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ARTICLE

Bronchial Asthma: Current Concepts in Pathophysiology and Management of Status Asthmaticus

EARLE B. WEISS, M.D., L. JACK FALING, M.D., STUART M. BROOKS, M.D., SHELDON MINTZ, M.D., F.R.C.P. (C), SANFORD CHODOSH, M.D., and MAURICE S. SEGAL, M.D.

From the Department of Medicine, Tufts University School of Medicine, and the Lung Station (Tufts), Boston City Hospital, Boston, Massachusetts

IN 1821 R. T. LAENNEC WROTE OF OBSTRUCTIVE airways disorders:

"The general symptoms of this affection are rather equivocal. Dyspnea being its most striking feature, it is one of the diseases usually confounded under the name of asthma. In it the respiration is habitually impeded, but is aggravated by occasional paroxysms which are quite irregular in their return and duration. Like dyspnea from any other cause, it is further increased by the usual causes, such as indigestion, mental emotion, elevated situation, violent exercise, especially that of mounting, etc. It is unaccompanied by any fever, and the pulse is, for the most part, regular. When the affection exists in a high degree, the skin assumes a dirty aspect, with a bluish tint in some places, especially the lips. In all cases I have seen, there was a slight degree of habitual cough, with a very slight mucous expectoration. The complaint often exists from childhood, and does not seem materially to abridge the duration of life. Like other dyspneas it frequently, in the end, gives rise to hypertrophia or dilation of the heart." (47)

Since this classical description of an asthmatic-like episode, bronchial asthma continues to be a distressing and frequently fatal disorder. In the United States, it is estimated that there are 3 million asthmatics with a fatality rate of 4000–7000 deaths/year (63). In 1962, Feldman observed that 1–3 per cent of patients hospitalized with bronchial asthma died. A review of asthmatic patients from 1948–1963 indicated an increasing mortality of 1.4 per cent–2.6 per cent respectively (24). This may be attributed to more critical selec-

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tion of patients, to use of newer agents or to the overuse of sedatives. It has been suggested that the majority of fatalities occur in older patients with intrinsic asthma, and that 15 per cent of those who died in status asthmaticus had symptoms less than a year, while in 50 per cent the illness was present less than 5 years (6). Alternatively, recent work from England and Wales cited that mortality was increasing from 1960–1965, most pronounced in the 10–14 year age group (77).

The major insult to the patient with bronchial asthma is status asthmaticus. Once this state supervenes, profound physiologic changes occur, and death may result. The natural history of this disease continues to be a challenge to the investigator and the clinician. Current concepts of the pathophysiology and the rational therapy of status asthmaticus will be reviewed.

Precise definitions are variable and indicate the complex nature of this disorder. Based on bronchiolar hyper-reactivity, bronchial asthma is characterized by acute, recurrent or chronic attacks of bronchial-bronchiolar obstruction. This is manifest by wheezing and dyspnea of variable severity and usually of brief duration. Multiple factors such as allergy, air pollution, infection, stress or emotional upset can initate, interact and intensify the process. Cough and mucoid sputum production may be present. The definition of the American Thoracic Society is useful: "Asthma is a disease characterized by an increased responsiveness of the trachea and bronchi to various stimuli and manifested by widespread narrowing of the airways that changes in severity either spontaneously or as a result of the therapy." (1).

Wheezing *per se* is not pathognomonic of bronchial asthma and the reader is reminded that other diseases must be considered in the differential diagnosis: cardiac failure; bronchitis; pulmonary emphysema; tracheobronchial or laryngeal disease; hypocalcemic laryngospasm; mechanical compression by enlarged thymus, thyroid, aortic aneurysm, mediastinal lymphadenopathy or neoplasm; carcinoid tumor; foreign bodies; angioneurotic edema; and pulmonary emboli.

CLINICAL CLASSIFICATION AND OBSERVATIONS

We find it useful to delineate asthmatic patients according to their clinical state. That is, they may be in an acute or chronic phase of varying severity. Either state can be mild to moderate in intensity and manageable on an ambulatory basis. The extreme, intractable form, status asthmaticus, is a medical emergency carrying the threat

of severe hypoxemia, respiratory failure and death. This development requires hospitalization for full evaluation and proper management.

"Extrinsic Asthma"

This condition occurs in the genetically prone, usually younger patient and is characterized by acute paroxysms of brief duration with relatively normal intervening periods. Even during these asymptomatic intervals a small increase in airway resistance (partially reversible) may be demonstrable (7). A family history of allergy usually exists, as well as a personal history of allergy to drugs (aspirin or penicillin), foods (eggs, fish, nuts, chocolate, spices), pollens, dusts, molds, animal danders, and insecticides, etc. Positive skin reactions to the offending allergens often occur, and their significance requires careful historical correlation. Thereafter, hyposensitization therapy may prove beneficial to some, especially if begun early and administered properly (30). In general, the prognosis for "extrinsic" asthma is good, unless significant infectious bronchitis or bronchiolitis supervene.

"Intrinsic Bronchial Asthma"

This condition occurs in those with a less definite allergic history and usually begins after the age of 35–40, although an earlier onset is occasionally noted. Frequently, nasal polyposis, chronic hyperplastic sinusitis, poorly resolved pneumonia or bronchitis can precede or initiate intrinsic asthma. The mechanism may be related to respiratory tract infecting agents. Cultures of secretions from these patients reveal a mixed flora, with *Hemophilus influenzae*, Pneumococcus, *Neisseria catarrhalis*, Streptococcus, *Klebsiella* and fungal forms, yet their precise role has been difficult to establish. These patients commonly manifest a significant bronchitic component (viz., asthmatic bronchitis); thus at a given time infection dominates the clinical pattern. The development of an infectious bronchitic component influences the clinical course and therapeutic approach. Anti-allergic therapy is often less effective with such infections, and antibiotics are required. On the other hand, mixed infection and allergy, or allergic reaction alone may predominate. With asthmatic bronchitis, progressive destruction of gas exchange units may develop and this carries a more serious prognosis.

In many cases the intrinsic and extrinsic types of asthma merge,

overlap or remain undetermined; thus any etiologic designation of these patients must include both causes.

Clinical Data

In the classical form of bronchial asthma, acute attacks follow "appropriate" exposure. The onset is often dramatic and is associated with tachypnea, a feeling of suffocation and anxiety. Cough, with or without sputum, often occurs. Obvious wheezing and expiratory difficulty develop, but it is of interest that many asthmatic patients complain of "not getting enough air *in*." The attack can resolve gradually, with or without the use of appropriate medication (often a bronchodilator inhaler), or may progress slowly or rapidly to an unrelenting state.

Severe or Status Phase

The patient can rarely ascertain which attack will result in status asthmaticus; however, he can provide certain historical features disclosing the nature of the precipitating event. In many instances, acute infectious bronchitis initiates the process and the predominant complaint is cough productive of thick, purulent sputum; severe wheezing and dyspnea generally supervene. A critical development in status asthmaticus is widespread bronchiolar plugging and inspissation, manifest clinically by severe dyspnea, wheezing, and a cough, minimally productive of sputum. Gross examination of this sputum often reveals tiny bronchiolar mucus plugs (Curschmann's Spirals). Other clues to a severe, intractable phase include: poor response to, or an increasing requirement for, bronchodilator aerosols or aminophylline; severe fatigue and physical exhaustion related to respiratory work; progressive dyspnea; significant sudden reduction in routine function tests (FEV_T, MVV, $FEV_{1.0}$) to less than 50 per cent of predicted; cyanosis, reflecting advanced hypoxemia; and central nervous system agitation or depression reflecting carbon dioxide retention and acidosis.

The physical examination will be of value in assessing the total pulmonary and medical involvement. The patient is usually agitated, fatigued and anxious, and the blood pressure normal or increased (catecholamine response). Tachycardia, flushing, cyanosis or diaphoresis may be present. The patient often prefers sitting upright. Prominent neck veins and the use of accessory respiratory muscles are observed. Cardiac auscultation is difficult because of adventitious

sounds and lung overinflation; sinus tachycardia and accentuated S_2P are common. The thorax shows diminished excursions and overinflation, with hyper-resonance to percussion. Rales or rhonchi indicate secretions and local post-tussive findings suggest a focal bronchiolar or pneumonic process. Breath sounds show expiratory prolongation, are often coarse, and can be loud or diminished; regional reductions suggest bronchial mucus obstruction with atelectasis. Widespread reduction in bronchovesicular sounds reflects a generalized obstructive process. Here the normally audible inspiratory and expiratory wheezing may become very soft or "tight" in quality. Laryngeal stridor should not be confused with peripheral airways obstruction. In elderly patients the presence of basilar rales and diffuse wheezes suggest coexistent cardiac failure. In those instances where severe hypoxemia and respiratory acidosis supervene, papilledema, neuromuscular abnormalities (asterixis, irritability), confusion, agitation, cardiac arrhythmias or shock may ensue.

Pathologic Features

Since the observations of Huber and Koessler in 1922, and more recently by Cardell and Bruce-Pearson, the pathologic features observed in patients with status asthmaticus have been described. These include submucosal edema, basement membrane thickening, eosinophilic infiltration, intraluminal viscous mucus plugs, and smooth muscle contraction.

The lungs of patients dying in status asthmaticus are pale, grossly overdistended, and do not deflate when the thorax is opened. Widespread tenacious mucus plugs in thickened bronchi and bronchioles are common, with regional parenchymal zones of overinflation and atelectasis (23). These plugs are intrinsically viscous and externally adhesive to local structures, and create intraluminal resistances to airflow. They contain PAS-positive material, eosinophils, and Charcot-Leyden crystals (degenerative crystalloids of the eosinophil). Broad detachments of bronchial epithelium denude the respiratory surface and may be seen as clumps (Creola bodies) in the sputum of asthmatics; these are absent in bronchitis (65).

Gross reduction in luminal diameter is compounded by the folding of the internal surface of the bronchiole and contraction of a thickened smooth muscle layer. Thickening of the entire wall because of edema, hyperemia, inflammatory cell infiltrates (polymorphonuclear, eosinophil and plasma cells), prominent mucous glands, and goblet cells creates further increases in airway resistance. The cellular reaction in uncomplicated asthma extends to bronchi of 1 mm. in diameter.

The extensive bronchial gland hypertrophy described with chronic bronchitis is not seen (73). Goblet cell hyperplasia is present in areas not denuded. The basement membrane is usually thick and hyalinized; and partial atrophy of bronchial cartilage can occur. Regional atelectasis, bronchopneumonia or overinflation may be a consequence of the above processes.

Despite such obstructive features and gross hyperinflation, the alveolar destructive findings of pulmonary emphysema are absent unless the disease is complicated by infections (bronchitis or bronchiolitis). In addition, the alveoli, alveolar ducts and respiratory bronchioles may be dilated without tissue destruction (51). It appears that bronchial asthma can occur without permanent pathologic changes pathognomonic of the disease (80).

Pulmonary Vascular Alterations

Pulmonary vascular alterations during status asthmaticus are difficult to determine. Exposure of asthmatic patients to histamine or specific antigen can cause increases in pulmonary artery pressure and a tendency to increased but reversible pulmonary vascular resistance (35). Despite this, chronic cor pulmonale is not common. Evidence of acute right heart strain by ECG criteria, however, may be related to pulmonary vasoreactivity due to hypoxemia, acidosis or pharmacologic mediators. Right ventricular enlargement has been described in some patients dying in status asthmaticus; great age variation, and coexistent medical and pulmonary disorders influence such findings (40).

Death in Asthma

It is claimed that asthma alone rarely causes death. In status asthmaticus, however, the lethal potential of the pathophysiologic sequelae and drug complications must be appreciated. Recent epidemiologic studies report a significant increase in mortality in England and Wales from 1960–1965. This was particularly evident in the age groups 5–34 years (77). In addition, several investigators stress that death often occurs unexpectedly (24,90). Relative adrenal insufficiency due to improper adrenal corticosteroid therapy, sedatives, and excessive use of adrenergic aerosol bronchodilators have been speculated upon as possible mechanisms. Since bronchodilator-induced hypoxemia and myocardial irritability may be deleterious side-effects of sympathomimetic aerosols, the patient and physician must guard

against their overzealous use. Clinical evidence of an intractable state is the excessive use of an "inhaler" with little or no beneficial effect.

In the context of the pathologic consequences of bronchiolitis, mucus inspissation, atelectasis, and bronchopneumonia, severe hypoxemia and respiratory acidosis may ensue. Here, cardiac or respiratory arrest may develop, and must be considered a significant complication of status asthmaticus. Interestingly, sudden death has been reported even with normal blood gas values (90). One can only conclude that all the variables have not been defined, but it is important to emphasize the potentially serious consequences of status asthmaticus, possibly compounded by the use of pharmacologic agents. The reader is referred to a recent editorial on death from asthma (49).

Immunology and Pharmacology

It is generally accepted that a genetic predisposition exists in bronchial asthma, but the evidence for immunologic mechanisms is less clear. In extrinsic asthma, the main allergic antibody is IgE (38). This is the reagenic (skin-sensitizing) antibody. Normally present in small concentrations, it is reported elevated in 63 per cent of patients with allergic asthma and in 5 per cent of normals and patients with intrinsic asthma (39). The IgE antibody appears to be specific and the level of IgE is higher if a patient has multiple allergies rather than a single allergy. It may also rise after hyposensitization. It has not been proven that *all* reagins are IgE (50). The chemical basis for genetic and immune considerations has been reviewed by Middleton (59). A simplified scheme is presented below:

genetically atopic individual (extrinsic asthma)
↓
exposure to antigen (inhalants, pollens, foods, drugs)
↓
formation of sensitizing antibody—IgE (skin, lung)
↓
reintroduction of specific antigen
↓
antigen-antibody reaction at sensitized cells
↓
release of pharmacologically active materials:

a. Histamine
b. Slow-reacting substance of anaphylaxis (SRS-A)
c. Bradykinin

} major mediators

d. Acetylcholine
e. Serotonin
f. Infectious: direct—bacterial, viral, fungal reaction
indirect—toxic responses

Producing:

1. Mucus hypersecretion
2. Increased capillary permeability (edema and congestion)
3. Smooth muscle contraction
4. Inflammatory reactions

SRS-A (slow-reacting substance of anaphylaxis) is an acidic, probably lipid substance, obtainable in good yield from the perfusate of human asthmatic lung challenged with the appropriate antigen in vitro. In minute concentrations, it causes a strong and well-maintained contraction of isolated human bronchioles (16). While SRS-A tissue sources are not identified, it is believed to play a role in the pathogenesis of human allergic asthma.

Histamine is released from perivascular mast cells following allergen-antibody interaction. It increases capillary permeability and induces a short-term bronchiolar smooth muscle constriction. Even though sensitized asthmatic patients may release histamine, evidence of its in vivo role is less convincing, based upon low blood histamine levels and ineffectiveness of antihistamines. At present, allergen-induced release of histamine may contribute to the pharmacologic mediation of bronchial asthma.

Kinins have become implicated in recent years. Their level increases approximately tenfold during an asthmatic attack (2). They cause bronchoconstriction both in vitro and in vivo (by inhalation) in asthmatics (76). This bronchoconstrictor effect shows marked tachyphylaxis (2). The evidence is only suggestive that kinins *may* play a role in human asthma. The role for serotonin is even less clear (16).

One may conclude that the exact nature of the sensitizing immunoglobulins, the target cells, and the pharmacologic mediators of bronchial asthma in man have not been established firmly.

LABORATORY STUDIES

Sputum Observations

Some understanding of the dynamics of the existing underlying abnormality is established by careful observation of the patient's

sputum. It is important to note that the absence of sputum in status asthmaticus may indicate progressive bronchiolar inspissation and plugging by secretions, thereby contributing to death.

Grossly, the expectorated sputum may be clear, mucoid, thick or thin. Grossly, small, spiral bronchiolar plugs (Curschmann's Spirals) are presumptive evidence for bronchial asthma. Difficult expectoration indicates altered adhesive qualities. Copious viscous plugs are raised as an attack is clearing, presumably because of therapeutic agents. The sputum may appear to be purulent. However, one should not assume infection from this gross observation alone since the degeneration of eosinophils can also impart a yellow-green color.

Cell Population

Microscopic examination of the sputum cellular population may reflect what is actually occurring in the bronchial tree. Technically, place a small portion of sputum on a glass slide; add an equal volume of an aqueous buffered crystal violet stain (0.02–0.06% crystal violet in a $\frac{1}{15}$ M Sörenson's buffer at a pH of 6.8–7.0); gently mix; apply a coverslip and examine under the light microscope.

The cellular composition in a patient with uncomplicated bronchial asthma, demonstrates three main cell types: eosinophils, bronchial epithelial cells and histiocytes (macrophages). The eosinophils can comprise up to 50–70 per cent of all cell types. These are intact or disrupted with release of refractile granules into the noncellular mucoprotein matrix. The latter finding is often noted when an attack is at its climax or when it is resolving. After a period, numerous elongated rhomboid-shaped crystals, the so-called Charcot-Leyden crystals, appear. These are believed to represent a coalescence of the released eosinophilic granules. The desquamated bronchial epithelial cells are unique in asthma, since these columnar cells are often intact with their ciliary tuft; this finding is unusual in chronic bronchitis. Individual bronchial epithelial cells are often swollen, or one can often observe them as large clusters with intact cilia (Creola bodies). Creola bodies are more numerous during status asthmaticus. In addition, large numbers of histiocytes are often present. Their direct relationship, other than macrophage function, to the pathophysiology of the disease is not understood. Neutrophils exist, even up to 25 per cent, without overt bacterial infection being present. The finding of *large* numbers of neutrophils, however, should lead one to suspect the presence of an infectious process. Since acute infections often

precipitate status asthmaticus, the interpretation of this cellular feature can be lifesaving.

In intrinsic or asthmatic bronchitis, the predominant cellular features are bronchitic, with eosinophils usually comprising only 3–25 per cent of the total cells. There are fewer intact ciliated bronchial epithelial cells and Creola bodies. The neutrophil is usually predominant. Increases in eosinophils, in the clinical context, however, may reflect an asthmatic or allergic component.

Laboratory Findings

1. *Blood:* leukocytosis may be present or absent. Immature polymorphonuclear cells suggest infection. Blood eosinophilia from 5–50% may occur; total eosinophils > 250 mm.^{3}.

2. *Chemistries:* no significant findings unless acidosis, alkalosis, electrolyte complications or dehydration coexist.

3. *EKG:* right or left axis deviation, prominent right atrial P waves, or right ventricular strain may be present. Sinus tachycardia is usually present and generally reversible.

4. *Sputum:* see appropriate section in text.

5. *X-ray:* overinflation is the result of expiratory airway obstruction with increased thoracic volume, hyperlucency of parenchyma, depressed diaphragms and deep retrosternal air space. The vascular markings may be widened, but their caliber and distribution are normal. The main pulmonary artery segments may appear prominent. The heart is normal or small relative to the size of the thorax. Associated parenchymal or cardiac disease may be clarified. Focal atelectasis or transient infiltrates are often due to mucoid impaction.

PHYSIOLOGY

Physiologic guidelines to evaluate the course of status asthmaticus and the effect of therapeutic agents are often limited by patient cooperation. Particularly valuable are serial measurements of simple pulmonary mechanics, airway resistance, lung volumes and arterial blood gases. The latter, while not delineating all the pathophysiologic processes, do provide an index of net respiratory function.

As a result of the numerous pathologic processes described previously, variable degrees of physiologic impairment may ensue. These vary with (a) age; (b) duration and severity of disease; (c) coexisting disorders, viz. bronchitis or pneumonia; and (d) therapy and patient cooperation.

Mechanics of Breathing

The initial pathophysiologic disturbance in bronchial asthma arises from predominantly expiratory airways obstruction as a result of bronchospasm, mucosal edema and inflammation, secretions, and effort-related dynamic airways collapse. Bronchial obstruction is characterized by an increased airways resistance and increased work of breathing. Thus, a greater transpulmonary pressure is necessary for a given tidal volume or airflow. In addition, the normally passive expiratory phase will require active work to complete gas emptying. Where expiratory time is short, increases in residual volume ensue. Pressure-volume or flow loops are shifted and show increased hysteresis, indicative of the increased respiratory work necessary to overcome the mechanical resistances to air flow.

Chronic Stable State

In the chronic stable state, the slow vital capacity (SVC) may be normal or reduced. Many patients, regardless of age or duration of disease, have a SVC of 4 L. or greater. A review of our data in 59 adult asthmatics who were asymptomatic, revealed great variation in SVC. Since the slow vital capacity is a static measurement, time-volume indices obtained from the forced expiratory spirogram (low resistance, high speed spirometer) are relied upon to demonstrate airways obstruction in the chronic stable state, with or without preservation of the vital capacity. Thus, 1-second and 3-second forced expiratory volumes ($FEV_{1.0}$ and $FEV_{3.0}$), measurement of peak expiratory flow rate (PEFR) ($FEF_{0-25\%}$), or maximum midexpiratory flow rate (MMEFR) ($FEF_{25-75\%}$), reflect resistances in the airways and are often reduced in stable asthma. When feasible, measurement of airways resistance will provide direct data, but is generally unnecessary. Forced inspiration flow values (FIF) indicating increased inspiratory airflow resistances may also be reduced in asthma, and thereby contribute to increases in the work of breathing.

Acute Attack

In the acute attack, slow and total forced vital capacity (forced expiratory volume or FEV_T) as well as air flow parameters are reduced. In general, the more severe the asthmatic attack, the more compromised are the FEV_T and/or timed-flow measurements. We consider acute reduction in the FEV_T to 1.0 L. or less as critical, re-

Table 1. Demonstrating Improvement in Bronchial Air Flow by Actual First Second Measurements Despite Constant Relationship of Per Cent One Second Parameter

	Before aerosol	*After aerosol**
FEV (liter, BTPS)	2.0	4.0
% predicted	44%	89%
$FEV_{1.0}$ (liter)	0.800	1.600
% 1 second $\left(\frac{FEV_{1.0}}{FEV_{observed}} \times 100\right)$	40%	40%

* Aerosol used was isoproterenol hydrochloride (Isuprel).

quiring careful medical supervision. It should be noted that the ratio (or % 1 second) $FEV_{0.1}/FEV_{total} \times 100$, may remain constant, from the symptom-free to the severe bronchospastic state, because falls (or improvements) in the total FEV may remain proportional to changes in the first second volume (Table 1). Thus, $FEV_{1.0\%}$ is not always a reliable index. In some cases of acute asthma, significant reductions in total FEV may occur without gross reduction in $FEV_{1.0\%}$; the pattern will appear to be a restrictive type defect. The cause of the latter appears related to the hyperinflated state in status asthmaticus, where increases in residual volume effectively decrease lung compliance and produce difficulties in inspiration and expiration. Other measurements of airways obstruction, namely peak expiratory flow rate and maximum voluntary ventilation (MVV), roughly parallel the increases in airway resistance noted with the forced expiratory spirogram.

Recent studies have correlated arterial blood gas changes with the changes of simple pulmonary mechanics. Palmer and Diament, in studying status asthmaticus, reported that the arterial oxygen tension correlated best with the forced VC and not at all with $FEV_{1.0\%}$. Thus, the greater the fall in FVC, the greater the hypoxemia (67). In these patients, changes in arterial CO_2 tension did not correlate with any of the above measurements. These patients, however, did not exhibit hypercapnia. Tai and Read noted that a $FEV_{1.0}$ of 1 L. or less was associated with a significant reduction in the arterial O_2 tension, and in a recent paper McFadden and Lyons noted that hypercapnia occurred only at extreme degrees of obstruction, i.e., when $FEV_{1.0}$ was less than 15 per cent of predicted value. Interestingly, the increases in $PaCO_2$ averaged only approximately 10 mm. Hg, despite the severe degree of airways obstruction.

Lung Volumes

With progressive obstruction, decreases in vital capacity develop, limiting the inspiratory and expiratory lung capacities. The residual volume compartment is increased as the result of air trapping. Such overinflation may be seen in the chest X-ray and is characteristically reversible. Within limits, such overinflation places the midposition of the thorax in a more advantageous mechanical position to perform work, and also tends to increase the diameter of the airways, thus facilitating air flow. It has been suggested that a reduction in residual volume, despite a constant FEV_T, indicates a lessening of the airways obstruction, and is a useful parameter in objective evaluation of therapy (92). In the symptom-free state, the residual volume tends to be normal.

Regional Lung Function in Bronchial Asthma

Many patients with bronchial asthma demonstrate regional abnormalities in the distribution of inspired gases and of pulmonary capillary blood flow. Uneven ventilation may exist during the symptom-free intervals or acute episodes (7). Bentivaglio, *et al.* demonstrated regional ventilatory abnormalities in 6 of 12 symptom-free patients with asthma using radioactive xenon^{133}. More recently, regional alveolar ventilation/perfusion ratios were studied with radioactive xenon^{133} in 10 asthmatics in remission. Four subjects demonstrated normal distribution of ventilation, 4 had hypoventilation in some regions and normal ventilation in others, and 2 patients had abnormal ventilation in almost *all* lung regions. Zones which were hypoventilated had low ventilation/perfusion ratios and tended to be hypoperfused (33).

The development of lung scanning techniques provided a simple and effective way of determining regional pulmonary arterial blood flow (82,85). Intravenous I^{131}-macroaggregated albumin is uniquely suited for study of acute bronchial asthma, since the radioactive particles lodge within the pulmonary arterioles and capillaries during their first passage through the lungs and remain there for *several* hours (82). The characteristic scan pattern during acute bronchial asthma is transient regional hypoperfusion returning to nearly normal scan patterns within 24 hours following the acute attacks (60,61,91). It has also been demonstrated that different zones are affected in different attacks in one-half of the patients studied (61). The recognition of transient regional hypoperfusion in patients with bronchial asthma is useful in the differential diagnosis of acute pulmonary embolism,

since up to 5 per cent of these patients manifest wheezing. This transient pattern is also beneficial in differentiating pulmonary emphysema from bronchial asthma. The mechanisms of regional perfusion changes in acute bronchial asthma are unknown, but may be related to (a) regional alveolar hypoxia causing pulmonary vasoconstriction (29), or (b) air-trapping producing mechanical impairment of alveolar capillary blood flow when intra-alveolar pressures exceed those in the pulmonary arterial system.

Diffusion

The diffusion capacity of the lung (D_{LCO}) in asthma, is subject to the following variables: (a) severity of disease; (b) D_{LCO} method; and (c) complicating disorders. In most instances during acute attacks (54), the resting steady state D_{LCO} is normal or nearly so, even with a bronchitic element. This indicates the preservation of a normal diffusing surface and usually serves to distinguish asthmatics from patients with emphysema in which D_{LCO} may be reduced. Occasional reduction of D_{LCO} in acute bronchial asthma may represent acquired ventilation-perfusion abnormalities. Thus, when confronted with a reduced D_{LCO} in asthma, one should generally suspect such contributory factors as pulmonary fibrosis, vascular disorders, anemia or diffuse emphysema.

Arterial Blood Gas and pH

As the consequence of airways obstruction, with its numerous physiologic disturbances, blood gas abnormalities are frequently present in the asthmatic patient. The type and extent of blood gas/pH abnormality that exists in any particular case can only be determined by arterial blood analysis. Sequential measurements are necessary to determine the patient's course, establish whether O_2 therapy or improved alveolar ventilation is required, and clarify the effects of therapy. The spectrum of arterial blood gas patterns observed in latent, acute or status asthmaticus includes:

a. normal PaO_2, $PaCO_2$, pH: stable state, no or minimal symptoms.
b. normal PaO_2, $PaCO_2 < 40$ with pH normal or alkalotic: stable state or mild asthma.
c. hypoxemia $PaO_2 < 80$–85 mm. Hg, $PaCO_2 < 40$, and pH normal or respiratory alkalosis: stable state or mild to severe asthma.
d. hypoxemia and "normal" (crossover) $PaCO_2$ (see below).
e. hypoxemia, hypercapnia ($PaCO_2 > 45$ mm. Hg) ± respiratory acidosis.

In chronic stable bronchial asthma, mild hypoxemia (in terms of arterial O_2 tension) occurs at frequencies not previously appreciated, and some degree of hypoxemia is present in many, if not all, asthmatics during an acute attack. In severe asthma or status asthmaticus, advanced hypoxemia frequently develops, and prompt oxygen therapy is required to prevent death and other hypoxemic complications. Such hypoxemia is usually the result of unequal ventilation/perfusion ($\dot{V}/\dot{Q}$) relationships initiated by the acute airways obstruction. Impaired diffusing capacity, and right to left shunts, are mechanisms which only occasionally contribute to the hypoxemia encountered (54). Generalized hypoventilation develops most commonly from the injudicious administration of depressant agents.

The arterial blood in acute asthma usually reveals hypocapnia with acute respiratory alkalosis. This hyperventilation is stimulated by altered chest wall and pulmonary parenchymal reflexes as well as by hypoxemia and psychological factors. With progressive disease, further inequalities in ventilation and perfusion develop, and initial compensatory increases in effective alveolar ventilation subsequently fail, because of further increases in airways resistance and associated excessive work of breathing. At the point where respiratory work becomes limiting, or when the effort is diminished (as by sedatives or fatigue), the patient with status asthmaticus will progress to gross hypercapnia and respiratory acidosis. Palmer and Diament have stressed that acute hypercapnia is an important sign of impending deterioration in status asthmaticus, and that vigorous therapeutic measures are necessary (68). An important point is that such deteriorations may occur rapidly.

As Indices of Severity

Weiss and Faling have recently stressed the need for serial arterial blood analysis as indicators of progressive $\dot{V}/\dot{Q}$ inequality and severity of disease (88). Specifically, the shift of $PaCO_2$ from hypocapnia to normocapnia may herald the "crossover" into hypercapnia and respiratory acidosis. The approach of Pco_2-pH data to the "crossover" range of normal values should alert the physician to reassess the clinical picture and to modify or intensify therapy if indicated. Obviously, this concept will not apply to improved patients who attain normal $PaCO_2$ and pH relationships.

The following case of status asthmaticus in a 46-year-old female illustrates: (1) the value of serial arterial bloods in detecting the "crossover" from hypo- to hypercapnia; (2) the rapid clinical deteri-

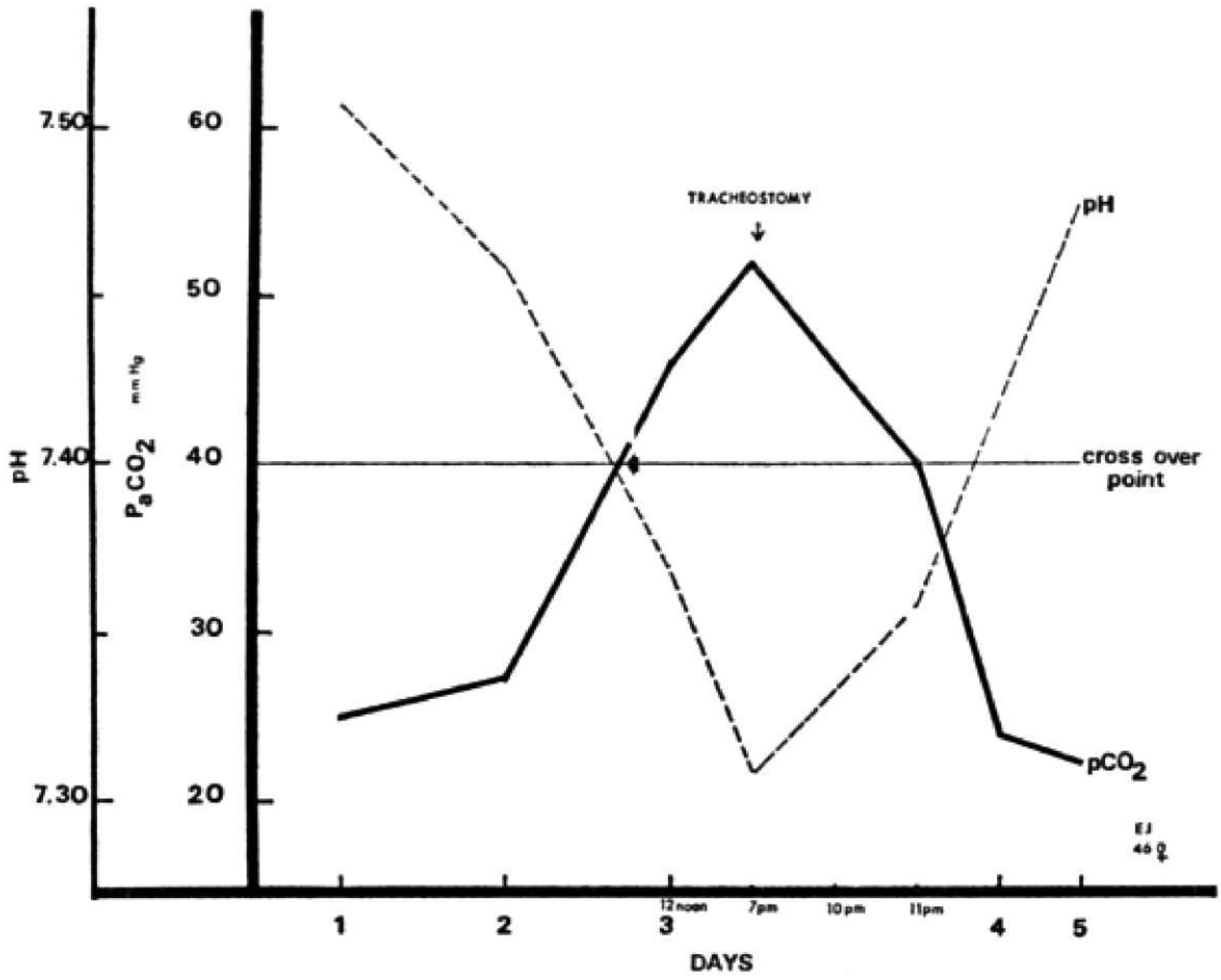

Fig. 1. **Arterial $PaCO_2$ and pH data in a 46-year-old Negro female in status asthmaticus. Note the initial hypocapnia and respiratory alkalosis progressing to a "crossover" phase with "normal" $PaCO_2$–pH values and then to frank respiratory acidosis. See text for details.**

oration which frequently occurs once the crossover point is reached; and (3) the need for immediate intensive care, including mechanical ventilation, to correct acute respiratory failure as well as the status state. (Figure 1).

Case 1

A 46-year-old Negro female was admitted in status asthmaticus. On medical treatment including adrenal corticosteroids and tetracycline, an arterial blood sample on the next day revealed $PaCO_2$ 25 mm. Hg, pH 7.51, and PaO_2 74 mm. Hg (on mask O_2).

Status asthmaticus persisted and on the third hospital day the $PaCO_2$ was 27 mm. Hg, pH 7.47, and PaO_2 80 mm. Hg (on O_2). Severe fatigue and clinical deterioration ensued, but repeat blood analysis was not obtained until noon of the fourth hospital day: $PaCO_2$ 46 mm. Hg, pH 7.37, and PaO_2 48 mm. Hg (on O_2). Despite renewed intensive treatment, a rapid downhill course developed over the next 7 hours, necessitating a tracheostomy ($PaCO_2$ 52 mm. Hg, pH 7.31). The patient was placed on assisted ventilation and 4 hours later was clinically improved ($PaCO_2$ 40 mm. Hg, pH 7.36 and PaO_2 120 mm. Hg). Thereafter, she recovered, manifesting hyperventilation until the tracheostomy was removed one week prior to discharge (88).

This case emphasizes the need for serial arterial blood determinations during the course of status asthmaticus, particularly if clinical improvement fails to occur. The crossover phase (Fig. 1) might have been appreciated by additional serial $PaCO_2$ and pH observations reflecting progressive $\dot{V}/\dot{Q}$ disturbance with reduced effective alveolar ventilation, and earlier attempts to reverse her course might have been successful. Thus, further medical observation and vigorous treatment are clearly indicated at this potentially critical point in an asthmatic's course.

TREATMENT OF STATUS ASTHMATICUS

Status asthmaticus may be defined as a state of continuous intractable asthma refractory to conventional therapy. Presentation in a state of extreme physiologic stress, anxiety, hypoxemia, (and respiratory acidosis), dehydration, and excessive respiratory work, creates a therapeutic challenge to the physician. The three critical changes occurring within the airways are (1) smooth muscle constriction; (2) bronchial mucosal edema; and (3) excessive respiratory secretions. Treatment with anti-inflammatory drugs, expectorants and bronchodilators in addition to physiologic support is necessary to reverse this state. Management during pregnancy follows the same principles, with due consideration to the possible maternal and fetal complications of drugs employed.

Precipitating Factors

Successful management requires careful consideration of the various responsible factors and the nature of the patient's response, both organically and psychologically. Removal of the offending allergens is of benefit. This is facilitated when the agent is known historically, but many environmental agents such as dusts, molds, pollens, etc. cannot be avoided entirely. Hyposensitization therapy with defined and properly timed injections of commercially available extracts in the presymptomatic period may prove useful for unavoidable allergens. If hyposensitization is successful, less symptomatic treatment will be required. Since (1) a search for responsible agents is difficult and often a variable success, and (2) desensitization is not feasible during status asthmaticus, emphasis on the allergic approach to management is deferred, and full supportive physiologic and drug therapy is employed at this time.

Multiple precipitating factors, often unrelated to the original causes,

may be responsible for acute deterioration into status asthmaticus and should be evaluated and dealt with, for successful therapy:

1. *Infection:* viral, bacterial, fungal (bronchitis, pneumonia, etc.) may initiate or complicate the clinical picture.
2. *Allergic Factors:* pollens, animal danders, dusts, foods, drugs (penicillin and salicylates), vaccines, fungal spores (Alternaria, Aspergillus, Hormodendrum), etc. These are identified by specific seasonal or perennial allergic sensitivity and confirmed by skin tests and history.
3. *Irritative Factors:* dusts, fumes, strong odors, smoke, cold air, air pollutants, anesthetic agents, hiatus hernia.
4. *Trigger Mechanisms:* sinobronchitic disease, nasal polypi, otitis media, weather and humidity changes, laughing, physical exertion.
5. *Emotional:* stress, fatigue. (Always rule out specific organic causes primarily.)
6. *Drugs:* propranalol, isoproterenol, salicylates (and nasal polyps).

The Airway

Bronchoscopy and Lavage

It is absolutely essential that a patent tracheobronchial airway is maintained at all times. Those patients capable of raising their own secretions will not require intubation. Those individuals who are severely obstructed, obtunded, or poorly cooperative, will require supportive measures such as endotracheal intubation or tracheostomy. Therapeutic bronchoscopy may be considered initially in those patients who are critically ill and unable to evacuate their own secretions. If performed early and successfully, it can prove lifesaving in moribund patients and endotracheal intubation or tracheostomy may be avoided. Appropriate endoscopic lavage with warm isotonic saline, N-acetylcysteine (Mucomyst), or pancreatic dornase (Dornavac) is advisable. In any patient receiving full medical support and appropriate inhalation therapy, but deteriorating because of persistent and tenacious sputum, therapeutic bronchoscopy with lavage is also indicated. A useful approach is to employ a Carlen's differential bronchospirometry catheter so that one lung can be ventilated while the other is lavaged, preferably segmentally. The patient *always* should be well *oxygenated* during these procedures. Bronchoscopy with lavage facilitates the aspiration of trapped secretions, improves drainage, and may help restore an effective cough mechanism. Cardiac

arrest can develop during bronchoscopy due to vagal reflexes or hypoxemia and/or acidosis, and this serious event should be anticipated. A word of *caution:* N-acetylcysteine may prove irritating and actually produce bronchoconstriction. It must be used with *great caution* and preferably mixed with small amounts of isoproterenol. N-acetylcysteine through the bronschoscope or tracheostomy tube is most effective, although the percutaneous transtracheal or aerosol route is often used.

Endotracheal Intubation

An oral or nasal endotracheal tube can be employed for several days to maintain a patent airway for ventilatory support and secretion evacuation. Periodic deflation of the inflated balloon, meticulous nursing care and avoidance of mechanical stress by mobility and malpositioning of this tube are necessary. Laryngeal necrosis and unilateral mainstream bronchus intubation are the frequent complications to be avoided. In many cases, this approach will avoid the serious complications of tracheostomy and may permit more rapid recovery with a shortened hospitalization. With proper use, prolonged endotracheal intubation alone can be employed for as long as 1 week without deleterious effects, but it is not generally recommended for more than 2–4 days. On the other hand, if mechanical ventilation appears necessary for longer periods, a tracheostomy will be required.

Tracheostomy

Tracheostomy is often a necessary and lifesaving move to facilitate the removal of secretions, and to provide a route for continuous ventilation. It should be established where the above measures have failed, or in the instance where more dramatic intervention is required. It is preferably performed in the operating room, over an endotracheal tube under controlled conditions, permitting adequate ventilation, oxygenation, and mobilization of secretions. When performed at the bedside under emergency conditions, the complication rate has been very high due to bleeding, hypoxemia, cardiac arrest and pneumothorax. An inflatable cuff should fit snugly around the end of the tracheostomy tube. Deflation is necessary for at least one minute every one-half hour whether on continuous mechanical ventilation or humidified oxygen. Frequent replacement of the tube, deflation of the balloon (always after suctioning above the cuff), cleansing of debris and strict aseptic techniques are mandatory for the success-

ful application of this approach. It is essential that adequate humidification of the airways be provided at all times. Heated humidifiers permit greater wetting of inspired air and should be employed with all mechanical ventilators as well as with the simple tracheostomy box.

Wound or tracheal infections occasionally ensue in the traumatized area, the organism varying with hospital environment. Isolation of the patient is useful in halting the spread of offending staphylococci. The introduction of gram-negative bacteria by contaminated humidifiers or nebulizers can be limited by the frequent cleansing of equipment and periodic replacement of sterile solutions. The presence of bacteria in the tracheal wound and/or secretions requires clinical evaluation for proper antimicrobial therapy. Minor colonization without symptoms or systemic response generally may go untreated.

Management of Secretions

Whether the patient is being managed with or without an artificial airway, appropriate attention to secretions is necessary. One of the most significant factors in precipitating, accentuating or perpetuating status asthmaticus is obstructing airway secretions. Their physical presence creates a series of physiological changes which can result in hypoxemia and/or hypercapnemia. Thus, their mobilization is mandatory and will contribute significantly to reversing the disorder. The causes of excessive secretions should be promptly identified to permit appropriate therapy. Usually, there are adequate clinical indications that secretions are a major problem. Not infrequently, however, the patient may be seen without such findings, and their presence should be suspected in any individual with known bronchopulmonary disease. Failure to achieve adequate mechanical ventilation may be an indication of inspissated secretions.

Liquefication and Suctioning of Sputum

There are two basic types of sputum, each requiring its own type of management. *Mucoid sputum* is white or opalescent, gelatinous and adhesive, due to mucopolysaccharide and mucoprotein gels. Clinical observations suggest that the more water this gel-sputum contains, the less viscid it becomes; conversely, when water is lost through dehydration, viscosity and adhesiveness increase. Mucoid sputum may be quite troublesome because of its viscous and adhesive properties and the fact that it cannot be altered by antibiotics. N-acetylcysteine,

by reducing disulfide bonds in mucopolysaccharide chains, tends to lower viscosity and adhesiveness and thereby facilitates removal.

On the other hand, *purulent sputum* contains fibers of desoxyribonucleic acid (DNA) from necrotic parenchymal and inflammatory cell nuclei. Large volumes of such material, with increased viscous and adhesive properties, can be generated by any infectious process. Pancreatic dornase is employed for the enzymatic degradation of DNA which assists in the removal of lodged and inspissated material. Additionally, antibiotics will abort the progression of the infectious process contributing to these sputum characteristics. Finally, where both components are present, combination therapy should be established. Five to 10 ml. q.i.d. of N-acetylcysteine, in the form of a 10% solution, may be instilled directly and aspirated through the tracheostomy tube, administered by a transtracheal catheter aseptically inserted into the subcricoid space, or used at the time of bronchoscopy. Again, since N-acetylcysteine carries the risk of bronchospasm it must be used with caution, and if employed should be mixed with 0.5 ml. of 1% isoproterenol per 10 ml. of solution. Pancreatic dornase (50,000 units, q.i.d.) can be instilled directly or aerosolized.

Changes in body position during the administration of such agents will facilitate their appropriate distribution and since they often liquify secretions quite rapidly, attention to proper suctioning is mandatory. Aerosol distribution of these agents will be limited by the obstructive features present within the airways during bronchospasm.

Tracheobronchial suctioning should be performed aseptically and with caution. Actual suction pressure should be activated only after the catheter has been gently inserted, otherwise denuding and destruction of the tracheal mucosa may occur. Each catheter is to be used only once and then discarded. During each maneuver, one should be certain that the catheter suctions beyond the length of the tracheostomy or endotracheal tube.

Hydration

Normally, inspired air is fully saturated with water by the mucosa of the upper airways. Dehydration limits intrabronchial humidity, causing dry and thick secretions. With fever, hyperpnea, and poor fluid intake, a "humidity deficit" may exist. During hyperpnea, the water lost from the lungs may be great. Tanked or wall oxygen is absolutely dry and must be humidified by means other than the bubble or flow-through humidifier used in most hospitals (89). With

poor humidification, any existing secretions will thicken because of water loss and become more tenacious and difficult to raise. Inspissated, crusted mucus and cellular debris create an environment favorable for regional bacterial growth.

Temperature is a major limiting factor for the water content in inspired air. The size of the droplets of moisture delivered in the gas is also of great importance. Particles of smaller diameter than 0.5 μ are largely swept out in the expiratory flow. On the other hand, particles larger than 10 μ are usually deposited in the oropharynx or trachea. Aerosol generators which baffle out particles larger than 10 μ and produce the majority of particles in the 3 μ size are the most effective. The aerosol should be delivered at body temperature or higher to achieve greater humidity.

Ultrasonic (high frequency) nebulization (De Vilbis-Monoghan-Macrosonic) provides a homogeneous, micron-sized fine mist of therapeutic substances, water and saline. These are more likely to be deposited into the peripheral bronchial tree. The maximum volumes to be nebulized can be controlled and limited. The nebulizer can be attached to face masks, body tents, and tracheostomy box units powered by air, oxygen or respirators. The less expensive cold vapor atomizers producing high outputs of atomized (large) particles of cold vapors may be similarly employed. Aerosols of saline or water, employing aerosol generators equipped with heating coils (Puriton or Mistogen units) powered by air or oxygen, can be directed into I.P.P.B. units or tracheostomies.

Adequate hydration by oral and/or intravenous routes is the other key approach to liquifying secretions. Agents such as tyloxapol (Alevaire) seem to be effective only by virtue of their water content and are not generally recommended. The expectorant properties of iodides administered either orally (10–30 gtts. of a saturated solution of potassium iodide b.i.d.–t.i.d.), or intravenously (1–2 Gm. NaI per liter) act presumably by liquefication of retained materials. A disagreeable metallic, bitter taste is commonly experienced. Side-effects include rash, conjunctivitis, bronchorrhea, adenopathy and iodide goiter in adolescents when prescribed for 6–12 months. Idiosyncrasy to iodides should be anticipated in all asthmatic patients. Glyceryl guaiacolate (Robitussin), in doses of 400–600 mg. q.i.d. (20–30 ml. of preparation) is also efficacious and particularly valuable in cases of iodide sensitivity; both can be used simultaneously. All of these measures improve bronchopulmonary drainage. However, suctioning techniques are necessary to evacuate loosened secretions in patients who have lost effective cough or have a tracheostomy. The debilitated

or semiconscious patient may literally drown in his own secretions if effective suctioning is not undertaken.

Ancillary Measures

There are several ancillary measures which aid in general management: (a) *Postural drainage:* in those patients whose sputum is liquefied, and who can cooperate, positional drainage is of benefit, even when their cough is somewhat depressed. With the patient properly positioned to utilize gravitational forces, chest tapping can liberate trapped and/or voluminous secretions; (b) *Antitussives:* coughing paroxysms in certain patients may be trigger mechanisms for inducing bronchospastic crises, expiratory air trapping and possible alveolar destruction. At no time should an effective, productive cough be eliminated. Taking the edge off an irritating cough is sometimes beneficial, however, particularly at night, when sleep is essential. Under select circumstances during status asthmaticus, one can justifiably employ narcotic suppressants, always with appropriate concern and monitoring for respiratory depression. In less pressing or chronic situations, the use of non-narcotic antitussives may be of benefit. Theratuss in doses of 20–60 mg. q.i.d. is useful. Although chlophedianol hydrochloride (ULO) is an effective antitussive, the incidence of neuropsychiatric side-effects limits its routine use.

Bronchodilators

Bronchodilator agents are an integral component in the management of status asthmaticus. In principle, they reduce airways obstruction, thereby improving gas distribution and alveolar ventilation. In addition, excessive respiratory work is reduced. Simultaneously, they improve the distribution of aerosolized medications to those regional zones of relative obstruction. Systemic and cardiovascular side-effects are common and bronchodilator use necessitates proper monitoring.

The bronchodilatory effect of isoproterenol, epinephrine and aminophylline in patients with bronchial asthma is established. Recently it has been appreciated, however, that these agents may also influence arterial blood oxygen tension (PaO_2). It has been shown that the PaO_2 is frequently, although usually moderately, decreased in subacute and chronic asthmatic patients after the administration of aerosol isoproterenol (45), subcutaneous epinephrine (72), or intravenous aminophylline (71). These patients usually show improvement in

ventilatory function tests and subjective improvement of dyspnea. The explanation for this blood gas change is attributed to either increases in the dead space ventilation ($\dot{V}_D/\dot{V}_E$) (45) or to an increase in blood flow to the underventilated lung regions (21).

The therapeutic benefit of these agents in status asthmaticus is undisputable at present. Despite these blood gas changes, bronchodilators reduce airways obstruction, improve regional alveolar ventilation and decrease the work of breathing. Reductions in arterial O_2 tensions must be accepted and are easily treated by enriching the inspired air with oxygen. In practice, this is usually provided to these patients.

Aminophylline

The xanthine derivatives are very useful because of their marked bronchodilator action as seen clinically and by increases in vital capacity. Other effects include respiratory stimulation, increased cardiac output, decreased pulmonary vascular resistance and increased renal blood flow with diuresis. In acute situations, 250 mg.–500 mg. intravenous aminophylline (theophylline ethylenediamine, 81%) is administered *very slowly* over a 15–20 minute period, since fatalities with aminophylline have been reported associated with rapid intravenous injection. This may be followed by the continuous infusion of 250–500 mg. aminophylline/liter of 5% dextrose and water at 20–30 drops per minute flow rate. We prefer not to exceed 1.5–2.0 Gm./day. The exact dosage should be tailored to the clinical situation with due regard to the patient's tolerance for aminophylline, age, weight, and possible side reactions. Relief is immediate and prolonged in some individuals, while others will require repeated or continuous administration. Aminophylline may be given rectally, as a retention enema, in similar doses when the patient has improved sufficiently to omit the intravenous infusions. The oral route and suppositories are not recommended in status asthmaticus; they are more useful in maintenance therapy. Other side-effects include: nausea, vomiting, local irritation, diaphoresis, hypotension, seizures, and palpitations.

Isoproterenol

This powerful sympathomimetic amine stimulates beta-receptors in the heart, smooth muscles of bronchi, vasculature, and other organs. Isoproterenol causes relaxation of bronchomotor tone and relief of bronchoconstriction. Reduction in airway resistance and improvement

in respiratory mechanics (i.e. MBC, FVC) will assist in alleviating the physiologic changes created by the attack of bronchial asthma. Isuprel is administered via commercial Freon-propelled inhalers, hand or ventilator nebulizers. For nebulization, 0.5 ml. (or less) of a 1:200 solution is diluted to 2 ml. with saline or sterile water, and prescribed 2–3 times in a 24-hour period. The *smallest* dose affording relief is selected. Precautions as with epinephrine should be observed. Side-effects are attributed to excessive systemic absorption and include dizziness, tachycardia, anxiety, angina, and palpitations. Sudden death may occur in asthmatic patients if adrenergic agents are used to excess (53). Van Metre and Lopez, in reviewing fatalities in status asthmaticus, suggested that patients can become refractory to isoproterenol. When the latter is discontinued, other therapy, previously ineffective, may be beneficial (83). In addition, a few patients appear to demonstrate a measurable *increase* in airway resistance following isoproterenol as compared with placebo aerosol (41). Both these factors should be considered in the refractory patient in status asthmaticus receiving aerosol isoproterenol.

Epinephrine

This catecholamine acts at specific alpha-and beta-receptor effector cell sites. In the lungs, epinephrine is of therapeutic value since it produces a bronchodilator and bronchial decongestant action. Subcutaneous injections of 0.3 ml. of a 1:1000 aqueous adrenalin solution can be repeated at 30–60 minute intervals as indicated. Subcutaneous Sus-Phrine suspension (0.2–0.3 ml. of a 1:200 solution) is sometimes used because of longer effect (up to 4 hours). Precautions should be taken with cardiac, hypertensive, hyperthyroid or cerebrovascular risk patients. Arrhythmias can develop, particularly in those with significant hypoxemia or co-existing cardiac disease, and may cause unexpected death. The intravenous route is not recommended. Aerosols of racemic epinephrine solution (2.25% Vaponefrin) are nebulized or administered via intermittent positive-pressure breathing (IPPB) (0.2–0.5 ml. with 2 ml. saline). Epinephrine refractoriness developing with repeated use (usually after 2–3 days) is possibly related to coexistant acidosis. Mithoefer has suggested that sodium bicarbonate, in correcting such acidosis, can restore responsiveness (62).

Heparin

Earlier reports suggested that heparin was capable of improving certain patients with acute bronchial asthma (13). A recent double-

blind study indicates, however, that heparin does not have a beneficial action in these patients (28).

Atropine and Related Belladonna Alkaloids

These preparations can be considered, particularly in "wet" asthmatics, if above agents fail. They are generally less potent than other bronchodilators and possess a drying action. This should be avoided by their judicious administration to prevent inspissation of bronchial secretions. Atropine sulfate, 0.5 mg., is prescribed orally, subcutaneously, or preferably as an aerosol, such as Dylephrin (2.5% racemic epinephrine and 0.5 Gm. atropine sulfate).

Adrenal Corticosteroids

Adrenal and pituitary function in bronchial asthma has been frequently studied, often with conflicting results. The renal excretion of both normal and diminished levels of adrenal metabolites has been noted; however more recent studies have reported normal plasma cortisol levels. Similarly, both a normal and decreased adrenal responsiveness to ACTH stimulation have been observed, and a normal metopirone test was demonstrated in one small group of uncomplicated asthmatics (12,25). Obviously, further studies are required with careful definition of disease, its duration and severity, as well as coexisting therapy and medical disorders.

Recently, interest has focused upon the following aspects of corticosteroids in relation to bronchial asthma: (1) long-term corticosteroid therapy; (2) cortisol metabolism; and (3) steroid resistance.

El-Shaboury recommended the use of adrenal steroids rather than ACTH during status asthmaticus, since the adrenal glands may fail to respond to ACTH following long-term steroid treatment (26). On the other hand, prolonged steroid administration (up to 13 years) was unassociated with increasing dose requirements and side-effects were related primarily to the dose employed (56). Weaning from steroids entails considerable risk, since withdrawal has been associated with a significant incidence of status asthmaticus, which is occasionally fatal. These severe relapses develop suddenly, are considered to result from failure of the pituitary-adrenal axis during stress, and require the immediate institution of high dose corticosteriod treatment (56).

Asthmatic patients on long-term steroid therapy exhibit increased cortisol metabolism, a finding not noted in nonsteroid treated asthmatic patients (25). Intravenous doses of hydrocortisone failed to

achieve expected plasma cortisol levels, and this low response correlated well with an unfavorable clinical course. Correction required large dose steroid administration.

Asthmatics requiring unusually large continuous doses of steroids for clinical control (>15 mg. prednisone q.d.) are described as steroid-resistant (74). In a recent study, 6 steroid-resistant patients were compared to 19 unselected patients who required either no steroids or from 2.5–10 mg. of prednisone, or its equivalent, daily. There were no other significant distinguishing characteristics between these two groups. The steroid-resistant group revealed a diminished eosinopenic response to cortisol and an accelerated plasma cortisol clearance (74). The reason for the difference in the two groups is unknown.

Thus, many aspects of corticosteroid metabolism and pituitary-adrenal responses remain unclear, and are often variable or indeterminate in patients with bronchial asthma. Chronic steroid therapy, steroid resistance, and/or rapid cortisol turnover are factors that must be considered in any patient not responding to the standard and "customary" dosages of corticosteroids. We must emphasize that a favorable biologic effect is the desired end-point following the use of these agents, and some cases will require immediate and/or larger corticosteroid blood levels to be effective.

Specific Indications

With critically ill patients, or those not responding to usual therapeutic measures, the use of adrenal corticosteroids is recommended. Reduction in mucosal edema, inflammatory reaction, epithelial desquamation and mucous gland activity contribute to the dramatic improvement seen when steroids are administered. In addition, asthmatic children reveal an improved bronchodilator response to catecholamines following steroid therapy (42). In the critical status state, 100–200 mg. of intravenous hydrocortisone is given immediately, followed by 300–1000 mg. in 5% D/W or D/normal saline over the subsequent 24 hours. Such doses are arbitrary and the effective dose is considered to be the least necessary to obtain a therapeutic result. A working guide to the biologic effectiveness of steroids is eosinopenia, and an effective dose will produce total eosinophil counts of 100/mm.^{3} or less, with larger counts indicating increased steroid requirements. When improvement is noted, adrenal corticosteroids should be tapered. Adrenocorticotropic hormone (ACTH) has been employed to restimulate the adrenal cortex during the withdrawal of exogenous steroids. Specific recommendations for such withdrawal

Table 2. Approximate Steroid Equivalents

Cortisone	25	mg.
Hydrocortisone	20	mg.
Prednisone	5	mg.
Prednisolone	5	mg.
Methyl prednisolone	4	mg.
Triamcinolone	4	mg.
Dexamethasone	0.75	mg.

have been reviewed by Thorn (81). If prolonged adrenal corticosteroid therapy is necessary, the use of alternate day oral agents (Table 2) administered in the early morning may reduce undesirable side-effects, such as occult and overt peptic ulceration with gastrointestinal hemorrhage, intensification of diabetes mellitus, hypokalemia, progressive osteoporosis, psychosis, fluid retention, hypertension, risk of infections, spread of a tuberculous process and other steroid stigmata.

The use of supplemental potassium (liquid KCl), regulation of sodium intake, adequate protein diet, antacid therapy, monitoring of blood sugar and electrolytes, and bone films will aid in management, particularly with continuous steroid therapy.

There is some suspicion that corticosteroids may contribute to therapeutic failures in asthma (43). Although such impressions may be valid, it is generally accepted that corticosteroids do not impose this risk (69).

The importance of such an observation is to stress the need for care during steroid therapy and for careful monitoring of adrenal function during steroid withdrawal.

New Agents

Immunosuppressive Drugs. Antimetabolic agents such as 6-mercaptopurine, nitrogen mustard, and azathioprine have been employed in refractory asthma. Improvement has been noted in some cases, poor responses in others. Existing data indicates the need for further study (4).

Disodium Cromoglycate and Diethylcarbamazine. These agents selectively inhibit the release of chemical mediators following allergen-reagin interaction. Disodium cromoglycate (Intal) probably acts by inhibiting the release of histamine (66), but does not possess anti-inflammatory, or bronchodilator effects, nor does it competitively inhibit histamine directly (20). In general, disodium cromoglycate has

been given by inhalation along with isoproterenol (58), thus limiting interpretation. One study with disodium cromoglycate *alone* (44) showed similar benefit. Results have not been dramatic but encouraging, particularly in extrinsic asthma. Subjective improvement has occurred more often than improvement in pulmonary function tests.

Diethylcarbamazine is presumed to inhibit release of SRS-A. While preliminary studies are encouraging, further data is required (55).

ADEQUATE GAS EXCHANGE

In addition to the careful clinical evaluation of the patient, it is necessary to document whether gas exchange is adequate. This means that the patient is well-oxygenated and that carbon dioxide is properly eliminated. As was described earlier in the section on physiology, hypoxemia is commonly present in status asthmaticus. This develops because of ventilation/perfusion ($\dot{V}/\dot{Q}$) imbalance (regional alveolar hypoventilation) or generalized alveolar hypoventilation. Hypocapnia is common with regional $\dot{V}/\dot{Q}$ abnormalities, with hypercapnia developing when the processes become advanced. In generalized hypoventilation, often induced by narcotics or sedatives, hypercapnia predictably accompanies the hypoxemia (19). Cyanosis is an unreliable clinical sign until oxyhemoglobin saturation falls to less than 75%, at which point arterial oxygen tensions may be in the range of 40–50 mm. Hg. Thus, arterial blood analysis is necessary to confirm the presence of significant hypoxemia, and serial samples must be obtained to assess the effectiveness of O_2 therapy over the clinical course. We have found an indwelling arterial plastic catheter useful for this purpose. Estimation of carbon dioxide exchange in terms of alveolar ventilation ($\dot{V}_A$) based on minute volumes alone (tidal volume $\times$ respiratory rate) or based on nomograms devised for normals (Radford, Ohio) are unreliable because of variable metabolic demands, alterations in perfusion and increases in dead space ventilation (70).

While alveolar ventilation can be measured accurately by expired and alveolar CO_2 values:

$$\dot{V}_A = \frac{\dot{V}_{CO_2}\text{ (volume of } CO_2 \text{ expired/minute)}}{\text{alveolar } CO_2 \text{ tension}} \times 0.863,$$

this time-consuming procedure is generally unnecessary. This is so because the volume of carbon dioxide excreted per unit time is relatively constant, and where alveolar P_{CO_2} is assumed equal to arterial P_{CO_2} then $\dot{V}_A$ is inversely proportional to arterial carbon dioxide tension. The use of an end tidal sample or rebreathing apparatus can

provide data on alveolar, and thereby arterial CO_2 tensions. "Arterialized" venous blood, obtained by warming the hand or arm for 10 minutes, may be used for P_{CO_2} tensions as an index of ventilatory adequacy. In practice, the *direct* measurement of *arterial* blood for P_{CO_2} is the simplest method of assessing effective alveolar ventilation, and also provides pH values as well as oxygen tensions. In this manner, while the many variables influencing gas exchange can not be absolutely clarified, the end result of the ventilatory process is established via these blood gas measurements. In general, an arterial oxygen tension of 60 mm. Hg or less, alone or with a $PaCO_2$ of 60 mm. Hg or more, and a pH of 7.25–7.30 in the clinical context, should be considered conclusive of respiratory failure, unless previously established data indicates that such values were present during a chronic stable phase.

Oxygen Therapy

As noted previously, many, if not all patients in status asthmaticus exhibit arterial hypoxemia of varying degrees, with minor to significant desaturation of hemoglobin. Therefore, adequate oxygen tensions should be maintained in the patient with status asthmaticus. When arterial P_{O_2} falls to 60 mm. Hg, increases in respiratory work develop as a compensatory response. Hypoxemia contributes to cardiac decompensation directly by influencing myocardial metabolism, or indirectly by increasing pulmonary vascular resistance. In addition, hypoxic encephalopathy with mental impairment, metabolic effects upon oxygen-dependent enzyme systems, increases in airway resistance, and reduced respiratory responses to increased CO_2 tensions which may contribute to ventilatory failure, result from hypoxemia. Significant in management is the fact that irreversible changes in the brain follow 3–5 minutes of complete anoxia. The distinction between arterial hypoxemia of pulmonary origin and tissue hypoxia is emphasized. The tissues require adequate arterial O_2 tensions, a normal cardiac output and distribution of blood flow, as well as a normal hemoglobin content and oxyhemoglobin dissociation curve.

For ***routine*** use, the double-pronged, plastic nasal cannula may deliver oxygen concentrations up to 35% in the inspired air with flow rates of 6–8 liters/min. The Eliot open-face tent will provide concentrations of 35–50% at 6–10 liters/min. flow rates in a system that can provide for humidification as well. The Cambell Venturi mask is useful for providing controlled low concentrations of oxygen (viz., 28% at flow rates of 4 liters/min.), where respiratory depression may be

a problem. If higher concentrations (80–100%) are indicated, one may employ a comfortably fitting but well-sealed reservoir rubber face-mask with a nonrebreathing valve to eliminate CO_2. With the endotracheal tube or tracheostomy, any mechanical ventilator unit may be enriched by appropriate adjustment of oxygen input. A soft plastic tracheostomy box should be used in the tracheostomy patient not requiring ventilators, with the oxygen supply flowing through a water aerosol chamber warmed to body temperature (Puritan Unit). It is mandatory in oxygen therapy that the gas be adequately humidified at all times, to prevent drying of secretions or irritative bronchitis. Table 3 provides comparison of O_2 administration (46). By these methods acceptable oxygen tensions and saturation can be achieved in most patients. Arterial blood gas analysis should be monitored serially to establish the adequacy of such therapy, particularly where hypoxemia is advanced or ventilatory depression is suspect.

In the few patients with chronic hypercapnea, oxygen depression of the carotid-aortic chemoreceptor centers must be avoided. Such patients are usually severely hypoxic, however, and desperately in need of oxygen. Low concentrations of oxygen, employing (1) the plastic nasal cannula, face-mask, or nasal catheter, at 2–4 liters/min., or (2) Ventimasks which deliver oxygen at predictable concentrations may be initiated and the patient observed. If this is tolerated, and carbon dioxide tensions do not rise greater than 5–10 mm. Hg over a several hour period, then the O_2 concentration can be gradually raised until the measured arterial Po_2 is in the range of 70–80 mm. Hg. Since mechanical ventilation via endotracheal or tracheostomy

Table 3. Comparison of Oxygen Administration (46)

Method of administering O_2	*Approximate per cent O_2 at alveolar level*	*O_2 flow required (liters/min.)*	*CO_2 accumulation (at 8 liters O_2 flow)*
Rubber oronasal mask	40	4	yes
(BLB)	50	6	yes
(OEM)	55	8	yes
	60	10	yes
Plastic face mask	30	4	no
Nasal catheter	40	5	no
Face tent	45	8	no
Nasal cannula	50	10	no
O_2 tent	25	6	no
	35	10	no
	43	15	no

tube is frequently associated with morbidity and mortality, it is advisable to initially attempt controlled, low concentrations of oxygen in all patients. It should be re-emphasized that oxygen must be given in states of advanced hypoxia and if depression of respiration ensues, adequate ventilation and oxygen enrichment must be established by the physician.

Oxygen Toxicity

Oxygen is a fundamental therapeutic agent. Its potential toxicity must be recognized, however, and it should be administered cautiously as indicated. At the cellular level, high levels of oxygen may inactivate some sulfhydryl enzyme systems. The eye, central nervous system and lungs are particularly susceptible at greater than 2 atmospheres pressure. Central nervous system toxicity is manifest by grand mal seizures.

In addition to respiratory depression, oxygen can be directly toxic to the tracheobronchial mucosa and the pulmonary parenchyma. Although exact tolerance limits are not defined, pulmonary oxygen toxicity occurs when the partial pressure of the inspired O_2 exceeds approximately 300 mm. Hg. The problem is complex; toxicity is enhanced by increasing partial pressures and duration of exposure; its onset is delayed by the presence of arterial hypoxemia or the intermittent breathing of ambient air. The precise mechanism(s) producing toxicity are unknown (34).

A fall in the vital capacity is one of the earliest measurable parameters of pulmonary oxygen toxicity (18). With continued exposure, a chemical tracheobronchitis may develop, characterized by substernal tightness or chest pain; adequate humidification of the inspired gas often reduces this reaction (37). Retardation of tracheal mucus flow and ciliary action occurs when inspired oxygen is greater than 40% (48).

Parenchymal lesions, occurring with the prolonged use of mechanical ventilators, have been associated with increasing respiratory distress, deteriorating pulmonary function and progressive difficulty in weaning from the respirator. The earliest lesions are capillary congestion, interstitial edema, hyaline membrane formation, alveolar edema and hemorrhage, and atelectasis (64). Some studies show an impairment in surfactant production (31). Although the acute stage is reversible, a later irreversible stage, characterized by capillary proliferation and progressive fibrosis, can develop unless exposure to oxygen at high partial pressures is discontinued. An important clinical con-

sideration is that *refractory* hypoxemia may have been induced by these mechanisms of toxicity.

In patients with persistent and significant arterial hypoxemia, the hazards of oxygen toxicity must be weighed against the dangers of tissue hypoxia. Humidified O_2 must be provided with a minimum of hazardous exposure (time and concentration) commensurate with tissue metabolic demands. In general, arterial Po_2 levels should not exceed 100 mm. Hg during the treatment of status asthmaticus.

Helium-Oxygen Mixtures

The density of gas flowing in the tracheobronchial tree is one of the determinants of airway resistance. The rationale for helium therapy is based on its lower specific gravity which exhibits less flow resistance through compromised larger airways compared with air or oxygen (5). In the smaller airways however, helium's greater viscosity should require greater driving pressures to create streamline air flow and may be disadvantageous. For clinical use, mixtures of 70–75% helium, balanced with oxygen are administered with the closed metered expiratory positive pressure mask (O.E.M.), IPPB unit or directly into the endotracheal or tracheostomy tube.

Providing Adequate Alveolar Ventilation

If the only blood gas abnormality is a decrease in PaO_2, and the patient can tolerate oxygen administration (section on O_2 therapy) without respiratory depression, then this is all that is required. If respiratory depression occurs with oxygen, or if advanced hypercapnea and acidosis are present and not responding to supportive measures (antibiotics, bronchodilators, removal of secretions, etc.), then adequate alveolar ventilation must be provided by other means.

This may be accomplished in numerous ways: manual compression of a rebreathing bag in a closed-or open-circuit system; tank respirator; electromechanical devices that supply variable amplitudes and frequencies of respiration automatically responding to signals from servomechanisms (activated by the arterial blood gases and pH); volume-cycled (Emerson unit) or pressure-cycled (IPPB) ventilators. Commonly, long-term ventilation with pressure or volume-cycled respirators is employed in maintaining adequate alveolar ventilation. No attempts should be made to ventilate a patient continuously for long periods by face-mask or mouthpiece. The endotracheal tube or tracheostomy techniques must be employed as described previously.

Once the patient is placed on the ventilator, appropriate tidal vol-

umes and respiratory rates should be established. The effectiveness of the arbitrarily selected minute volume must be ascertained by arterial Po_2, Pco_2, and pH determinations. Additionally, it is imperative to prevent either alveolar hyperventilation or hypoventilation. Hyperventilation in patients with respiratory acidosis can create an alkalotic state leading to seizures or circulatory collapse.

Assisted and Controlled Ventilation

Pressure-cycled ventilators (IPPB) commonly available (Bennett, Bird) operate on a pressure limiting principle; inspiration terminates when the pressure within the airway reaches any pre-set value. The respirator is triggered in inspiration by a slight negative pressure from the patient; this is termed *assisted* ventilation. It may be administered periodically or continuously, depending upon the clinical needs and patient cooperation. Several models have adjustable inspiratory flow rate controls that allow for low flow rates, thereby improving gas distribution and alveolar ventilation. Their low cost, durability, ease of operation and independence of electrical supply are desirable features. The major problems are: (1) occasional inability to achieve high driving pressures; (2) unadaptable minute volumes when airway resistance and tissue compliance vary; and (3) inaccuracy in inspired O_2 concentration (a 40% O_2 setting often delivers 60–80% O_2).

Volume-cycled respirators (Emerson, Moersh, Bennett) deliver a predetermined volume at variable respiratory rates, and provide a relatively constant minute volume. Except for the Bennett volume respirator, these ventilators are fully automatic and provide only *controlled* ventilation. Desirable models incorporate an automatic sighing device for periodic hyperinflation. The duration of inspiration and expiration is adjustable in most respirators, and while basically operating at ambient air, O_2 is added as required.

Intermittent positive pressure breathing therapy, with bronchodilator aerosols, is effective for periodic *assisted* breathing for periods of 15–20 minutes, 4–6 times a day. The effect of hyperventilation with IPPB therapy is often transient, and sustained lowering or elevated carbon dioxide levels cannot be accomplished by brief periodic treatments. It has been documented, however, that assisted IPPB, "tailored" to the patient's respiratory pattern, can produce effective and prolonged improvements in blood gas parameters (11). Some improvement in the patient being treated with IPPB is due to the more effective delivery of bronchodilator aerosols, which reduce bronchoconstriction and augment expectoration.

In general, *assisted* mechanical ventilation is employed in the moderately ill and cooperative patient, whereas *controlled* mechanical cycle with IPPB is useful for the critically ill, poorly cooperative or obtunded individual. *Controlled* ventilation with IPPB is indicated for ventilatory support when *assisted* ventilation fails. The purpose of controlled ventilation is to reduce ineffective respiratory patterns and excessive thoracic work, and to substitute adequate artificial, mechanical ventilation under constant physiological monitoring. This thereby provides time for appropriate medical therapy to reverse the acute precipitating factors. With improvement, the patient's own ventilatory effort may then be capable of maintaining normal or clinically stable balance. Such an approach is often beneficial to the patient in status asthmaticus in respiratory failure not responding to conventional assisted ventilation.

Controlled Ventilation—Indications and Modalities

Since controlled cycle requires greater medical intervention, every attempt should be made to improve assisted ventilation, so that effective oxygenation and CO_2 elimination is feasible. In a recent evaluation from this laboratory, (87) the indications for controlled ventilation as the result of failure of assisted IPPB were observed to be:

1. Failure of patient to cooperate for assisted cycle, being stuperous or agitated and refusing to accept, trigger or phase with the respirator.
2. Failure to reduce or prevent a rise in $PaCO_2$ on *assisted* IPPB with progressive clinical deterioration.
3. Persistent tachypnea, physical exhaustion, obvious excessive work of breathing (which is often quite marked in status asthmaticus).
4. Oxygen depression of ventilation on assisted IPPB.

Thus, *synchronization* of the patient to the respirator with elimination of excessive respiratory work is the key to effective *controlled* ventilation. The following modalities may be employed to institute *controlled* ventilation:

A. *Machine cycle:* Many patients will accept the pressure respirator which is preset to cycle automatically at a rate of 10–15/minute. Appropriate pressure and flow settings are established for adequate minute ventilation. This approach seems most successful in the obtunded or comatose patient.
B. *Oxygen depression and machine cycle:* Since ventilation in certain patients with chronic hypercapnea is depressed by oxygen,

100% O_2 may be given (with this purpose in mind) by assisted IPPB, cannula or tracheostomy box until agitation is reduced. This must be followed immediately with machine cycle as described above (A). This modality is not effective in all patients, but can be valuable, since the use of depressant drugs is thus avoided.

C. *Drug suppression and machine cycle:* In agitated, confused, or uncooperative patients whose blood gases are deteriorating, and in whom ventilation and oxygenation are essential, depressant drugs may be administered to reduce agitation and thereby facilitate machine coordination. We have found the titration of small intravenous doses of morphine sulfate (2–10 mg), Meperidine (Demerol) 50 mg., or succinylcholine (40 mg. intravenously) valuable for this purpose; barbiturates or diazepam (Valium) have also been used. It is imperative that machine cycle as in (A) be instituted immediately, once relaxation occurs.

In our recent experience (Weiss) in 19 selected patients with 21 episodes of advanced acute ventilatory failure, many in status asth-

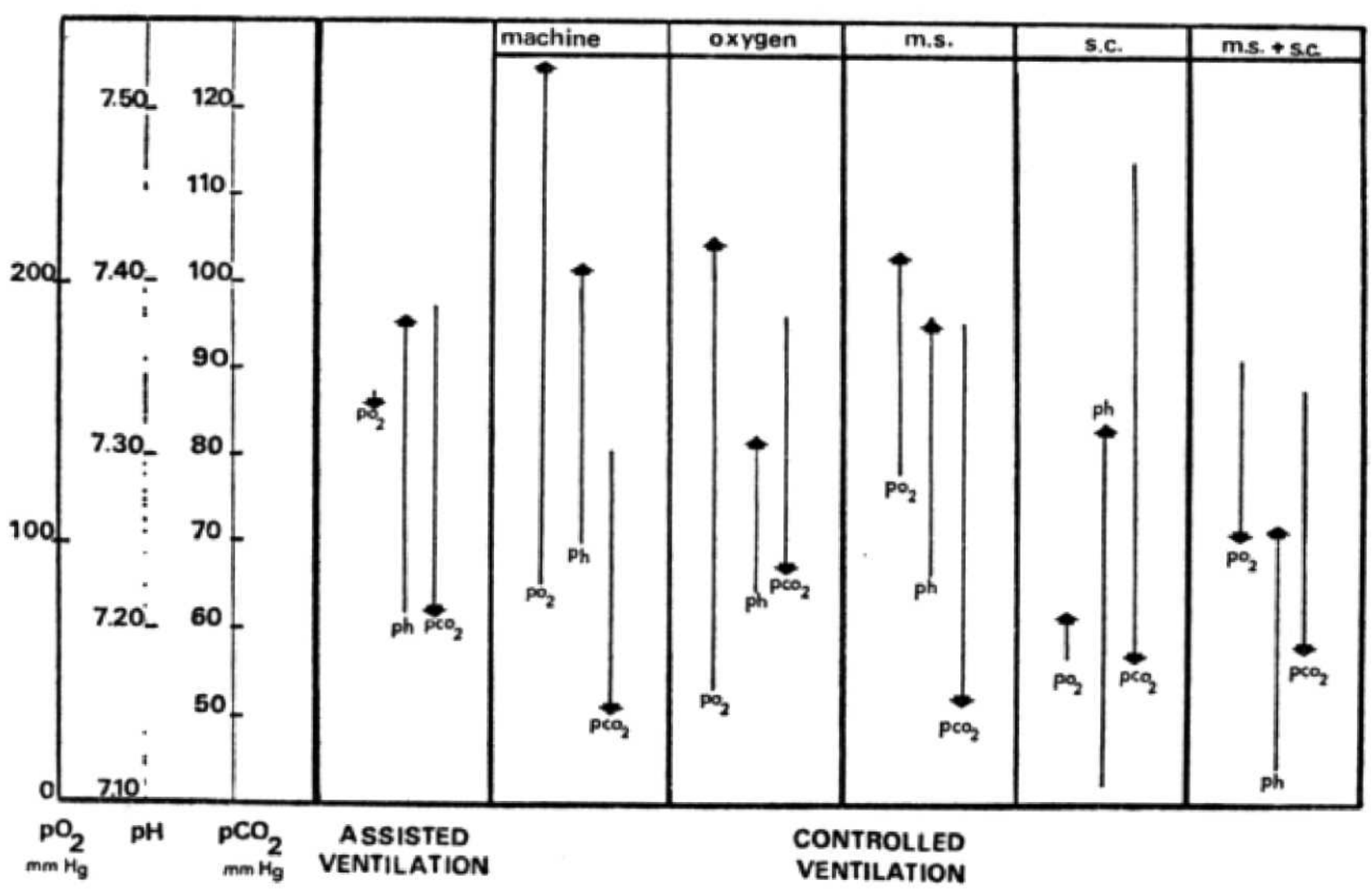

Fig. 2. **Changes in arterial blood PaO_2, $PaCO_2$, and pH (mean values) in patients with chronic obstructive lung disease and bronchial asthma in acute ventilatory failure managed with assisted versus controlled ventilation via a pressure-limited respirator. The direction of the arrows indicate the changes observed from the onset of supportive ventilation to the period of prolonged ventilation (hyperventilation phase). (MS = morphine sulfate, SC = succinylcholine). See text for details.**

maticus, only four trials could be managed by assisted IPPB. The remaining 17 episodes were treated by controlled ventilation in the following sequence employing either endotracheal intubation or tracheostomy: automatic machine cycle, oxygen depression, and drug suppression. Simple machine cycle was effective in 41 per cent of instances, particularly in the obtunded, comatose patient. With agitated, uncooperative patients, oxygen depression in 18 per cent and drug suppression (morphine and/or succinylcholine) in 41 per cent were effective in establishing control.

Proper synchronization with the respirator was a prerequisite for proper controlled ventilation. Thereafter, effective ventilation could be achieved. Mean falls of 30–57 mm. Hg in $PaCO_2$, improvement in pH of 0.09–0.21 units, and adequate PaO_2 tensions were observed in contrast to the lack of improvement during assisted ventilation (Fig. 2). Such improvements were associated with slow respiratory rates and increased tidal volumes, rather than gross increases in minute ventilation (Fig. 3). In all cases, $PaCO_2$ tensions were lowered

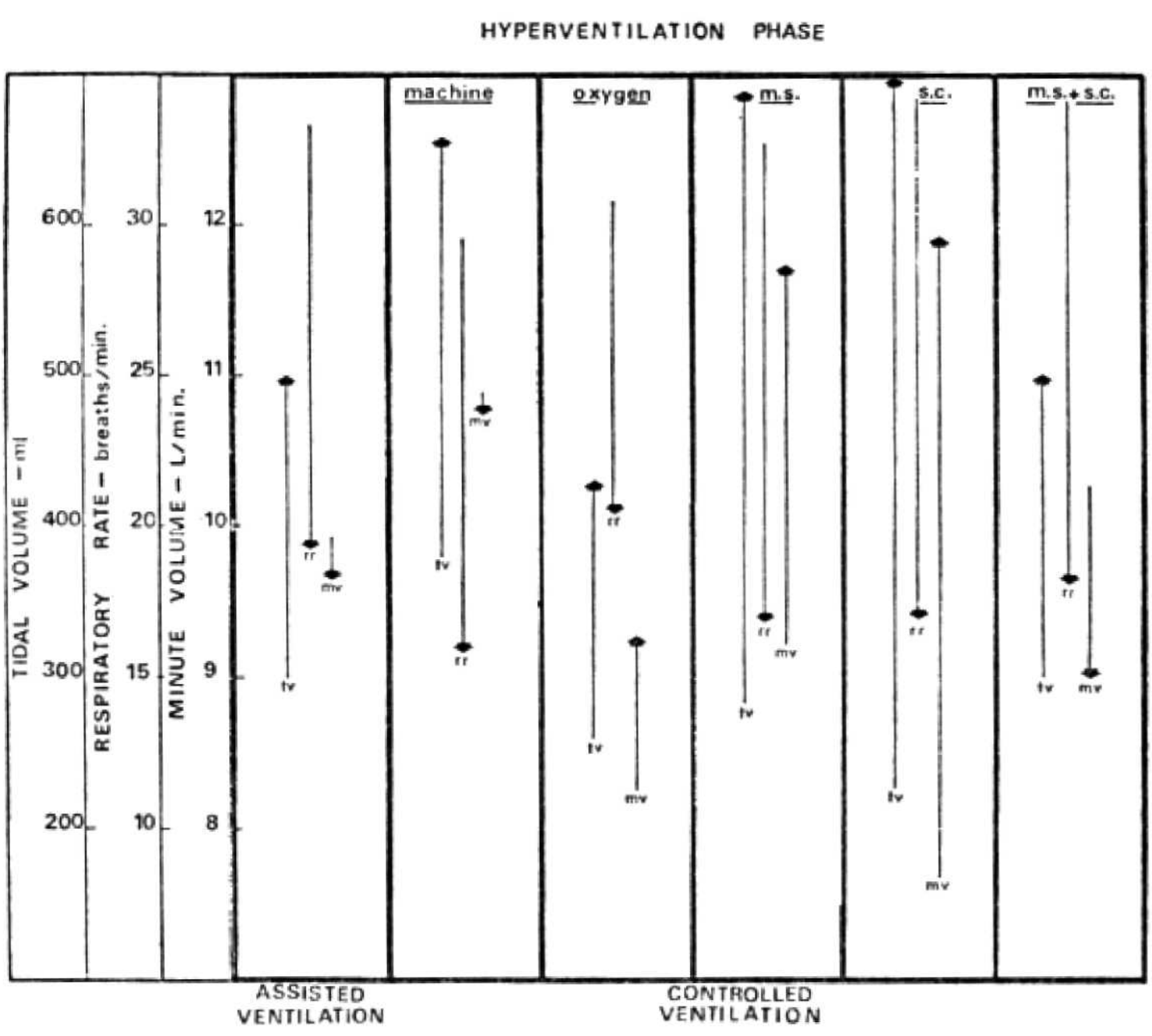

Fig. 3. **Tidal volume, respiratory rate and minute volume (mean data) in conjunction with arterial blood gas and pH changes of Figure 2. Important feature is that effective controlled ventilation is associated with increases in tidal volume and reduction in respiratory rate, rather than gross increases in minute ventilation, though this was observed in some cases.**

gradually to avoid detrimental alkalosis. Inspiratory to expiratory time periods were maintained at a ratio of 1:2 or 1:3 to permit effective gas distribution.

High respiratory pressures with moderate inspiratory and slow expiratory flow rates were employed with relative safety except for a reversible hypotension encountered with high inspiratory pressures (35–40 cm. H_2O). If cardiac output falls, consideration of the immediate ventilatory requirement must be balanced by this adverse effect. Transient falls in cardiac output may have to be accepted. Complications such as gastrointestinal bleeding, cardiac arrest, arrhythmias, pulmonary emboli, and shock (cardiogenic or bacteremic) had an adverse effect upon survival and might be a consequence of the procedure. The over-all mortality rate was 41 per cent. In the context of severely ill patients, one might anticipate greater mortality if adequate ventilation were not provided, and in fact, a *survival rate* of 59 per cent was encountered in this particular series of patients in far advanced ventilatory failure managed by the modality of controlled ventilation (87).

Drug-controlled Respiration

An example of drug control of respiration is given in the following case report:

Case 2

A 35-year-old white man was admitted to the Boston City Hospital with a history of chronic asthmatic bronchitis and a recent increase in productive cough, wheeze, and dyspnea. The deterioration was due to bronchopulmonary infection and related airways obstruction. Initial therapy consisted of intravenous fluids, aminophylline, iodides, penicillin (on basis of sputum Gram stain), methylprednisolone sodium succinate (Solu-Medrol), and IPPB via assisted (mask) ventilation with nebulized isoproterenol and 40% oxygen. Blood gases on admission are noted in Table 4. Early the next day, progressive bronchospasm and retention of secretions were associated with severe agitation, confusion and poor cooperation for IPPB. Tracheostomy was performed and assisted ventilation with the Bird Mark VII Respirator was begun. Blood gases under these conditions were $PaCO_2$ of 87 mm. Hg, pH 7.15 and PaO_2 173 mm. Hg (Table 4).

Consultation with the Lung Station (Tufts) was requested because of obvious clinical deterioration and blood-gas evidence of inadequate ventilatory support by assisted ventilation. The latter was limited because of severe motor agitation and extreme uncooperation, even with high pressures and moderate flow rates on the IPPB. Ten milligrams of morphine sulfate was then given intravenously with only moderate respiratory depression and persistence of motor agitation. Because of this, 40 mg. of succinylcholine

Table 4. Example of Drug Control of Respiration

	Admission—assisted IPPB	*Next day—assisted (on tracheostomy)*		*Controlled ventilation (hours after No. 2)*				
		No. 1	No. 2*	1.45	2.50	4.00	5.50	Next day
$PaCO_2$ (mm. Hg)	41	57	87	71	71	58	46	46
pH	7.40	7.31	7.15	7.18	7.19	7.27	7.26	7.46
PaO_2 (mm. Hg)	56	38	173	250	168	245	101	
Tidal volume (ml.)	220		350	500	550	450	400	400
Respiratory rate (per min.)	30		34	18	18	16	16	14

* One hour later than No. 1 measurement.

was administered intravenously, resulting in complete apnea. Controlled machine ventilation with preset tidal volume, pressure, and rate was immediately instituted. The favorable blood-gas results over the next few hours are presented in Table 4. With continued careful management of bronchospasm and secretions, clinical improvement was noted. When semi-awake, 6 hours later, the patient was able to cooperate fully on an assisted ventilation schedule and complete recovery was noted thereafter.

Where possible it is advisable to provide brief rest periods during assisted IPPB therapy. Repeated overdistension of the lungs may depress the Herring-Breuer reflex, reduce the effective ventilatory drive, and impede the weaning process. In addition, periodic (several breaths/hour) overinflation (sighing) is necessary to prevent significant atelectasis from developing. With *continuous* assisted or controlled IPPB therapy, tidal volume should be measured periodically through the exhalation port, with a Wright respirometer or a similar meter, so that adequate minute ventilation is provided. An arterial blood sample for P_{CO_2}, P_{O_2}, and pH should be obtained periodically, however, to correlate the above and establish the effectiveness of artificial ventilatory support. For example, a patient with an initial tidal volume of 500 ml. at 15 cm. H_2O pressure on the IPPB unit, might, as secretions collect and pulmonary compliance falls (stiffer lung), develop a tidal volume of 200 ml., and yet the pressure setting on the IPPB unit would still remain at 15 cm. of water. Hence, the gas exchange would be significantly impaired. The IPPB pressure setting should be the minimum that will provide adequate ventilation. This may require frequent adjustment of flow and rate dials to achieve effective minute volumes. Leaks can develop around the tracheostomy tube and machine autocompensation will not follow (unless fitted with flow accelerative adaptors); hence, inadequate tidal volumes

will be delivered. This requires immediate attention. Assiduous nursing care and careful monitoring of equipment throughout the period of controlled cycle is mandatory.

Finally, as described previously, patients on long-term assisted or continuous IPPB should not receive high concentrations of oxygen because of the dangers of oxygen toxicity. In these patients, inspired concentrations of 30–40% resulting in arterial tensions of 70–80 mm. will usually suffice.

ACID-BASE DISORDERS

The level of arterial CO_2 tension is fixed by the rate of its production and alveolar clearance:

$$PaCO_2 = \frac{\dot{V}co_2 \text{ (tissue production)}}{\dot{V}_A \text{ (alveolar ventilation)}} \times 0.863.$$

During respiratory failure, reduction in effective V_A leads to a rise in CO_2 which rapidly shifts into all cell compartments; this effectively becomes hydrogen ion activity $[H^+]$; i.e., respiratory acidosis:

$$CO_2 + H_2O \underset{\text{carbonic anhydrase}}{\overset{\longrightarrow}{\longleftarrow}} H_2CO_3 \rightleftarrows [H^+] + HCO_3^-$$

The relationships are described by the Henderson-Hasselbalch equation:

$$pH_a = pK_a' + \log \frac{[HCO_3^-]_a}{[H_2CO_3]_a}$$

where $H_2CO_3 = 0.03 \times PaCO_2$: if $PaCO_2 = 40$ mm. Hg, then $H_2CO_3 = 1.2$ nM./liter. Clearly the final pH_a is dependent upon the ratio of bicarbonate ion and carbonic acid. Maintaining the relative ratio of $\frac{[HCO_3^-]}{[H_2CO_3]}$ at approximately 20/1 is the role of body buffers.

An increase in $[H^+]$ from hypercapnia generates extracellular bicarbonate from: (1) blood buffers, (2) tissue buffers, and (3) renal mechanisms. This rise in plasma bicarbonate concentration has been divided temporally into an *acute* and *chronic* phase. The *acute* buffering is via blood and tissues and may be viewed as follows:

$$H_2CO_3 + ROH \dashrightarrow R^+HCO_3^- + H_2O$$

In Figure 4, the buffering response to acute hypercapnia in normal man is presented. The generated $[HCO_3^-]$ is a function of increasing $PaCO_2$, but is inadequate to effectively buffer *acute* $[H^+]$ increments.

Additionally, about this acute "whole body" CO_2 titration curve 95 per cent confidence limits have been established for definition of appropriate bicarbonate and pH responses to acute hypercapnia, and may thereby be employed to distinguish uncomplicated respiratory acidosis from complicating metabolic acid-base disorders. (14)

Chronic Phase

In the *chronic phase*, under the stimulus of chronic retention of carbon dioxide, renal excretion of $[H^+]$ and generation of $[HCO_3^-]$ provides a further rise in plasma $[HCO_3^-]$, and a greater defense of pH than by tissue buffers alone (Fig. 4). Similar confidence bands for chronic stable hypercapnia permit definition of coexisting metabolic disorders for patients with chronic obstructive lung disease under stable state conditions of CO_2 retention (22,75,84).

In patients with chronic airways disease and chronic hypercapnia who experience acute respiratory failure and thus superimposed acute

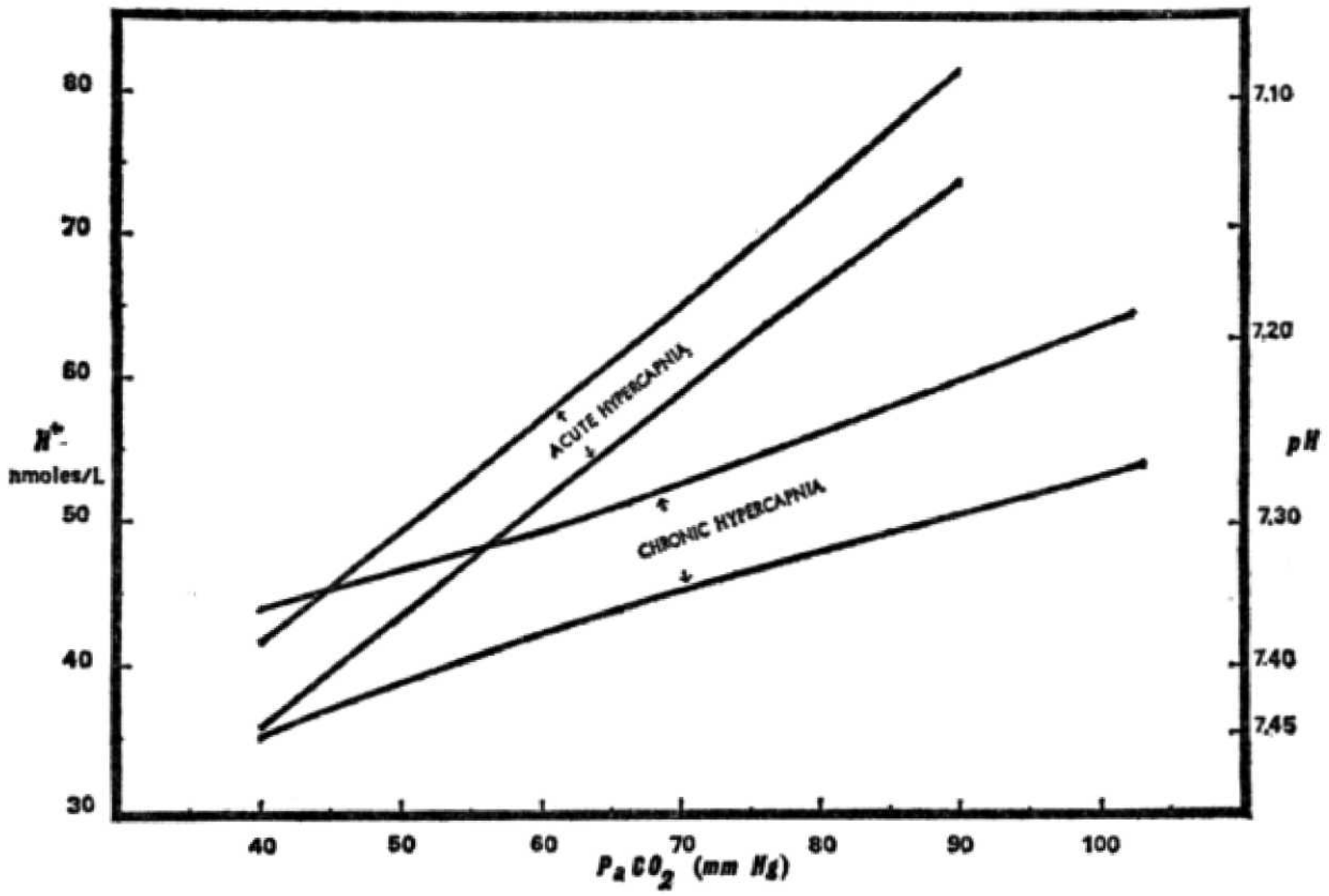

Fig. 4. **Confidence bands for acute hypercapnia in normal man and chronic stable hypercapnia in chronic obstructive lung disease based on $PaCO_2$–hydrogen ion relationships (14,84). In uncomplicated acute or chronic hypercapnia, there is a 95 per cent probability that values of Pco_2–pH will fall within the band. Any values lying above appropriate band indicate complicating metabolic acidosis; values below appropriate band indicate complicating metabolic alkalosis. See text.**

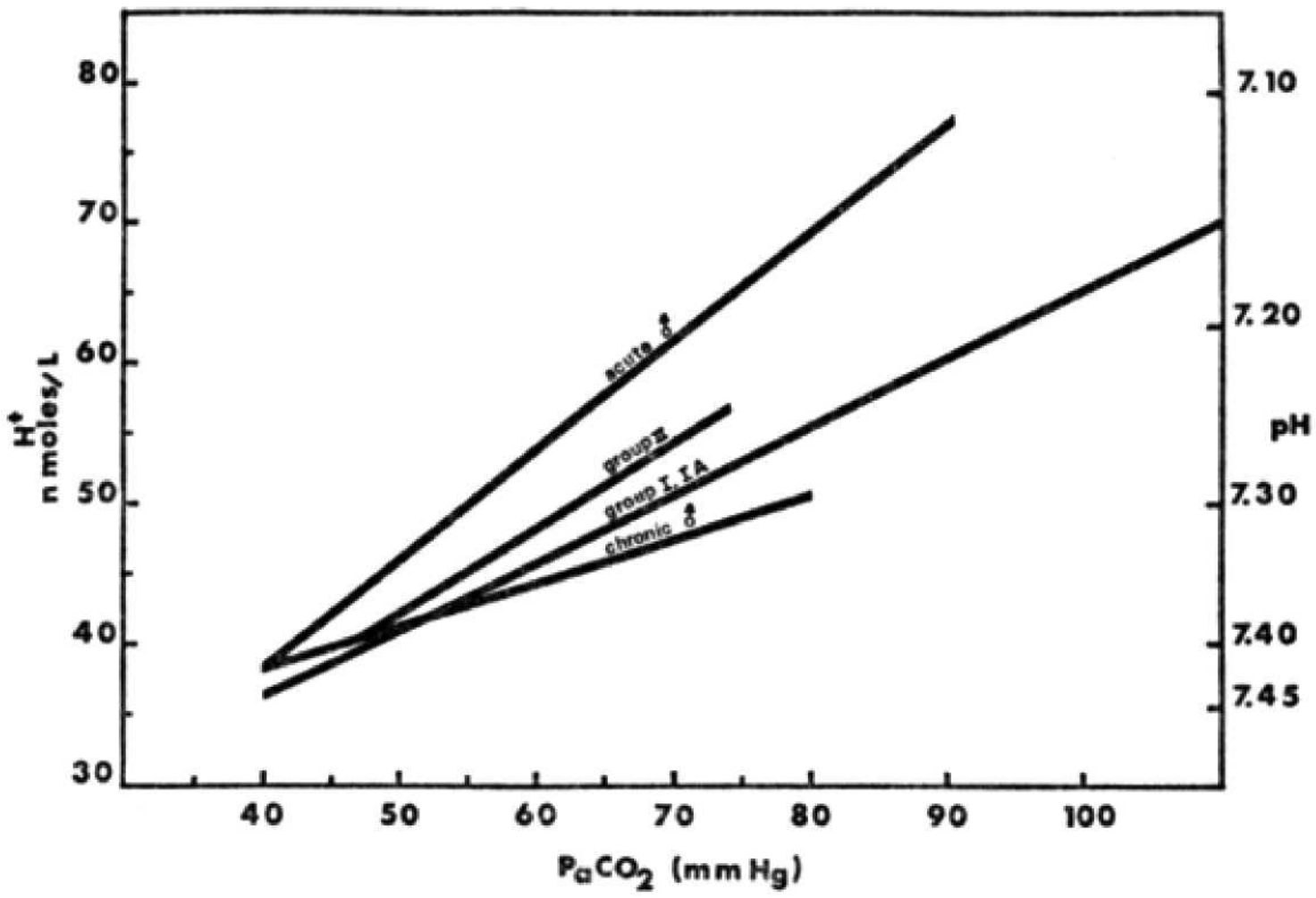

Fig. 5. **Relationship between hydrogen ion concentration and $PaCO_2$ during acute hypercapnia in patients with chronic obstructive lung disease. Acute carbon dioxide titration curve in man is based on data of Brackett, Cohen, and Schwartz (14); chronic curve is that reported by van Ypersele de Strihour, Brasseur, and DeConnick (84); groups I and IA represent response to acute hypercapnia occuring in chronic obstructive lung disease patients in whom chronic stable Pco_2–pH relationships are not defined (group I) and those in whom the chronic stable Pco_2–pH were known (IA). Changes in pH to acute alveolar hypoventilation induced by 100% oxygen for 30 minutes in patients with chronic hypercapnia are shown by group II. Limits of reported observations are indicated by lengths of the regression lines. Data suggests that uncomplicated acute hypercapnia *superimposed* upon chronic hypercapnia in patients with chronic obstructive airways disease limits use of prediction "bands" established for stable state chronic hypercapnia or steady state acute hypercapnia in man. See text for details.**

acidosis, steady state conditions are not present and variable in vivo carbon dioxide $[H^+] + [HCO_3^-]$ responses result. The defense of the extracellular pH is then primarily related *temporally* to renal buffering mechanisms (86) (Fig. 5). The above-cited prediction relationships for steady state acute hypercapnia in normal man or stable chronic hypercapnia are then not valid for the interpretation of coexisting metabolic acidosis or alkalosis. This concept is important clinically where pure respiratory acidosis must be distinguished from the multiple extrapulmonary metabolic disturbances patients may present with. In this circumstance, interpretation of the acid-base disorder will require clinical reconstruction and judgment.

tion may ensue, the effects of the drugs must be assessed clinically, and *confirmed* with arterial blood gas analysis whenever they are employed. Additionally, any sedative which suppresses a "useful" cough and dries secretion must be avoided.

Ether by rectum (57) or general anesthesia (10) (cyclopropane) are considered in those patients who are continuing problems. This approach has been reported to provide relief in unyielding attacks by mechanisms not entirely clear, other than general relaxation. Concomitant bronchoscopic lavage may be performed at the time of anesthetic administration. Adequate ventilation and oxygenation must be maintained throughout. Halothane is considered the preferred anesthetic agent (93), though it may occasionally precipitate ventricular arrhythmias (possibly potentiated by prior use of epinephrine) and must be employed with great caution, particularly in hypoxemic patients. Halothane is generally nonirritating to the airways, capable of relaxing bronchial smooth muscles and affording relief during status asthmaticus. Ether is administered rectally in doses of 60–90 ml. dissolved in equal amounts of olive oil. This may be repeated after several hours.

THERAPY OF INFECTIONS

Viral and bacterial infections of the respiratory tract often precipitate, aggravate or perpetuate status asthmaticus. When bacterial infections are documented or implicated, it is imperative to treat promptly and vigorously, even though the exact organism is not immediately definable or appropriate diagnostic material is not available. A gram stain of the sputum (tracheobronchial washings or percutaneous transtracheal aspirate) will aid in defining the flora. The initial antibiotic choice is modified once culture and sensitivity data are provided. Periodic follow-up evaluation of the sputum is necessary to detect changes in bacterial flora having clinical significance. It is important that this initial antibiotic selection be based upon an adequate fresh sputum specimen. This can be ascertained by the crystal violet method previously described. The presence of alveolar macrophages (histiocytes) and bronchial epithelial cells with a minimum of oral squamous cells suggest a representative bronchopulmonary specimen. This same aliquot can be used for the gram stain analysis, since crystal violet is the major constituent of the gentian violet of the gram procedure. The presence of tuberculosis or fungal lesions as precipitating or perpetuating factors must be kept in mind. Each patient should be screened and observed for sensitivity to the selected antibiotic, since

Other Respiratory and Metabolic Disturbances

Other acid-base disturbances may develop in status asthmaticus and the physician must be aware of these complications.

A. Respiratory alkalosis: endogenous or exogenous hyperventilation by mechanical respirator, and uncovering of increased compensatory HCO_3^- levels.

The consequences of this acute alkalosis include central nervous system findings, seizures, coma, hypotension, apnea and death. Additionally, the O_2 dissociation curve is shifted to the left and release of O_2 to tissues is impaired.

B. Metabolic alkalosis: from chloride or potassium depletion; commonly dietary, diuretics, steroids, or chloruresis during development of respiratory acidosis.
C. Metabolic acidosis: excess $[H^+]$ formation, excess intake, reduced excretion.

The treatment of respiratory acidosis is *primarily* directed to controlling all causes of ventilatory failure. Improvement in net alveolar ventilation and reduction in $PaCO_2$ is the logical and acceptable method of dealing with excess hydrogen ion activity. When severe acidosis exists during status asthmaticus (8,87) (either pure respiratory or mixed with metabolic acidosis) and while ventilatory support is being established, exogenous buffers or alkali may be administered. When the pH drops to 7.20 or less, the acidemia may be life-threatening, and the infusion of bicarbonate is indicated. With serial pH measurements to clarify the end points, intravenous infusion of 80–120 mg. of $NaHCO_3$ will temper the pH and permit time for all other supportive measures to become effective. Sodium-free THAM (Trishydroxy methyl aminomethane) can be employed where Na^+ restriction is mandatory; it, however, may depress respiration causing further hypoxia and acidosis in some patients; we prefer $NaHCO_3$.

Finally, since chloride depletion is common during the stage of acidosis, the recovery phase is occasionally associated with a persistent hypochloremic and/or hypokalemic alkalosis; this requires proper electrolyte replacement.

An example of the application of prediction acid-base nomograms can be illustrated by reference to the patient discussed in Table 4.

The arterial pH (nM) and P_{CO_2} data of this case of asthmatic bronchitis in ventilatory failure are shown in Figure 6. Note that in the initial decompensation phase, the $PaCO_2$ and pH_a relationships

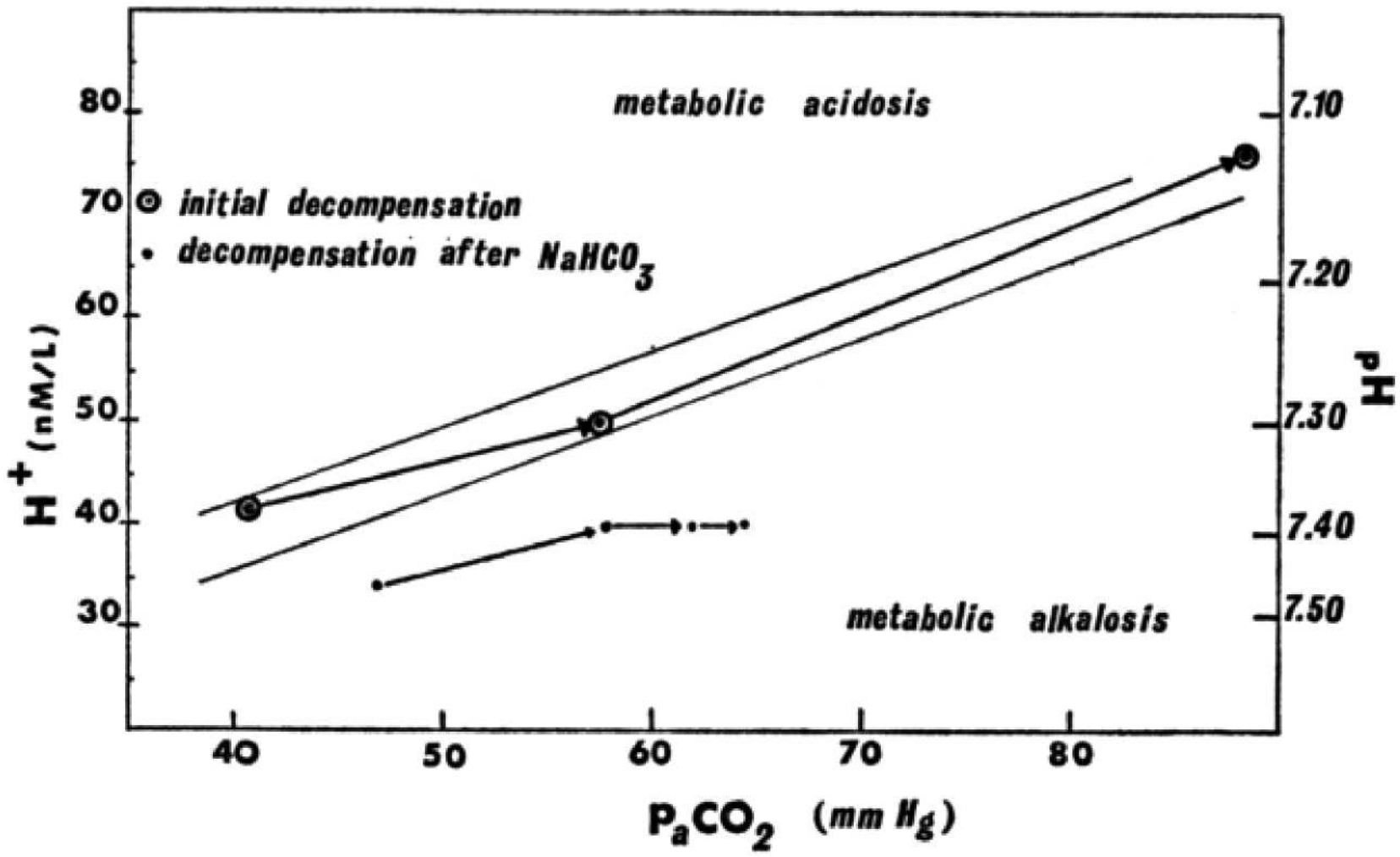

Fig. 6. **Application of confidence band. Nomogram defining acute predicted responses of [H⁺] to increments in $PaCO_2$. See text for illustrative case.**

fall within the predicted band for acute hypercapnea established by Schwartz. This would indicate that the developing acidosis was entirely respiratory in basis. Several days later the patient was given sodium bicarbonate; a subsequent milder ventilatory decompensation ensued. The relationships are now shifted toward the alkalotic side of the acute band indicating, as was known, the presence of a complicating metabolic alkalosis. Thus, in practice, complicating metabolic factors can be evaluated by the use of such nomograms.

Sedation

Moderate sedation has been considered an aspect of treatment, since fear, anxiety and agitation may influence over-all management. The use of barbiturates, tranquilizers, and even opiates may be beneficial, though the degree to which such agents depress respiration is often not fully realized, particularly in the patient with ventilatory insufficiency. Many patients with an acidemia in the range of pH 7.20 will be poorly responsive or comatose; i.e., self-narcotized. It must further be emphasized that the quiet patient is not always an improved patient. Auscultation may show much less wheezing, but the concomitant decrease in breath sounds may indicate poor ventilation and significant lodging of secretions. The absence of obvious respiratory distress *under sedation* may be *misinterpreted* by the physician as the patient actually deteriorates. (See section on crossover.) Since opiates and sedatives have been incriminated as causes of death in asthma, and since respiratory depression with alveolar hypoventila-

tion may ensue, the effects of the drugs must be assessed clinically, and *confirmed* with arterial blood gas analysis whenever they are employed. Additionally, any sedative which suppresses a "useful" cough and dries secretion must be avoided.

Ether by rectum (57) or general anesthesia (10) (cyclopropane) are considered in those patients who are continuing problems. This approach has been reported to provide relief in unyielding attacks by mechanisms not entirely clear, other than general relaxation. Concomitant bronchoscopic lavage may be performed at the time of anesthetic administration. Adequate ventilation and oxygenation must be maintained throughout. Halothane is considered the preferred anesthetic agent (93), though it may occasionally precipitate ventricular arrhythmias (possibly potentiated by prior use of epinephrine) and must be employed with great caution, particularly in hypoxemic patients. Halothane is generally nonirritating to the airways, capable of relaxing bronchial smooth muscles and affording relief during status asthmaticus. Ether is administered rectally in doses of 60–90 ml. dissolved in equal amounts of olive oil. This may be repeated after several hours.

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drug hypersensitivity may be responsible for persistent or intensifying bronchospasm. The possibility that an extrapulmonary infection is contributing to the asthmatic state, should always prompt a search for an associated ear or paranasal sinus infection.

When a successful regimen has been instituted, it should be continued for a minimum of 7 days (we prefer 10–14 days or longer) since rebound of the infection may occur, particularly with *H. influenzae* or other gram-negative bacilli. The following simplified Table 5 can serve as a guide to antibiotic selection for some of the more commonly encountered bacteria; the order of listing does not imply an order of therapeutic choice.

When it appears that the antibiotic is not effective, one should consider that the bacterial flora has changed, that resistant organisms

Table 5. Antibiotic Selection in Status Asthmaticus

Responsible organism		*Choice of antibiotic*	
Culture	*Gram stain*	*Ambulatory patient*	*Hospitalized patient*
Diplococcus pneumoniae	Encapsulated gram-positive diplococci	Penicillin (2–3 million U/day) Erythromycin (2 Gm. q.d.) Tetracycline (2–4 Gm./day)	Penicillin G (parenteral) Erythromycin Tetracycline
Hemophilus influenzae	Small, pleomorphic, gram-negative cocco-bacillary forms	Tetracycline, ampicillin (2–4 Gm./day), chloramphenicol (2–4 Gm./day)*	Penicillin (20–40 × 10^6 units IV/day) plus streptomycin (1 Gm./day), or chloramphenicol, or tetracycline
Mixed types, no specific pathogen predominant	Same	Tetracycline Ampicillin Chloramphenicol	Same, plus penicillin parenterally (consider high dose)
When significant infection is present but no material is available for examination		As above	Penicillin (20–40 × 10^6 units IV/day) plus streptomycin, or kanamycin (1 Gm./day), or chloramphenicol
Staphylococcus, Streptococcus, Neisseria, Proteus, Pseudomonas, K.A. group		Use standard criteria including sensitivity studies	

* 4 Gm. for 1–2 days, then 2 Gm. thereafter. Careful observation mandatory.

have developed, that the responsible organism was not initially identified because the infected area was not draining, that lung atelectasis, abscess or empyema have developed, or that the location of the infection is other than the respiratory tract. As with all other aspects of the management of the seriously ill patient with asthma, infections must be continuously evaluated.

ANTIHISTAMINES

The antihistamines, with chemical structures similar to histamine, act as competitive antagonists at receptor sites. Theoretically, the antihistamines should block the changes which are attributed to histamine: i.e. bronchial smooth muscle contraction and congestion of the mucous membranes of the bronchial tree secondary to vasodilatation and increased vascular permeability. Experimentally, such effects are slight (15) and in practice, these drugs have not uniformly fulfilled their theoretical role. Their effectiveness in some individuals with asthma, however, may be significant. Thus, they should be given a therapeutic trial, particularly during "seasonal" attacks of those with defined allergy. We employ the maximally tolerable dose before discarding treatment with any one of the antihistamines, and a number of these agents should be employed before they are considered ineffective. A drying atropine-like effect is beneficial to a few patients by decreasing sputum volume, but in many others it produces dry, tenacious sputum which is difficult to raise. All antihistamines possess some anticholinergic action, but this varies from drug to drug and one should select the antihistamine-anticholinergic balance by the best response of the patient. A beneficial side-effect is the sedative action of these agents.

Table 6 notes a few of the commonly employed antihistamines with usual dosage schedules for adults:

Table 6. Commonly Employed Antihistamines

Antihistamine	*Unit dose*	*Schedule*
Diphenhydramine hydrochloride (Benadryl)	25–100 mg.	q.i.d.
Chlorpheniramine maleate (Chlor-Trimeton, Teldrin)	4–8 mg.	q.i.d.
Tripelennamine (Pyribenzamine)	25–100 mg.	q.i.d.
Brompheniramine maleate (Dimetane)	2–8 mg.	q.i.d.
Promethazine hydrochloride (Phenergan)	6.25–25 mg.	q.i.d.
Dimethindene maleate (Forhistal)	1–2 mg.	q.i.d.

As a general rule, full medical therapy and paramedical care is necessary for recovery and survival. Cardiac failure, arrhythmias, other infectious foci, fluid and electrolyte imbalance, etc., must be controlled in the environment of constant nursing care and preferentially in an intensive care respiratory unit, where serial and essential physiological monitoring is possible.

SUMMARY

Status asthmaticus is a potentially fatal medical emergency and requires an intensive multidisciplinary approach by the physician and his staff. The patient is best managed in the intensive care respiratory unit, in view of the need for physiological monitoring and the hazards of respiratory and cardiac arrest. Evaluation of background disease, precipitating factors, and extent of physiological impairment is necessary for appropriate management. The importance of establishing and maintaining a patent airway, removing secretions, providing adequate oxygenation and alveolar ventilation and use of steroids, bronchodilators, antibiotics, appropriate sedation, etc. has been stressed. Didactic, defined approaches are difficult to establish and each physician, aware of the complexity of the disease and therapeutic modalities, must adopt his own approach to the patient. In view of the increasing therapeutic armamentarium available, the iatrogenic influences of the physician should be carefully kept in mind at all times. While basic measures should be observed, each patient will require a personalized approach to minimize complications and achieve survival.

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Bronchial Asthma: Current Concepts in Pathophysiology and Management of Status Asthmaticus

EARLE B. WEISS, M.D., L. JACK FALING, M.D., STUART M. BROOKS, M.D., SHELDON MINTZ, M.D., F.R.C.P. (C), SANFORD CHODOSH, M.D., and MAURICE S. SEGAL, M.D.

From the Department of Medicine, Tufts University School of Medicine, and the Lung Station (Tufts), Boston City Hospital, Boston, Massachusetts