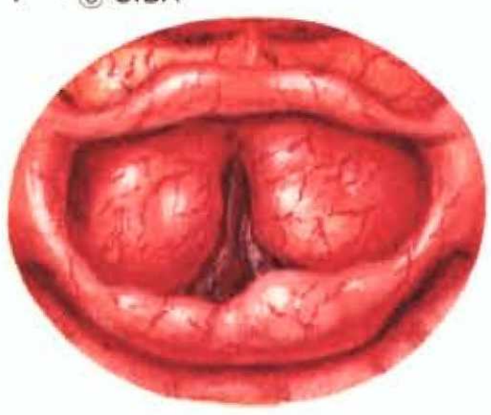
Congenital constrictive vascular rings



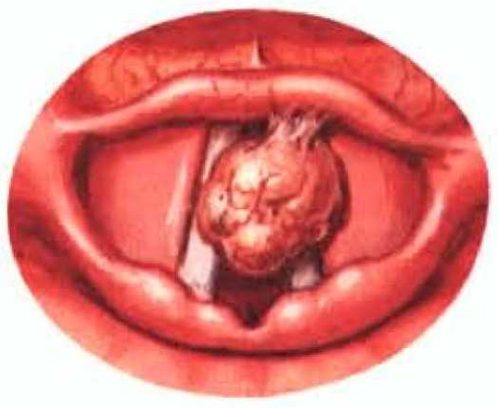
Aortic aneurysm



Hiatal hernia with reflux



Laryngeal edema (croup)



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

Anxiety hyperventilation

Clinical and Laboratory Considerations

Symptoms and Clinical Findings. Symptoms and signs of bronchial asthma range from acute, discrete episodes of shortness of breath, wheezing and cough, followed by significant 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. An asthmatic attack can be a terrifying experience, especially for patients who are aware of its potentially progressive nature.

Symptoms of an asthmatic episode may develop gradually or suddenly, and are at times preceded by an episode of allergic rhinitis or upper respiratory tract infection. Many patients complain of a sensation of retrosternal chest tightness and mention greater difficulty in breathing in than out. Expiratory and often inspiratory wheezing is audible and is associated with variable degrees of dyspnea. Cough is likely to be present and may be productive of sputum. The inability to raise secretions is ominous, and indicates severe and widespread bronchiolar plugging with tenacious mucus, often exacerbated by dehydration.

The patient prefers to sit upright; visible nasal alar flaring and use of the accessory respiratory muscles reflect the augmented work of breathing. Anxiety and apprehension generally relate to the

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Bronchial Asthma
(Continued)

intensity of the attack. Tachypnea may be the result of fear, airway obstruction or changes in blood and tissue gas tensions or pH. Hypertension and tachycardia both reflect increased catecholamine output, although a pulse rate greater than 110 to 130 beats/minute may indicate significant hypoxemia (Pa_{O_2} <60 mm Hg) and the seriousness of the episode. Pulsus paradoxus (10 mm Hg or higher) accompanies pulmonary hyperinflation, occurring when the FEV_1 is 1.25 liters or less. Flushing or perspiration and monosyllabic speech also signal the gravity of the attack. If severe hypoxemia and hypercapnia with respiratory acidosis supervene, the patient is usually cyanotic, fatigued, confused and agitated, or may show neuromuscular abnormalities such as asterixis and papilledema.

Chest examination reveals 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. With low-grade obstruction, wheezing may be slight or even absent but can be accentuated by rapid, deep breathing. Its pitch tends to rise with progressive obstruction, but when this is extensive, airflow is severely reduced and the chest may become paradoxically silent. This ominous finding may be inadvertently induced or worsened by administration of hypnotics, tranquilizers or sedatives which depress respiration. At the point where airflow is so decreased that the chest becomes silent, cough becomes ineffective and ventilatory failure supervenes. This requires immediate intensive therapy.

Complicating diseases such as pneumonitis, pleurisy, atelectasis, heart failure, pulmonary emboli or pneumothorax can contribute additional characteristic physical findings. Cardiac auscultation is frequently limited by the adventitious noises within the chest and by the increase in residual air. However, tachycardia and accentuated pulmonic second sound are often discernible. Laryngeal stridor or central airway obstruction from tracheal masses (*e.g.*, tumors) should not be confused with diffuse asthmatic obstruction. The primary clue here is a monophonic wheeze of similar sound quality throughout the thorax, loudest at its point of upper airway origin. In elderly patients, heart failure is readily diagnosed when the typical findings are present. These include prominent neck veins, basilar rales, cyanosis, cardiomegaly, gallop rhythm and peripheral edema. Finger clubbing is unusual in asthma, and its presence should alert the physician to possible suppurative, neoplastic or other hypoxemic disease processes. The careful evaluation of the ears, nose, sinuses, skin, abdomen and extremities is essential, and may disclose such complicating or precipitating processes as sinusitis, nasal polyps, hiatal hernia with aspiration or sources for pulmonary emboli.

Differential Diagnosis

The erroneous concept that wheezing is synonymous with asthma is still regrettably prevalent. Accordingly, the cliché "all that wheezes is not asthma" serves as a reminder that wheezing is not pathognomonic of asthma. For the patient who is wheezing, a combination of history, physical examination and laboratory findings should establish a diagnosis. Diseases to be considered in the differential evaluation are depicted in Plate 22. Pulmonary disorders other than those illustrated include cystic fibrosis, pneumoconiosis and systemic vasculitis involving the lungs. In addition, wheezing episodes have been described following exposure to cotton fibers or inhalation of toluene diisocyanate in plastics manufacturing (polyvinyl chloride in meat wrappers), or baker's asthma from wheat flour sensitivity. In these cases

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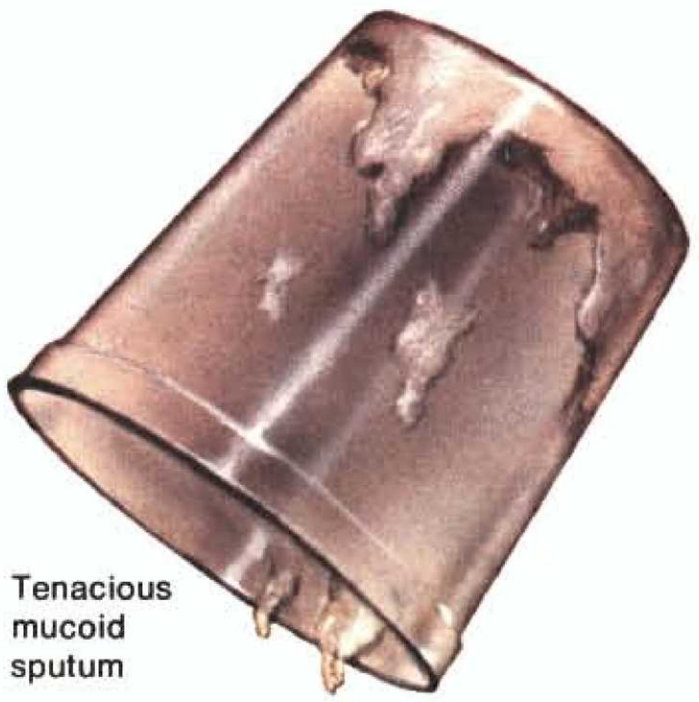
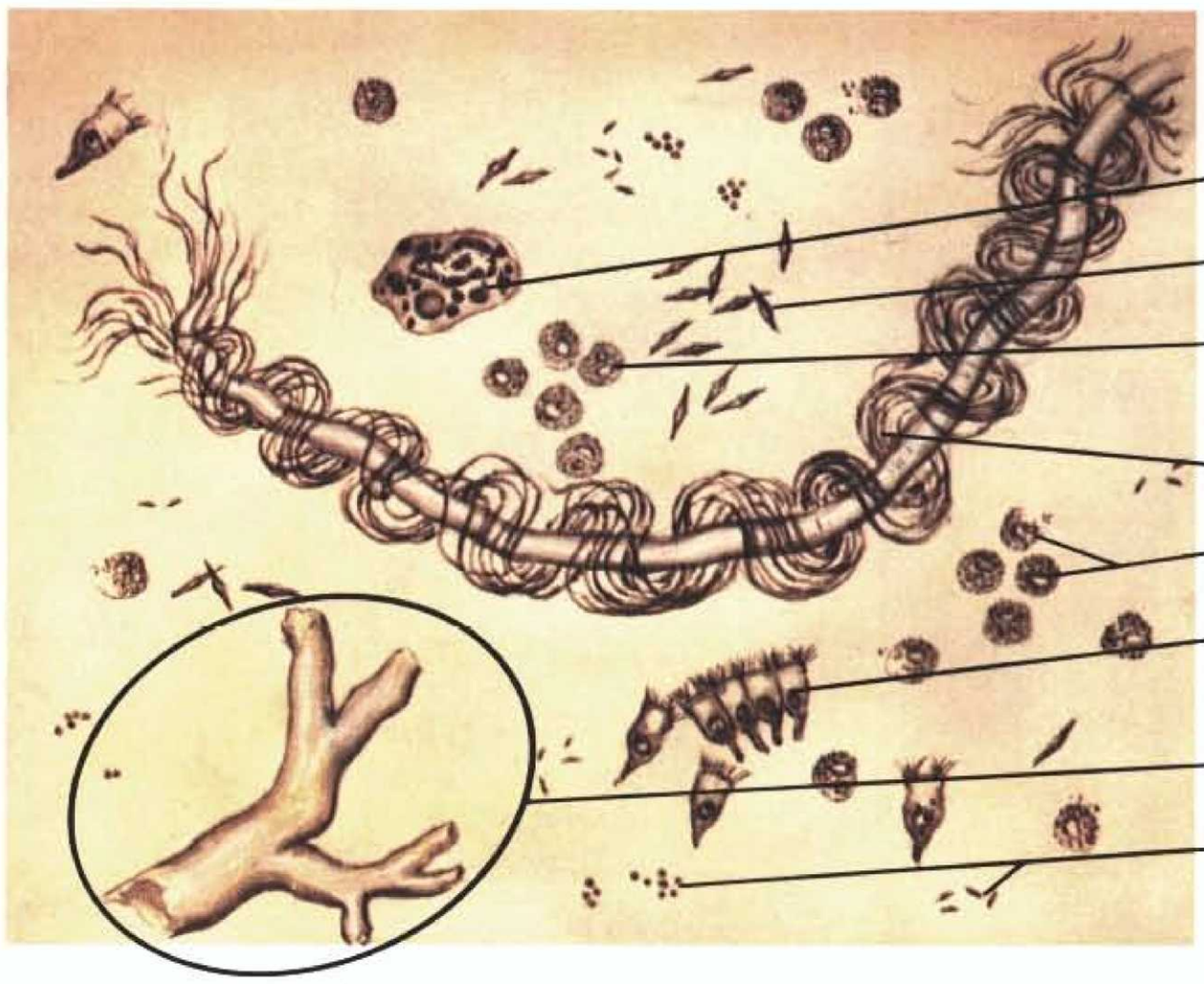
Sputum in Bronchial Asthma

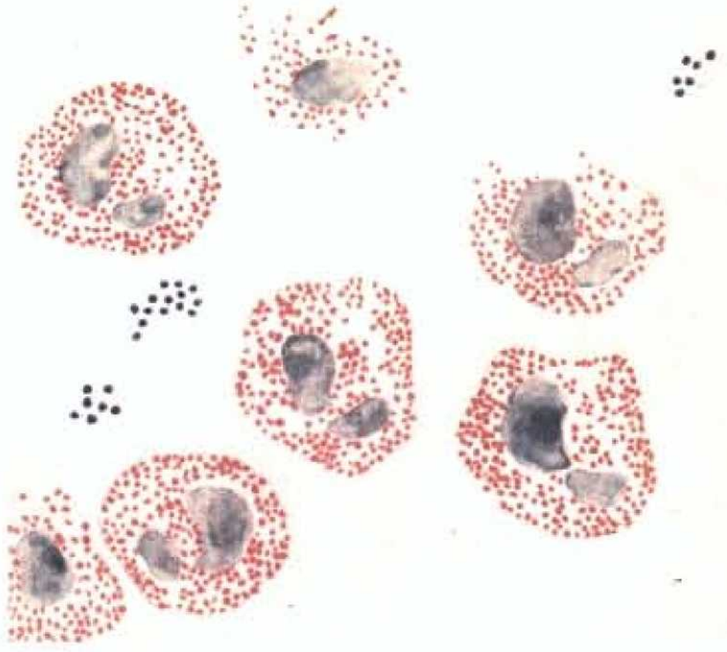


Tenacious mucoid sputum

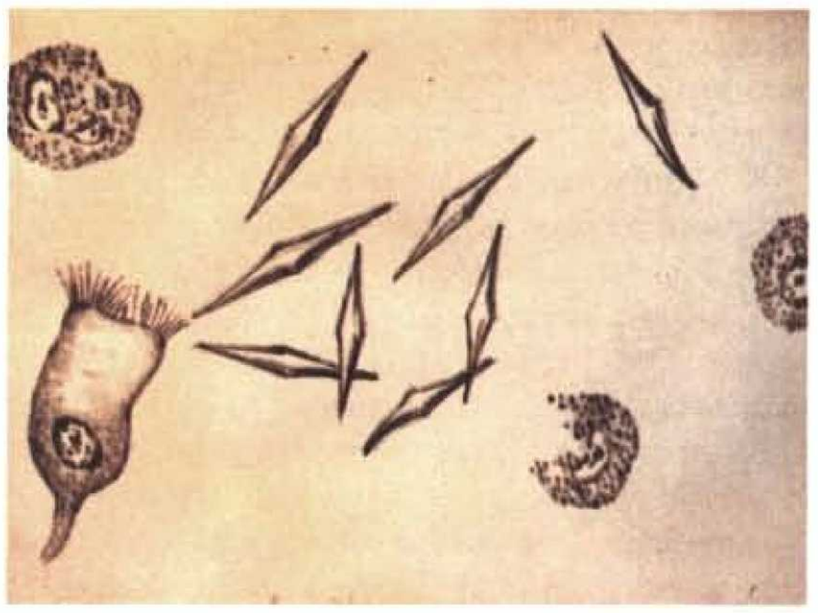
Purulent sputum



Unstained smear of asthmatic sputum; schematic (low power)



Eosinophils and staphylococci in stained smear



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

Bronchial Asthma
(Continued)

a history of specific occupational exposure and laboratory appraisal will aid in diagnosis.

Specific therapy of acute asthma is aided by various laboratory diagnostic tests which evaluate pulmonary function, assess the relative roles of infection and allergy, and determine whether complicating conditions coexist.

Radiography. The primary value of radiography is to exclude other diseases and to determine whether pneumonia, atelectasis, pneumothorax, pneumomediastinum or bronchiectasis exists. In mild asthma, the chest x-ray film will show no abnormalities. With severe obstruction, however, a characteristic reversible hyperlucency of the lung is evident, with widening of costal interspaces, depressed diaphragms and increased retrosternal air. In contrast to pulmonary emphysema in which vascular branching is attenuated and distorted, vascular caliber and distribution in asthma are generally undisturbed. Heart size remains normal or small unless cardiac disease coexists.

Focal atelectasis, a complication of asthma, is caused by impaction or inspissation of mucus. In children, even complete collapse of a lobe may be observed. Atelectatic shadows may be transient as mucus impaction shifts from one lung zone to another. When sputum is appropriately liquefied and mobilized, these patterns resolve.

Radiography is also useful in evaluating coexisting paranasal sinusitis. An upper gastrointestinal series is indicated if hiatal hernia with recurrent aspiration is suspected. Lung scans or angiography may be required if pulmonary emboli are believed to mimic asthma.

Sputum. Tracheal mucus velocity is impaired because of changes in viscosity, volume or chemical alterations. Gross and microscopic examination of any expectorated sputum is valuable for assessing airway pathology (Plate 23).

Sputum may be mucoid, frankly purulent or a mixture of both. *Mucoid sputum* is an opalescent or white gelatinous substance, generated in purely allergic insults and often very difficult to expectorate. It is quite adhesive to contiguous structures, and is internally viscous because of the presence of mucopolysaccharide and glycoprotein fibers, as well as transudated serum albumin. The more water mucoid sputum contains, the less viscous and adhesive it is. Recognition of mucoid sputum is based on its color, tenacity and adherence (*i.e.*, to the patient's tongue or sputum jar). Clinically, these qualities promote stasis and impaction of secretions leading to critical airway plugging and obstruction and often to secondary infection.

Purulent sputum is yellow, gray or green and may be produced in large volumes. Like mucoid sputum, it can be thick or viscous, a property resulting from deoxyribonucleic acid fibers arising in necrotic debris of inflammatory cells, bacteria or parenchymal cells.

Sputum should be examined microscopically, stained with aqueous crystal violet, or viewed simply as a wet preparation under a coverslip. Thin spiral bronchiolar casts (Curschmann's spirals), measuring up to several centimeters in length, are often detected grossly and are strongly indicative of asthma. Ciliated columnar bronchial epithelial cells are frequently found. They may be recognized by their 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. Creola bodies are clumps of such bronchial epithelial cells with moving cilia; they are very characteristic of severe asthma. Another cell easily recognized by its granular cytoplasm and, in wet preparations, by its brownian movement, is the polymorphonuclear neutrophil leukocyte (PMN), 10 to 15 microns in diameter. In purely infectious exacerbations of asthma, the PMN is the predominant cell.

In allergic asthma, eosinophils are stimulated and may constitute 10 to 90% of the sputum cell population. Eosinophils are structurally similar to PMN's except that the nucleus is often bilobed and the cytoplasmic granules are larger, more uniform and highly refractile. The latter property can be detected by focusing the microscope up and down. Large numbers of crystalloid derivatives of eosinophils can also be identified. These colorless fragments (20 to 40 microns in length), called Charcot-Leyden crystals, are elongated and octahedral. Macrophages are large cells (10 to 40 microns in diameter) and have numerous inclusion bodies. Adequate numbers (greater than 10 to 15% of the cell population) reflect appropriate cellular defenses.

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

The amount of sputum raised often indicates the effectiveness of secretion mobilization. Early in status asthmaticus sputum is likely to be sparse, emphasizing the need for therapeutic mobilization of secretions. This feature is also responsible, in part, for the slow lysis of an asthmatic paroxsym compared to the rapid reversibility achieved with bronchodilator drugs when smooth muscle spasm is the dominant abnormality. A 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.

Blood Tests. Because of stress, dehydration or infection, leukocytosis may occur. An increase (15,000/mm^3) in PMN's indicates superimposed infection. A low blood eosinophil count may be seen in the early stages of the asthmatic episode or when infection is present; a count of greater than 5% may imply an allergic cause. Total eosinophil counts (TEC) are more quantitative and of greater clinical significance. They can be used serially to judge the efficacy of treatment, particularly with corticosteroid drugs. TEC values higher than the normal 250/mm^3 (often 800 to 1000/mm^3) suggest a severe allergic reaction. TEC's of 4000/mm^3 are often due to parasitic infection. Conversely, the absence of eosinophils does not exclude asthma. If during therapy with corticosteroids the eosinophil count does not fall, steroid-resistant bronchial asthma may exist, necessitating still higher doses of these drugs for resolution.

Usually, blood chemistry findings are normal unless secondary complications develop—vomiting, diarrhea or severe dehydration. In patients receiving diuretics or corticosteroids, complicating hypochloremic hypokalemic alkalosis may contribute to ventilatory depression. If pulmonary emboli, heart failure or connective tissue disorders are masquerading as bronchial asthma, appropriate blood tests may be of diagnostic value. When recurrent infections appear to be causative, immunoglobulins should be assayed. A sweat test for cystic fibrosis or stool examination for ova and parasites are indicated, if these are suspected.

Electrocardiogram. A tachycardia of greater than 120 beats/minute may indicate serious hypoxemia (Pa_{O_2} <40 to 60 mm Hg). The sinus tachycardia of an asthmatic attack will revert to normal with remission. During a severe episode, pulmonary hypertension may cause reversible right ventricular strain with right 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 dysrhythmias or myocardial ischemia may be precipitated. Dysrhythmias can also be produced by heart-stimulating drugs such as epinephrine or isoproterenol, particularly in the hypoxemic individual with coronary artery disease, valvular disorders or a cardiomyopathy.

Principles of Management

Prompt treatment of an acute asthmatic episode is imperative, but *prevention* of asthma is basic to any therapeutic program. Each patient must be thoroughly evaluated to determine all possible causative and contributing factors, as long-term management depends on their elimination or control. The acute attack requires prompt specific drug therapy since any episode may progress to life-threatening status asthmaticus.

Treatment of Acute Episode

Aqueous epinephrine is preferred for its rapid and predominant beta stimulatory action (Plate 24). Formulations of epinephrine that provide more prolonged relief also have slower absorption; aerosol preparations are available but have generally been replaced by selective $beta_2$ adrenergic drugs.

Aerosolized isoproterenol, the most potent sympathomimetic amine, can also be used in an acute attack. An unexpected bronchoconstrictive effect has been reported with isoproterenol which may be related to the formation of a metabolite with a beta blocking action, and a paradoxical fall in arterial oxygen tension may be observed in some patients.

$Beta_2$ selective adrenergic bronchodilators have a preferential airway effect with a longer duration of action than isoproterenol, and are reputed to

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Bronchial Asthma
(Continued)

cause fewer cardiovascular side effects and less hypoxemic induction. These include such agents as isoetharine or metaproterenol sulfate, available in aerosol form, and terbutaline sulfate, which is given by subcutaneous injection or orally. Ephedrine's usefulness is limited in an acute attack because of a slower and less potent action; it may be of value orally for maintenance therapy. In the hypertensive, hyperthyroid or cardiac patient, epinephrine must be used with caution or preferably not at all. Intravenous epinephrine is never recommended because ventricular dysrhythmias or cerebral hemorrhage may occur.

The initial response to epinephrine may be inadequate, or the patient may exhibit refractoriness with repeated use. Initial therapeutic resistance has been ascribed in part to coexisting respiratory acidosis, which is partially reversible by intravenous administration of bicarbonate. When this is persistent, repeated injections are of no value and may be detrimental because of side effects. In this event, aminophylline, which is longer acting and may have an additive effect with sympathomimetic drugs, can be administered intravenously, *very slowly* over 15 minutes. Too rapid administration can cause hypotension and even death, but other routes are seldom effective in an acute attack. The bronchodilating activity of aminophylline is generally related to its plasma concentration; effective levels range from 10 to 20 μg/ml. Although aminophylline is preferred for older patients, those with liver disease or heart failure should be monitored carefully since toxic reactions become more likely. Overdosing can be associated with convulsions, coma, cardiac irregularities or fatality.

When an asthmatic attack does not respond to the therapy described above, a short course of corticosteroids may be added, although their peak action usually does not occur until 6 to 12 hours after intravenous or intramuscular administration.

Important supportive measures in an acute episode include appropriate antimicrobial therapy if infection is present, adequate hydration and oxygen. Expectorants and oral ephedrine may be added.

Status Asthmaticus

Status asthmaticus is a medical emergency in which respiratory distress reflects refractoriness to conventional pharmacologic therapy for an acute asthmatic attack. Because of the nursing care and continuous monitoring required, hospitalization in an intensive care unit is mandatory. It is the stage of asthma with the most severe gas exchange defects and accounts for its greatest morbidity and mortality. It may be defined as an attack resistant to several standard doses of epinephrine and/or aminophylline within a reasonable period of time. Multiple factors are often responsible for the extreme degree of airway obstruction seen, and every effort must be made to identify and correct them.

Changes in Blood Gases and pH. As a consequence of advanced airway obstruction, serious ventilation-perfusion disturbances arise, causing major changes in arterial oxygen and carbon dioxide tensions and pH (Plate 25). In fact, dangerous levels of hypoxemia sometimes develop with alarming rapidity and, at least initially, without retention of carbon dioxide. This phenomenon may lead to sudden death.

These changes in blood gases and pH cannot be quantitated by simple clinical observation, but certain findings may be correlative. The degree of arterial hypoxemia will roughly correlate with the severity of airways obstruction. Hypercapnia is generally not seen until the FEV_1 is less than 1 liter (or 25 to 30% of that predicted). Precise documentation of blood gas and pH measurements must be obtained and followed repeatedly to evaluate serial changes in gas exchange and the response to therapy. There may be rapid

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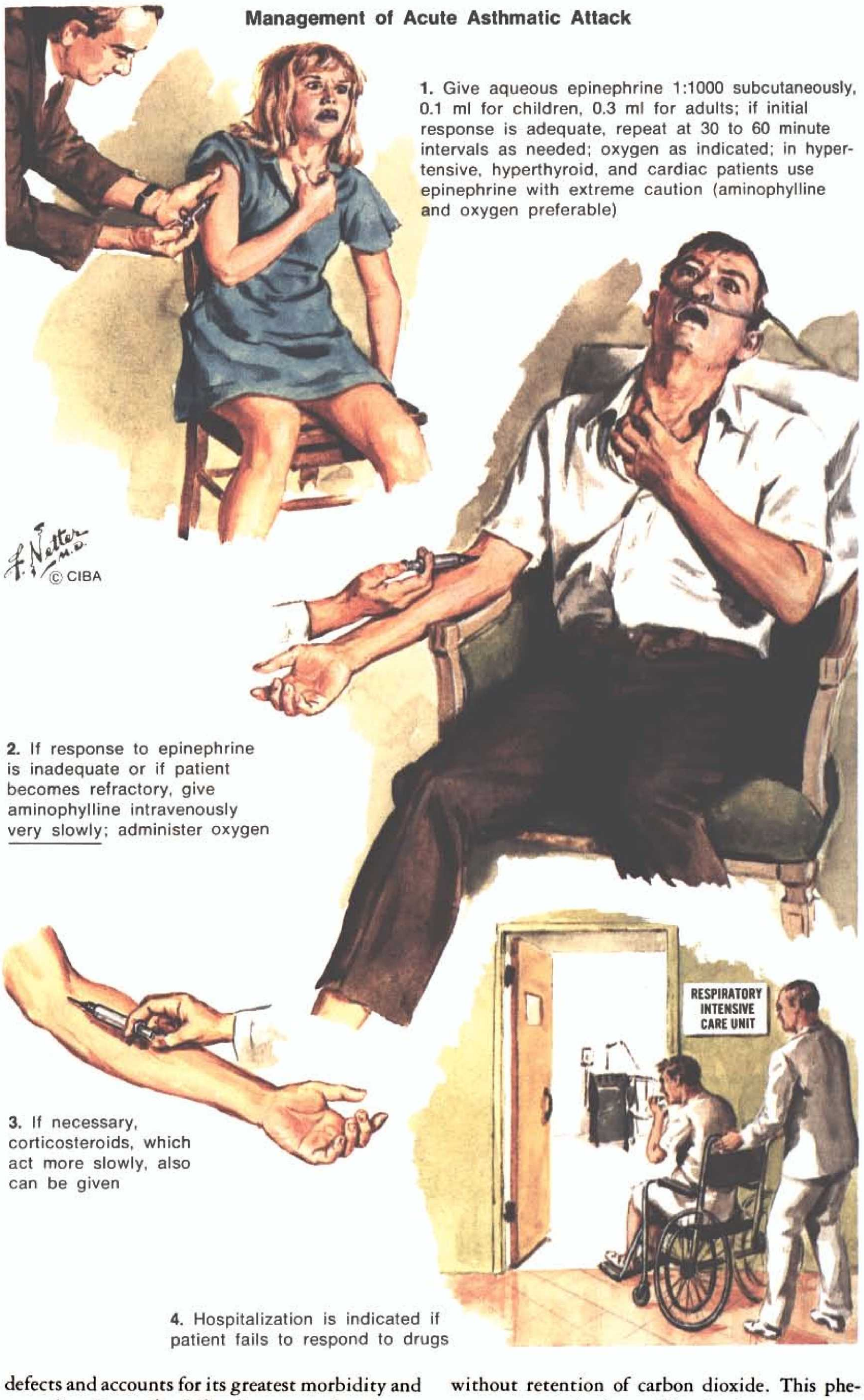

Bronchial Asthma
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progression from normal values to severe hypoxemia, hypercapnia and respiratory acidosis.

In an early stage, hypoxemia (Pa_{O_2} 55 to 75 mm Hg) and hypocapnia (Pa_{CO_2} <35 mm Hg) may be noted, leading to respiratory alkalosis with a variable degree of compensation.

Spirometry may show only moderately impaired breathing capacity, and this phase will often respond favorably to bronchodilators or other drugs.

With more severe obstruction, Pa_{O_2} decreases to the range of 50 to 55 mm Hg and Pa_{CO_2} is less than 30 mm Hg; respiratory alkalosis (pH >7.50) is apparent. This profile is associated with an acute, moderately severe episode of status asthmaticus. Flow and volume indexes are significantly impaired, and response to bronchodilators is variable. At this point, all therapeutic efforts must be intensified.

Frank ventilatory failure is associated with severe hypoxemia (Pa_{O_2} <55 mm Hg); hypercapnia (Pa_{CO_2} >45 mm Hg) and respiratory acidosis (pH <7.35). This profile is typical of advanced status asthmaticus with its limited or absent response to bronchodilators. Tracheal intubation and ventilatory support will be required.

Management of Status Asthmaticus

Because the primary basis for the arterial blood gas and pH changes in status asthmaticus is airway obstruction, establishing and maintaining airway patency is fundamental to the clearing of secretions.

Mobilizing Secretions and Clearing the Airway. In conjunction with control of allergy and infection (including possible ear and paranasal sinus infection), rapid mobilization of secretions and cellular debris will help terminate the asthmatic episode. Multiple approaches are established in therapy:

1. Adequate hydration: dehydration resulting from limited fluid intake, insensible water loss and fever contributes to secretion retention, and hypovolemia increases the mortality. Replacement and maintenance fluids are essential.

2. Expectorant agents: hydration and airway humidification are most effective for mobilizing secretions. Oral SSKI, sodium iodide by infusion or oral glyceryl guaiacolate may be tried. Aerosolized *N*-acetylcysteine lyses mucoproteins but should be used with caution in asthma, which it may aggravate, and always with a bronchodilator agent.

3. Mechanical measures: once the patient is hydrated, the raising of secretions may be encouraged by physical therapy measures. Nasotracheal suctioning and occasionally bronchoscopy may be necessary.

4. Oxygen: well-humidified oxygen should be provided throughout to maintain a Pa_{O_2} of 70 to 80 mm Hg. Oxygen-induced hypoventilation can be controlled by mechanical ventilation.

5. Bronchodilators: the effectiveness of epinephrine may be limited by pharmacologic refractoriness. Isoproterenol aerosol can be provided by a hand bulb or compressor-driven nebulizer or with IPPB. Isoproterenol may reduce airway resistance and alleviate respiratory overwork, but by inducing a $\dot{V}_A/\dot{Q}_C$ mismatch it may occasionally aggravate hypoxemia; hence increased supplemental oxygen may be required. Aminophylline is generally a major and most useful foundation for bronchodilator therapy. Isoetharine, terbutaline or other bronchodilators may also prove valuable. In children (and in a limited number of adults), intravenous isoproterenol has been advocated as an added form of therapy with the rationale that it saves time in allowing corticosteroids to become maximally effective. Thus the need for tracheal intubation and ventilation and their attendant complications are minimized. This approach must be conducted with continuous, adequate cardiac and blood gas monitoring.

6. Sedatives: sedatives are absolutely contraindicated unless supportive mechanical ventilation is to be used.

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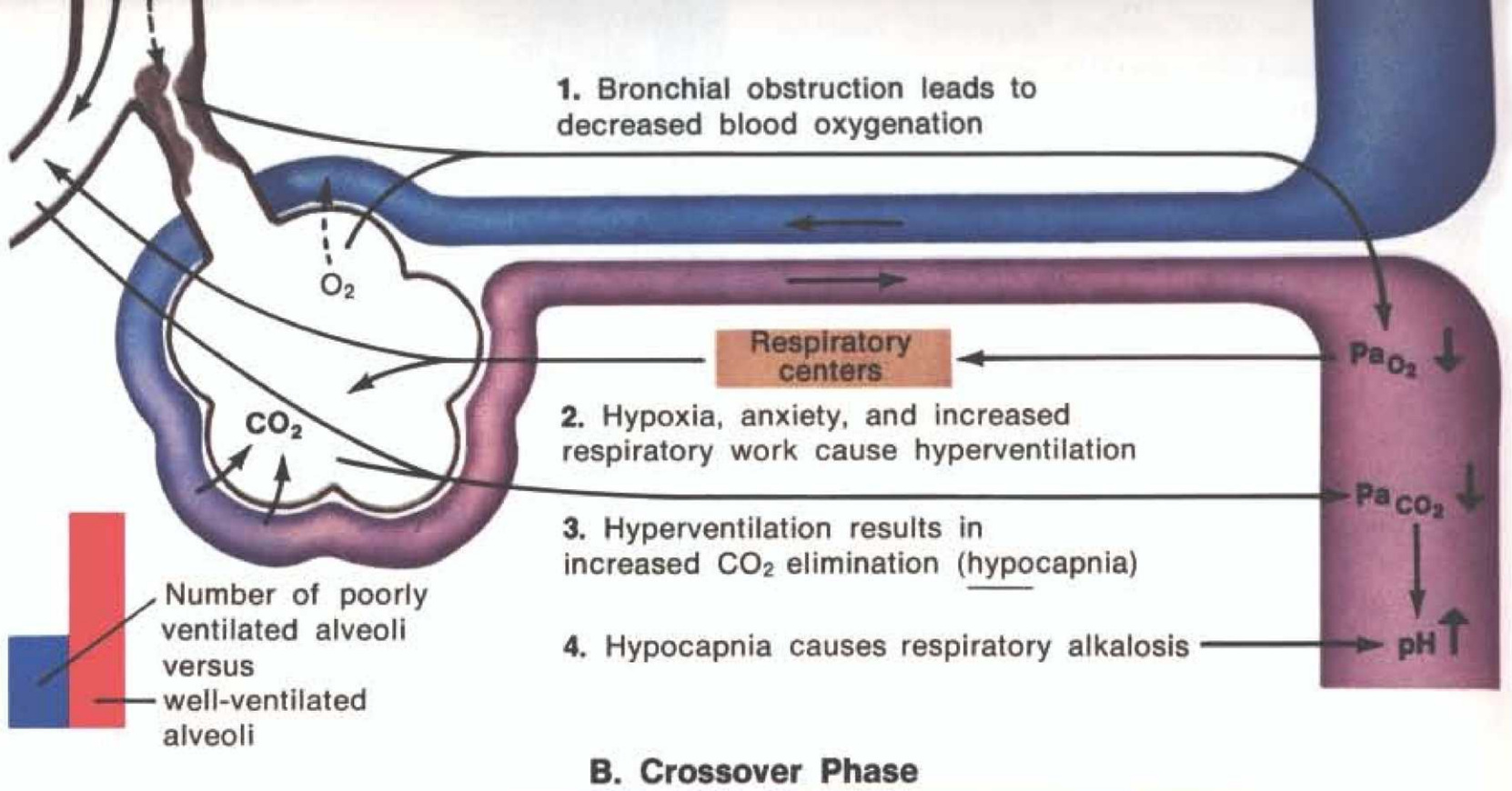
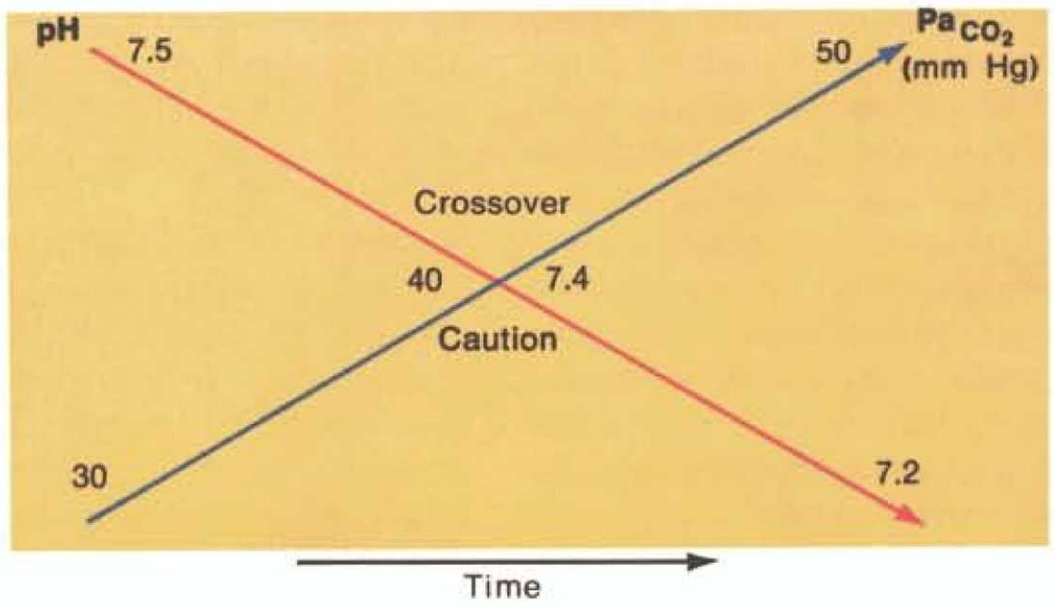
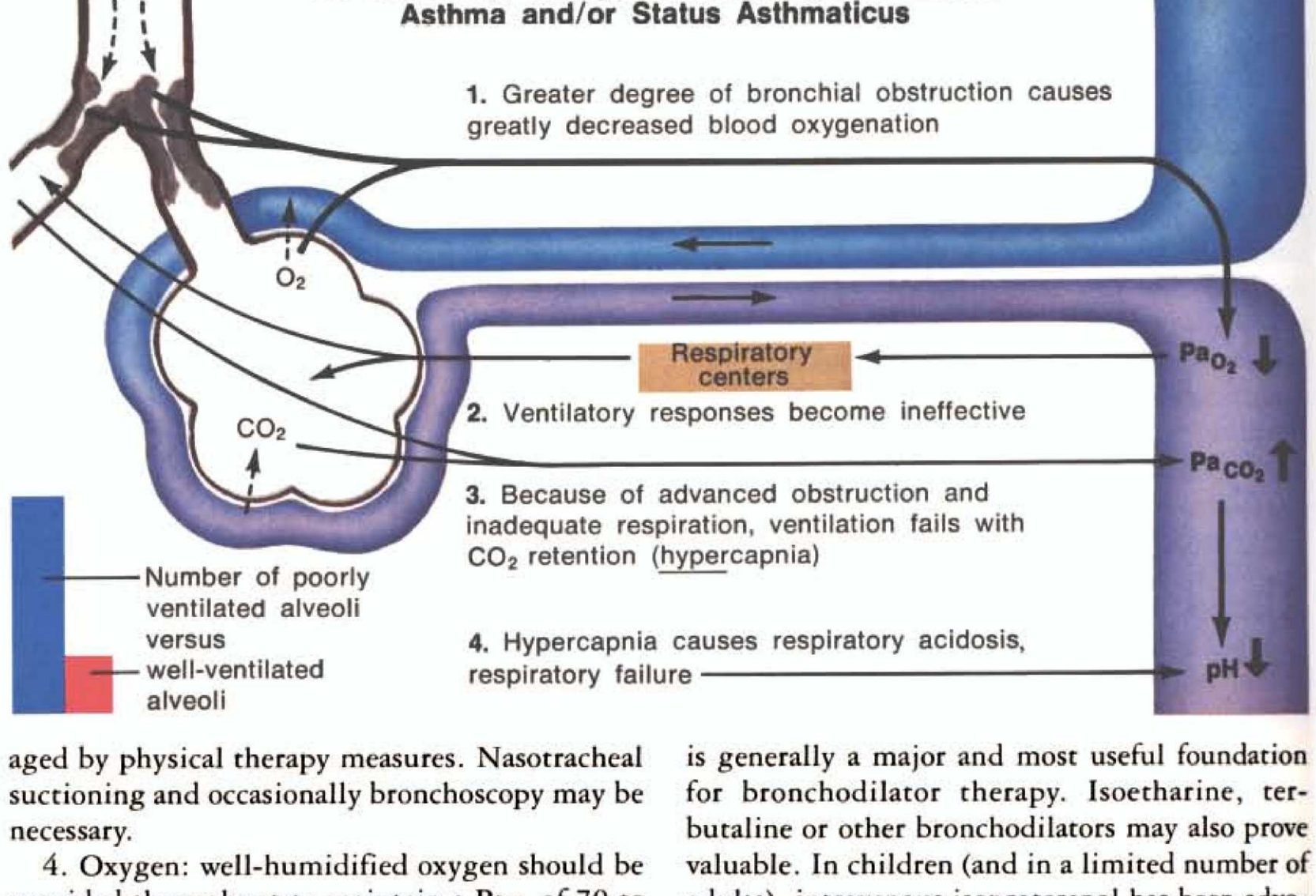


B. Crossover Phase



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



Bronchial Asthma
(Continued)

7. Mechanical ventilation: details are described elsewhere (see page 294). Ventilatory failure is a dangerous and often lethal phase of status asthmaticus. Indications for tracheal intubation and mechanical ventilation include (a) apnea, (b) rising Pa_{CO_2} of 5 to 10 mm Hg/hour despite full therapy, (c) patient exhaustion, (d) absolute Pa_{CO_2} of 50 mm Hg or greater with respiratory acidosis, (e) refractory hypoxemia. Volume-limited ventilators are preferred. Serial blood gas samples and pH measurements are necessary for optimal management.

8. Antibiotics: if evidence of infection exists, administer antibiotics preferably based on sputum culture results if available.

9. Adrenal corticosteroids: by several actions (Plate 19), corticosteroids significantly relieve otherwise uncontrollable asthmatic symptoms and may be lifesaving. Pharmacologically, they restore and potentiate the effectiveness of catecholamines on beta adrenergic receptors and also inhibit the enzyme phosphodiesterase. Early administration in high doses is advisable, particularly for critically ill patients, or those who have been on prior corticosteroid therapy.

The exact dosage or type of corticosteroids in status asthmaticus is unresolved, but generally moderate doses by the parenteral route are preferred. Treatment should be sustained until clinical improvement warrants a gradual reduction and eventual elimination of corticosteroid therapy. This precaution is particularly important for children because adrenal suppression may occur more rapidly than in adults. ACTH is not recommended in status asthmaticus because, presumably, the adrenal cortex is already maximally stimulated.

Undesirable side effects of corticosteroid medication are not usually encountered in short-term therapy.

Long-term Management of Asthma

Long-term management is required to prevent the occurrence of asthma or control its symptoms. As many diverse stimuli can interact to produce asthma, multiple therapeutic approaches are essential.

General Principles. The patient must practice moderation in daily activities and avoid exposure to precipitating agents. The home environment, particularly the bedroom, should have the factors which are shown in Plate 26 eliminated. Humidifiers are particularly important during the winter when decreased humidity may cause irritation to mucous membranes or drying of secretions. A relative humidity of 50% or greater is desirable. Nose, sinus or throat infection or polyps must be appropriately treated.

Avoidance of all precipitants is not always possible (Plate 20). Incriminated drugs or foods are easier to avoid than airborne inhalants. If only one allergen such as dust or dog dander is causative, avoidance may be beneficial. Exposure and activity should be limited during periods of high air pollution.

Psychologic Management. The physician should understand the patient's mechanisms for coping with his stressful disease and encourage rapport and open communication as well as provide adequate instruction about its general nature. A pleasant home environment and an understanding family are essential, particularly with children. Because extrinsic asthma often abates with growth, an optimistic attitude should be fostered. Parental resentment or excessive protectiveness should be minimized. Counseling with the child's teachers may also help. If serious emotional disturbances or socioeconomic or occupational problems exist, proper evaluation and counseling are indicated.

Apprehension and fear are seen in almost every patient during an acute episode and at times may be perpetuating or even precipitating factors. However, in severe asthma or status asthmaticus,

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General Management Principles for Asthmatic Patient

Good health measures

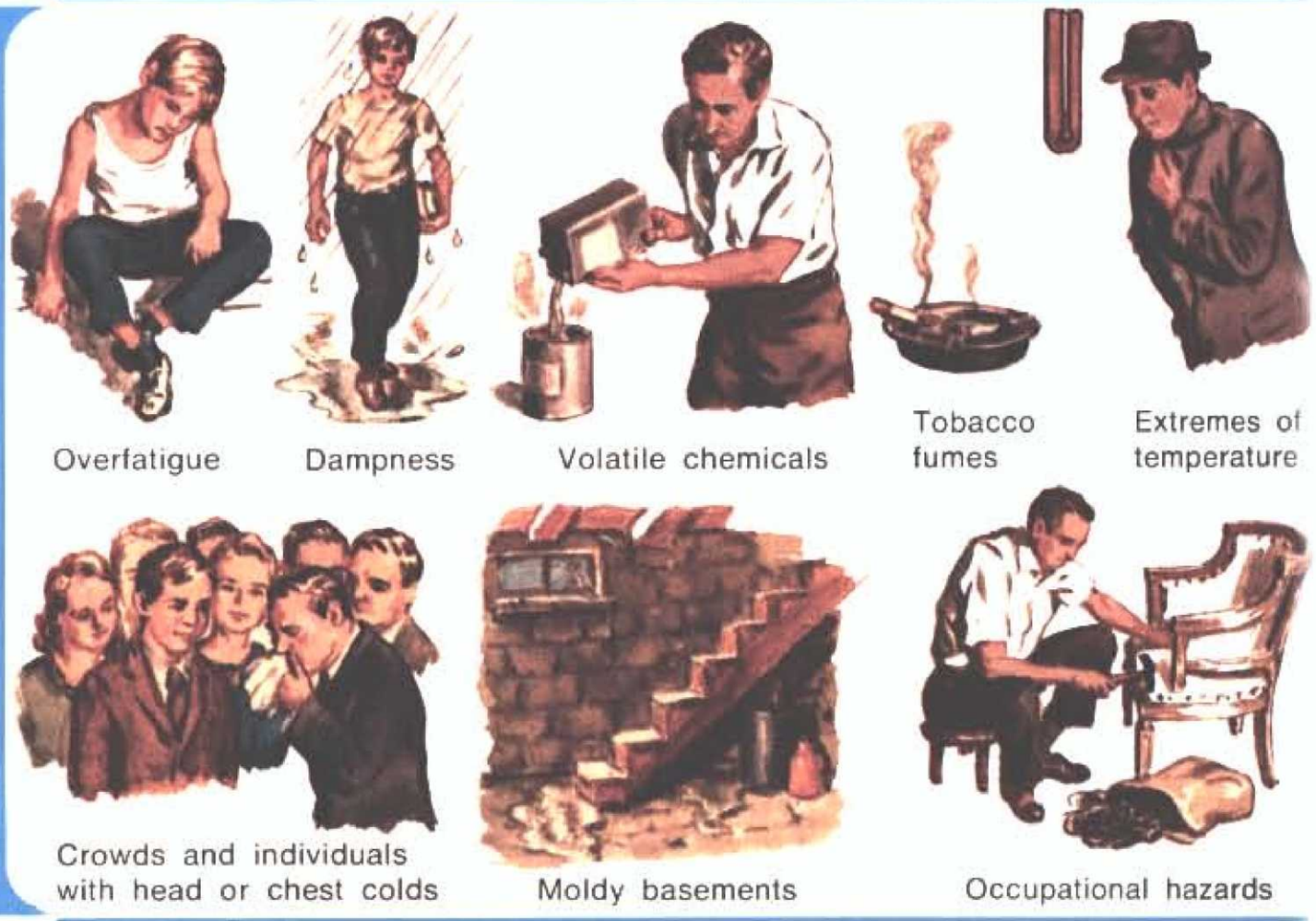
Nourishing nonallergenic diet

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

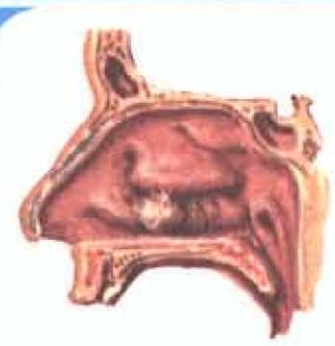
Wool blankets

Pets

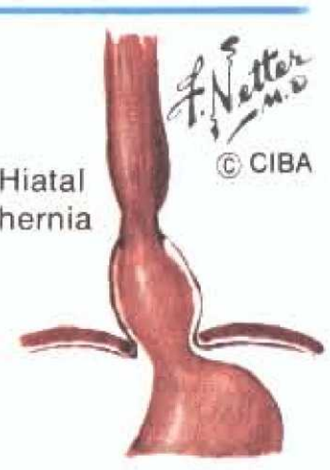
Mechanical or electronic aids

Air conditioners, humidifiers, filters, electronic air cleaners

Elimination or control of precipitating causes



Sinus infection, nasal polyps



Hiatal hernia

Bronchial Asthma
(Continued)

psychogenic factors must be considered secondary rather than primary causes.

Ambulatory Medication. Medications include bronchodilators (orally or by aerosol), antihistamines, corticosteroids, decongestants and expectorants. Daily use of drugs will prevent attacks and lessen chronic symptoms, although if corticosteroids have to be used, an alternate-day regimen is preferred.

Patients with moderate asthma respond well to maintenance therapy with aminophylline preparations administered orally. Aminophylline is the foundation of long-term ambulatory management and should be individualized. Some patients may benefit from a trial of antihistamines.

Aerosol preparations containing either epinephrine, isoproterenol or isoetharine are generally not primary forms of drug therapy and should never be dispensed without appropriate instruction about correct usage, proper dose and danger of overdosing. A patient may become dependent and overuse aerosol nebulizers, prompted by habit rather than by therapeutic need. The dangers of overdosage are increased, and drug propellant–induced cardiotoxic effects are more likely. Sudden death can occur in severe asthma, and, in one survey done in Great Britain, this was noted especially in children between 10 and 14 years of age who had overused gas-propelled isoproterenol nebulizers. A direct cardiotoxic effect of the propellant may have been responsible, or the deaths may have resulted from drug overdose leading to cardiac arrhythmias or a significant, paradoxical fall in Pa_{O_2}. Most of these children had severe, diffuse, secretional obstruction of their airways, and the relationship of death to treatment is uncertain. Thus, proper instruction about avoidance of the excessive use of nebulizers is imperative. Patients should notify their physicians whenever increased use of nebulizers is associated with decreased response.

Selective $beta_2$ stimulating drugs theoretically are expected to have fewer adverse cardiovascular effects, because $beta_2$ receptors are absent from the heart. Two such agents, terbutaline and salbutamol, have more prolonged action than isoproterenol.

At the first sign of an acute bacterial infection, culture specimens should be obtained and antimicrobial therapy started. Tetracycline or erythromycin may be used initially, but other antimicrobials can be substituted later, as indicated by the results of cultures and sensitivity studies. 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, and for them viral vaccines have been used prophylactically. However, their effectiveness and that of stock or autogenous bacterial vaccines remains disputed.

For ambulatory patients with severe asthma, corticosteroids are prescribed under close medical supervision (see page 133). They should be used on a long-term basis only if the response to comprehensive conventional therapy fails.

Chronic therapy may cause adrenal suppression, edema, hypertension, aggravation of diabetes mellitus, exacerbation or spread of infection, osteoporosis, myopathy, aseptic necrosis of the femoral or humeral heads, subcapsular cataracts, peptic ulceration with bleeding, psychosis, pseudotumor cerebri and hypokalemic alkalosis. To prevent these adverse effects, potassium supplements should be given; sodium restricted to less than 1 g/day; serum electrolytes and blood sugar monitored; and antacids prescribed. More important, for long-term use the drug should be administered on an alternate day schedule or by aerosol. Only careful and continuous follow-up of the patient will minimize these adverse sequelae.

In recent years new drugs have been introduced which may be of benefit in long-term management and in the prevention of acute attacks. Cromolyn sodium, a derivative of the smooth muscle relaxant khellin, acts by stabilizing the mast cell membrane and thus inhibiting the release of bronchoconstricting mediators. It is thus not a bronchodilator and is of no use in reversing established bronchospasm. It needs to be used in strictly prophylactic fashion, by inhalation using a special hand-held inhaler. Particularly in younger patients, both allergen- and exercise-induced asthma can be prevented when cromolyn sodium is given prior to such challenges. A major advantage is its ability to permit reduction or complete elimination of corticosteroids.

Aerosol preparations of corticosteroids are deposited directly in the airways and produce an adequate therapeutic response. Since they are not significantly absorbed, this topical route may reduce the need for oral administration and the complications of this type of treatment, including adrenal suppression. However, it must be clear that maintenance doses of aerosol corticosteroids do not have the same pharmacologic actions as sympathomimetic bronchodilators and therefore should not be used for the same purpose. In children, a major benefit has been a reduction in the incidence of steroid-caused growth retardation.

Hyposensitization. For patients in whom allergy plays a significant role, specific hyposensitization is an important element in long-term management. Such a program causes some discomfort, is time-consuming, and can be costly. Hence, it should be undertaken only if the asthma is sufficiently problematic, and if general avoidance measures and drug therapy are ineffective.

A hyposensitization program depends on results of skin testing and the exposure history. Since many antigens are available for skin testing, the physician must use clinical judgment in selecting those most likely to be allergenic for a particular patient.

Preferably, skin tests are performed by a scratch (prick) technique (Plate 27) using commercial aqueous extracts of common antigens—molds, pollens, fungi, house dusts, feathers, foods or animal danders. Mixtures of unrelated antigens should not be used. If skin-sensitizing antibodies to the antigen are present, a wheal-and-flare reaction develops within 15 to 30 minutes; a control test with saline diluent should show little or no reaction.

Optimally, both the history and dermal reactivity will give corresponding results. However, some patients have positive histories but negative or questionable skin tests. In other patients negative histories and positive skin tests indicate immunologic reactivity which is clinically insignificant. Equivocal results require careful evaluation. If further testing is called for because scratch test results were inconclusive, intradermal tests may be indicated. This approach is more sensitive than scratch tests, but it is time-consuming and more likely to produce systemic or acute asthmatic reactions.

Bronchial provocation tests (BPT) are a more direct method of determining the causative role of a specific airborne allergen when a patient with a negative skin reaction has a strongly positive clinical history. Serial measurements of pulmonary function (spirometry or body plethysmography) are made after inhalation of a suspected aqueous antigenic aerosol. There appears to be good correlation among skin tests, specific serum IgE antibodies and bronchial provocation test reactions. BPT are also useful in documenting late asthmatic reactions. Here, an early fall in FEV_1 is followed several hours later by a further drop which is often more severe and of longer duration. Another diagnostic maneuver is the inhalation of aerosolized methacholine. Patients with asthma will exhibit a noticeable increase in airway resistance at dilutions which do not affect normal subjects.

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, oxygen, emergency drugs (corticosteroids, aminophylline, vasopressors) and equipment to establish an airway should be readily accessible.

Results of skin or inhalation tests must be correlated with the clinical history. Best responses can be anticipated when pollens are the offending agents. Weekly injections of dilute extracts of antigen are administered under the supervision of a physician in gradually increasing doses until maximum protection is achieved. Hyposensitization schedules may be perennial, coseasonal or preseasonal. The patient's responses must be reevaluated periodically; if they are less than expected, new sensitivity to other antigens should 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 that of IgE, and therefore, it combines with the antigen more readily. A correlation between IgG titer and clinical improvement in

(Continued)

Bronchial Asthma
(Continued)

hay fever victims seems to exist. Serum IgE levels in treated patients are apparently decreased, possibly by IgG feedback. Or inhibition of IgE may be related to T cell function, which appears necessary for IgE antibody synthesis. A reduction in the cellular release of histamine may be another mechanism of immunotherapy.

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

Other Considerations. Some patients with refractory asthmatic symptoms may benefit by relocation to another climate. Because no geographic area is devoid of airborne allergens or irritants, the response to such a move is highly variable. However, living in a less humid or less industrialized area often proves beneficial. Optimally, a trial vacation or a period of residence in the prospective region will facilitate this decision.

Physical therapy benefits certain patients. This includes breathing exercises to improve effort tolerance and relaxation techniques to temper the distress of an acute attack. Postural drainage can also be used by patients with copious secretions.

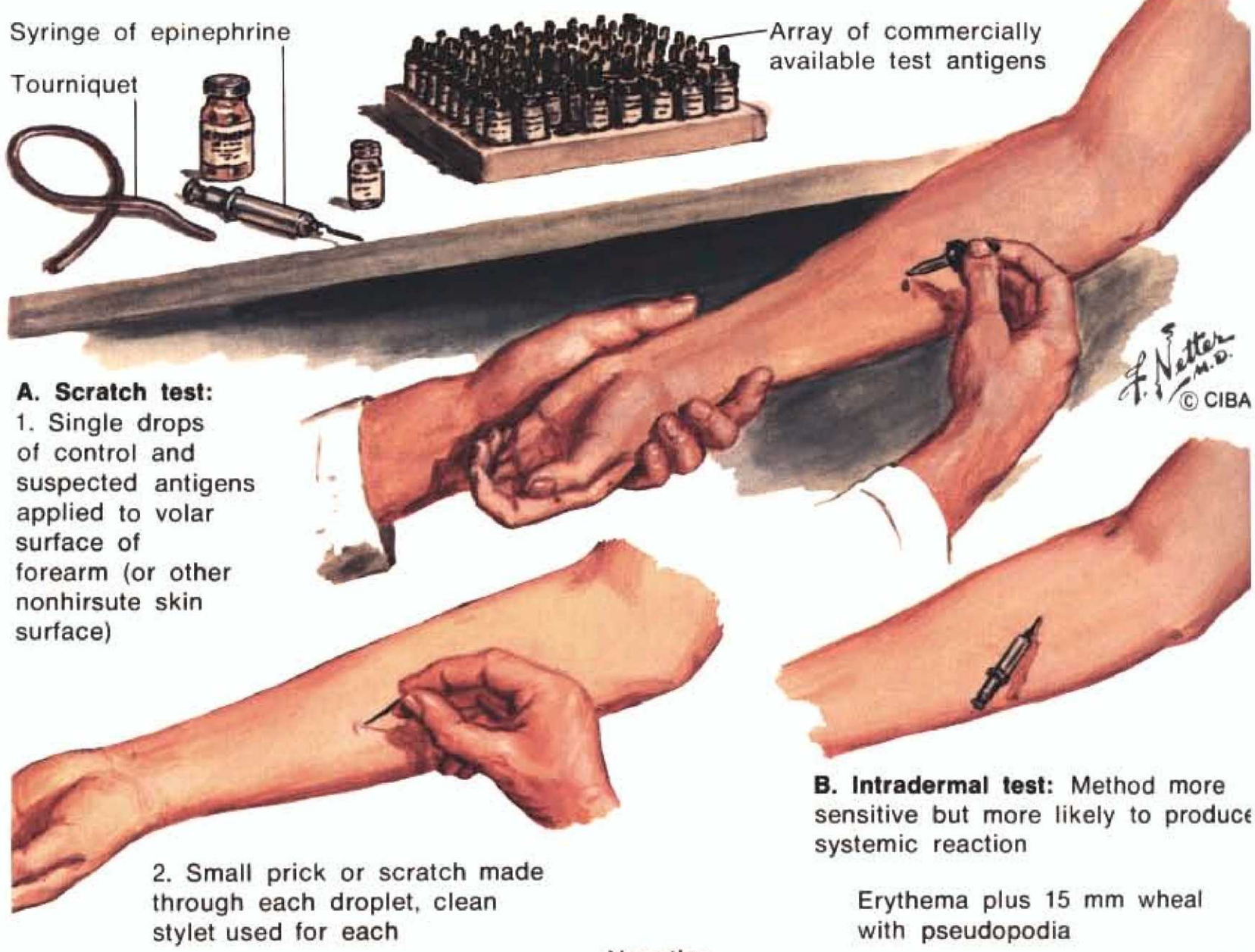
Surgical procedures are rarely indicated for asthma.

Conclusions

Of the 6 to 8 million asthmatics in the United States, between 4000 and 7000 die each year. Of this total, 1.5 million are children, yet less than 200 children die annually of causes related to asthma. The greatest danger of death occurs during severe attacks or in status asthmaticus. Prevention of such deaths requires intensive, individualized treatment based on the principles presented. Young asthmatic patients can anticipate significant relief of symptoms by the time they reach puberty. Even in adults, symptoms can be substantially alleviated by treatment.

Long-term management is based on *prevention* and requires an individualized therapy program for each patient. This program depends on the identification of the particular causes of asthma and mandates open communication and trust between patient, physician and other family members. Bronchial asthma is reversible with proper management, and its progression to permanent respiratory disability can be prevented.

Skin Testing for Allergy

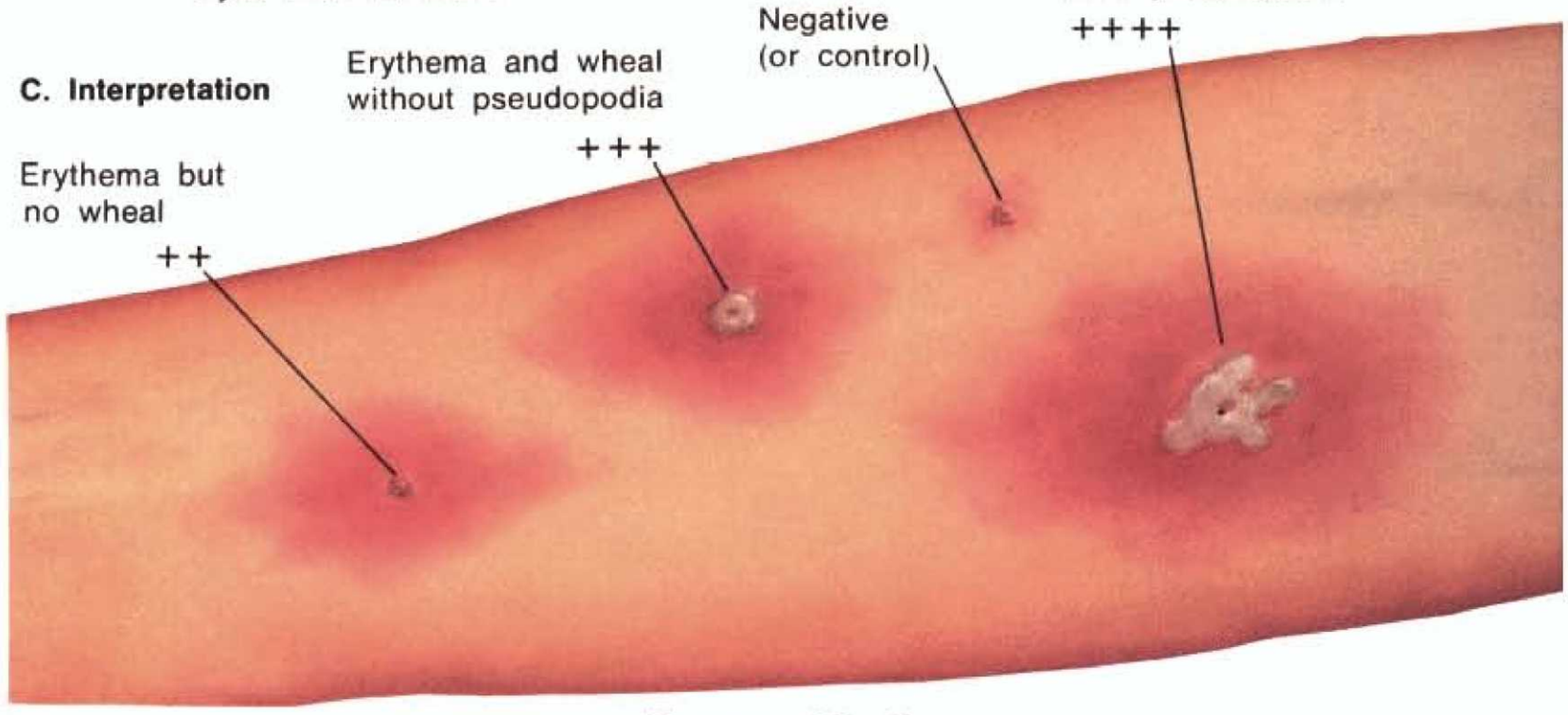


A. Scratch test:
1. Single drops of control and suspected antigens applied to volar surface of forearm (or other nonhirsute skin surface)

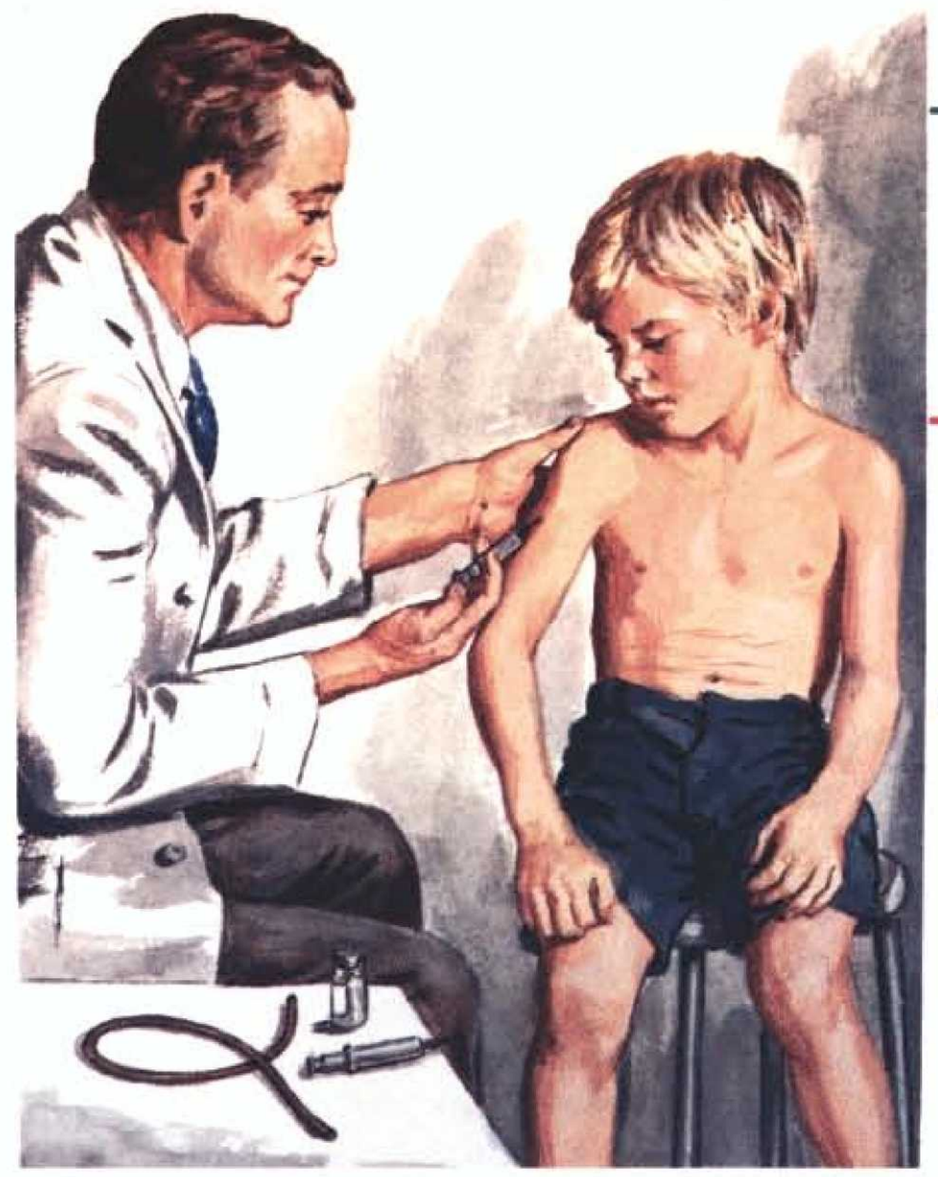
2. Small prick or scratch made through each droplet, clean stylet used for each

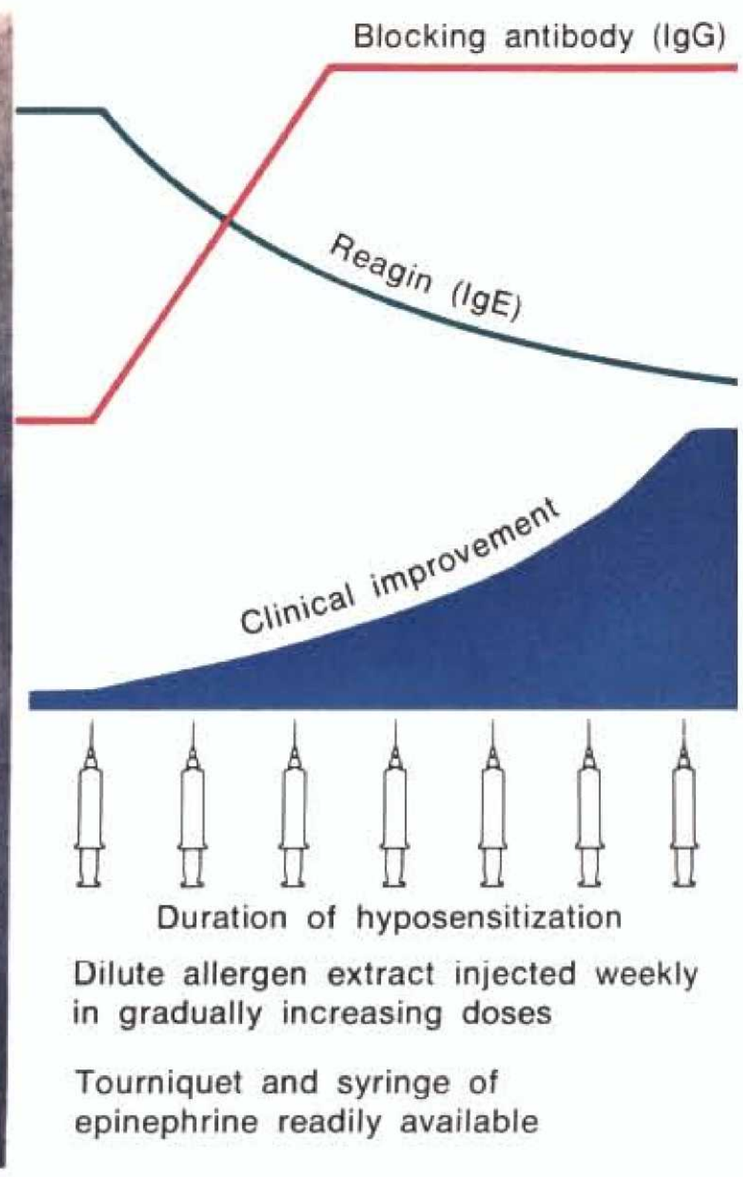
B. Intradermal test: Method more sensitive but more likely to produce systemic reaction

C. Interpretation



Hyposensitization





Dilute allergen extract injected weekly in gradually increasing doses

Tourniquet and syringe of epinephrine readily available