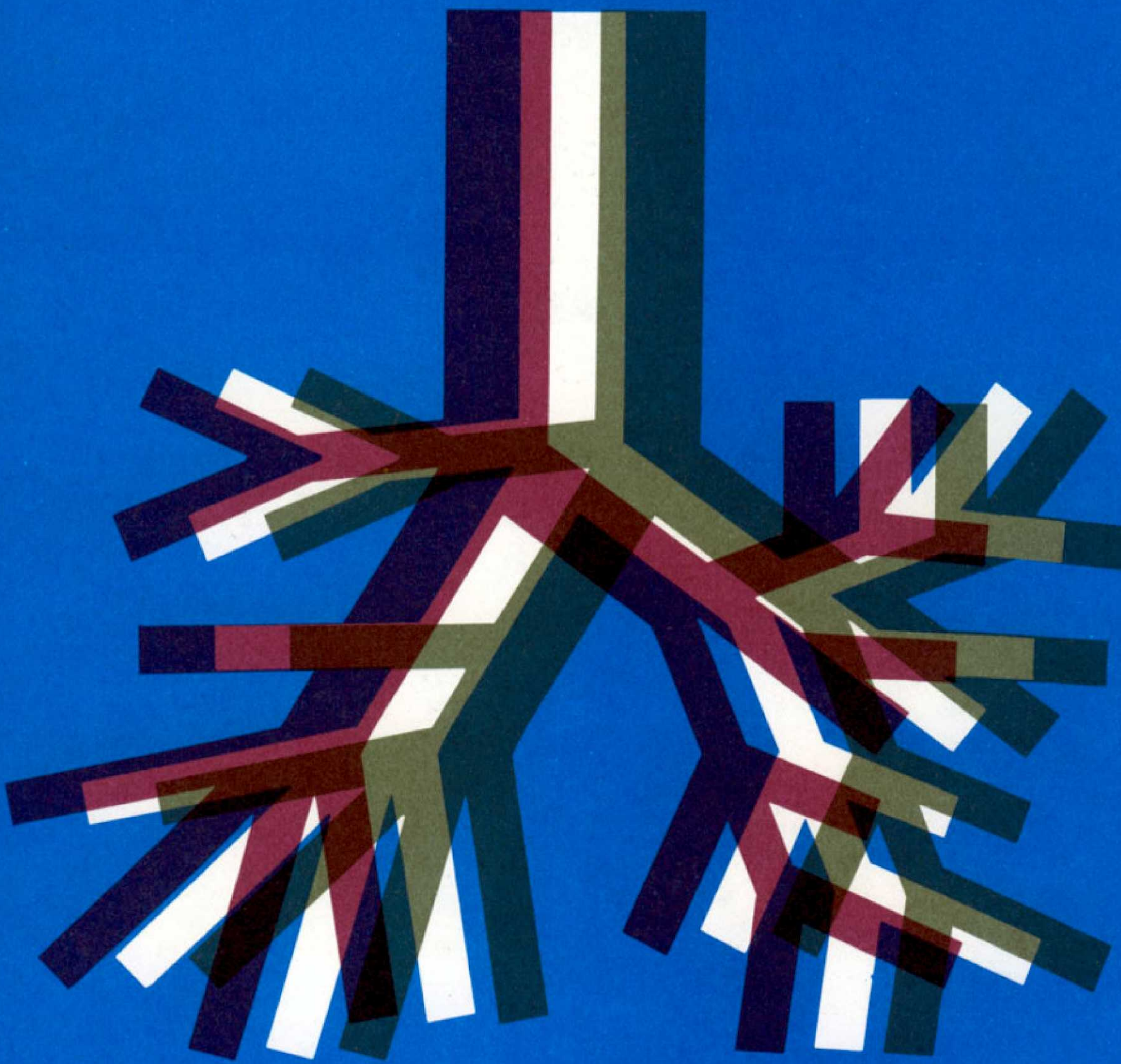
Bronchial Asthma

Mechanisms and Therapeutics

Edited by Earle B. Weiss, M.D.
and Maurice S. Segal, M.D.



60 Status Asthmaticus

Earle B. Weiss

There are two simple generalizations concerning status asthmaticus: first, this condition should be prevented; second, if it occurs, it can be treated.

Status asthmaticus is a medical emergency whose life-threatening stress accounts for most deaths from asthma. While the major clinical features are dyspnea and wheeze in association with severe gas-exchange defects, it is defined as a severe exacerbation of asthma *initially* unresponsive to usual therapy as epinephrine or theophylline. Widespread narrowing of the airways by spasm of the bronchial muscles, tenacious intraluminal secretions, and inflammatory congestion of the bronchial wall appear to be the major causes. Time factors and exact drugs or doses will not be rigidly specified, thus providing for some variability in patient response. Before it is certain that status asthmaticus is present, the physician must determine that the apparent refractoriness is not due to other causes such as acute bronchitis or bronchiolitis, croup, or pulmonary embolization (see Chapter 46). *However, when an attack is resistant to several standard doses of rapidly active epinephrine within a reasonable interval of 30 to 60 minutes (occasionally within several hours), generally by lack of improvement in clinical findings, status asthmaticus exists.* This approach is often supported with theophylline, oxygen, and fluids.

In extrinsic, atopic children, failure of response to three doses of aqueous epinephrine (1:1,000) of 0.01 ml/kg body weight subcutaneously, at 20-minute intervals, is a reasonable index [15]. Adult criteria may be more elusive, but a dose of aqueous epinephrine of 0.3 to 0.5 ml is given initially, followed by 0.3 ml subcutaneously, at 30 to 60 minute intervals, not to exceed 1.5 ml (average 70 kg values) total in adults. Aerosol isoproterenol appears less useful at this point of the acute paroxysm. Concurrently, aminophylline can be administered IV in a dose of 5.6 mg/kg *slowly* over 15 to 20 minutes. For elderly or high risk patients with hypertensive-cardiovascular disease, aminophylline alone is preferred to epinephrine. Oral or rectal routes of administration are not indicated. Although parenteral corticosteroids can be instituted, their peak action is delayed for several hours, and their use as a criterion is thereby limited; initiation of antimicrobials, hydration, and expectorants is ancillary. It is desirable to administer oxygen throughout this initial evaluation process. At this time, the details of recent drug use by the patient will aid in the decision processes and also prevent unneeded cumulative drug toxicity.

Additional supportive criteria for an inadequate response may include (1) persistent (12 to 24 hours) or recurrent (within a few days) symptoms or episodes despite proper therapy; (2) critically low spirometric parameters, for example, forced vital capacity (FVC) <1.0 liter, forced 1-second expiratory volume ($FEV_{1.0\%}$) <50%, or actual values of 0.5 to 0.6 liter, peak expiratory flow rate (PEFR) <60 to 100 liters/minute in the adult; and not improving; (3) refractory or critical hypoxemia (on room air, Pa_{O_2} 40–60 torr [mm Hg]); (4) Pa_{CO_2} 38 to 42 torr and rising, or absolutely >45 to 50 torr in an acute attack; (5) acute respiratory acidosis (even mild); (6) severe respiratory work, fatigue, or exhaustion in this context. Borderline patients, including those receiving corticosteroids or with a history of recurrent attacks, should be ad-

mitted in any instance of uncertainty. Once the diagnosis is made, three corollaries arise:

1. Bronchial asthma is now life threatening.
2. Status asthmaticus is a medical emergency: all efforts are to be alerted and intensified.
3. Mandatory hospitalization is required immediately for diagnostic studies, intensive treatment, nursing care, and elimination of offending agent(s).

The acute attack is usually not difficult to recognize. Most episodes crescendo in severity (an anaphylactic episode may occur catastrophically), with the rate of evolution occurring in most instances within hours to days of the initial change in symptoms. Some patients are distinguished by recurring exacerbations for which appropriate therapy will bring only temporary relief, reflecting intractability; thus, the essential element is a new episode that fails to respond to standard therapy, however repeated.

EPIDEMIOLOGY

Precise incidence data of status asthmaticus are limited. The 1945 edition of Unger's text cited 500,000 persons diagnosed as suffering from bronchial asthma in the United States (incidence of from 3.5 to 10%) [165]. From 1951 to 1959 there were 3 million cases, and in 1970 United States vital statistics estimated 6 to 8 million asthmatic patients in the general U.S. population of over 200 million [107, 167]. From this asthma population, a relatively low but disturbingly persistent incidence of hospitalizations continues, presumably, mostly for status asthmaticus. For example, there were 434 admissions for asthma from 1933 to 1948, and 269 admissions from 1948 to 1963, in one New York City hospital; and 1,000 of 56,000 admissions to the Peter Bent Brigham Hospital in Boston in 1947 were for asthma [33, 43]. At the Bronx Municipal Hospital Center in 1962, 500 asthma admissions were reported from 16,000 sequential adult and pediatric cases, whereas in 1973 less than 10 percent of asthmatic patients were hospitalized in the same institution [48, 185]. Of 269 admissions for acute respiratory failure to a university hospital, 6.7 percent were for asthma [115]. These figures may not account for deaths arising before hospitalization, and partially reflect admissions despite improvements in ambulatory care. It may also suggest that currently hospitalized patients represent a more refractory form(s) of the disease.

Of the total 3 million asthmatic patients cited for 1951 to 1959, it is estimated that deaths occurred in 4,000 to 7,000 per year, whereas in 1970 2,322 died: 342 mortalities were in the 5 to 34 year age group, a feature which presumably reflects uncomplicated asthma [107, 168]. Stolley's studies in the age group 5 to 34 years indicate a stable U.S. death rate of approximately 0.40 per 100,000 persons from 1959 to 1968, in comparison with the increased trends seen in Great Britain and Wales (see Chapter 4) [152]. These population figures establish an overall low, but persistent, average death rate in the United States in the recent decades of about 1.5 deaths per 1,000 cases. Smaller hospital series reveal a 1 to 3 percent mortality range in patients who are hospitalized [14, 20], and in one review of the Pavillion Service of the New York Hospital from 1948 to 1963, an increasing mortality from 1.4 to 2.6 percent, respectively, was observed [43]. Younger children appear at great risk, with 68 percent younger than age 5 years in one study [130]. Demise in children prior to 1950 appears to have been less common, although subject to variations as one increased trend from 1937 to 1963 was discovered in Los Angeles [130]. Infection, sedative abuse, aminophylline and epinephrine toxicity, and failure to initiate early therapy were considered major causative factors (see Chapter 62). Recently, Buranakul and his associates in reviewing the years 1949 to 1972 observed a decrease in the death rate in New Orleans Parish, Louisiana, among both children and adults since 1967 [15]. This and other data thus suggest a probable decrease in the death rate because of early intervention and improved treatment, but overall these incidence figures are subject to serious interpretative limitations including coding techniques, definition, and reporting mechanisms and will require further study. Of importance are a new awareness of the problem of deaths in asthma, and the fact that there still exists a disturbing

mortality despite major advances in our knowledge.

As education and improved diagnostics are contributing to an inevitable reduction in morbidity, recent trends and risk factors in life-threatening status asthmaticus must be monitored to quantitate and qualitate the net effects of therapy. A classification of mortality in status asthmaticus can provide a basis for a clearer understanding of this problem.

1. Acute death prior to supervised therapy. This is often sudden or unexpected, arising from hypoxemia, respiratory acidosis, or drug toxicity (adrenergics, theophylline, depressants), before the patient seeks a physician. Asphyxiation or fatal arrhythmias may be a common pathway, possibly intensified by paradoxical increases in airway resistance from drugs [77, 171]. Some deaths may be functional with an unremarkable necropsy, but most reveal extensive mucous plugging of the airways; dehydration with hypovolemia and circulatory collapse may be contributory [153].
2. Acute demise during therapy. Here, therapeutic commissions, omissions, or abuses may be causative, for example, sedation, toxic doses of bronchodilator agents, or inadequate steroids in steroid-dependent patients. In many cases the gravity is not realized and/or arterial blood gas and pH analyses have not been performed to alert the physician of the severity.
3. Gradually progressive deterioration leading to death. Generally, this occurs when proper therapy is not provided, but occasionally despite it. For example, deaths in elderly hospitalized patients are associated with progressive hypercapnia [157].
4. Deaths due to complications or coexisting conditions, for example, coronary occlusion, pneumothorax, bacteremia. Messer's studies indicated that 10 percent of asthmatic patients died from complications of the disease [102]. The first three mechanisms generally exhibit the common feature of extensive mucous plugging of bronchi and bronchioles (see Chapter 73).

A historical accounting by Alexander found that, among all age groups, deaths were almost unknown prior to 1930 [3]. "Between 1886 and 1906, when autopsies could be obtained more easily than nowadays, only seven autopsy cases of status asthmaticus were published. Evidently, hardly ever did anybody die of an asthmatic attack; the consultants with the most extensive practice wrote that they knew of only one of two fatalities due to bronchial asthma. These were the days when patients with an acute asthma attack received only potassium iodide to render the bronchial secretions more liquid, together with small doses of sodium bromide to soothe the acuteness of their discomfort" [147]. In 1930 Coke observed little mucous occlusions of the airways on the postmortems of patients with pure asthma [29]. This feature either changed quickly or was readily disproved, for Mallory easily identified such plugs in 1941, before the use of common contemporary drugs [3]. Messer's studies indicated that 11 percent of patients with status asthmaticus die, and that 97 percent of those succumbing were over the age of 20 years. Sixty percent of these deaths occurred in patients 50 years of age or older [102]. The observations by Dunnill and others suggested that this risk relates to the duration of disease, being more common in those with symptoms for about 20 years, and with a slight prevalence in females [40, 102, 184]. Other sources claim that mortality is more likely in those with symptoms for less than one year, and in 50 percent the problem had existed for only 5 years or less [162]. An important point is that *repeated* episodes of status asthmaticus is apparently characteristic of many who die. This was a common feature of the tragic losses in England from 1961 to 1967 of children who also exhibited previously severe episodes of asthma [143].

Even in the hospital the risk of death persists. One retrospective study noted the following liabilities shortly before death: (1) marked decrease in the use of sympathomimetic drugs, (2) inadequate amounts of corticosteroids and fluids (<4 liters/24 hours) administered, (3) a silent chest on auscultation, and (4) use of sedatives in 20 percent [53]. In 1943 Unger pointed out the association of mortality with the inappropriate use of sedatives to alleviate symptoms, provide for sleep, or allay anxiety [166]. Deaths in children are also ascribed to this abuse [15].

In a Swedish review, death was more common in those patients who had received larger doses of epinephrine than the survivors; but the dose can be explained by a greater severity in the former patients [65]. The development of a "locked-lung syndrome" described by Keighley is another drug-related problem in which tolerance to aerosol isoproterenol is followed by bronchoconstriction [77]. Independently of this effect, isoproterenol can induce arterial hypoxemia, caused by $\dot{V}/\dot{Q}$ mismatch, and fatal arrhythmias more pronounced in the presence of heart failure. This can contribute to drug-induced deaths in or out of the hospital [56, 66, 73]. Fluoromethane aerosol propellants also appear to be a risk factor, compounded by cardiac irritability from their epinephrine and isoproterenol constituents, especially in high concentrations. The toxic effects of propellants include bronchospasm, fall in pulmonary compliance and tidal volume, depression of myocardial contractability, or sensitization to epinephrine [6, 7]. Thus, drug problems play an important role in patient mortality and survival.

Survival in recent years must be interpreted in view of the significant advances in pharmacotherapeutics and the introduction of ventilator support. The use of steroids (discussed below), for example, may have created some risks, particularly with chronic users, but it has been invaluable for many other asthmatic patients. Similarly, many more severe patients are salvageable by the use of ventilators; indeed some deaths 15 to 20 years ago occurred because ventilators were not generally employed. In 1972 Lyons reviewed 70 episodes of status asthmaticus in 46 patients treated in a respiratory care unit. There was no mortality in a group of patients with a $Paco_2 \leq 40$ torr and who did not require intubation, but two deaths occurred in 22 patients requiring intubation and mechanical ventilation, indicating the persisting risk of death even with such support [141]. However, a summary of current series employing mechanical ventilation reveals an aggregate of 18 deaths in 149 obviously severe patients, or an average mortality rate of only 8.3 percent [65, 96, 128, 131, 141, 186]. In this regard it is difficult to extrapolate survival data prior to the introduction of controlled versus assisted ventilation into medical practice. However, survival with ventilatory support is not the only issue, because in 58 *severe* patients reported in a 1973 series, only one case required ventilatory support, with a good outcome in all those not receiving ventilators [127].

What may we then conclude regarding the incidence, morbidity, and survival in status asthmaticus? Asthma is more common by absolute increases in the general population, yet progress at eliminating the fundamental causes(s) of the problem has been limited. In the United States, about 8 million persons currently are afflicted with asthma, and of these from 2,500 to 4,000 will die per year. Despite numerous major advances in ambulatory care, status asthmaticus persists, and death is most likely to occur at this period. Aside from the recent, tragic increase in deaths in children aged 10 to 14 years, which occurred in the 1960s in Great Britain and Wales because of aerosol abuse (see Chapter 4), the relatively large numbers of children afflicted with asthma is fortunately offset by a low mortality rate. Death can occur prior to hospitalization, because of ignorance or neglect, drug abuse or toxicity, or rapidly crescending ventilatory failure. These factors cannot be quantitated, but they are real problems and should be avoided. Hospitalizations in adult asthmatic patients reflect a frequency of status asthmaticus of from 5 to 10 percent. Here, the risk of death is apparently low, though persistent, being 1 to 3 percent of those admitted. The overall major risks from death are associated with several factors: (1) age—either less than 5 years or older age (from 20 to 50 years), (2) duration of disease—a shorter duration appears a greater risk particularly in older onset patients, (3) severity or greater duration of attack—this generally relates to the extent of acute occlusive airway plugs; it is aggravated by limited pulmonary reserve from previously severe chronic asthma, (4) repeated episodes, (5) delay in diagnosis, (6) delay in or omissions of proper therapy; iatrogenic excesses, or commissions of therapy (sedatives, dehydration, bronchodilators) prior to or during hospitalization, (7) failure to hospitalize, (8) failure to monitor critical laboratory tests including arterial blood gases and pH, (9) corticosteroid requirement or steroid resistance. Reports that sudden death can occur within 48 hours of admission to the hospital [140]

restresses the need to monitor all patients throughout this and all periods of this serious disorder.

MECHANISMS AND CAUSES

No single factor has been incriminated in precipitating status asthmaticus. Rather, many factors may initiate, intensify, or propagate the process, and these may be difficult to recognize initially. In some instances inadequate understanding of therapy is a basic cause. For most patients, status asthmaticus begins as any other attack, and only as it becomes resistant to drugs does it reveal its true character. One retrospective study failed to identify any special predisposing factor(s); thus, most attacks can be provoked by the usual precipitating events in asthma (see Table 30-3) including allergic insults, infections, or toxic exposures: exercise, cold air, or emotional stress are less intense stimuli. Infectious exacerbations are more common in intrinsic asthma, whereas allergic factors are incriminated more in those with extrinsic atopic patterns.

The differences between extrinsic asthma and intrinsic disease suggest that no specific mechanism may explain refractoriness (Table 60-1). Thus, status asthmaticus in the allergic, extrinsic patient represents an intense reaction by immunological-pharmacological mediators as direct agonists, whereas this phenomenon has not been established in intrinsic or nonatopic refractoriness. However, both types may share a common, nonimmunological defect such as cholinergic predominance or beta-adrenergic receptor blockade. These effects can be complicated by hypercapneic acidosis, which inhibits the effectivess of beta-adrenergic agents. Collectively, these features could explain the refractoriness to sympathomimetic amines. This pharmacological defect is, however, not absolute for it can be partially overcome with increasing doses or by IV isoproterenol. This action of isoproterenol has been shown largely (but not exclusively) in children and may reflect mainly changes in bronchomotor tone, because these patients are more likely to suffer a rapidly reversible bronchial muscle contractile component. This is in contrast to the more resistant, slowly resolving patterns associated with secretional obstruction, where beta adrenergic refractoriness seems not a problem exclusively of membrane receptor blockade, but one compounded by intraairway mechanical obstruction from glandular secretions and inflammatory matrix. These matters may be more complex. A recent study suggested that in acute asthma the adenyl cyclase system was already maximally stimulated by circulating catecholamines. Hence, further stimulation with exogenous sympathomimetic drugs would appear to result in an adrenalin-fast state [4], perhaps aggravated by excessive use of a drug such as isoproterenol, with an accumulation of metabolites having beta-adrenergic blocking properties [70]. A maximal adrenergic receptor activation does not, however, clarify why methylxanthines are still effective in bypassing the membrane molecular site of abnormality and raise cyclic 3′,5′-AMP via cytoplasmic phosphodiesterase inhibition. Currently, then, status asthmaticus seems to be at least a quantitatively severe, final common pathway to many inciting mechanisms. An understanding that divergent opinions of the pharmacological basis for refractoriness exists should provoke further questions while qualitative features and reactivity differences among patients and nonasthmatic subjects have yet to be determined.

Concerning allergens, no one incitant appears particularly noteworthy. Inhalant antigens are important by their sheer incidence, but in any given case other allergens can be important and will require eventual identification. Fever, emotional or physical stress, dehydration, or hypermetabolic demands are

Table 60-1
Possible Causes of Refractoriness

Pharmacological-chemical causes
1. Beta-adrenergic blockade; intrinsic or acquired
2. Endogenous catecholamine deficiency
3. Alpha-receptor influences
4. Parasympathetic preponderance
5. Acidosis
Pathomechanical causes
1. Tenacious mucous airway secretions: infection, allergens, toxins, vagal
2. Mucosal inflammation and edema
3. Smooth muscle hypertrophy and spasm
4. Defects in clearance mechanisms
Immunological causes
Agonist pharmacological mediators

ancillary factors, but they all are of therapeutic importance. Current information of occupational hazards is limited, but they do not appear to be a major consideration (see Chapter 34). This includes asthma associated with exposure to isocyanates, enzyme detergents, baking, plastic wrapping, cotton or flax dust, certain wood dusts, and metal compounds such as nickel or platinum salts [137]. Nonasthmatic, occupational toxic insults must be distinguished because acute chemical bronchiolitis can mimic status asthmaticus. Also, cigarette smoking can intensify any insult. Exceptions to these occupational considerations are cautioned, for *once an attack is precipitated by any cause, it may progress to status asthmaticus in any patient.*

Patients with allergic respiratory diseases exhibit an increased morbidity and mortality during periods of high air pollution with particulates, ozone, oxides of sulfur, carbon monoxide, metals, and photochemicals, as well as during periods of temperature inversions and climate changes. In one serious epidemic in Donora, Pennsylvania, about 90 percent of the asthmatic population was affected, compared to 40 percent for the total population [54]. Also, hospital emergency room visits in urban areas increase at periods of air stagnation; common examples cited occurred in New Orleans and in Yokohama, "Yokohama asthma" being a nonspecific effect of air pollutants in susceptible persons (see Chapter 33) [150, 175]. In other instances, wind forces from a city dump were related to similar outbreaks [85]. Status asthmaticus and deaths have occurred with such exposure to industrial pollutants, temperature, and atmospheric or geographic changes, and appropriate protective measures should be encouraged.

Bacterial and viral infections are commonly incriminated as major causes of status asthmaticus. This rationale is based upon autopsy findings of pneumonia in asthma, bacterial hypersensitivity or beta-adrenergic blockade and the beneficial effect of antibiotics [58, 130]. In one review of 200 asthmatic patients, an infectious cause was recognized in 100 [156]. Viral provocations in the adult appear less common than in children, but although viral infections can trigger a serious exacerbation of asthma, including secondary bacterial implantation, a direct relationship to the development of status asthmaticus is not easily proved beyond this simple association. Overall, estimates of from 10 to 40 percent implicate a viral cause in children requiring hospitalization, with incidence variability arising from age differences, serological methods, or patient selection; respiratory syncytial, parainfluenza II, coronavirus, and rhinovirus are commonly identified [38, 94]. Mycoplasma is an infrequent finding aside from its general frequency [10].

Bacterial infection in childhood status asthmaticus is perhaps greater in nonatopic children or those with immunological deficiency, while precipitating bacterial infections in adults may include infective bronchitis or sinusitis. There may also be a predisposition in corticosteroid-treated patients, for one study revealed an increased infection rate in a steroid-treated group [34, 103], but this risk is not necessarily high in alternate-day therapy programs [35]. Furthermore it is believed that asthma predisposes to infectious complications; for example, in one study 11 percent of asthmatic children experienced recurrent bacterial pneumonia [79]. However, not all bacterial infections result in asthmatic exacerbations, but the association of infected sputum, the response to antibiotics, and the presumed prophylactic role of bacterial vaccines do suggest a major relationship. It is controversial whether bacteria act as exciting allergens or as direct infective agents, or by bronchial toxic effects, inflammatory leukocyte mediator release, or beta-adrenergic blockade [8]. Interestingly, not all series of status asthmaticus in adults indicate the risk of bacterial infections [185], and a recent double-blind study of prophylactic ampicillin in children without signs of bacterial infection in status asthmaticus failed to substantiate any differences in outcome of treated vs. nontreated groups [139]. In uncomplicated asthma, secondary bacterial infection is not an important feature, possibly because of the brevity of such attacks [99].

Based upon clinical observations, many attacks are multifactorial in cause, that is, a primary allergic reaction and coexisting infection may be compounded by fever, anxiety, dehydration, or drug reactions such as that to aspirin in the sensitive patient. Inappropriate drugs, or undermedication in the chronic stable patient or in the early, reversible phases of a paroxysm are also added causal

influences. It should be stressed that drug excess can contribute to death even if severe status asthmaticus has not fully developed from these common incitants.

Adrenal corticosteroid dependency is another predisposing factor, which may also index a greater, underlying severity of asthma, and includes these risks: (1) exacerbations of asthma, (2) more frequent infections, (3) limited response to nonspecific stress, and (4) complications or side effects; in one series of 250 patients, 10 percent died from the asthmatic exacerbations and 2 percent from therapy complications [89]. These problems are notable, particularly when steroid doses are inadequate and asthmatic exacerbation, stress, or infection supervene. In many patients, the risk of life-threatening asthma is greatest in those requiring steroids for control, and further caution and earlier aggressive therapy is indicated. This is exemplified by one evaluation in children with continuous asthma, refractory to epinephrine and aminophylline: only modest increases in endogenous plasma corticosteroids occurred in those previously on daily prednisone regimens in contrast to those not on steroids [110]. Similarly, in adults on <10 mg prednisone daily, basal cortisol levels were less than those of a normal matched population [21]. In some patients with acute asthma, plasma cortisol levels of <10.0 μg% were well below that anticipated in response to stress [31].

The extent of hypothalamic-pituitary-adrenal (HPA) suppression relates to the duration and to the daily and/or total dose of steroids. Patients on chronic therapy and impaired HPA axis responsiveness can be sorted into those with or without steroid resistance (see Chapters 52–54).

Patients on continuous steroids and/or those with steroid resistance (≧15 mg prednisone a day for 2 months) carry a greater risk and require more diligence since they exhibit increased cortisol metabolism during an acute attack, decreased eosinopenia (despite added steroid doses), and associated lack of clinical improvement [138]. Steroid-resistant patients require unusually large doses (2 to 3 times the usually effective levels) for control during an exacerbation. Steroid-dependent patients require immediate increased doses during either nonspecific stress, such as fever or surgery, or with specific allergic or infectious prodromes. Also, abrupt termination of steroids may precipitate an acute attack, or even death, if there is a delay in administration [92]. Thus, adrenal insufficiency has been suspected in some patients previously treated with corticosteroids (even death has occurred), and the clinician should be alerted to this possible presentation. These findings stress that an impaired adrenal cortical reserve can emerge during the crisis period of status asthmaticus, a liability which can be minimized by the use of alternate-day maintenance therapy schedules [155]. Regrettably, HPA responsiveness during status asthmaticus per se has not been extensively evaluated. Recently, the Children's Asthma & Research Institute (CARI) in Denver reported that the percentages of children requiring prolonged steroid therapy rose from 23 percent to 46 percent over a 10-year period [12], suggesting more reliance upon these drugs and/or selection of patients with greater severity. Feldman, however, in a limited analysis of 12 fatalities from 16,000 admissions, did not conclude an adverse influence by steroids [48]. Certainly, normal HPA function does not prevent the occurrence of status asthmaticus!

A final question asks which patients are predisposed to status asthmaticus. For the majority of relapses, the relationship between bronchial reactivity (or hypersensitivity), organ threshold, and severity of response have not been examined. Theoretically, a predisposition to minor exacerbations could lead to a risk of increased frequency of status asthmaticus. For example, increases in total serum IgE are frequently, although not invariably, associated with more severe and frequent episodes of asthma in atopic children, and a rough parallel between exercise severity and bronchoconstriction is described [61, 144]. Bronchial provocation testing reveals that asthmatic patients are more sensitive or hyperreactive than are normal control subjects to histamine, allergens, or acetylcholine [59]. However, considering that minute amounts of allergen can induce histamine release in vitro (and that blood histamine can be increased during an asthmatic attack, with patients exhibiting more sensitivity to inhaled histamine), no direct correlation of histamine levels with severity or status asthmaticus is known. Alternatively, some in-

Table 60-2
Clues to Impending Status Asthmaticus

HISTORY
1. A change in pattern of symptoms
   a. wheezing: more severe or frequent, particularly at night
   b. worsening dyspnea: progressive exercise limitations, dyspnea at rest, orthopnea, or fatigue
   c. cough with tenacious sputum: difficult to expectorate, or a substantial decrease in daily volume; changes in sputum color from white to yellow, gray, or green
2. Refractoriness to drugs: increasing use with less relief to otherwise efficacious drugs; loss of improvement in spirometry following administration of bronchodilator drugs
3. Constitutional: personality changes (irritability, confusion), anxiety, anorexia, and insomnia

EXAMINATION
These findings are present in a mild form.
1. Anxiety, increased respiratory efforts
2. Expiratory prolongation and onset of inspiratory wheeze
3. Use of accessory respiratory muscles; hyperinflated thorax with diminished diaphragmatic excursions, hyperresonance to percussion, and quieter breath sounds
4. Dyspnea limiting speech
5. Pursed-lipped breathing
6. Cyanosis (a late sign)
7. Tachypnea
8. Sympathetic discharge (diaphoresis, tachycardia, flushing, ↑BP)
9. ↑S_2P—hyperdynamic heart
10. Paradoxical pulse

LABORATORY DATA
1. Falling flow or volume indices: FVC, $FEV_{1.0}$, MMEFR, PEFR, or reduction in FVC with rising FRC: e.g., FVC <50% predicted, PEFR <100 liters/minute, $FEV_{1.0}$ ≤50% of predicted (approximations only).
2. Failure or limited response to bronchodilator (by spirometry)
3. Progressive or absolutely severe hypoxemia (Pa_{O_2} <55 torr)
4. Hypocapnia (<35 torr)
5. X-ray: hyperinflation (or pneumonia or atelectasis)
6. Eosinophils in blood or sputum: high values or a shift from chronic state levels
7. Leukocytosis; purulent sputum

stances may represent a state of reduced availability of endogenous catecholamines during stress [97]. Such fragments indicate that severity can relate to immune or bronchoreactivity factors and circumstances which favor exacerbations may then lead to status asthmaticus in infection-susceptible or severely allergic patients. Although it is more difficult to be precise about emotional crisis as an initial cause, this factor appears capable of intensifying an established episode.

PRESTATUS ASTHMATICUS

A prodromal period of "prestatus" asthmaticus exists (Table 60-2). This state should be recognized because early intervention is more likely to abort overt status asthmaticus. Perhaps the now well-described British epidemic of asthmatic deaths attributed to an unsupervised, excessive aerosol dosing of concentrated isoproterenol exemplified the extreme of this "prestatus" problem; here, progressive symptoms led to more frequent use of bronchodilator agents rather than to direct medical care. In one report, for example, 42 of 52 children or adolescents who died, did so, suddenly, at home [148]. It is important for patient and physician alike to be aware of this period, for it is easier and safer to abort a massive insult than to treat it, and to recognize that it is urgent for the physician not to underestimate the likelihood of death in status asthmaticus, a process which begins at this stage. In this regard, no single observation, or groups of observations, is a reliable prognostic feature, and all patients must be regarded as having the potential for mortality although some observations are suggestive (see following table). Thus, even with full intensive therapy, continuous observations and monitoring are required.

Features of Poor Prognosis in Status Asthmaticus

1. Complete refractoriness to all bronchodilators and all other supportive therapy
2. Use of inappropriate drugs, or inappropriate dosages, or delay in initiating therapy
3. Greater duration of attack
4. A silent chest, nonmobilization of secretions, and increasing dyspnea
5. Hypercapnia, respiratory acidosis
6. Severe hypoxemia despite full therapy
7. Cardiac arrhythmias, hypotension
8. Abuse of sedatives or respiratory depressants
9. Underlying cardiopulmonary disease

PATHOLOGY

The flagrant findings of status asthmaticus have been the most easy to characterize, and these will be recapitulated. Significant differences between intrinsic and extrinsic asthma apparently do not exist. Characteristically, hypersecretion of a thick, viscous, and adhesive mucous exudate is seen within the airways in histological secretions of a patient dying in status asthmaticus. This mucus causes the striking occlusion with widespread plugs extending from segmental bronchi to terminal bronchioles (see Chapter 23) [42, 64]. This is a major feature of status asthmaticus, whatever the inciting mechanism. It contributes most to the pathofunctional disturbance, it limits acute bronchodilator response, and it is therefore a major therapeutic consideration. Simple exacerbations of asthma which respond rapidly to adrenalin are less commonly associated with significant sputum volumes and represent bronchial smooth muscle spasm. This mucus is distinctive by its low water content, by the presence of immunoglobulins, and by a high histamine concentration. In addition, these secretions frequently contain bronchial epithelial cells, alone or in clumps as Creola bodies, and many eosinophils. Intense inflammation of the mucosa with denuded epithelium can interrupt the normal epithelium and these exfoliated zones show some correlation with the severity of an attack as well as favoring microbial invasion and contributing to intractability.

Paralleling severity are other inflammatory changes including mucosal edema, vascular congestion, and cellular infiltration as well as gross mucosal irregularities with swollen pseudopolypoid folds. In infectious exacerbations, eosinophilic infiltrates can be observed, but they are not as dramatic as seen in allergic insults; here, extensive eosinophilic infiltration into the bronchial wall and mucosa, mucous plugs, and surrounding parenchyma are notable. Although increased mast cell numbers can reflect the severity of asthma, they are not routinely observed because of mast cell degranulation processes. Other characteristic, but nonspecific features include a reversible, nonemphysematous hyperinflation of the lungs, foci of atelectasis, pneumonia, or fibrosis; the intervening lung parenchyma is otherwise normal. Hyperplasia of the goblet cells extending to the bronchioles and extensive mucous gland hyperplasia (perhaps caused by cholinergic stimulation) are not as extensive as in chronic bronchitis.

Smooth muscle hypertrophy and hyperplasia are severe and imply severity or chronicity, and not simply muscle *spasm* contributing to the obstructive events [63, 159]. Some patients with asthma show a thickened bronchial basement membrane with immunoglobulin deposits of antigen-antibody complexes or antibodies to antigen or microbial materials, but cases of status asthmaticus are not necessarily included in these analyses [17, 90, 174]. Immunofluorescent studies in status asthmaticus have revealed complement and patterns of IgA, IgG, and IgM in the basement membrane area [18]. IgE deposition is noted, but is not necessarily related to severity or to status asthmaticus.

These pathological features are also presumably a quantitative, morphological extension of the hyperreaction of the airway components involved in asthma. Overall, the major changes of smooth muscle contraction, mucosal inflammation, edema and accompanying damage, and hypersecretion of thick and tenacious sputum set the basis for the airways obstruction, and hence gas exchange defects and clinical symptoms. The treatment rationale of status asthmaticus requires a clear understanding that these changes are *reversible*.

PHYSIOLOGY

A notable physiological feature of status asthmaticus is its advanced gas exchange defects, and only in this phase of asthma is advanced hypoxemia associated with various *levels* of ventilatory competence; thus, the Pa_{CO_2} may be low, "normal," or elevated. Despite differences in clinical profiles, only minor physiological distinctions exist in spirometry, lung volumes, diffusion, or arterial blood gas and pH values between extrinsic vs. intrinsic asthma, except for slight increases in residual volume (RV) in the former [119]. Similar to pathological resolution, recovery from an episode will lead to normal or near-normal function. Only those physiological alterations germane to status asthmaticus will be reviewed here (Fig. 60-1).

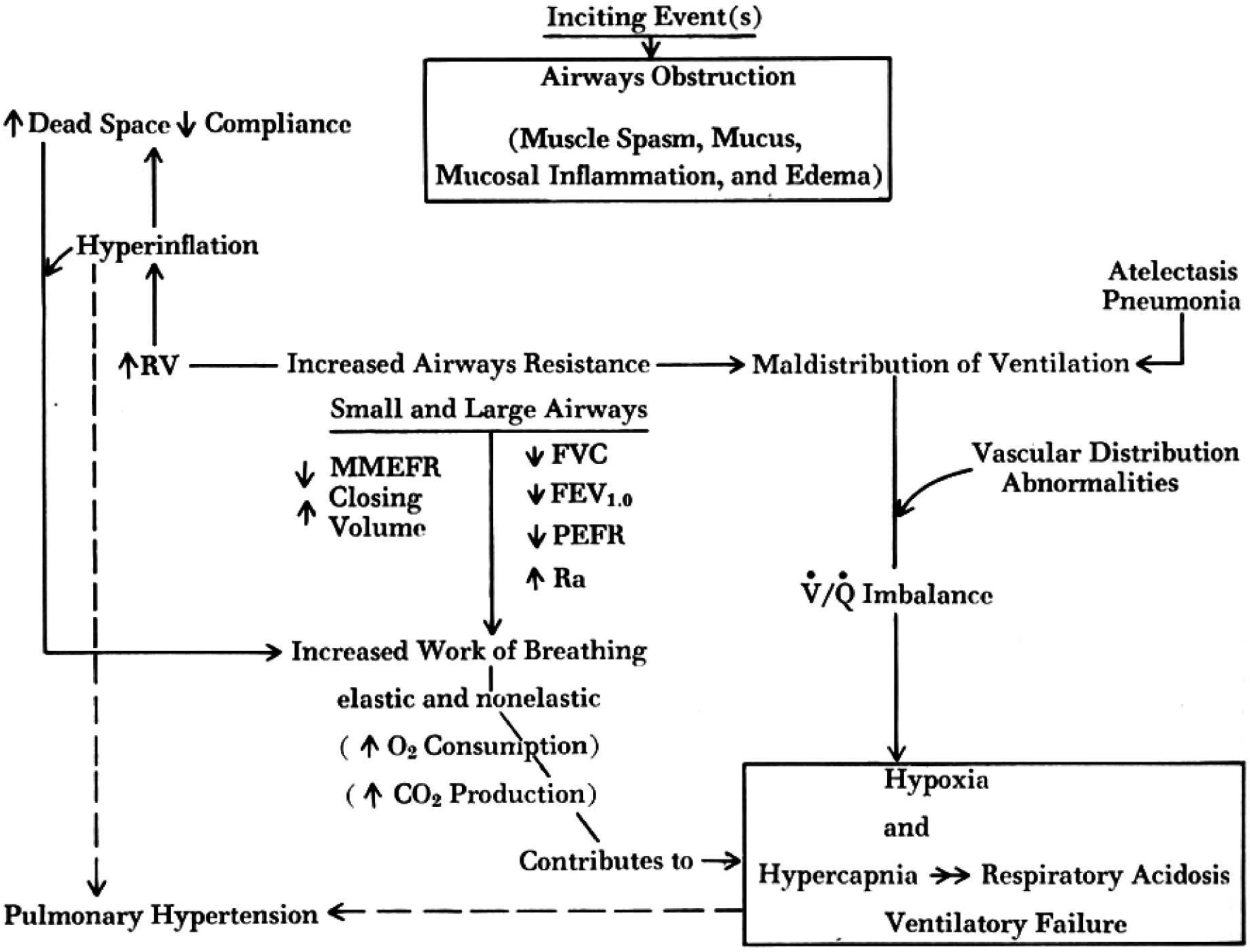


Figure 60-1
Physiological events in status asthmaticus.

Airway Dynamics

The primary mechanical event is progressive increases in air flow resistance caused by multiple features, including intraluminal secretions, airway wall inflammation and edema, muscle spasm, turbulent air flow, expiratory airway compression, and coexistent bronchitis. As a result, increases in elastic and resistive work occur and cause greater inspiratory pressures (or total thoracic work) for alveolar ventilation. To meet ventilatory demands under these conditions, active expiratory work is an added feature which will contribute to the energy cost of breathing; it can also lead to compression of intrapulmonary airways. With more severe obstruction, there will be a failure to exhale fully the previous tidal air, and this will lead to a characteristic overinflation of residual volume (RV), functional residual capacity (FRC), and total lung capacity (TLC).

The precise level of routine measurements of forced vital capacity (FVC), forced 1-second expiratory volume ($FEV_{1.0}$), MMEFR, or specific conductance at which status asthmaticus exists has not been exactly, or realistically, defined, but these values will be substantially decreased. For example, the series of Stanescu and Teculescu [151] revealed average values for VC of 67 percent predicted (range 38–99%), of Rebuck and Read mean FVC = 1.20 ± 0.63 liter and $FEV_{1.0}$ = 0.54 ± 0.28 liter [127], and $FEV_{1.0\%}$

of 17.6 and 34.9 percent of predicted in severe and moderate asthma, respectively [93]. During an acute attack, an FVC of 1.0 liter (range 0.7 to 1.85) and $FEV_{1.0}$ of 0.46 liter (range 0.2 to 0.8 liter) were recorded in adults [128], while in children an $FEV_{1.0\%}$ of 55 percent was measured [183]. A PEFR of 80 to 100 liter/minute, or less, may be a useful guide to severity because this peak flow rate has been shown to correlate with deaths in asthma [185]. Last, a constant $FEV_{1.0}$ percent (observed) has been suggested as an index of fixed obstruction in the evolution of severity [189, 190].

Asthma was formerly considered to be a process limited to the larger airways, and only recently has it become apparent that both large and small peripheral (<2 mm) airways are involved [92], a feature that is extensive in status asthmaticus. Although the major resistances during status asthmaticus are undoubtedly in intermediate or larger airways, a major contribution by small airways is an added critical problem because their large cross-sectional area is now reduced by intraluminal secretions whose mobilization is arduous, but *mandatory*, for complete relief.

The nature and distribution of airways obstruction is important in the definition of refractoriness. In asthma, a basic requisite is bronchoreversibility, conventionally accepted to be 15 percent (or greater), increases in $FEV_{1.0}$ percent, MMEFR, or airway conductance within 10 to 15 minutes of bronchodilator drug administration. Status asthmaticus, by definition, does not exhibit this acute reversibility for reasons previously discussed. In addition, drug refractoriness can be exaggerated by the inability of aerosol dilator drugs to reach peripheral airway zones and the obvious inability of such drugs to reverse airways obstruction due to extensive mucous plugging. Also, to fully assess airways responsiveness, various techniques and measurements must be employed because mechanics values are not interchangeable and apparently reflect flow at different airway segments, and this feature should be appreciated in analyzing a limited response to a bronchodilator.

A further complication of intraluminal secretions is that they impair air flow in inspiration as well as in expiration. Clinicians are familiar with complaints of the inability to inspire, or of inspiratory wheezing in status asthmaticus, features which can be explained by the inspiratory obstruction as well as by the increases in FRC which intensifies elastic work. This is in contrast to emphysema, in which the major flow limitations are largely in expiration. Thus, the asthmatic patient must additionally exert increased inspiratory work—from two to ten times normal, and actual measurements of inspiratory flow resistance exemplify this problem with one series citing a mean value of 27 cm H_2O/liter/sec in contrast to a normal range of 2 to 3 cm H_2O/liter/sec [182].

Air flow patterns are also a consideration in advanced asthma. To meet the demands of basal gas exchange, as well as those additionally imposed by fever, infection, "stress," and the augmented work of the respiratory muscles, total ventilation must be increased. When this state occurs, concurrent increases in air flow are not proportional to higher driving pressures, and become alinear, leading to turbulent flow patterns. Energy losses resulting from these increased gas velocities, eddy currents, and gas vortices from bronchospasm, airway secretions, and swollen, inflamed mucosa must be then met by greater changes in alveolar pressure by the respiratory muscles. Resistance to air flow over and through intra-airway secretions is estimated to occur with viscid sputum and when secretional thickness exceeds 300 μm [26]. These flow patterns are more extreme in larger airways where turbulency is influenced by the gas density. Further, transbronchial pressure gradients are now shifted so that peripheral airways are subject to expiratory air flow limitations earlier than in normal subjects. Also, tracheal and large bronchi compression may complicate the process when active expiration or cough elevates the intrathoracic pressure [37].

Several features of the work of breathing indicate the severity of the problem which confronts the patient with status asthmaticus. The nonelastic component (airway resistance, or Ra) of respiratory work rises, often to extreme levels, in status asthmaticus; Ra values of 16 to 50 cm H_2O/liters/sec (normal 2.0) are described [19, 182]. In addition, hyperinflation reduces the efficiency of the respiratory muscles, and active expiratory muscle contraction adds further to the work

demands placed upon the thorax. Respiratory work will, therefore, increase, and estimates of as much as 5 to 25 times over normal subjects at rest have been made [182]. As ventilatory demands rise during an attack, O_2 consumption by the respiratory muscles also increases. Faced with these impedances, a given amount of ventilation will consume more O_2 in contrast to normal subjects. As an illustration, if minute ventilation rises to 60 liters/min, O_2 consumption per minute of the respiratory muscles may rise to over 100 to 200 ml with airways obstruction, in contrast to only 20 ml in normal subjects. Clinically, fatigue and exhaustion will be obvious when these factors accumulate in status asthmaticus. Besides this inefficiency of the O_2 cost, total work may fall below that required to dissipate CO_2, and hypercapnia will ensue. Noelpp et al. demonstrated that in animal-induced bronchospasm the work of breathing against elastic resistance increased 44-fold and the total work of breathing 12.5-fold [112, 113]. Parallel findings in human asthma for both overall elastic work and expiratory air flow resistances were observed by Attinger et al: [5].

Lung Volumes

Lung volumes in severe asthma are characterized by large, but reversible, increases in RV, FRC, and TLC. This hyperinflation results from air trapping as progressive obstruction creates a time dependent, ball-valve mechanism preventing complete expiration. In addition, intersegmental collateral air drift may allow access to alveoli distal to obstruction. However, the exact cause of increased air is still not clarified (see Chapter 19). The resulting rise in resting expiratory level reduces the vital capacity by limiting both inspiratory capacity and expiratory reserve volume. The RV may rise to 200 to 300 percent of predicted values, or from 1 to 4 or 5 liters. Discrepancies in FRC measurements by dilution vs. plethysmographic methods are due to impaired ventilation or to trapped air behind areas of advanced obstruction, hence, RV will be greater measured by plethysmography than by inert gas or washout studies [101, 190]. As stated, the rise in FRC offers some mechanical advantage because it creates a radial tractional effect that enlarges the airway caliber, but the advantage is offset by the shift in tidal ventilation to a flatter portion of the pressure volume (PV) curve (see Chapter 19). This results in a stiffer lung, that is, a lower lung compliance, which increases the elastic work of breathing for a required minute ventilation. These factors can contribute to clinical dyspnea. Some patients with chronic asthma exhibit static PV curves which are shifted left and upwards, indicating a decrease in elastic recoil with possible limitation of flow in expiration [55]. As yet unresolved, such a reversible shift during status asthmaticus could facilitate adequate tidal volumes with less pressure changes.

It is estimated that, depending upon the rise in FRC, the elastic work in inspiration could rise 2- to 10-fold. Other disadvantages of hyperinflation include impaired muscle inefficiency, greater work of accessory respiratory muscles, and a prolonged equilibration time in mean alveolar gas composition. A practical finding is that serial changes in FRC can be used to assess the severity of asthma; even with a constant $FEV_{1.0}$ percent, a fall in FRC is indicative of a lysis in the obstruction [190].

Such increases in residual volume may mimic pulmonary emphysema: a chest radiograph with flat diaphragms and attenuated pulmonary vasculature, physical examination revealing use of accessory musculature (implying a temporary, mechanical disadvantage of the diaphragm), low-lying diaphragms, hyperresonance, and diminished intensity of breath sounds caused by the elevated air-tissue ratio. However, destructive emphysema is not present, and these findings are reversible.

Blood Gas and pH

Impairment of inspired gas distribution with marked variation in the time constant of various lung zones is characteristic of bronchial asthma. Progressive obstruction leads to further maldistribution of inspired air with adverse consequences upon $\dot{V}/\dot{Q}$ matching and a predominance of hypoventilated, but relatively perfused alveoli. This causes an increase in respiratory frequency and increased minute volume as well as in alveolar ventilation. At some point in the process, however, ventilation fails and hypoventilation will oc-

cur [93]. For many years the extent of arterial hypoxemia (Pa_{O_2}) in asthma was underestimated. Now it is clear that mild or chronic stable asthma has some impairment of oxygen transfer whereas severer clinical states exhibit advanced hypoxemia caused by further $\dot{V}/\dot{Q}$ disturbances proportional to the distribution and population of these low ($\dot{V}A/\dot{Q}C$ <0.8) ratios [187]. With complete airway obstruction, anatomical right-to-left shunting will intensify this cause of hypoxemia. In some instances, zones of increased $\dot{V}/\dot{Q}$ ratios occur and lead to an increase in physiological dead space which can increase respiratory work. Diffusion does not limit oxygen transfer and may be elevated by a perfusional redistribution to the lung apices [181].

In severe asthma or status asthmaticus, dangerous levels of hypoxemia may develop, frequently rapidly, and without hypercapnia. In addition, marginal Pa_{O_2} levels (60 torr) may quickly lead to dangerous hypoxemia if there is a further (perhaps even small) decrease in airway patency, a feature that can contribute to sudden death. Generally, the extent of hypoxemia correlates well with the severity of obstruction; a reduction in FVC or $FEV_{1.0\%}$ (or degree of pulmonary hyperinflation) or greater duration of an attack shows a parallel decrease in Pa_{O_2} (Fig. 60-2). For example, in 101 patients, McFadden and Lyons found such a correlation; for mean $FEV_{1.0\%}$ of 59, 35, and 18 percent of predicted, the mean Pa_{O_2} was 83, 71, and 63 torr, respectively [93]. In another series, a Pa_{O_2} of <60 torr was common with an $FEV_{1.0}$ of <0.5 liter or <30 percent of predicted [49].

The primary gas exchange defect of hypoxemia *with hypocapnia* is due to $\dot{V}/\dot{Q}$ inhomogeneity. However, with progressive obstruction, effective ventilation will fall and hypercapnia will supervene (Fig. 60-3; see also Fig. 21-3). The incidence of hypercapnia is cited from 10 to 50 percent [39, 93, 158]. It must be stressed that alveolar hypoventilation with respiratory acidosis is critical because it carries a high mortality rate [118], and survival may require ventilator intervention.

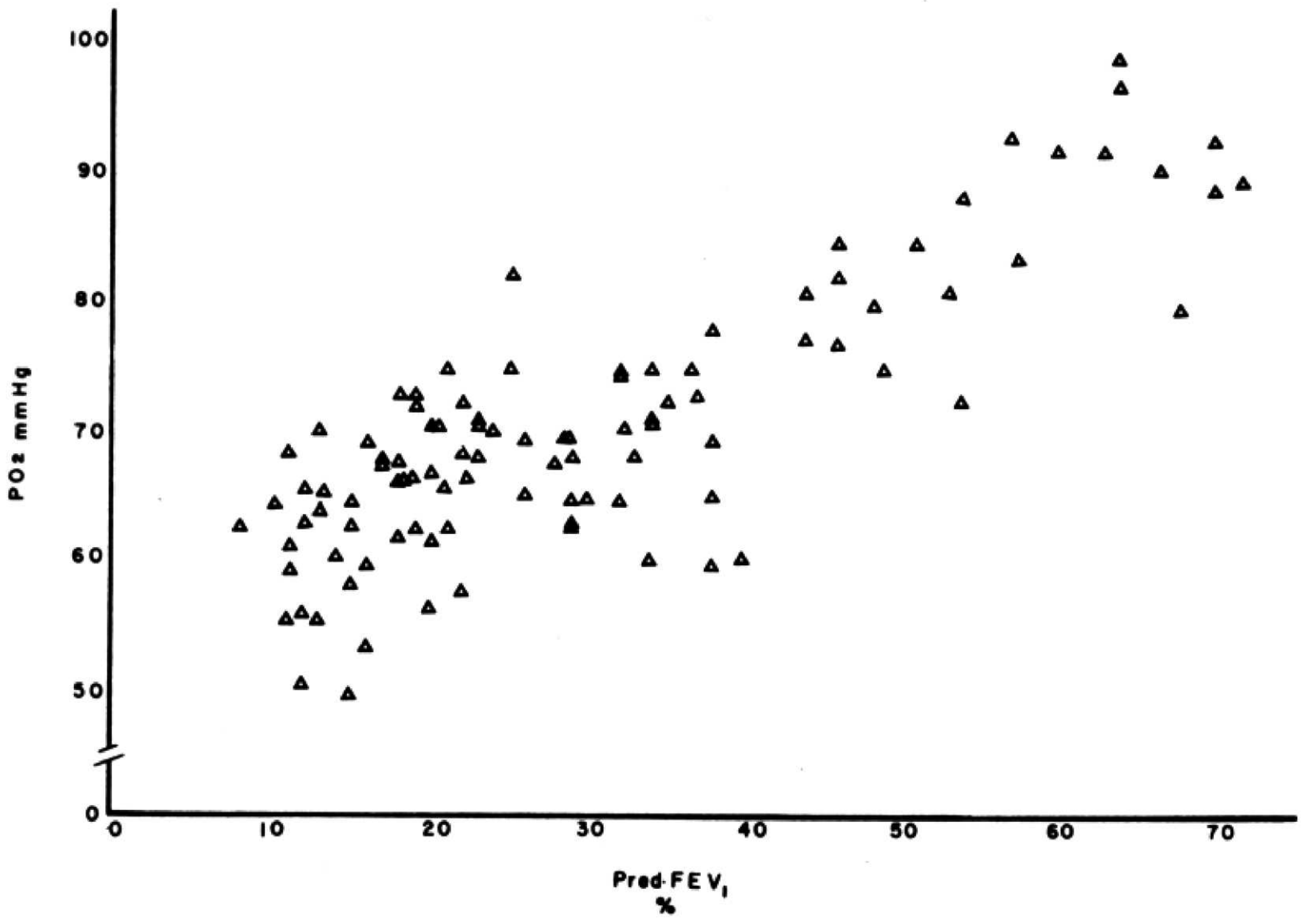


Figure 60-2
Pa_{O_2} vs. $FEV_{1.0}$ in acute asthma. (Reprinted with permission from McFadden, E. R., Jr., and Lyons, H. A., Arterial blood gas tension in asthma. *New England Journal of Medicine* 278:1027, 1968.)

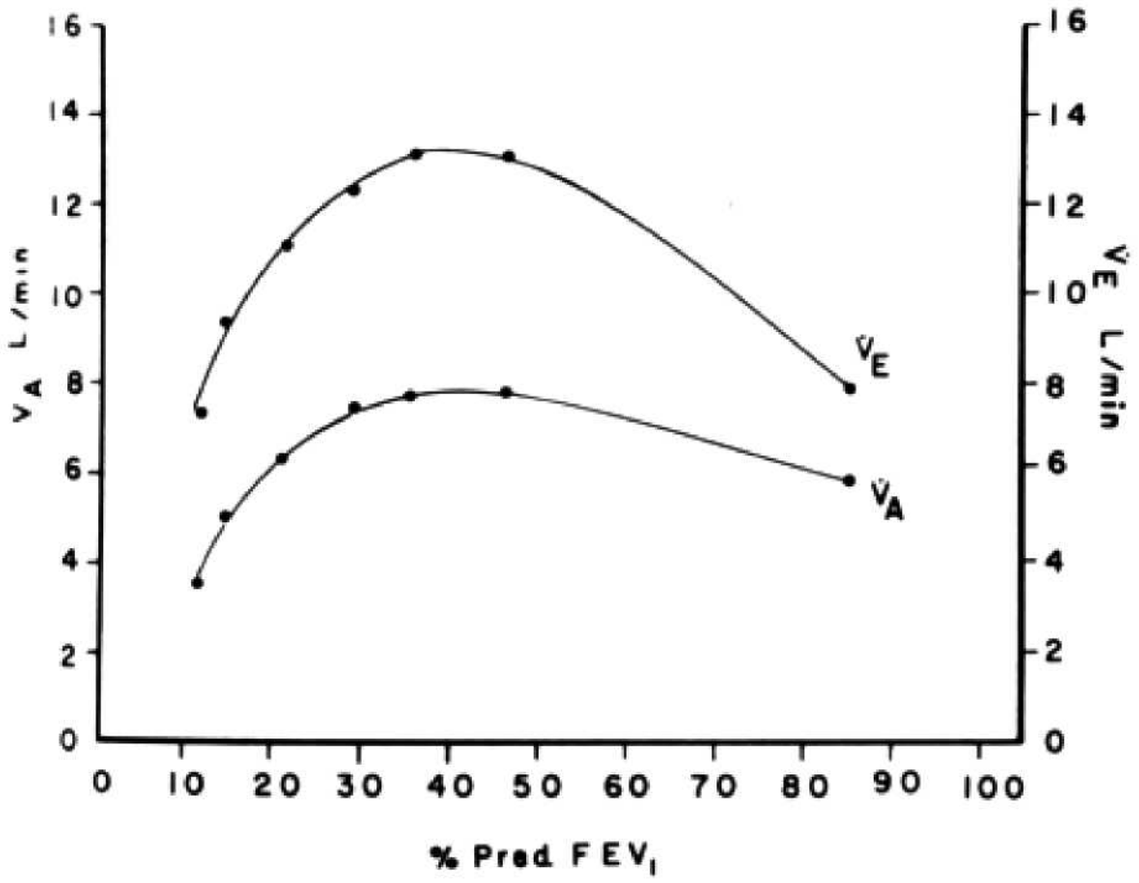


Figure 60-3
Alveolar ($\dot{V}A$) and minute ventilation ($\dot{V}E$) (BTPS) vs $FEV_{1.0}$ in acute asthma. (Reprinted with permission from McFadden, E. R., Jr., and Lyons, H. A., Arterial blood gas tension in asthma, *New England Journal of Medicine* 278: 1027, 1968.)

However, only a relatively small number of patients exhibit respiratory acidosis; yet this acidosis may be severe when it occurs. In 101 adults, 7 had respiratory acidosis, 21 a normal pH, and 73 respiratory alkalosis [93]; in 25 episodes the pH was normal or alkalotic in all but 6 [128]. In children higher incidences of acidosis may exist [39, 146]. Because an arterial Po_2 of <60 torr may be associated with $Paco_2$ varying from 30 to 80 torr, and even hypocapnia can exist with $FEV_{1.0}$ ranges from 0.5 to 1.0 liters, such divergencies require blood gas and pH documentation of ventilatory adequacy and acid-base status.

No one single pattern of Pao_2, $Paco_2$, or pH changes is characteristic of status asthmaticus, rather, evolving stages of severity can be categorized (Table 60-3; see also Chapter 21). Significant advances in the management of status asthmaticus have emerged by used of these arterial blood gas and pH profiles, particularly with serial observations and because gas exchange severity *cannot* be judged clinically. Arterial hypoxemia intensifies as the obstruction becomes severe, and even Pao_2 values of 30 or 40 torr can be encountered.

Such hypoxia with mild hypocapnia and respiratory alkalosis (because of hyperventilation from hypoxia, anxiety, infection, or catecholamine release) characterizes the least severe gas exchange disturbance, stage I. Here, $\dot{V}/\dot{Q}$ disturbances are insufficient to lead to ventilatory failure and respiratory work remains effective in eliminating CO_2. A

Table 60-3
Blood Gas and pH in Status Asthmaticus

Stage	Obstructive Severity	$Paco_2$ (torr)	Ventilatory Status	Pao_2 (not on supplemental O_2) (torr)	Sao_2	Uncomplicated pH_a
I	+	35–42	Early hyperventilation (compensatory and other stimuli) a. mild, self-limiting attack b. chronic stable c. early status asthmaticus	Normal or mild reduction, 75–80	≧94%	≧7.40
II	++	<35	Late hyperventilation	55–75	85–94%	≧7.45–7.50
III		38–42	Eucapnia or "crossover"			≅7.40 + 0.4
	+		a. normalization, or	≧70–85	≧94%	
	+++		b. progressive abnormality	<70 (more likely <50)*	<85%	
IV	++++	>42–45	Hypoventilation, ventilatory failure	<50	<85%	<7.35

* Can be normal range with therapeutic O_2.
Pao_2 = arterial oxygen tension.
$Paco_2$ = arterial carbon dioxide tension.
Sao_2 = oxyhemoglobin saturation, %.
++++ = most severe.

therapeutic program requires supplemental O_2 and supportive measures, and bronchoreversibility may be readily restored. Stage II reflects greater obstruction with more advanced hypoxemia, but CO_2 elimination is still not hampered and more severe hyperventilation and respiratory alkalosis are observed; these patients are typically quite tachypneic and dyspneic and exhibit respiratory distress. With proper therapy, many of these patients will respond. Disturbingly, others remain refractory and will progress to greater severity with continued drug refractoriness.

The next phase, stage III, is a critical point in the evolution of obstruction and refractoriness and can be evidence of even further serious deterioration. Here, the Pa_{CO_2} and pH are paradoxically in a "normal range" despite the obvious continued clinical severity of the disease. This normalization of the Pa_{CO_2}-pH now is an index to the progression of asthma, since it reflects advancing $\dot{V}/\dot{Q}$ disturbances and is, in fact, a relative hypoventilation. The author has stressed this "cross-over" period (Fig. 60-4) to alert the physician of the transition between the *hyperventilating* (stages I and II) and the hypoventilating (stage IV) phases of status asthmaticus [180]. Because the next stage, IV, with frank hypoventilation and respiratory acidosis, can develop from this eucapnia level with alarming rapidity, as does the risk of death, the "cross-over" point is one of concern and reaction in which treatment must be modified and intensified to prevent

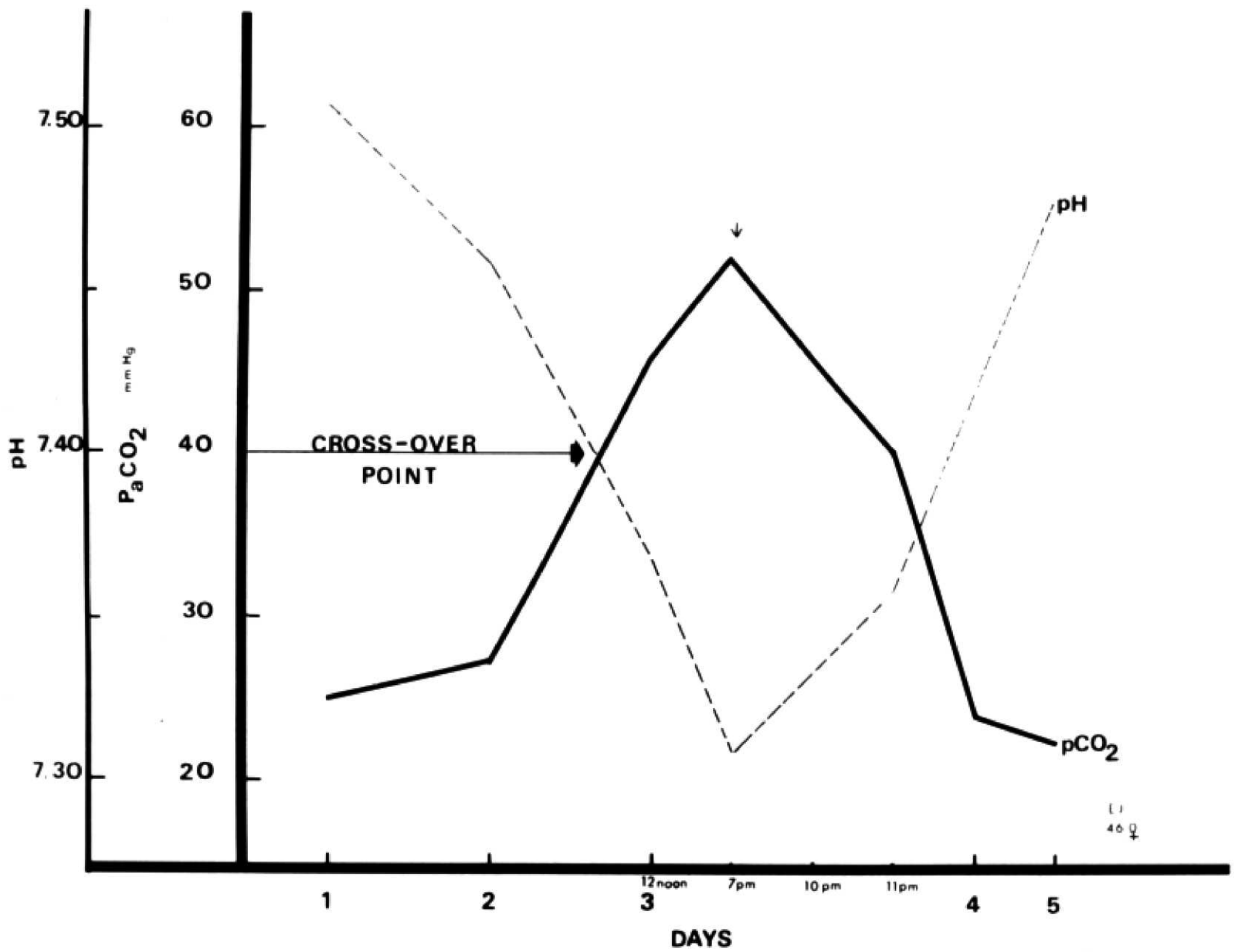


Figure 60-4
An example of cross-over stage III. Pa_{CO_2} and pH in a 46-year-old female in status asthmaticus. Note initial hypocapnia and respiratory alkalosis progressing to normal Pa_{CO_2}-pH relationships as a prelude to frank respiratory acidosis despite full medical therapy. Pa_{O_2} on supplemental O_2 at the cross-over point was 80 torr. The vertical arrow indicates institution of intubation and ventilatory support. The patient fully recovered. Note the rapid development of acidosis; it can occur in an hour. (Reprinted with permission from Weiss, E. B., and Faling, L. J., Clinical significance of Pa_{CO_2} during status asthma: The cross-over point. *Annals of Allergy* 26:545, 1968.)

further deterioration. The interpretation of a Pa_{CO_2} in the range of 40 torr, pH 7.35 to 7.45, and Pa_{O_2} of 70 torr (or greater, because of therapeutic oxygen) without reference to the clinical status, is obviously important because some patients will exhibit this profile and be either deteriorating or essentially asymptomatic (or in stage I).

Finally, in stage IV advanced hypoxemia is now complicated by hypercapnia and respiratory acidosis, and the immediate response to bronchodilator and other supportive measures is very limited. If a patient progresses through stage III to stage IV despite full therapy, then support of ventilation will be required because of the associated high mortality rate. Some patients presenting initially in stage IV may be managed conservatively; others will require mechanical ventilatory support if they are exhausted, obtunded, or have critical Pa_{O_2} or Pa_{CO_2}-pH values, as discussed below. Irresponsible causes of hypoventilation, such as sedative use, drying agents, or uncontrolled O_2 administration, must be identified as reversible, but contributing, factors.

All aspects of oxygen delivery are important because of the dangers of hypoxic injury or death. Cardiovascular limitations are not prominent in uncomplicated status asthmaticus (see Chapter 22), unless shock, heart failure, or arrhythmias supervene. Recently, shifts in oxyhemoglobin affinity (P_{50}) have been emphasized. With conditions of hypoxia, a rightward shift of the whole-blood oxyhemoglobin dissociation curve (increase in P_{50}) develops, postulated to be an adaptative mechanism favoring the release of oxygen from hemoglobin. Besides physiochemical Bohr or temperature effects, increasing concentrations of intraerythrocytic 2,3-diphosphoglycerate (2,3-DPG), which binds preferentially to reduced hemoglobin, are related to this rightward shift in a variety of pulmonary disorders such as stable chronic bronchitis, emphysema, pulmonary fibrosis, anemia, and congestive heart failure. The major influences in this 2,3-DPG shift are intracellular pH and a time-averaged mixed venous oxygen saturation, and the two influences in status asthmaticus which could elevate red cell 2,3-DPG are hypoxia and respiratory alkalosis. In one study of chronic stable bronchial asthma with mild hypoxemia, P_{50} was normal. Then, acute asthma was divided into hyperventilating and hypoventilating (acidotic) groups, but neither exhibited a significant net shift or an increase in physiological P_{50} or 2,3-DPG despite significant oxyhemoglobin desaturation [177]. This affinity state may still be physiological, but the actual influence upon oxygen delivery is not resolved. Although these matters are still unresolved, such factors could influence tissue hypoxia and stress the requirement for assuring adequate blood oxygenation as well as total oxygen delivery during status asthmaticus.

CLINICAL CONSIDERATIONS

The onset of status asthmaticus can be rapid, often dramatic, with a terribly oppressive air hunger, but for some patients this evolution may take several days or longer. The severity and reversibility of an attack may be directly related to the development time [41]. Clinical clues to impending status asthmaticus are cited in Table 60-2. Dyspnea is a key feature, associated with audible wheezing and interrupted irregularly by a distressing hacking cough, productive of gelatinous or colored phlegm. But sputum is rarely copious at the outset, a paucity reflecting its mechanical inspissation caused by thick and sticky characteristics from internal viscosity and surface adhesiveness changes. A clinical guideline is that most attacks will not remit until adequate secretion mobilization occurs, although this does not apply to atopic extrinsic asthmatic patients with pure bronchospasm, who respond rapidly to bronchodilator drugs.

The patient is usually agitated, fatigued, and anxious with a normal or slight elevation of blood pressure from catecholamine release. Dyspnea limits speech, which is interrupted by frequent pauses for breath. Regular tachycardia, flushing, and diaphoresis are common and cyanosis, when present, is a feature of advanced hemoglobin desaturation. A pulse rate of greater than 130/minute may indicate hypoxemia with Pa_{O_2} ranging to <40 torr, or it may relate to catecholamine response, or arise from adrenergic drugs, or a combination of factors [128]. Prominent neck vessels and —at times—the violent use of accessory respiratory muscles are observed. The breathing pattern is altered, with a rapid inspiration followed by a prolonged expiration, and both

exhibiting wheezing. Breath sounds are often coarse and loud, but regional reductions in intensity may imply bronchial mucous obstruction with significant atelectasis. Thoracic excursions are initially exaggerated and later diminished with greater disease severity. Adventitious sounds and lung overinflation may impair cardiac auscultation, usually revealing a regular tachycardia and accentuated S_2P. Musical rhonchi reflect looser airway secretions, and local, persistent post-tussive inspiratory rales and/or ergophony suggest a focal pneumonic or consolidative process; the emergence of nosier rhonchi parallels the mobilization of secretions. Overinflation yields not only a hyperresonant percussion note, but also contributes to the widespread attenuation in vesicular sound caused by generalized obstruction. In severe asthma, inspiratory wheezing is an added major finding. With severe obstruction, tidal volume and flow rates fall and the normally audible inspiratory and expiratory wheezing may become ominously soft or "tight" (high frequency dominance) in quality. At this stage, dyspnea is increased, paralleling the decrease in breath sounds and poor mobilization of sputum, and the chest may, in fact, be silent to auscultation.

Laryngeal stridor or other focal obstructive processes of the trachea and upper bronchi should not be confused with diffuse asthmatic airways obstruction; in the former instance the wheeze is monophonic, and its intensity diminishes from the site of its generation. In elderly patients, the presence of basilar rales (ventricular gallop or rises in central venous pressure) with diffuse wheezing indicates coexistent cardiac failure, although wheezing can be the only presenting initial sign of cardiac decompensation. If severe hypoxemia and hypercapnia supervene, papilledema, neuromuscular abnormalities (asterixis, irritability), confusion, agitation, cardiac arrhythmias, hypotension, or shock may ensue and add their respective findings; rarely some patients, especially children, may present obtunded.

As severe hyperinflation compromises diaphragmatic excursions, the patient prefers to sit upright fixing his shoulder girdle to enhance the effectiveness of the accessory respiratory muscles. With progressive obstruction and a rise in the midposition of the lungs, tidal excursions now occur near full inspiratory capacity. This hyperinflation leads to the typical findings of hyperresonance, caudally displaced and limited diaphragmatic excursions, reduced breath sounds, and pulsus paradoxus. The latter arises when an increased FRC and a high intra-alveolar pressure impair cardiac output, leading to a fall in arterial blood pressure during inspiration. In the studies of Rebuck and Read, the paradoxus fluctuations ranged from 10 to 130 mm Hg and was present when the $FEV_{1.0}$ was 1.25 liters or less; a reduction in this physical finding parallels improvement [126, 127]. Other clinical changes in asthma have functional correlations. For example, an $FEV_{1.0}$ of approximately 0.65 liters in adults during an acute attack is associated with retraction of the sternocleidomastoid muscles [91]. Most patients whose FVC or $FEV_{1.0}$ is <30 to 50 percent of predicted will exhibit serious hypoxemia, with a poor correlation between Pa_{CO_2} and VC or $FEV_{1.0}$ until the $FEV_{1.0}$ is less than 1.0 liter; then a correlation with CO_2 retention is observed.

A sequence of clinical recovery reflects reversal of the pathology. First, intercostal and neck muscle retractions disappear, then the dyspnea, and finally a decrease in expiratory wheeze reflecting the patency of the larger airways. Smaller airway patency is noted by improvements in Pa_{O_2} and flow rate indices as MMEFR [91]. Complications of the acute episode with physical findings include pneumothorax (pneumomediastinum, even pneumopericardium), mucous plugs with atelectasis, pneumonia, and occasionally rib fractures or cough syncope.

LABORATORY PROCEDURES

X-Ray

The principal value of the chest radiograph in status asthmaticus is to determine (1) specific precipitating causes as pneumonitis, or (2) complicating processes as pneumothorax, atelectasis, or cardiac decompensation. Hiatus hernia, pulmonary infarction, or pleural disorders may be inferred or diagnosed on these plain films, and appropriate examination of sinuses, cardiac series, or gastrointestinal contrast studies can be of additional value.

Extreme hyperinflation is common, and foci of bronchial mucoid impaction may be

observed, but the pulmonary vascular distribution and branching pattern is preserved. Clinical data make the diagnosis of pulmonary emphysema unlikely, and reduction in overdistention and return of diaphragmatic excursions is confirmatory. This distinction is easy in young, reversible, extrinsic asthmatic patients but it is less clear in those with intrinsic and infective bronchitic elements or where asthma complicates destructive emphysema. Bullae with concavity or serrations of the diaphragm, or persistently attenuated peripheral vasculature are atypical for uncomplicated status asthmaticus. Transient infiltrates may be a feature of extrinsic asthma with segmental or subsegmental distributions caused by mucous plugs, with or without *Aspergillus*. Similar infiltrates in intrinsic asthma are more likely to be bronchopneumonic foci. In children, intermittent attacks are associated with normal chest x-rays, whereas marked abnormalities (diaphragm below anterior rib level of 6.5, lung length ≧ lung width, narrow vertical heart, hilar vessels large relative to lung vessels) are invariably present with moderately severe and continuous asthma [145]. The severity of airways obstruction frequently relates to some of these x-ray changes [190].

Electrocardiogram

Because of hypoxemia, pH shifts, pulmonary hypertension, and right heart strain, the ECG may become abnormal with reversible axis shifts, conduction defects, or alterations in wave form. For example, a frequency in one series cited 19 percent right axis deviation, 14 percent clockwise rotation, 3 percent RBBB, 9 percent ST-T wave changes, 3 percent ventricular ectopics, and 12 percent right ventricular dominance with RV_1, SV_5 [127]. Turiaf et al. cited ECG alterations in 50 percent of cases [164]. Sinus tachycardia, the most common rhythm pattern, may be intensified by chronotropic sympathomimetic drugs [45]. In young patients serious ECG changes may be indices of greater severity, whereas interpretation in older asthmatic patients is influenced by possible underlying cardiac disease. The latter is a serious liability during the stress period of status asthmaticus. Acute right heart strain, with wheeze or dyspnea, can also mimic pulmonary embolization or acute myocardial injury. A complicating feature that should be recalled in interpreting the ECG is the use or abuse of fluorocarbon-propelled bronchodilator aerosols with cardiotoxicity or arrhythmiagenesis, or intensification of preexisting hypoxemia. Cited ECG changes of these propellants include sinus bradycardia, T-wave depression, and A-V block in hypoxemic mice, or cardiac irritability by non-$beta_2$-selective adrenergic drugs with ventricular irritability or lethal arryhthmias [160]. Some patients receiving oxygen do not exhibit ECG changes despite vigorous sympathomimetic therapy, suggesting that oxygen may be protective under these conditions [127].

Hemogram and Chemistry

Leukocytosis may be modest. Counts ≧ 15,000/mm³ are likely due to infection, especially with an immature polymorphonuclear cell shift, and stress or dehydration may influence these white blood cell or hematocrit values. No particular changes in serum electrolytes are characteristic for severe asthma unless complicating disorders, or the effects of therapy such as corticosteroids, coexist with, for example, hypokalemic alkalosis. Hypokalemia is reported but other studies indicate serum sodium, chloride, and potassium to be within normal limits [128]. Increased levels of serum glutamic-oxaloacetic transaminase (SGOT) and serum glutamic-pyruvic transaminase (SGPT), and liver-specific ornithine carbamal transferase caused by hypoxic or hypercapneic hepatic injury can occur [30]. Elevated isoenzyme lactic dehydrogenase (LDH) patterns from lung and liver show no relationship of total LDH activity to the length or severity of an asthmatic episode [169]. A sweat test and quantitative immunoglobulins if cystic fibrosis or immune deficiency respectively are suspect, may be indicated.

Eosinophilia

Blood eosinophils measured as a quantitative total eosinophil count/mm³ (TEC) is valuable in diagnosis and therapy. This count provides an overall clue to the allergic reaction as well as indexing adrenal-corticosteroid

function and the efficacy of glucocorticoid therapy. Minimal eosinophilia occurs during infectious exacerbations, whereas greater blood or sputum eosinophilia is common during an allergic relapse [88]. Improvements in pulmonary function with falls in TEC parallel appropriate therapy. Steroid-resistant asthmatic patients with accelerated plasma cortisol clearances have high TEC (>400 cells/mm^3) and require high steroid doses to achieve eosinopenia (<50–100/mm^3) and clinical remission; in one series, TEC fell 75 percent in steroid-responsive patients, but only 36 percent in resistant asthmatic patients after 40 mg IV cortisol [138].

Normal TEC averages 100 to 200/mm^3; this count is slightly increased in asymptomatic atopic patients (200/mm^3) and can become greater with more extensive allergic insults [88]. In status asthmaticus it may reach 1,000 to 1,500/mm^3, but such counts should not specifically imply this as a diagnosis. High TECs are seen in both intrinsic and extrinsic asthma; values of more than 4,000/mm^3 are likely due to such causes as parasitic involvement [173]. In addition, although the presence of eosinophils is not diagnostic for asthma, their absence does not exclude this diagnosis. Adrenergic agents, theophylline, and cromolyn, as well as emotional stress and infection, all can reduce eosinophil numbers [81]. Serial TEC measurements are useful in predicting exacerbations as well as reflecting the adequacy of therapy. For example, in one study, corticosteroid treatment was necessary for clinical resolution when eosinophil counts exceeded 1,200/mm^3 [62]. With or without steroid resistance, patients in status asthmaticus will generally require corticosteroids, and if eosinophilia is present, the titration of steroid doses to clinical resolution will be facilitated by serial measurements of TEC. Greater and more prolonged steroid requirements and other therapeutic measures will be necessary for patients not improving clinically and/or when eosinopenia has not occurred.

SPUTUM

Intra-airway secretions, which mechanically contribute to refractoriness, also reflect certain pathological changes in the expectorated sputum. Thus, noninfected mucoid sputum with eosinophils or infected purulent material with bacteria offers clues to etiology. In the early phases of status asthmaticus only small volumes are apparent because of diffuse inspissation and probably not because of hyposecretion. Before therapy, sputum is thick, opalescent, and adhesive, sticking tenaciously to dehydrated oral mucosa or sputum cups and later clinical improvement is preceded by a greater facility in expectoration of a thinner, moist sputum. Gross inspection often reveals fine, threadlike mucinous strands, composed of glycoproteins, debris, and dislodged epithelial cells, mixed with larger coils or Curschmann's spirals. These coiled whorls with eosinophils are highly suggestive of asthma although spirals can occur also in bronchiolitis, pneumonitis, or chronic bronchitis [27].

Sputum cytology, as it reflects allergic and inflammatory elements, is also useful in diagnosis or therapy (see Chapter 45). The Creola body, characteristic of a severe asthma attack, is a clump or cluster of columnar bronchial-epithelial cells with intact and active cilia observed in wet preparations [108]. It indexes severity because intense reactions are needed for transudation of submucosal edema to dehisce the clump from its basement membrane attachment. Large numbers of sputum eosinophils or Charcot-Leyden crystals, their crystalloid derivatives, reflect both an intense allergic element and extensive tissue infiltration as well as mast cell mediator release (including eosinophil chemotactic factor of anaphylaxis [ECFA]). In chronic bronchitis, sputum eosinophils constitute <10 to 15 percent of all cell types. Higher values tend to characterize allergic asthma, reflecting, as in blood, a greater severity, but this issue is not entirely resolved [83, 100]. Inspissated airway plugs with eosinophils having ill-defined morphology indicate protracted obstruction, and the reemergence of recognizable free cells occurs with improved sputum mobilization [136]. Thus, shifts in sputum eosinophils may be caused by (1) inability to raise mucous plugs containing these cells, (2) the introduction of eosinopenic measures (allergen removal, corticosteroids), or (3) nonallergic episode with predominant polymorphonuclear neutrophil leukocytes (PMN).

Finally, a gram stain is necessary to evaluate bacteria. Brown discoloration may be

caused by *Aspergillus* and this should be evaluated.

Select biochemical and immunological features of sputum include the presence of certain pharmacological mediators such as histamine, kinin released by kallikrein enzymes, IgE, secreted or transudated IgG (as high as 20 to 50 mg per 100 ml), locally secreted bacteriostatic IgA, lysozymes, and lactoferrin. IgE concentration is about 50 μg% in asthmatic sputum and is absent in normal secretions [67]. Physiochemical differences in status asthmaticus such as glycoproteins, serum proteins, sialic acid, deoxyribonucleic acid (DNA), pH, water content, internal viscosity, or surface consistency are not yet resolved. Sputum viscosity may depend more upon its gross macroscopic status (e.g., purulent or mucoid) than on the inciting disease. However, in one study asthmatic sputum was found to be more viscous than specimens from cystic fibrosis, chronic bronchitis, or bronchiectasis [23]; others claim this difference exists for mucoid secretions [117]. It will be of value to determine both the drugs which can enhance an optimal viscoelastic state favoring expectoration, and the pharmacological measures which promote clearance or suppress synthesis of secretions. For example, clinical observations of increased viscosity during status asthmaticus have some laboratory substantiation in vitro where a reduction in viscosity is shown to be proportional to water content [86]. Also, the neuraminic acid content of sputum contributes to the physical properties of mucoid sputum, and a positive correlation to sputum viscosity was shown by Keal in chronic bronchitis and in some cases of asthma [75]. In asthmatic patients with profuse bronchorrhea, high neuraminic acid levels have been observed and could serve as an index for therapy, especially for steroids. Concerning the implications of water content, some studies delineate two major sputum components, one actively secreted by mucous glands, and another passively transudated; patients with asthma may additionally have an inflammatory transudation of serum albumin, fibrin, and other plasma proteins. In status asthmaticus, rapid absorption of water from sputum or the mucous blanket by systemic or local dehydration with protein polymerization processes will produce a more viscous gel causing the typical inspissated bronchial plugs. The therapeutic reaction is proper hydration.

THERAPY

A history, physical examination, and appropriate laboratory studies should be obtained quickly and thoroughly. This includes spirometry (if cooperation permits), arterial blood gas and pH tests, x-ray studies, sputum examination, hemogram, eosinophil count, blood chemistries, urine analysis, and ECG. The history or prior records may indicate recent durg use, sensitivity, or responses to these agents, as well as any plausible inciting factors. In this evaluation, the possibility of continued exposure to an inciting agent contributing to bronchodilator refractoriness should be carefully considered and eliminated if feasible. From the outset, the physician's calm and confident manner will support the patient emotionally, and the physician should assure the patient of recovery.

The goal of therapy is to correct the processes creating the gas exchange abnormalities; hence, a patent airway is a primary step in management. Most patients will respond to conservative but intensive schedules with oxygen, drug programs, humidification, and possibly IPPB treatments, and not need an artificial airway. The proper sequence in these instances is to institute the full scope of measures outlined below, each tailored to individual patient requirements. During the course, frequent clinical and laboratory data as arterial blood gas and pH must be obtained to evaluate the adequacy of the program. The therapeutic plan will depend upon what stage (see Table 60-3) the patient is in and the progress, or lack of it, while on therapy. Thus, some patients in stages I through IV may be managed without intubation or ventilator support, whereas others in stage III or particularly in stage IV will appear in obvious difficulties and have a high priority for intubation with ventilatory assistance.

Oxygen

Deaths, including those acute and unexpected, or serious biochemical disturbances are often due to hypoxic extremes with adverse end-organ effects as impaired myocardial function, pulmonary hypertension, increased tho-

racic work, and hypoxic encephalopathy. *Thus, continuous and adequate oxygen tensions are mandatory from the outset in all patients.* A Pa_{O_2} of 60 torr and a corresponding Sa_{O_2} of 85 to 90 percent are physiological levels, assuming that red blood cell (RBC) mass, P_{50}, cardiac output, and systemic blood flow are appropriate to meet tissue demands. Higher tensions of 80 to 100 torr provide a margin of safety from the potentially adverse hypoxic effects of suctioning or of bronchodilator drugs and such levels are advised. Because tank or wall oxygen sources are absolutely dry, adequate humidification is needed to minimize drying of secretions or bronchial irritation. Appropriate concentrations of oxygen can be delivered by nasal cannulae or face masks, or with ventilators.

Despite a graded severity of hypoxemia, many instances are easily corrected by oxygen, and inspired concentrations of 30 to 50 percent will be adequate, because the average Pa_{O_2} ranges from 50 to 70 torr. However, Pa_{O_2} values poised at the descending slope of the Hb-O_2 dissociation curve could lead rapidly to dangerous levels of hypoxemia. Additionally, several series cite a greater severity of initial arterial hypoxemia, from 30 to 50 torr, even in children, and without hypercapnia [39, 93, 128]. Anatomical right-to-left shunting or even alveolar hypoventilation can contribute further to this hypoxemia. Thus, even greater O_2 may have to be supplied. If the Pa_{O_2} remains <50 to 60 torr (without hypercapnia and with a $F_{I_{O_2}}$ of 0.25–0.40), then venous admixture can be surmised from extensive secretions, atelectasis, or pneumonia. This will demand more oxygen as well as active sputum mobilization measures. If the Pa_{CO_2} is elevated, other causes of central alveolar hypoventilation contributing to hypoxemia should be considered as well.

A fall in Pa_{O_2} by isoproterenol, epinephrine, or aminophylline is another problem, since the use of these drugs is mandatory for the relief of airways obstruction. This danger is greatest when they are prescribed without supplemental oxygen. In stable asthma, isoproterenol dosing is not invariably associated with progressive hypoxemia, nor does concurrent administration of aminophylline protect against a fall in Pa_{O_2} [13]. The rational use of oxygen requires repeated arterial blood documentation of adequacy even during such drug therapy and is *not* supplanted by spirometry or clinical measurements.

Relatively few uncomplicated asthmatic patients will significantly suppress their chemoreceptor hypoxic respiratory drive by oxygen administration. An exception is those asthmatic patients with evolving hypercarbia [128]. Oxygen-induced alveolar hypoventilation has also been described caused perhaps by coexisting metabolic alkalosis, or chronic hypercapnia from chronic bronchitis, or inappropriate sedative use [146]. Adequate oxygenation must be assured in these cases commencing with low flow oxygen at 2 to 4 liters/minute flow with a nasal cannula or catheter, or by Venturimasks which will deliver relatively precise O_2 concentrations. If this approach is tolerated, good O_2 tensions with modest increases in CO_2 (e.g., <5 torr) will be possible. But if respiratory depression occurs, mechanical ventilation with O_2 enrichment must be instituted. Potential oxygen toxicity from a $F_{I_{O_2}}$ >0.6 should be avoided; the lowest concentrations providing physiological tensions are best. However, for all practical purposes, anoxia is a greater risk than oxygen toxicity, and advantage should be taken of the substantial increase in oxygen deliverable by modest increases in $F_{I_{O_2}}$. The use of light gas helium-oxygen mixtures (75% He) may take advantage of lower flow resistances and reduced respiratory work. Although a reduction in $\dot{V}O_2/\dot{V}E$ and in pulmonary resistance at high work loads occurs, the practicability of helium use in status asthmaticus has not been fully examined (see Chapter 65).

Bronchodilator Agents

Bronchodilator drugs are fundamental in management and should be administered at once. Their primary effect is upon a labile or reversible bronchial smooth contraction, with little obvious action on the inflammatory processes and secretions which are more fixed and resolve slowly. The relative contribution of these elements varies from case to case, a difference which should be appreciated in evaluating therapeutic effectiveness [74]. Because the methods for evaluating bronchodilator efficacy in status asthmaticus are limited, maximum or optimum results are difficult to

define. Furthermore, by definition, immediate responses are precluded, and their effectiveness is deduced from stable-state human or animal studies. Besides hypoxemia induction, a less common problem is a delayed bronchoconstrictive effect from isoproterenol which can be responsible for refractory obstruction. Thus, bronchodilator drugs must be prescribed with established effective dose schedules and observed for benefits and adverse effects.

XANTHINES (see also Chapter 51)

Aminophylline (80% theophylline ethylenediamine) is a rapidly acting, potent, and relatively long-acting bronchodilator drug whose half-life averages 312 ± 84 minutes in adults and about 202 minutes in children, but with wide ranges, particularly in the latter, from 110 to 600 minutes [71, 111]. Its primary benefit is its presumptive, continued activity despite epinephrine fastness and/or when coronary artery disease precludes the use of cardiac stimulants. Thus, it should be instituted and continued through the management period. Increases in vital capacity and reduction in airway and pulmonary vascular resistance result, whereas cardiovascular side effects are modest [71, 105]. The correlation between clinical response and plasma concentrations appears good [105, 111, 122], and based on average theophylline clearances, effective serum levels of between 10 and 20 μg/ml should be maintained on a 24-hour basis. It should be administered immediately, with an initial IV loading dose of 250 to 500 mg *slowly* over 15 to 20 minutes, or added to infusions for the average 70 kg adult; or 5.6 mg/kg over 15 to 20 minutes; this is followed by 40 to 60 mg/hour (0.9 mg/kg/hour), not to exceed 1.5 to 2.0 gm or about 20 mg/kg per day for adults, allowing for individual responses. It is necessary to titrate clinical response against toxicity or intolerances [111], and reductions in maintenance infusions may be needed with heart failure or severe liver disease because of resulting higher blood concentrations. Side effects and toxicity relate to serum levels and are common at concentrations ≥20–25 μg/ml; but at times below these levels when nausea, vomiting, tachycardia, or diarrhea supervene, and these side effects are best minimized by reducing dosages, not by completely stopping the drug. Before administration, it is important to determine when the patient had previously used the drug, and in what quantity in order to avoid acute cumulative toxicity. Overdosing can be associated with convulsions, arrhythmias, coma, or fatalities [69]. Oral or rectal preparations are not indicated in status asthmaticus. Caution has been advised in the oral combination of ephedrine and theophylline in severe asthma, for toxicity may be greater and the combination is no more effective than theophylline alone [176].

The average formulations for adults may exhibit wide fluctuations in acute peak and trough levels beyond the desirable 10 and 20 μg/ml range by variations in distribution, absorption, rates of excretion, and metabolic clearance as well as possible hepatoenteric circulation. After IV dosing, half-life data of from 181 to 571 minutes suggest variations in actual blood levels and, hence, the benefit-toxic ratio will require careful monitoring, if not periodic serum (or salivary) theophylline assays [71, 84]. In other instances, standard doses may be inadequate for improvement [51, 122]. Controlled trials of theophylline in status asthmaticus are limited, but one recent study with parenteral aminophylline indicated an apparent bronchodilator effect at *blood* concentrations of 2.0 to 8.0 μg/ml [111]. Effective doses should be continued throughout as a main component of bronchodilator maintenance therapy, for few patients develop tachyphylaxis or intolerance to the drug.

SYMPATHOMIMETIC DRUGS

Sympathomimetic drugs may be employed in conjunction with all other supportive measures. The effectiveness of epinephrine, a potent adrenergic stimulator, and other sympathomimetic agents early in treatment of status asthmaticus is limited, and repeated dosing is not desirable. In adults, 0.3 ml (1:1,000 aqueous) initial doses may be tried subcutaneously, once each 30 minutes for two or three doses, depending upon effect or to establish refractoriness if indicated. Thereafter, it should be used sparingly if at all. Later in the course, small doses could be reattempted at intervals (e.g., 0.1 ml SQ, t.i.d.), for responsiveness to the drug might return

during therapy. Small repetitive doses are recommended for safety and to minimize toxicity. Caution is advised, not only to avoid toxicity, but because of bronchospasm which could theoretically intensify in the presence of beta blockade by an alpha-adrenergic stimulation effect. There is no special advantage in longer acting (up to 4 hours) preparations as Sus-Phrine. Aerosols of 1% epinephrine and racemic epinephrine (2.25% Vaponefrin) can be attempted, and nebulized (DeVilbis No. 40 or 42), or given by IPPB units. The average dose of racemic epinephrine is 0.25 to 0.5 ml in 2.0 ml saline solution delivered over 15 minutes and given once every 6 hours. When prescribed, the patient should be encouraged to take deep breaths to facilitate drug distribution, which is limited in severe obstruction. Intravenous use is not recommended. Extreme caution is advised in all patients, especially in elderly or risk patients with hypertensive cardiovascular-cerebrovascular diseases, or if the pulse exceeds 120/minute. Epinephrine resistance may be reversed by sodium bicarbonate if acidosis exists, but this subject is not entirely resolved [106, 170]. Theophylline or steroids may similarly restore some of its effectiveness.

Combination therapy containing phenylephrine, an alpha-stimulating agent, to reduce vascular congestion and edema and prolong bronchodilator action have little data of effective schedules in status asthmaticus.

ISOPROTERENOL

As a powerful, rapid acting, pure (nonselective), $beta_1$ and $beta_2$ adrenergic stimulator, isoproterenol is commonly employed as an aerosol, with 0.25 to 0.5 ml (1:200) in 2.0 ml sterile saline solution or water delivered pneumatically over 15 minutes on a 4- to 6-hour basis for the average sized adult. It is estimated that this form of delivery loses about 70 percent of the dose in the exhaled air. Freon or hand bulbs are occasionally used. The drug's effect is short-lived, with rapid absorption and inactivation by metabolic conversion via catechol-*O*-methyl transferase. Thus, $FEV_{1.0}$ reaches a peak in 15 minutes and declines steadily thereafter [124]. Inasmuch as blood levels of isoproterenol are not commonly available, the smallest dose effective by clinical-laboratory findings is recommended (e.g., decreases in respiratory work, wheezing, Pa_{CO_2}, peak ventilator pressures, or increases in Pa_{O_2} or tidal volume [Vt]). Adverse reactions include cardiac stimulation and arrhythmias, dizziness, palpitation, anxiety, hypotension, and angina; clinically, many mysterious tachyarrhythmias can be resolved by reviewing the order sheets. Derivatives of isoproterenol, such as isoetharine and metaproterenol (Alupent), used as aerosols have insufficient data of efficacy in status asthmaticus, but can be tried (see Chapter 49).

Several considerations concerning isoproterenol should be emphasized: (1) hypoxemic induction mandates concurrent oxygen therapy; (2) excessive dosing is to be avoided, for cardiotoxicity or sudden death may occur [87]; (3) aerosol dispersion does not assure delivery to obstructed airways, for paths of least air flow resistance will receive more drug; absorption from airways, oral mucosa, or stomach will lead to systemic-cardiovascular side effects; (4) repeated dosing may lead to refractiveness by (a) beta-blockade from its metabolite, 3-*O*-methylisoproterenol, or (b) direct myospasm [77, 120, 134]; (5) persistent obstruction may require discontinuation of the drug, then other previously ineffective therapy may become beneficial [171]. It is interesting that some studies have failed to corroborate a cumulative effect on heart rate or Pa_{O_2} falls by repeated dosing of isoproterenol [13, 142]. Overall, these features require a close supervision of the patient.

Current interest in relatively selective beta-2 adrenergic bronchodilators is great, for beside equipotency to isoproterenol, they are purported to have less cardiovascular side effects or toxicity as well as less hypoxemic induction. Favorable characteristics are their stability, longer duration of action, and absence of known beta-blocking metabolites (see Chapters 49 and 50). Albuteral (salbutamol) is used extensively in England; terbutaline is now available in the United States for parenteral or oral use. In status asthmaticus limited studies are available. A comparison of isoproterenol and salbutamol aerosol in stable, nonhypoxemic asthmatic patients found an optimal effect and minimal chronotropic cardiac action with a solution of 0.5% salbutamol [25]. Streeton and Morgan [154] nebulized 0.5% aqueous salbutamol over 15 to 20 minutes every 4 to 6 hours to nearly 100 critically

ill patients, including those in status asthmaticus, and the following responses were noted: (a) rapid decrease in Ra, (b) clinical improvement, and (c) minor side effects and a minor fall in Pa_{O_2}. Similar improvements in specific airway conductance were reported in four patients with status asthmaticus following 400 μg Freon-propelled aerosol salbutamol, but MMEFR and $FEV_{1.0}$ changes were not significant [133]. The full role of these agents in status asthmaticus is yet to be evaluated. A suggested dose schedule for terbutaline is 0.25 to 0.50 mg, b.i.d. to t.i.d., subcutaneously.

Intravenous isoproterenol has recently been advocated in an attempt to improve therapy and reduce ventilator complications in childhood status asthmaticus. In one evaluation of 19 children with respiratory failure (Pa_{CO_2} > 54 torr) refractory to epinephrine and theophylline, 17 children responded with a fall in Pa_{CO_2} to ≤48 torr in 10 hours following continuous IV infusion of doses ranging from 0.08 to 2.7 μg/kg/minute. One child required ventilation, another had reversible ventricular tachycardia; none exhibited myocardial injury [188]. Bypassing the problems of aerosol delivery and because of rapid metabolism, such sustained infusions may be an effective method of continuous airway muscle (or mast cell) delivery of isoproterenol for competitive antagonism of beta-blockade. Studies in adults are scant. Paterson et al. [121] infused graded doses of 0.11 to 2.2 μg/minute of IV isoproterenol in *stable* asthma, comparing it to a similar infusion of salbutamol (0.54 to 2.2 μg/min). Both increased $FEV_{1.0}$. At doses of 1.1 μg/minute the drugs were considered equipotent bronchodilators, but salbutamol had a 7-fold less effect on heart rate. Quite recently, one trial in acute asthma demonstrated some effectiveness of IV isoproterenol in adults. A major cited advantage in this approach is that precious time is saved to allow for corticosteroid effect, which may then minimize the need for endotracheal intubation and assisted ventilation [80]. Finally, a recent British double-blind trial of intravenous salbutamol (500 μg) versus aminophylline (0.5 gm) in acute asthma yielded statistically equivalent acute improvements in PEFR for both drugs; however, it was felt that, in this small series of twenty patients, side effects were less with salbutamol [186a]. Thus this agent may have an increasing role in management of status asthmaticus in the future.

OTHER AGENTS

Even though cromolyn sodium is not indicated in status asthmaticus, there are no data of ill effects if it is continued, but delivery will be limited. Antihistamines have little documented effect and may be detrimental because of a dessicant action on secretions. They cannot be generally recommended. Ephedrine, 25 mg orally every 4 to 6 hours, seems best reserved for recovery period or ambulatory use because of side effects and tachyphylaxis. At present, atropine or newer, related anticholinergic derivatives do not have a role in treatment (see Chapter 49).

Steroids

Adrenal corticosteroids are vital and usually mandatory in management. Considerations of morbidity from brief therapy are small in contrast to their effectiveness. An added benefit of steroids is an enhancement of adrenergic bronchodilator responsiveness [78] and in one double-blind trial of injectable corticosteroids in children, there was an unexplained rise in Pa_{O_2} in 24 hours, compared to control subjects (63 vs. 77 torr) [123]. It would be advantageous if the status of endogenous adrenal function were known since baseline free and total plasma 17-hydrocorticosteroid levels could be useful in establishing relative risks to stress and requirements of extra glucocorticoids. For example, one study of status asthmaticus revealed significantly low admission plasma cortisol levels, the highest value being 55 μg per 100 ml whereas patients with the stress of cardiogenic shock had levels of 155 μg per 100 ml [21]. In practice, this approach is limited, and steroids are generally indicated in all instances of status asthmaticus.

Steroids should be administered immediately once bronchodilator refractoriness is established. Although their maximum action is delayed for several hours, they can exhibit an effect within 30 to 60 minutes [45a]. In children, some physicians temporize for the initial 24 hours; others prescribe them immediately for all hospitalized cases. However, there should be no hesitation in those patients previously on maintenance steroids or if they

have had similar attacks requiring steroids for lysis. Initially, IV doses are preferable to obviate erratic gastrointestinal absorption. Initial recommendations vary from 100 to 200 mg IV methylprednisolone sodium succinate (Solu-Medrol), or equivalent, immediately and then up to 300 to 500 mg in 24 hours for a 70-kg adult, maintained, and then tapered with improvement; recommendations do vary in such doses, and lower as well as higher recommendations exist in the literature [30a, 68, 72]. We use about 100 to 200 mg methylprednisolone initially, followed by 200 to 400 mg total, in divided doses, in the first 24 hours. Relatively high doses of 100 mg every 8 to 12 hours are then continued daily until clearing is observed. The antiinflammatory effectiveness of prednisone-prednisolone, their low mineralocorticoid properties, and their immediate action without conversion to an active form, as is necessary with cortisone, are favorable features. Hydrocortisone sodium succinate in doses of 100 to 200 mg IV initially, or 4 mg/kg, followed by divided doses up to a 1,000 to 2,000 mg total (or more) may be required in the first 24 hours (see Chapter 53). Known steroid-resistant patients may have even greater requirements (see Chapter 54). ACTH is not recommended because the adrenal cortex is already presumably maximally stimulated, and resulting cortisol levels could be suboptimal. Collins recently reported, however, that acute asthma patients not previously on corticosteroids did respond well to daily depot tetracosactrin [30a].

The proper dose is one which is clinically effective, and this effect must be estimated by clinical-pulmonary end points (including FVC and $FEV_{1.0}$) and by biological effectiveness. Particularly useful for this estimation are total eosinophil counts where effective steroid doses will yield values of $<100/mm^3$ or less within 24 to 36 hours. Greater cell counts indicate a need for further and higher steroid dosages (and antigen elimination).

Measurements of plasma 11-hydroxycorticosteroids, (11-OHCS) are of some benefit in achieving accurate therapeutic levels in acute asthma [31]. Normally, 95 percent of plasma cortisol as bound to the gamma globulin transcortin is biologically inactive, and only free cortisol can diffuse through membranes into the tissues and exert a therapeutic effect [32, 36]. This is accomplished when plasma levels reach 100 to 150 μg/100 ml and can be achieved by 4 mg hydrocortisone/kg/every 220 minutes by IV administration (approximately 1,600 mg/24 hr in a 70-kg patient) [31, 44]. However, critical analysis of this formulation did not necessarily find asthmalysis with strict plasma level schedules [21], and higher doses may be necessary in those on chronic maintenance steroids because of accelerated metabolic clearance rates [44]. It is also suggested that *continuous* IV infusions of hydrocortisone (3 mg/kg/q6h) are preferable to bolus doses in achieving maintenance plasma cortisol levels with a smaller total daily dose [30a]. Aerosol corticosteroids have not yet been evaluated in the treatment of status asthmaticus, but particle delivery may limit their role.

When clinical improvement is sustained, steroids can be gradually tapered by approximately 50 to 70 mg prednisone a day, or about 25% every two or three days. For those not previously on chronic therapy, the drug can be lowered to oral 15 to 20 mg prednisone, then to alternate days for one or several weeks, and finally discontinued. During this process, doses are best titrated with clinical symptoms and signs, and with spirometric values, and any relapse may require their temporary increase. Patients previously on alternate-day schedules are tapered to their previous maintenance levels (see Chapter 53). Finally, evaluation of HPA function can be conducted during remissions to identify liabilities in anticipation of such stress as surgery or exacerbations of asthma. The use of simple ACTH stimulation and other tests appear useful and reliable (see Chapter 52) [76].

Complications of brief, high-dose steroid therapy appear to be minimal [123]. Nonspecific gastrointestinal bleeding is not unique, nevertheless, we routinely provide antacids. Acute psychotic reactions or other mental changes do occur and may be confused with abnormalities from hypoxia or pH changes. Sodium and fluid retention, and particularly hypokalemia following large doses of steroids, requires monitoring and correction; hypokalemic alkalosis with muscle weakness and hypoventilation is an unnecessary complication. Dexamethasone and prednisone exhibit accelerated plasma clearances when phenobarbital is administered, and ad-

justment of their dosages may be necessary if there is ever any need to employ long-acting barbiturates. The great hazards of acute bacterial superinfections in the intubated patient on steroids can be minimized by diligent aseptic techniques during suctioning, cleanliness of ventilators and their tubing, and maintaining sterility of mainstream nebulizers. Sputum and tracheal aspirates should be cultured regularly in this circumstance.

Hydration and Sputum Mobilization

Whether the patient is managed with or without an artificial airway, mobilization of secretions is a vital step. Under normal conditions, the inspired air is warmed and saturated with water vapor in the upper respiratory tract and major airways. Impaired humidification affects existing secretions, which then lose water and become thickened, tenacious, and thus more difficult to raise. These circumstances also impair mucociliary action and hence favor stasis with bacterial invasion. In status asthmaticus, hyperpnea, perspiration, fever, and reduced oral fluid intake contribute to a relative humidity defect that can be aggravated by therapeutic oxygen if not properly humidified. Unheated bubble humidifiers produce only 20 percent of the required moisture. Furthermore, intubation or tracheostomy bypasses the upper airways humidifying mechanism. Therefore, adequate hydration and appropriate reduction and/or removal of secretions are mandatory, for secretions are a major feature in precipitating, intensifying, or perpetuating the clinical state. Generally, there will be ample evidence of the presence of sputum, yet it must be suspect even without obvious findings as occurs with diffuse inspissations. Their composition should be promptly identified as infectious or allergic—or mixtures—to aid in treatment decisions.

Water appears to be the best expectorant. Adequate hydration may be achieved by mouth, but, in status asthmaticus, IV routes supported by humidification of the inspired air are initially preferred to assure an adequate daily intake. In the absence of edema-forming states (CHF), for the average 70 kg adult initial hydration of 2.5 to 4.0 liters of 5% dextrose in water or 0.5*N* saline solution is suggested. This is followed by maintenance IV fluids of about 1.6 liters/m^2/day (or 2.5–4.0 liters) depending upon urine losses, tachypnea, and fever. Requirements are greater for severely dehydrated patients. Besides expectorant effects, an important contribution in fluid management arose from the studies which emphasized the dangers of hypovolemia. True decreases in blood volume with hemoconcentration were present in some instances of status asthmaticus, and circulatory collapse was conjectured as a cause of sudden, unexpected death. Improvement with prompt volume replacement supported the concept that dehydration is dangerous, and volumes even greater than maintenance must be replaced when the hematocrit is increased or if hypotension exists [153]. In the presence of a normal renal function, a low urine specific gravity, low osmolarity, or urine Na^+ of 30 to 40 mEq/liter may be taken as evidence of adequate hydration. Serum sodium measurements will indicate the relative requirements for sodium and water; for example, a serum sodium of 150 mEq/liter requires, primarily, water, whereas normal or lower Na^+ values can be treated with 0.5*N* or 1.0*N* saline solutions. Daily observations of fluid intake and output and daily body weights are important precautions, particularly where fluid retention could be a problem, as in the patient with underlying cardiac disease and/or those receiving corticosteroids. In some instances a Swan-Ganz catheter may aid in fluid management.

Expectorant drugs, such as sodium or potassium iodide (SSKI) or glyceryl guaiacolate, may also be beneficial. Iodides apparently increase the aqueous output of the respiratory tract as well as cause proteolysis, and limited studies in children substantiate some expectorant value for the drug [46, 47]. They are prescribed as sodium iodide, 0.5 to 1.5 gm/24 hours added to IV infusions or as SSKI orally (1.0 gm/ml) 10 to 15 drops in water/b.i.d.-q.i.d. A critical evaluation of iodides is given by Boyd et al. [11]. Skin eruptions, enlargement of salivary glands, fever, angioedema, rhinorrhea, and eosinophilia are infrequent side reactions; sodium loading, as NaI, is low (6.5 mEq/gm). Hypersensitivity reactions are more problematic. Glyceryl guaiacolate is purportedly effective orally in doses of 100 to 200 mg q.i.d. It is unavailable for parenteral use, but may be beneficial if an iodide reaction occurs. Theoretical contrain-

dications to its use include active peptic ulceration, or bleeding diathesis because of a decrease in platelet adhesiveness. Its value in asthma has not been well documented [60]. Finally, ammonium chloride (1–2 gm orally/day) has no specific indications for asthma.

Mucolytic and proteolytic agents chemically decrease sputum viscosity to some "optimal" point at which expectoration is facilitated. Purulent sputum, high in DNA content generated from necrotic inflammatory or parenchymal cells, may respond to proteolysis by deoxyribonuclease (Pancreatic Dornase) employed as an aerosol, 50,000 units/3 ml saline solution t.i.d., or instilled during bronchoscopy. The major side effect is bronchospasm. The drug is recommended when significant *purulent* sputum cannot be coughed or suctioned. Antibiotics, however, are the first line of treatment for purulent secretions. *N*-acetylcysteine (Mucomyst) reduces the viscosity of mucoid or purulent secretions by chemical reduction of mucopolysaccharides and mucoproteins. It has theoretical advantages for predominantly mucoid sputa which are uninfluenced by antibiotics, but irritative bronchospasm largely limits its use. It is not generally recommended, but if employed it should be used with caution and a bronchodilator, usually isoproterenol, must be added: 3.0 to 5.0 ml 10% *N*-actylcysteine with 0.25 ml of 1:200 isoproterenol, is used as an aerosol, or instilled through an endotracheal tube or bronchoscope. Immediate suctioning is mandatory because bronchorrhea or excessive thinning of secretions may cause asphyxiation in a patient with an ineffective cough or in one who is intubated. Other enzymes or detergents are discussed in Chapter 55, and streptokinase, propylene glycol, Alevaire, or emetic ipecac have not been proved particularly effective.

Airway humidification can complement the expectorant process by continuous or intermittent nebulization and/or humidification. Continuous nebulizer-humidification devices may be tolerated quite well, yet many asthmatic patients experience suffocation with the fine, dense mist of the ultrasonic nebulizer. The latter is better prescribed for 5 to 15 minute treatment (2–3 ml/minute output, every 4 to 6 hours), or as tolerated by the patient and delivered after a bronchodilator. Normal or 0.45% saline solution is preferred to 5% saline solution or distilled water in COAD (chronic obstructive airway disease) patients [89]. Unheated ultrasonic nebulizers increase airway resistance in patients with COAD caused partially by direct irritation or reflex bronchoconstriction, and may also swell intrabronchial mucus and could, therefore, aggravate secretional obstruction [1]. In children, overhydration with an increased A-aO_2 gradient can result from their improper use. A rise in airway resistance with V/Q disturbances, limited peripheral airway delivery, and the general intolerances of such mists may limit their effectiveness in status asthmaticus.

Nebulizers powered by oxygen or compressed air will deliver water or saline aerosols continuously or intermittently by a mouthpiece, face tent, mask, or endotracheal tube. Because temperature is a major factor influencing the volume of water vapor, humidifying units should be heated sufficiently to deliver the gases at body temperature. Commonly employed heated humidifier-nebulizer units are aceptable devices for the delivery of aerosol fluids; other therapeutic substances as bronchodilator or proteolytic agents can be added periodically if indicated. Slow, deep breathing and changes in body position may achieve more effective penetration and deposition. If secretions liquify rapidly, attention to proper suctioning is clearly needed.

Once these bronchodilating and expectorant measures are instituted and are effective, cough will become productive, and then postural drainage with gentle percussion and vibration maneuvers can be of value. The alert, cooperative patient with an effective cough may be managed by such supportive measures. In others, gentle tracheal suction is added to stimulated cough, but this must be conducted with caution because bronchospasm may result. Occasionally, cautious transcricothyroid catheterization with fluid instillation may be beneficial. In view of the problems inherent to status asthmaticus, antitussive preparations cannot be recommended to retard any productive cough.

The Airway

It is mandatory that a patent airway is established and maintained at all times. This is the

first step in management. Patients adequately raising secretions should be provided with the intensive measures outlined above. Those who cannot mobilize secretions, or who are obtunded, comatose, or obstructed with advanced gas exchange defects will need immediate endotracheal intubation and ventilation. The intubation procedure may assist in a decision of bronchoscopic lavage.

Lavage Procedures

A therapeutic bronchoscopy can occasionally be life-saving in moribund patients or in some who, despite full therapy, continue to deteriorate because of persistent and tenacious sputum. Bronchoscopy with lavage not only facilitates the aspiration of retained secretions, it may also initiate drainage and help restore an effective cough. A therapeutic bronchoscopy may also precede definitive intubation. Criteria for its use are based on clinical observations, and includes circumstances with profuse airway secretions or *inspissated bronchial* mucous plugs (often characterized by a nonproductive cough), refractory to other forms of simpler therapy. The literature is scanty for this therapeutic modality, and it has often been employed under emergency conditions, followed by mechanical ventilation. Here, a "life-saving" capability is stressed, especially when rapid inspissation and occlusion have occurred [172, 186]. Reisman recommends a segmental lavage with 500 ml saline lavage to each bronchus with 15 to 20 ml introduced and suctioned at a time [129]. Another approach employs a large volume of 0.9% saline through one port of a double lumen tube while the contralateral lung is ventilated with oxygen enrichment, thus reducing the problems inherent to a rigid bronchoscope, which has limited access to distal airways. The dual lumen also permits use of mechanical ventilation. If the endoscopy is performed under general anesthesia, for example, halothane (plane 3, stage III), bronchodilation may also occur (see Chapter 67). In status asthmaticus, good recovery of large and small casts and improvement in FVC, $FEV_{1.0}$, and Pa_{O_2} have been reported [82, 132]. In selected cases of obviously tenacious secretions which are proximally visible, mucolytic agents can be lavaged with the schedules described previously. Advantages of fiberoptic bronchoscopy in asthma are drawn from its use in acute respiratory failure of COAD or from severe atelectasis. Adequate ventilation and oxygenation with ECG monitoring must be provided during these endoscopic procedures, for ventricular arrhythmias are a serious danger.

Endotracheal Intubation

An oral or nasal endotracheal tube can be placed for several days to maintain a patent airway for ventilatory support and removal of secretions. Periodic deflation of the inflated cuff, meticulous nursing care, avoidance of torsional stress by undue mobility, and proper positioning of this tube are necessary. Low pressure cuffs are recommended and with their use, a minimum of 5 to 7 days of endotracheal intubation is feasible, particularly since the average duration of intubation in status asthmaticus is not greater than 72 hours [141]. Throughout, complications should be assiduously avoided, such as pressure necrosis of larynx or trachea, secondary infection, unilateral bronchial intubation or kinking of tube, or obstructive accretion of secretions in the lumen.

Tracheostomy

Rarely indicated on an emergency basis, tracheostomy is best avoided unless coincident upper airways obstruction, unusual problems with tenacious secretions, or prolonged endotracheal intubation supervene; then, optimally it should be conducted in the operating room over an endotracheal tube with full control of ventilation and data monitoring. With the upper airway humidifying mechanism bypassed, it becomes essential that adequate humidification be provided at all times. Tracheobronchial suctioning should be gentle, performed aseptically and with caution. Actual suction pressure should be activated only after the catheter has been gently inserted, and jamming maneuvers avoided; otherwise, denudation and injury of the tracheal mucosa may occur.

Ventilatory Assistance and IPPB Treatments

It is unresolved whether periodic assistance of thoracic mechanical work by IPPB in im-

pending or early acute ventilatory failure might avoid intubation and continuous ventilation in status asthmaticus. However, it may be effective in some early cases, and if used, such support will require stringent, clinical monitoring, with serial arterial blood gas and pH data. Any psychological assurance of this measure must be matched with objective benefits. Simple IPPB treatments employed intermittently, for example 10 minutes (time to empty a side-stream nebulizer) every 2 to 4 hours, may deliver aerosol bronchodilators and/or transiently improve ventilation or alleviate the work of breathing. Suggested schedules of 5 to 15 minutes every half-hour employing 0.5 ml 1:200 isoproterenol do not have data to support their efficacy [16]. One comparison of isoproterenol with salbutamol via IPPB did show FVC and $FEV_{1.0}$ improvements in stable asthma [25, 149], but because appropriate trials in status asthmaticus are incomplete, the use of IPPB treatments in this manner remains controversial [9]. One benefit of IPPB is the improved delivery of aerosol medications. Although this can be achieved by hand nebulization, deep breathing, or Freon units [22, 24], positive pressure delivery seems more effective in severely ill patients who cannot achieve adequate airway delivery of particles because of an inability to cooperate or to take a deep inspiration [50, 160].

Continuous Ventilation

If the only serious blood gas abnormality is hypoxemia without CO_2 retention, and oxygen administration with medical support is effective, then this is all that is required. However, when frank ventilatory failure occurs or is imminent despite the intensive therapy described above, continuous ventilation is imperative. Clinical guidelines, although suggestive, are not reliable nor quantitative indices of effective alveolar ventilation, and hypercapnia in acute asthma bears a poor correlation with spirometry until extremes of obstruction exists. These diversions reemphasize the need for measurements of CO_2 tension and pH for proof of ventilatory failure. The following are *guidelines* for ventilatory support in status asthmaticus.

1. Respiratory arrest—apnea
2. Rising Pa_{CO_2} >40 to 50 torr, despite complete and aggressive therapy, with obvious patient distress. A rise of ≧5 to 10 torr Pa_{CO_2}/hour is a poor prognostic sign when associated with acute respiratory acidosis [52, 128]
3. Absolute Pa_{CO_2} ≧50 to 55 torr, with acute respiratory acidosis
4. Refractory hypoxemia despite oxygen administration or O_2 suppression of ventilation
5. Physiological data
   a. vital capacity <10 ml/kg
   b. VD/VT ≧0.6
   c. P_A-aDO_2 >350 torr on 100% O_2

Clinical observations should abort emergency ventilator intervention as a desperate, hasty decision. Even though presentation in an advanced or near terminal state will occur in some instances, in most circumstances ventilation can be introduced at an appropriate point in a deteriorating patient.

Volume-limited ventilators are recommended during continuous mechanical ventilation for their ease of operation and ability to generate greater cycling pressures; peak inspiratory pressures >60 cm H_2O may be required [138]. For adults, initial ventilator settings may include Rf (respiratory frequency) 15 to 20/minute, Vt = 10 to 15 ml/kg, pressure 35 to 45 cm H_2O, I:E = 1:3, 50% inspired oxygen, and readjust within ½ to 1 hour, if necessary, following arterial blood gas analysis of effectiveness. Many patients will cycle effectively on a patient-initiated mode (assisted ventilation); others are too confused, exhausted, frightened, or tachypneic to coordinate effectively with the ventilator [178]. Then, controlled ventilation is necessary to reduce ineffective respiratory patterns and excessive thoracic work while providing fully supportive mechanical ventilation, thereby also providing time for appropriate medical therapy to reverse the acute precipitating factors. With improvement, the patient's own ventilatory effort will then be capable of maintaining clinical stability. This approach is often beneficial for the patient in status asthmaticus in respiratory failure not responding to conventional assisted ventilation. Failure of assisted schedules is determined by clinical observations of patient stupor or fatigue, of poor coordination (e.g., exhaling prematurely), or

struggling with the ventilator, of inappropriately high respiratory frequency or low tidal ventilation; these should be confirmed by a concurrent rise in Pa_{CO_2} and a fall in pH.

Synchronization of the patient with the respirator, resulting in elimination of excessive respiratory work, is the key to effective, controlled ventilation. Controlled ventilation is facilitated with sedatives, or morphine, or occasionally neuromuscular-blocking drugs [178]. Although morphine or tubocurarine cause bronchoconstriction, any effect is undoubtedly offset by bronchodilators or the work of the ventilator [125]. Morphine venodilation and hypovolemia may result in systemic hypotension, especially if high cycling pressures are encountered. It is best to titrate diazepam (5–10 mg IV) or morphine (5–10 mg IV) as *initial* adult doses to the desired end point of relaxation or sedation; additional small doses can be added later as needed. Succinylcholine, pancuronium bromide (little histamine release), or gallamine triethiodide on occasion can be used to provide immediate relaxation by paralysis and hence synchronization with the ventilator, but this procedure must be conducted with caution and *absolute airway* and ventilatory control. Many patients will remain synchronized after one paralyzing dose, followed by appropriate sedation. During mechanical ventilation, high blood CO_2 levels should be lowered gradually, 5 to 10 torr/hour or to whatever limits hypocapneic alkalosis. Monitoring of such data as blood gases, ventilator functions, ECG, and vital signs is mandatory throughout the period of ventilator support and the combined talents of physicians, nurses, anesthesiologists, and respiratory therapists should be organized to accomplish this goal (see Chapter 61).

Survival in ventilatory failure from status asthmaticus is rather good considering the gravity of the disorder. Over the past decade, the major reported series in adults averaged 18 fatalities in 149 patients requiring intubation or tracheostomy and mechanical ventilation, for an 88 percent survival rate (Table 60-4). Nevertheless, ventilatory support is not always required. The series of Rebuck and Read [127] included 76 admissions in 58 patients with hypercapnia (>45 torr) in 19 occasions. Only one patient, who was sedated, required endotracheal intubation and ventilation. It was maintained that because hypercapnia is of short duration and is invariably associated with voluminous secretions, vigorous therapy including high doses of corticosteroids will be adequate for most. However, many patients do not exhibit this initial bronchorrhea, and this may explain an apparent discrepancy. Generally, then, in status asthmaticus the major setting for ventilatory support is those cases with endogenous ventilatory failure; in some instances this condition is complicated by injudicious sedation or uncontrolled oxygen. In all instances, Pa_{CO_2} and pH in the clinical setting will be the major determining factors in this decision.

Table 60-4
Survival in Status Asthmaticus Supported with Mechanical Ventilation

Date	Reference	% Survival
1966	[96]	80
1962–1966	[131]	82
1968	[157]	100
1968	[128]	89
1968	[186]	89
1972	[141]	91

Finally, during ventilatory support, certain complications and hazards have been recognized. In one pediatric series, complications included subcutaneous emphysema 23 percent, pneumothorax 7 percent, tension pneumothorax and cardiac tamponade 3 percent, cardiac arrest 13 percent, postextubation subglottic stenosis 10 percent, and death from sepsis 3 percent [39]. In adults, a recent review of 354 episodes of assisted ventilation cited these nonfatal problems: pneumonia (4%), pneumothorax (4.2%), atelectasis (4.5%), gastric distention (2%), and ventilator malfunction (21%); serious complications associated with increased mortality were unilateral mainstem intubation, tube malfunction, and alveolar hypoventilation [191]. Deliberate, frequent, and careful observations can prevent these unnecessary problems.

Antimicrobial Agents

The role of viral and/or bacterial infections in status asthmaticus was reviewed earlier. Bronchial infection is more frequent than pneumonia per se, yet pneumonia can account for many fatalities if it occurs. In 10

children who died of status asthmaticus complicated by pneumonia, treatment with antibiotics had not been given early enough [130]. Bacterial infection is more likely in older or intrinsic asthmatic patients and viral infections with asthma exacerbations in children. When a bacterial cause is documented or suspected, prompt antimicrobial therapy is imperative, a decision based initially upon a sputum gram stain and confirmed with culture and sensitivity studies; thereafter, the antibiotic is modified as indicated. Inflammatory cytological examination and a Ziehl-Neelsen or fungal stain can be included, if necessary, in the initial evaluation. Periodic reevaluation of sputum flora will detect shifts in organisms with clinical significance. The recovery of bacteria may not reflect actual infection, nor does it necessarily correlate with clinically significant infection. In general, colonization occurs rapidly in the debilitated, in the elderly, or in those receiving antibiotics or steroids. Although the distinction between infection and colonization is difficult, antibiotic regimens are indicated in many cases, and are often recommended routinely. Individual considerations are of importance, for controlled trials are sparse and not all instances require antibiotics. Antibiotic drugs are optimal when a specific bacterial disease is present, such as pneumonia, purulent bronchitis, otitis media, or bacterial sinusitis. Criteria for infection in asthma include diaphoresis, leukocytosis, or secretion purulency. Fever may not be a reliable criterion because infection can precede pyrexia by several days; this supports the early use of antibiotic agents in appropriate circumstances [57].

For broad spectrum coverage, ampicillin (2 gm/day), erythromycin (2 gm/day), or tetracycline (2 mg/day) may be used. *Hemophilus influenzae* and *Diplococcus pneumoniae* are common pathogenic bacteria in children and require specific penicillin or ampicillin therapy. In adults, such broad spectrum coverage will suffice unless examination reveals staphylococci or gram-negative bacilli; generally, a decision for antibiotic use, if indicated, should not await return of cultures. Dosages should then be continued for at least 10 days. Drug-related bronchospasm should be monitored, for example penicillin reactions, and also changes in bacterial flora should be followed, particularly for patients on ventilators. Persistent fever might otherwise indicate a focus of atelectasis or an extrapulmonary infection. Isoniazid (INH) may be given in tuberculin-positive patients receiving corticosteroids. With viral causes, paired serum titer studies may be diagnostic, but they are, of course, limited in therapeutic value.

Acid-Base Considerations

The spectrum of acid-base disturbances in status asthmaticus may include: (1) *respiratory alkalosis* caused by hyperventilation; this condition can be mild or severe and therapy is to the inciting asthma. When inadvertently caused by respirator overventilation, seizures, coma, and hypotension can occur. (2) *Metabolic acidosis* stems from hypoxic lactic acidosis or from complications or disorders such as diarrhea. Therapy is O_2, adequate perfusion, or to the coexisting causes. (3) *Metabolic alkalosis* arises from chloride or potassium depletion by limited electrolyte intake, steroids or diuretic use. Electrolytes should be monitored and replacement therapy instituted. (4) *Respiratory acidosis* will be discussed below.

Initially, a hypocapneic alkalosis deteriorates to respiratory acidosis, both of varying severity and with compensatory renal adjustments. These pH/P_{CO_2} relationships may be analyzed by in vivo nomograms, but it is generally necessary to relate clinical events to the interpretation of blood acid-base status to clarify compensatory mechanisms from treatable complications, for example a complicating metabolic alkalosis from appropriate renal bicarbonate resorption. Also, dynamic and rapid alterations in Pa_{CO_2} and pH in status asthmaticus limit the value of nomogram confidence bands [179]. The importance of clarifying pH changes is also significant because of the Bohr effect or DPG influences on oxygen binding. For example, in acidotic patients rapid correction of pH with $NaHCO_3$ could acutely impair oxygen delivery [2]. The *logical* approach to correcting severe pH shifts is essentially to the underlying events and the stage of disease. Thus, severe hypercapneic acidosis will require all standard pharmacological and medical measures and even ventilator support to improve alveolar ventilation and reduce Pa_{CO_2} and $[H^+]$.

It must be emphasized that respiratory aci-

dosis can occur with alarming rapidity, within hours or less, and is associated with significant mortality. When respiratory acidosis is extreme (for example, pH ≤7.15), it may be valuable to reduce its severity. This also applies if the acidosis is complicated with a base deficit or a metabolic component, or if apnea occurs, or if there is an undue delay before definitive ventilatory control is established. The effectiveness of epinephrine may also be restored. Although associated, severe circulatory disturbances and tissue hypoxia might lead to complicating metabolic (lactic) acidemia, this condition does not appear common in adults. In 101 patients none had evidence of metabolic acidosis [93]. In the studies of Rees et al. [128], one patient of 24 had a pH less than 7.30, of 7.05, and two fatal cases had a mixed metabolic and respiratory acidosis. The data of Sheehy et al. are similar [141]. Figure 60-5 summarizes other series, with most values lying within the confidence bands for acute hypercapnia in man [49]. In children, however, complicating metabolic acidosis with ketonemia has been reported, but arterial lactate and pyruvate levels are not necessarily elevated [39, 146].

In severe acidosis, exogenous alkalizing agents such as sodium bicarbonate may be administered while adequate ventilation is being implemented. For an adult, from 45 to 90 mEq (50–100 ml of 7.5% solution) of $NaHCO_3$ is infused slowly over 10 to 20 minutes, and serial pH (arterial or venous) is titrated to an approximate pH range of 7.25. Greater correction is unnecessary and can result in nonvolatile alkalemia when adequate ventilation excretes carbon dioxide. The use and effectiveness of $NaHCO_3$ is, however, limited unless CO_2 thus generated can be eliminated [116]. Therefore, this recommendation must be evaluated for each clinical circumstance, particularly in view of the lack of controlled data and where clinical experience suggests that a modest increase in bicarbonate is desirable. Supplemental oxygen should be given in view of reported falls in arterial Pa_{O_2} following 50 to 100 mEq bicarbonate IV doses, but extrapolation of this finding to status asthmaticus may not be entirely justified [104]. Sodium-free tris-hydroxymethylaminoethane (THAM) has been advocated when sodium intake is to be severely curtailed; but it may depress respiration. Complicating metabolic alkalosis (hypochloremic or hypokalemic) can be anticipated from vomiting, diuretics, gastric suction, corticosteroids, or exogenous bicarbonate. Because alkalosis can depress ventilation and retard weaning programs, serial electrolytes and preventative replacement therapies should be instituted to limit this complication.

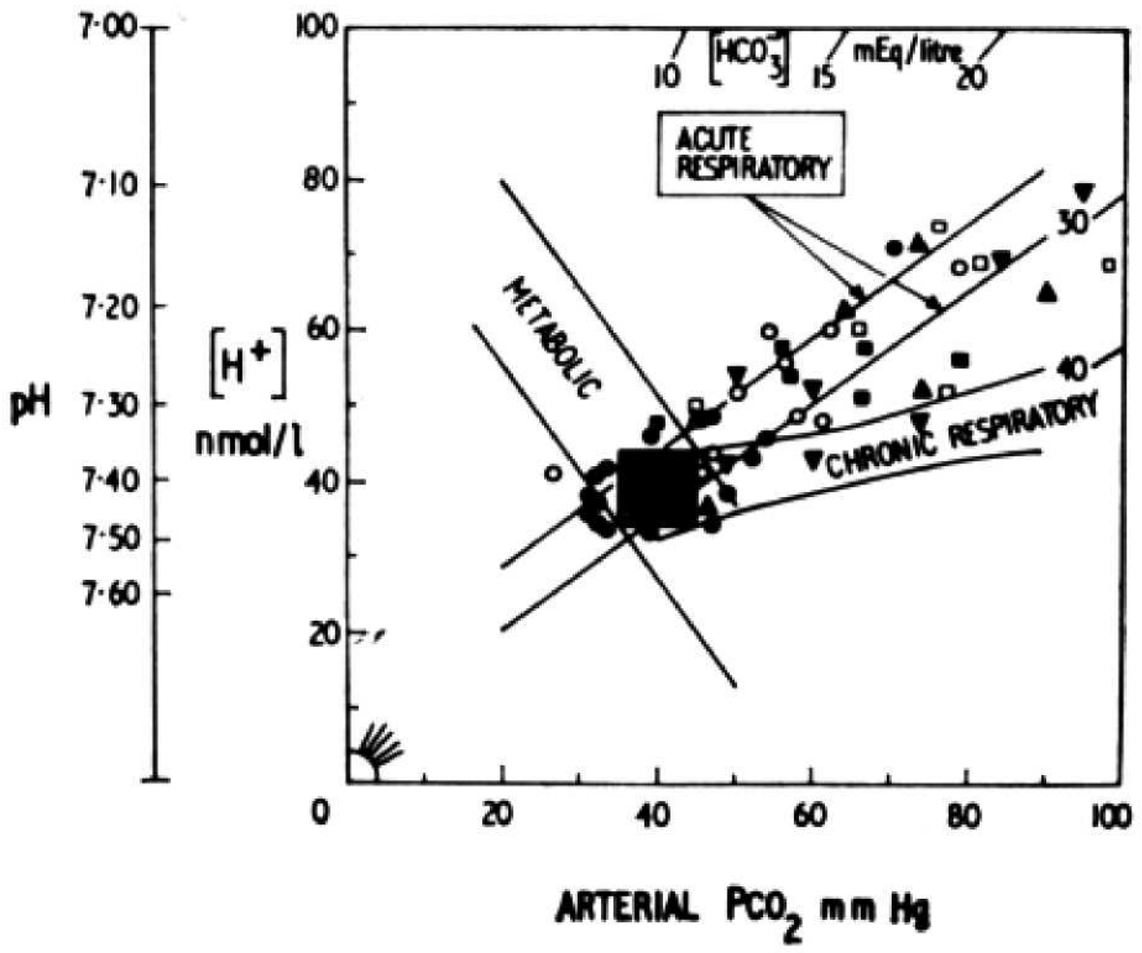


Figure 60-5
Acid-base relationships in severe asthma. Each symbol represents data summarized from various series of severe asthma. (Reprinted with permission from Flenley, D. C., Blood gas tensions in severe asthma. *Proceedings of the Royal Society of Medicine* 64:65, 1971.)

Sedatives

Sedative or psychopharmacological drugs are important considerations in status asthmaticus, for their inappropriate use is implicated in death [15, 53, 114, 184]. The 1860 warning by Salter against the use of opium in asthma is still valid [135]; similarly, a 1938 review of the pathology of status asthmaticus concluded that "morphine and atropine should never be used in the management of status asthmaticus" [163]. Thus quieted, the unagitated patient removes an important signal from the physician and generates a false sense of security for both. The relationship between a decrease in the breath sound amplitude by the fall in volume or velocity of tidal breathing explains the effect of sedative respiratory depression upon auscultation, where now quiet sounds can be spuriously inter-

preted as clinical improvement. Because it is recognized that the anxiety, restlessness, and behavioral abnormalities arise from the asthma process, their reversal and supportive care are the essential remedy, particularly because sedation does not eliminate the obstructive process. These drugs should also be considered contributory in case of unexplained deterioration. Other problems arising from sedation are accelerated steroid clearance, cough depression, drying of secretions, and potentiation of convulsive seizures of phenothiazine by xanthines. Although controlled trials of sedatives with mortality are unavailable, it appears that many patients who expire have been excessively sedated [109]. What is excessive sedation? Do patients with extreme anxiety provoke the physician to employ such agents? In one series of status asthmaticus in which sedation was prohibited from use, progressive asthma severity, sufficient for intubation, still occurred in some patients [141]. In one pediatric series, death was only conjectured to be due to sedation—or oversedation—but it could not be firmly asserted [15]. In other series of fatalities, a sedative cause is hardly noted [48], and recently in adults, mortality was equal among patients irrespective of sedative use [28]. At present, it is mandatory to avoid such drugs, especially strong depressants such as morphine and barbiturates, and probably antihistamines. Cautious and small titrated doses of tranquilizers such as chlordiazepoxide hydrochloride or diazepam can be provided to palliate anxiety in very select situations, but the actual effect of these agents may be hard to discern and will require proper monitoring. In short, the association of a decrease in breath sounds and abatement of wheeze by sedative use or abuse should always be kept in mind. The sedative and bronchodilator benefits of ether per rectum are inconclusive, but some practitioners have recommended its use, and the use of anesthetics is discussed in Chapter 67.

CONCLUSION

Because many patients are first seen during a status asthmaticus attack and no one feature characterizes how the patient will respond, intensive palliative treatment must be initiated. Once controlled, all possible contributing causes must be investigated and a proper program of symptomatic control established, because the long-term goal is to eliminate offending causes and to minimize recurrences. This program is necessary for total rehabilitation. The risks and benefits of therapy and the nature of the problem should be clarified with the patient, who should be encouraged to believe that asthma can be well controlled with optimal management. It should be stressed that the long-term prognosis is good. Conversely, there is no place for complacency in the total management of these patients, because there is no reliable guide for predicting their course or of status asthmaticus. Thoroughout management, it is mandatory that careful observations support a rational therapy program.

REFERENCES

1. Abernethy, J. D. Effects of inhalation of artificial fog. *Thorax* 23:421, 1968.
2. Alberti, K. G. M. M., Darley, J. H., Emerson, P. M., and Hockaday, T. D. R. 2,3-Diphosphoglycerate and tissue oxygenation in uncontrolled diabetes mellitus. *Lancet* 2:391, 1972.
3. Alexander, H. L. A historical account of death from asthma. *J. Allergy Clin. Immunol.* 34:305, 1963.
4. Alston, W. C., Patel, K. R., and Kerr, J. W. Response of leucocyte adenyl cyclase to isoprenaline and effect of alpha-blocking drugs in extrinsic bronchial asthma. *Br. Med. J.* 1:90, 1974.
5. Attinger, E. O., Goldstein, M. M., and Segal, M. S. The mechanics of breathing in normal subjects and in patients with cardiopulmonary disease. *Ann. Intern. Med.* 48:1269, 1958.
6. Aviado, D. M. Toxicity of propellants. In *Progress in Drug Research.* Basel: Birkhauser Verlag, 1974. Vol. 18.
7. Aviado, D. M. Toxicity of aerosols. *J. Clin. Pharmacol.* 16:86, 1975.
8. Baird, K. A. Background and history of interest in the role of bacteria in allergic diseases. In Frazier, C. A. (Ed.), *Annual Review of Allergy 1973.* Flushing, N.Y.: Medical Examination, 1974. P. 362.
9. Baker, J. P. Magnitude of Usage of Intermittent Positive Pressure Breathing. *Am. Rev. Respir. Dis.* 110 part 2:176, 1974.
10. Berkovich, S., Millian, S. J., and Snyder,

R. D. Association of viral and mycoplasma infections with recurrence of wheezing in the asthmatic child. *Ann. Allergy* 28:43, 1970.
11. Boyd, E. M., Sheppard, E. P., and Boyd, C. E. The pharmacological bases of the expectorant action of glyceryl guiacolate. *Appl. Ther.* 9:55, 1967.
12. Brook, S. M. In drug therapy in asthma: More rational, still complex. *Hosp. Prac.* 10:27, 1975.
13. Brooks, S. M., Mintz, S., and Weiss, E. B. Patterns of responses to bronchodilators in patients with bronchial asthma. *J. Lab. Clin. Med.* 79:367, 1972.
14. Bullen, S. S. Correlation of clinical and autopsy findings in 176 cases of asthma. *J. Allergy Clin. Immunol.* 23:193, 1952.
15. Buranakul, B., Washington, J., Hilman, B., Mancuso, J., and Sly, R. Causes of death during acute asthma in children. *Am. J. Dis. Child.* 128:343, 1974.
16. Busey, J. F., Fenger, E. P. K., Hepper, N. G., Kent, D. C., Kilburn, K. H., Matthes, L. W., Simpson, D. G., and Grzybowski, S. Management of status asthmaticus: A statement by the committee on therapy. *Am. Rev. Respir. Dis.* 97:735, 1968.
17. Callerame, M. L., Condemi, J. J., Bohrod, M. G., and Vaughan, J. H. Immunologic reactions of bronchial tissue in asthma. *New Engl. J. Med.* 289:459, 1971.
18. Callerame, M. L., Condemi, J. J., Ishizaka, K., Johansson, S. G. O., and Vaughan, J. H. Immunoglobulins in bronchial tissues from patients with asthma, with special reference to immunoglobulin E. *J. Allergy Clin. Immunol.* 47:107, 1971.
19. Campbell, E. J. M. Mechanics of airway obstruction in emphysema and asthma. *Proc. R. Soc. Med.* 51:108, 1958.
20. Cardell, B. S., and Bruce-Pearson, R. S. Death in asthmatics. *Thorax* 14:341, 1959.
21. Cayton, R. M., and Howard, P. Plasma cortisol and the use of hydrocortisone in the treatment of status asthmaticus. *Thorax* 28: 567, 1973.
22. Chang, N., and Levison, H. Effect of a nebulized bronchodilator administered with or without intermittent positive pressure breathing on ventilatory function in children with cystic fibrosis and asthma. *Am. Rev. Respir. Dis.* 106:867, 1972.
23. Charman, J., and Reid, L. Sputum viscosity in chronic bronchitis, bronchiectasis, asthma, and cystic fibrosis. *Biorheology* 9: 185, 1972.
24. Chester, E. H., Racz, I., Barlow, P. B., and and Baum, G. L. Bronchodilator therapy: Comparison of acute response to three methods of administration. *Chest* 62:394, 1972.
25. Choo-Kang, Y. F. J., Parker, S. S., and Grant, I. W. B. Response of asthmatics to isoprenaline and salbutamol aerosols administered by intermittent positive pressure ventilation. *Br. Med. J.* 4:465, 1970.
26. Clarke, S. W., Jones, J. G., and Oliver, B. R. Resistance to two-phase gas-liquid flow in airways. *J. Appl. Physiol.* 29:464, 1970.
27. Clifford, R. *The Sputum, Its Examination and Clinical Significance.* New York: Macmillan, 1932.
28. Cochrane, G. M., and Clark, T. J. H. A survey of asthma mortality between ages 35 and 64 in greater London hospitals in 1971. *Thorax* 30:300, 1975.
29. Coke, F. *Asthma.* Baltimore: Williams & Wilkins, 1930. P. 89.
30. Colldahl, H. A study of serum enzymes in patients suffering from periods of respiratory insufficiency, especially asthma and emphysema. *Acta Med. Scand.* 166:399, 1960.
30a. Collins, J. V., Clark, T. J. H., Brown, D., and Townsend, J. The use of corticosteroids in the treatment of acute asthma. *Q. J. Med.* 174:259, 1975.
31. Collins, J. V., Harris, P. W. R., Clark, T. J. H. and Townsend, J. Intravenous corticosteroids in treatment of acute bronchial asthma. *Lancet*, 2:1047, 1970.
32. Cope, C. L. *Adrenal Steroids and Disease.* London: Pitman, 1964. Chapters 3, 11.
33. Craige, B. Fatal bronchial asthma. *Arch. Intern. Med.* 67:399, 1941.
34. Cua-Lim, F., and Lim, M. G. Relationship of acute bacterial (suppurative sinusitis) and viral (pneumonitis) infections to status asthmaticus. *J. Asthma. Res.* 9:31, 1971.
35. Dale, D. D., Fauci, A. S., and Wolff, S. M. Alternate-day prednisone, leukocyte kinetics and susceptibility to infections. *N. Engl. J. Med.* 291:1154, 1974.
36. Daughday, W. H. Binding of corticosteroids by plasma proteins. *J. Clin. Invest.* 37: 519, 1958.
37. Dekker, E., and Groen, J. Asthmatic wheezing: Compression of the trachea and major bronchi as a cause. *Lancet* 1:1064, 1957.
38. Disney, M. E., Matthews, R., and Williams, J. D. The role of infection in the morbidity of asthmatic children admitted to hospital. *Clin. Allergy* 1:399, 1971.
39. Downes, J. J., Wood, D. W., Striker, T. W., and Pittman, J. C. Arterial blood gas and acid-base disorders in infants and children

with status asthmaticus. *Pediatrics*, 42:238, 1968.
40. Dunnill, M. S. The pathology of asthma, with special reference to changes in the bronchial mucosa. *J. Clin. Path.* 13:27, 1960.
41. Dunnill, M. S. Morphometry of the Human Lung in Health and Disease. In Cumming, G., and Hunt, L. B. (Eds.), *Form and Function in the Human Lung*. Baltimore: Williams & Wilkins, 1968. P. 19.
42. Dunnill, M. S. The pathology of asthma. In Porter, R., and Birch, J. (Eds.), *Identification of Asthma*, Ciba Foundation Study Group No. 38. Edinburgh and London: Churchill Livingstone, 1971.
43. Dworetzky, M., and Philson, A. D. Review of asthmatic patients hospitalized in the pavilion service of the New York Hospital 1948 to 1963, with emphasis on mortality rate. *J. Allergy Clin. Immunol.* 41: 181, 1968.
44. Dwyer, J., Lazarus, L., and Hickie, J. B. Study of cortisol metabolism in patients with chronic asthma. *Aust. Ann. Med.* 16: 297, 1967.
45. Editorial: Treatment of status asthmaticus. *Brit. Med. J.* 4:563, 1974.
45a. Ellul-Micallef, R., and Frenech, F. Intravenous prednisolone in chronic bronchial asthma. *Thorax* 30:312, 1975.
46. Falliers, C. J. Comments on preceding articles. *J. Allergy* 42:279, 1968.
47. Falliers, C. J., McCahn, W. P., Chai, H., Ellis, E. F., and Yazdi, N. Controlled study of iodotherapy for childhood asthma. *J. Allergy Clin. Immunol.* 38:183, 1966.
48. Feldman, R. Recognition and treatment of potentially fatal bronchial asthma. *Ann. Intern. Med.* 57:29, 1962.
49. Flenley, D. C. Blood gas tensions in severe asthma. *Proc. R. Soc. Med.* 64:65, 1971.
50. Froeb, H. F. On the relief of bronchospasm and the induction of alveolar hyperventilation: A comparative study of nebulized bronchodilators by deep breathing and intermittent positive pressure. *Chest* 38:483, 1960.
51. Fuleihan, F. J. D., Abdel-Baki, N., and Arslanian, A. The effect of intravenous aminophylline on pulmonary function in asthma. *Chest* 56:481, 1969.
52. Gandevia, B. Changing pattern of mortality from asthma in Australia. *Med. J. Aust.* 1:747, 1968.
53. Ghannam, R. D., Schreier, L., and Vanselow, N. A. Fatal bronchial asthma: An analysis of terminal treatment in twenty cases. *Ann. Allergy*, 26:194, 1968.
54. Girsh, L. S. Air Pollutants and Weather and Their Effect on Bronchial Asthma. In Frazier, C. A. (Ed.), *Annual Review of Allergy 1973*. Flushing, N.H.: Medical Examination, 1974. Chapter 12, p. 237.
55. Gold, W. M., Kaufman, H. S., and Nadel, J. A. Elastic recoil of the lungs in chronic asthmatic patients before and after therapy. *J. Appl. Physiol.* 23:433, 1967.
56. Grant, I. W. B., Kennedy, W. P. U., and Malone, D. N. Deaths from asthma. *Br. Med. J.* 2:429, 1968.
57. Green, M. A., and Soloman, B. A. Microscopic studies of nasal secretions in infectious asthma. *Ann. Allergy* 20:373, 1962.
58. Hampton, S., Johnson, M. C., and Galakatos, E. Studies of bacterial hypersensitivity in asthma. *J. Allergy Clin. Immunol.* 34:63, 1963.
59. Herxheimer, H. Provocation Tests for Studying Bronchial Reactivity. In Serafini, U., Frankland, A. W., Masala, C., and Jamar, J. M. (Eds.), *New Concepts in Allergy and Clinical Immunology*. Amsterdam: Excerpta Medica, 1971. P. 122.
60. Hirsh, S. R., Viernes, P. F., and Kory, R. C. The expectorant effects of glyceryl guaiacolate in patients with chronic bronchitis. *Chest* 63:9, 1973; 64:543, 1973.
61. Hogarth-Scott, R. S., Howlett, B. J., McNicol, K. N., Simons, M. J., and Williams, H. G. IgE levels in the sera of asthmatic children. *Clin. Exp. Immunol.* 9:571, 1971.
62. Honsinger, R. W., Jr., Silverstein, P., and Van Arsdale, P. P., Jr. The eosinophil and allergy: Why? *J. Allergy Clin. Immunol.* 49:142, 1972.
63. Hossain, S., and Heard, B. E. Hyperplasia of bronchial muscle in chronic bronchitis. *J. Path.* 101:171, 1970.
64. Huber, H. L., and Koessler, K. K. The pathology of bronchial asthma. *Arch. Intern. Med.* 30:689, 1922.
65. Iisalo, E. I., Iisalo, E. U. M., and Tala, E. J. Deaths from asthma, with special reference to the last drug treatment. *Acta Med. Scand.* 185:45, 1969.
66. Ingram, R. H., Jr., Krumpe, P. E., Duffell, G. M., and Maniscalco, B. Ventilation-perfusion changes after aerosolized isoproterenol in asthma. *Am. Rev. Respir. Dis.* 101:364, 1970.
67. Ishizaka, K., and Newcomb, R. W. Presence of γE in nasal washings and sputum from asthmatic patients. *J. Allergy Clin. Immunol.* 46:197, 1970.
68. Itkin, L. H. Fundamentals of the treatment of asthma. *Am. Fam. Physician* 4:82, 1971.

69. Jacobs, M. H., and Senior, R. M., III. Theophylline toxicity due to impaired theophylline degradation. *Am. Rev. Respir. Dis.* 110:342, 1974.
70. Jenkinson, D. H. Classification and properties of peripheral adrenergic receptors. *Br. Med. Bull.* 29:142, 1973.
71. Jenne, J. W., Wyze, E., Rood, F. S., and MacDonald, F. M. Pharmakinetics of theophylline, application to adjustment of the clinical dose of aminophylline. *Clin. Pharmacol Ther.* 13:349, 1972.
72. Jones, E. S. The intensive therapy of asthma. *Proc. R. Soc. Med.* 64:1151, 1971.
73. Jones, G. R. Deaths from asthma. *Br. Med. J.* 2:698, 1968.
74. Jones, R. S. Physiology and management of childhood asthma. *Postgrad. Med. J.* 47: 171, 1971.
75. Keal, E. E. Biochemistry and rheology of sputum in asthma. *Postgrad. Med. J.* 47: 171, 1971.
76. Kehlet, H., and Binder, C. Value of an ACTH test in assessing hypothalamic-pituitary-adrenocortical functions in glucocorticoid-treated patients. *Br. Med. J. Selections*, 2:147, 1973.
77. Keighley, J. F. Iatrogenic asthma associated with adrenergic aerosols. *Ann. Intern. Med.* 65:985, 1966.
78. Kennedy, M. C. S., and Pelham-Thursby, D. C. Cortisone in treatment of children with chronic asthma. *Br. Med. J.* 1:1511, 1956.
79. Kjellman, B. Bronchial asthma and recurrent pneumonia in children. Clinical evaluation of 14 children. *Acta Ped. Scand.* 56: 651, 1967.
80. Klaustermeyer, W. B., Di Bernardo, R. L., and Hale, F. C. Intravenous isoproterenol: Rationale for bronchial asthma. *J. Allergy Clin. Immunol.* 55:325, 1975.
81. Koch-Weser, J. Beta adrenergic blockade and circulating eosinophil. *Arch. Intern. Med.* 121:255, 1968.
82. Kylstra, J. A., Rausch, D. C., Hall, K. D., et al. Volume-controlled lung lavage in the treatment of asthma, bronchiectasis, and mucoviscoidosis. *Am. Rev. Respir. Dis.* 103:651, 1971.
83. Leopold, J. G. A Contrast of Bronchitis and Asthma. Paper given at Symposium on the nature of asthma, King Edward VII Hospital, Midhurst, 1964. P. 30.
84. Levy, G., Ellis, E. F., and Koysooko, R. Indirect plasma-theophylline monitoring in asthmatic children by determination of theophylline concentration in saliva. *Pediatrics* 53:873, 1974.
85. Lewis, R. Epidemic asthma in New Orleans: Summary of knowledge to date. *J. La. State Med. Soc.* 115:300, 1963.
86. Lifschitz, M. I., and Denning, C. R. Quantitative interaction of water and cystic fibrosis sputum. *Am. Rev. Respir. Dis.* 102: 456, 1970.
87. Lockett, M. F. Dangerous effects of isoprenaline in myocardial failure. *Lancet*, 1: 104, 1965.
88. Lowell, F. C. Clinical aspects of eosinophylia in atopic disease. *J.A.M.A.* 202:875, 1967.
89. McAllen, M. K. National statistics on asthma deaths and side effects of bronchodilators. *Respiration* 26:103, 1969.
90. McCarter, J. H., Vazquez, J. J., and Durham, J. J. The bronchial basement membrane in asthma. *Arch. Pathol.* 32:328, 1966.
91. McFadden, E. R., Jr., Kiser, R., and deGruot, W. J. Acute bronchial asthma: Relations between clinical and physiological manifestations. *N. Engl. J. Med.* 288:221, 1973.
92. McFadden, E. R., Jr., and Lyons, H. A. Airway resistance and uneven ventilation in bronchial asthma. *J. Appl. Physiol.* 25: 365, 1968.
93. McFadden, E. R., Jr., and Lyons, H. A. Arterial blood gas tension in asthma. *N. Engl. J. Med.* 278:1027, 1968.
94. McIntosh, K., Ellis, E. F., Hoffman, L. S., Lybass, T. B., Eller, J. J., and Fulginti, V. A. The association of viral and bacterial respiratory infection with exacerbation of wheezing in young asthmatic children. *J. Allergy Clin. Immunol.* Abstract 94, 1972. P. 131.
95. Malik, S. K., and Jenkins, D. E. Alterations in airway dynamics following inhalation of ultrasonic mist. *Chest* 62:660, 1972.
96. Marchand, P., and Van Hasselt, H. Last-resort treatment of status asthmaticus. *Lancet* 1:227, 1966.
97. Mathé, A. A. Decreased circulating epinephrine possibly secondary to decreased hypothalamic adrenomedullary discharge. A supplementary hypothesis of bronchial asthma pathogenesis. *J. Psychosom. Res.* 15: 349, 1971.
98. Maunsell, K., Bruce-Pearson, R. S., and Livingstone, J. L. Long term corticosteroid treatment of asthma. *Br. Med. J.* 1:661, 1968.
99. May, J. R. *Chemotherapy of Chronic Bronchitis and Allied Disorders*, London: The English Universities Press, 1968. P. 83.
100. Medici, T. C., and Chodosh, S. Nonmalig-

nant exfoliative sputum cytology. In Dulfano, M. J. (Ed.), *Sputum, Fundamentals and Clinical Pathology*. Springfield, Ill.: Thomas, 1973.
101. Meisner, P., and Hugh-Jones, P. Pulmonary function in bronchial asthma. *Brit. Med. J.* 1:470, 1968.
102. Messer, J. W., Peters, G. A., and Bennets, W. A. Causes of death and pathologic findings in 304 cases of bronchial asthma. *Chest* 38:616, 1960.
103. Michel, H., and Zander, M. V. Frequency of bacterial complications in patients treated with corticosteroids for bronchial asthma. *Klin. Wochenschr.* 45:1250, 1967.
104. Milledge, J. S., and Benjamin, S. Arterial desaturation after sodium bicarbonate therapy in bronchial asthma. *Am. Rev. Respir.* Dis. 105:126, 1972.
105. Mitenko, P. A., and Ogilvie, R. I. Rational intravenous use of theophylline. *N. Engl. J. Med.* 289:600, 1973.
106. Mithoefer, J. C., Rusner, R. H., and Kanetzky, M. S. Use of sodium bicarbonate in the treatment of acute bronchial asthma. *N. Engl. J. Med.* 272:1200, 1965.
107. Mustacchi, P., Lucia, S. P., and Jassy, L. Bronchial asthma: Patterns of morbidity and mortality in United States, 1951–1959. *Calif. Med.* 96:196, 1962.
108. Naylor, B. The shedding of the mucosa of the bronchial tree in asthma. *Thorax* 17:69, 1962.
109. Neder, G. A., Derbes, V. J., Carpenter, C. S., and Zeskin, M. M. Death in status asthmaticus. *Chest* 44:263, 1963.
110. Neuman, I., Morris, H., and Ellis, E. Endogenous corticosteroid concentrations during status asthmaticus. Abstract, Annual Meeting. *J. Allergy Clin. Immunol.* 49:127, 1972.
111. Nicholson, D. P., and Chick, T. W. A reevaluation of parenteral aminophylline. *Am. Rev. Respir. Dis.* 108:241, 1973.
112. Noelpp, B., and Noelpp-Eschenhagen, I. Der experimentelle asthma bronchiale des Meerschweinchens I. Mitteilung. Methoden zur objektiven Erfasung (Registrierung) des Asthmaanfalles. *Int. Arch. Allergy Appl. Immunol.* 2:308, 1951.
113. Noelpp, B., and Noelpp-Eschenhagen, I. II. Mitteilung. Die rolle bedingter reflexe in der pathogenese des asthma bronchiale. *Int. Arch. Allergy Appl. Immunol.* 2:321, 1951.
114. O'Brien, M. M., and Ferguson, M. J. Unexpected death in bronchial asthma: A warning sign with a clinicopathologic correlation. *Ann. Intern. Med.* 53:1162, 1960.
115. O'Donohue, W. J., Jr., Baker, J. P., Bell, G. M., Muren, O., and Patterson, J. L., Jr. The management of acute respiratory failure in a respiratory intensive care unit. *Chest* 58:603, 1970.
116. Ostrea, E. M., Jr., and Odell, G. B. The influence of bicarbonate administration on blood pH in a "closed system." Clinical implications. *J. Pediatr.* 80:671, 1972.
117. Palmer, K. N. V., Ballantyne, D., Diament, M. L., and Hamilton, W. F. D. The rheology of bronchitic sputum. *Br. J. Dis. Chest* 64:185, 1970.
118. Palmer, K. N. V., and Diament, M. L. Hypoxaemia in bronchial asthma. *Lancet* 1: 318, 1968.
119. Palmer, K. V. N., and Kelman, G. P. A comparison of pulmonary functions in extrinsic and intrinsic bronchial asthma. *Am. Rev. Respir. Dis.* 107:940, 1973.
120. Paterson, J. W., Conolly, M. E., Davies, D. S., et al. Isoprenaline resistance and the use of pressurized aerosols in asthma. *Lancet* 2:426, 1968.
121. Paterson, J. W., Courtenay Evans, R. J., and Prime, F. J. Selectivity of bronchodilator action of salbutamol in asthmatic patients. *Br. J. Dis. Chest* 65:23, 1971.
122. Piafsky, K. M., and Ogilvie, R. I. Dosage of theophylline in bronchial asthma. *N. Engl. J. Med.* 292:1218, 1975.
123. Pierson, W. E., Bierman, C. W., and Kelley, V. C. A double-blind trial of corticosteroid therapy in status asthmaticus. *Pediatrics* 54:282, 1974.
124. Pierson, R. N., and Grieco, M. H. Isoproterenol aerosol in normal and asthmatic subjects: Time relationship of pulmonary and hemodynamic responses. *Am. Rev. Respir. Dis.* 100:533, 1969.
125. Pontoppidan, H., Geffin, B., and Lowenstein, E. Morphine for severe asthma. *N. Engl. J. Med.* 288:50, 1973.
126. Rebuck, A. S., and Pengelly, L. D. Development of pulsus paradoxus in the presence of airways obstruction. *N. Engl. J. Med.* 288:66, 1973.
127. Rebuck, A. S., and Read, J. Assessment and management of severe asthma. *Am. J. Med.* 51:788, 1971.
128. Rees, H. A., Millar, J. S., and Donald, K. W. A study of the clinical course and arterial blood gas tensions on patients in status asthmaticus. *Q. J. Med.* 37:541, 1968.
129. Reisman, R. E., Friedman, I., and Arbesman, C. E. Severe status asthmaticus: Prolonged treatment with assisted ventilation. *J. Allergy Clin. Immunol.* 41:37, 1968.
130. Richards, W., and Patrick, J. R. Death

from asthma in children. *Am. J. Dis. Child.* 110:4, 1965.
131. Riding, W. D., and Ambiavagar, M. Resuscitation of the moribund asthmatic. *Postgrad. Med. J.* 43:234, 1967.
132. Rogers, R. M., Braunstein, M. S., and Shuman, J. F. Role of bronchopulmonary lavage in the treatment of respiratory failure: A review. *Chest* 62 [Suppl.] (part 2):95S, 1972.
133. Roncoroni, A. J., Puy, R. J. M., and Goldman, E. The effect of salbutamol on airways obstruction in patients with status asthmaticus. *Postgrad. Med. J.* [Suppl.] 47: 128, 1971.
134. Ross, S. B. In vivo inactivation of catecholamines in mice. *Acta Pharmacol. Toxicol.* (Kbh) 20:267, 1963.
135. Salter, H. H. Excerpts. In Samter, M. (Ed.), *Classics in Allergy*. Columbus, Ohio: Ross Laboratories, 1969. P. 16.
136. Sanerkin, N. G., and Evans, D. M. D. The sputum in bronchial asthma: Pathognomonic patterns. *J. Pathol.* 89:535, 1965.
137. Schlueter, D. P. Response of the lung to inhaled antigens. *Am. J. Med.* 57:476, 1974.
138. Schwartz, H., Lowell, F. C., and Melby, S. C. Steroid resistance in bronchial asthma. *Ann. Intern. Med.* 69:493, 1968.
139. Shapiro, G. G., Eggleston, P. A., Pierson, W. E., Ray, G. G., and Bierman, C. W. Double-blind study of the effectiveness of a broad spectrum antibiotic in status asthmaticus. *Pediatrics* 53:867, 1974.
140. Shapiro, J. B., and Tate, C. F. Death in status asthmaticus: A clinical analysis of eighteen cases. *Chest* 48:484, 1965.
141. Sheehy, A. F., DiBenedetto, R., Lefrak, S., and Lyons, H. A. Treatment of status asthmaticus. *Arch. Intern. Med.* 130:37, 1972.
142. Shim, C., and Williams, M. H., Jr. Cardiac response to repeated doses of isoproterenol aerosol. *Ann. Intern. Med.* 83:208, 1975.
143. Silverglade, A. Management of asthma in childhood. *J.A.M.A.* 230:963, 1974.
144. Silverman, M., and Anderson, S. Standardization of exercise tests in asthmatic children. *Arch. Dis. Child.* 47:882, 1972.
145. Simon, G., Connolly, N., Littlejohns, D. W., and McAllen, M. Radiological abnormalities in children with asthma and their relation to clinicial findings and some respiratory function tests. *Thorax* 28:115, 1973.
146. Simpson, H., Forfar, J. O., and Grubb, D. J. Arterial blood gas tensions and pH in acute asthma in childhood. *Br. Med. J.* 3:460, 1968.
147. Snapper, I., and Kahn, A. I. *Bedside Medicine*. New York: Grune & Stratton, 1967. 2nd ed., p. 296.
148. Speizer, F. E., Doll, R., and Heaf, P. Observations on recent increase in mortality from asthma. *Br. Med. J.* 1:335, 1968.
149. Spitzer, S. A., Goldschmidt, Z., and Dubrawsky, C. The bronchodilator effect of salbutamol administered by IPPB to patients with asthma. *Chest* 62:273, 1972.
150. Sponitz, M. Significance of yokahama asthma. *Am. Rev. Respir. Dis.* 92:371, 1965.
151. Stanescu, D. C., and Teculescu, D. B. Pulmonary function in status asthmaticus effect of therapy. *Thorax* 25:581, 1970.
152. Stolley, P. D. Asthma mortality. Why the United States was spared an epidemic of deaths due to asthma. *Am. Rev. Respir. Dis.* 105:883, 1972.
153. Straub, P. W., Buhlmann, A. A., and Rossier, P. H. Hypovolemia in status asthmaticus. *Lancet* 2:923, 1969.
154. Streeton, J. A., and Morgan, E. B. Salbutamol in status asthmaticus and severe chronic obstructive bronchitis. *Postgrad. Med. J.* [Suppl.] 47:125, 1971.
155. Sundberg, M., and Jakobson, T. Comparison of pituitary adrenocortical function in asthmatic patients given long-term corticosteroid therapy and in asthmatics who have not received adrenal steroids. *Acta. Allergol.* (Kbh) 24:11, 1969.
156. Swineford, O., Jr. Infectious asthma: An analysis of its major problems. *Ann. Allergy* 33:37, 1974.
157. Tabb, W. C., and Guerrant, J. L. Life-threatening asthma. *J. Allergy Clin. Immunol.* 42:249, 1968.
158. Tai, E., and Read, J. Blood-gas tensions in bronchial asthma. *Lancet* 1:644, 1967.
159. Takizawa, T., and Thurlbeck, W. M. Muscle and mucous gland size in the major bronchi of patients with chronic bronchitis, asthma, and asthmatic bronchitis. *Am. Rev. Respir. Dis.* 104:331, 1971.
160. Taylor, G. J., IV, and Harris, W. S. Cardiac toxicity of aerosol propellants. *J.A.M.A.* 214:81, 1970.
161. Taylor, W. F., Heimlich, E. M., Strick, L., and Busser, R. J. Intermittent positive pressure breathing versus freon-unit nebulized isoproterenol in asthmatic children. *J. Allergy Clin. Immunol.* 38:257, 1966.
162. Terr, A. I. Bronchial Asthma. In Baum, C. L. (Ed.), *Textbook of Pulmonary Diseases*. Boston: Little, Brown 1974. 2nd ed., p. 421.
163. Thieme, E. T., and Sheldon, J. M. A correlation of the clinical and pathological

findings in bronchial asthma. *J. Allergy Clin. Immunol.* 9:246, 1938.
164. Turiaf, J., Marland, P., Basset, G., and Georges, R. Intérêt de la sang pour la sécurité et l'efficacité de traitement de l'Etat de mal asthmatique grave, XXXIII[e] Congrès Français de Medicine. Paris: Masson, 1961.
165. Unger, L. *Bronchial Asthma.* Springfield, Ill.: Thomas, 1964. P. 35.
166. Unger, L., and Wolf, A. A. Treatment of bronchial asthma: Survey of value of treatment in 459 cases during 20 years. *J.A.M.A.* 121:325, 1943.
167. U.S. Department of Health, Education and Welfare, PHS Health Resources Administration. Prevalence of selected chronic respiratory conditions United States, 1970. *Vital and Health Statistics Series 10*, No. 84. Washington, D.C.: GPO, 1973.
168. U.S. Department of Health, Education and Welfare, PHS Health Resources Administration. Summary report final mortality statistics, 1970. *Monthly Vital Statistics Report* [Suppl.] 22, 1974.
169. Usher, J., Sheperd, R. J., and Deegan, T. Serum lactate dehydrogenase isoenzyme activities in patients with asthma. *Thorax* 29: 685, 1974.
170. van den Brink, T. G. The pharmacology of bronchida muscle relaxation. *Bull. Physiopathol. Respir.* 8:3, 415, 1972.
171. Van Metre, T. E., Jr. Adverse effects of inhalation of excessive amounts of nebulized isoproterenol in status asthmaticus. *J. Allergy Clin. Immunol.* 43:101, 1969.
172. Walker, P. E., and Marshall, M. Bronchial lavage in status asthmaticus. *Br. Med. J.* 3:5661, 1969.
173. Warren, K. S. Worms. In Samter, M., et al. (Eds.), *Immunological Disease.* Boston: Little, Brown, 1971. Vol. 1, p. 668.
174. Warwick, M. T., and Haslam, P. Smooth muscle antibody in bronchial asthma. *Clin. Exp. Immunol.* 7:31, 1970.
175. Weill, H. Ziskind, M. M., Dickerson, R., and Derbes, V. J. Epidemic asthma in New Orleans. *J.A.M.A.* 190:811, 1964.
176. Weinberger, M. M., and Bronsky, E. A. Evaluation of oral bronchodilator therapy in asthmatic children. Bronchodilators. *J. Pediatr.* 84:421, 1974.
177. Weiss, E. B., and Desforges, J. Oxyhemoglobin affinity in bronchial asthma: Chronic stable state, acute, and status asthmaticus. *Chest* 62:709, 1972.
178. Weiss, E. B., and Dulfano, M. J. Controlled ventilation with I.P.P.B. in the management of acute ventilatory failure associated with chronic obstructive pulmonary disease. *Ann. Intern. Med.* 67:556, 1967.
179. Weiss, E. B., and Dulfano, M. J. The quantitative acid-base dynamics in chronic pulmonary disease: Defense of pH during acute respiratory acidosis superimposed upon chronic hypercapnia. *Ann. Intern. Med.* 69:263, 1968.
180. Weiss, E. B., and Faling, L. J. Clinical significance of Pa_{CO_2} during status asthma: The cross-over point. *Ann. Allergy* 26:545, 1968.
181. Weitzman, R. H., and Wilson, A. F. Diffusing capacity and overall ventilation: perfusion. *Am. J. Med.* 57:767, 1974.
182. Wells, R. E., Jr. Mechanics of respiration in bronchial asthma. *Am. J. Med.* 26:384, 1959.
183. Weng, T. R., and Levinson, H. Pulmonary function in children with asthma at acute attack and symptom free status. *Am. Rev. Respir. Dis.* 99:719, 1969.
184. Williams, D. A., and Leopold, J. G. Death from bronchial asthma. *Acta. Allergol.* (Kbh), 14:83, 1959.
185. Williams, M. H., Jr. Pathophysiology and treatment of severe asthma. *N.Y. State J. Med.* 73:2446, 1973.
186. Williams, N. E., and Crooke, J. W. The practical management of severe status asthmaticus. *Lancet* 1:1081, 1968.
186a. Williams, S. J., Parrish, R. W., and Seaton, A. Comparison of intravenous aminophylline and salbutamol in severe asthma. *Br. Med. J.* 4:685, 1975.
187. Wilson, A. F., Surprenant, E. L., Beall, G. L., Siegel, S. C., Simmons, D. H., and Bennet, L. R. The significance of regional pulmonary function changes in bronchial asthma. *Am. J. Med.* 48:416, 1970.
188. Wood, D. W., Downes, J. J., Scheinkopf, H., et al. Intravenous isoproterenol in the management of respiratory failure in childhood status asthmaticus. *J. Allergy Clin. Immunol.* 50:75, 1972.
189. Woolcock, A. J., and Read, J. Improvement in bronchial asthma not reflected in forced expiratory volume. *Lancet,* 2:1323, 1965.
190. Woolcock, A. J., and Read, J. Lung volumes in exacerbations of asthma. *Am. J. Med.* 41:259, 1966.
191. Zwillich, C. W., Pierson, D. J., Creagh, C. E. et al. Complications of assisted ventilation—a prospective study of 354 consecutive episodes. *Am. J. Med.* 57:161, 1974.