EMERGENT MANAGEMENT OF ASTHMA

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INTRODUCTION

Management of asthma remains a frequent cause for emergency room visits and hospitalization just as it did the last time this topic was reviewed in Medical Grand Rounds by Gary Hart[1]. Dr. Hart cited 4% as the proportion of E.R. visits prompted by asthma in his 1981 review. This was similar to Karetzky's report from Morrisania Hospital in the South Bronx in the early 70's where 5.02% to 6.21% of E.R. visits from July 1971 through June 1974 were asthma related[2]. There is no reason to suspect a decline in these figures, and, indeed the number may be even higher now[3,4]. Mullally, et. al., cite figures suggesting an increase in the numbers, as well as the severity of asthma admissions among children's hospitals in Washington, D.C.[5] (Figure 1.). Unfortunately, good prevalence data are unavailable for given areas and, therefore, substantiation of Mullally's data is not possible. McFadden estimates prevalence figures of about 5% of adults[6]. Karetzky's report from the South Bronx noted that 8% of adult medical admissions were due to asthma during the aforementioned three year period[2]. Rose quotes Davis' work (also from the early 1970's) citing 134,000 hospitalizations annually for asthma in the United States[7].

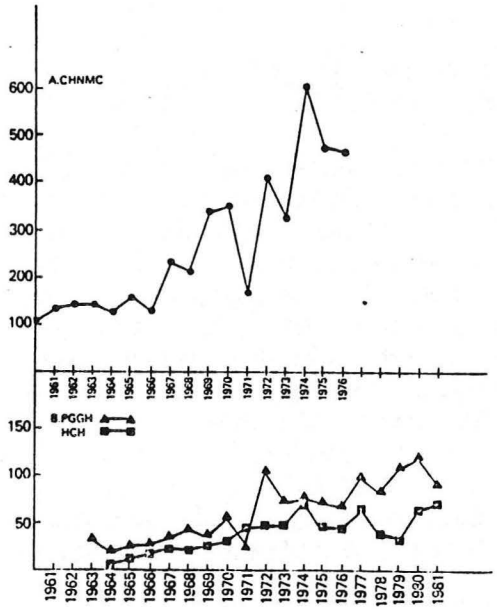

Figure 1. Asthma Admissions in 3 Washington, D.C. Hospitals, (Mullally, et al.[5]).

The rise of mortality for asthma noted in the 1981 Grand Rounds referred to the United Kingdom, Australia, and New Zealand predominantly (Figure 2.). The United States had been spared to that point[8-10]. A recent news item in The Journal of the American Medical Association suggests that that grace period has ended[11] and

is supported by Sly's[12] evaluation of mortality statistics as well as a 1986 report in MMWR[13] (Figure 3.). The etiologies of the epidemics of fatal asthma here and abroad over the past 20 years remain uncertain. However, several possible causes have been discussed over the years and will be addressed in this review.

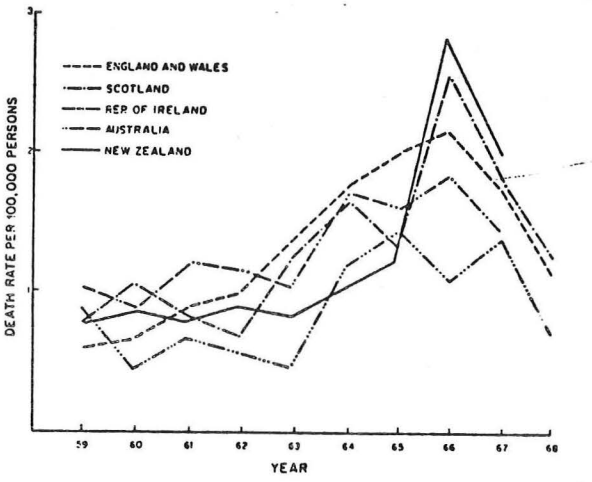

Figure 2. "Asthma Death Epidemic" of the 1960's (Stolley, 1972[10])

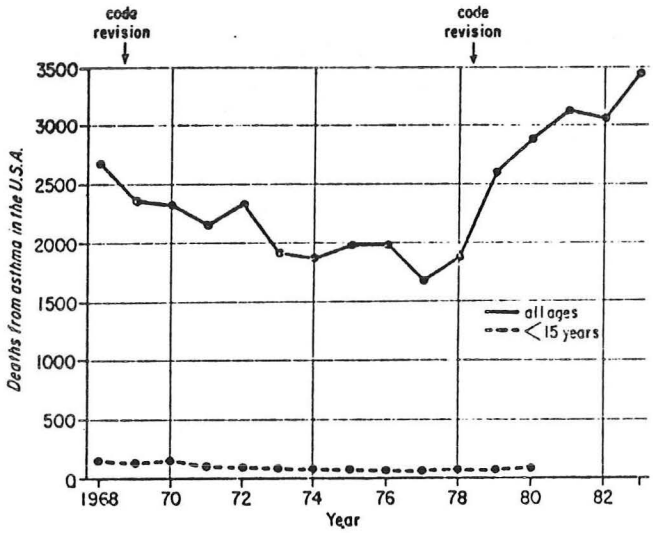

Figure 3. Asthma Deaths in the U.S.. (Sly, 1984[12])

There has been some recent change in the therapeutic options for asthma as well as reevaluation of long established therapies. A number of studies evaluating aminophylline in the emergency room management of asthma have been published in the past five years and have made a more scientific approach to asthma more feasible. Likewise, considerable data on the use of corticosteroids in emergency room therapy of asthma have been published in that interim. Anticholinergic therapy of asthma has at last become more formalized in the U.S. with the release of ipratropium bromide. Consequently, review of the available data on its use in the acute setting are in order. Lastly, the advent of chamber delivery systems for aerosols may suggest a method to decrease costs in the emergency room therapy and decrease exacerbations in the chronic therapy of asthma.

Hence, considering the aforementioned developments, a reexamination of the topic of emergent management of asthma as it stands in 1989 seems appropriate. The topics of chronic outpatient therapy, allergic components, and in-hospital management (except as they apply to emergency therapy) will not be covered.

The definition of asthma offered up by the American Thoracic Society in 1962 is still regarded as the standard. Asthma was defined as a disease "characterized by an increased responsiveness

of the trachea and bronchi to various stimuli and manifested by a widespread narrowing of the airways that changes in severity either spontaneously or as a result of therapy"[14]. This group emphasized a host defect prompting inappropriate smooth muscle contraction and mucus secretion in the tracheo-bronchial tree in response to commonly encountered stimuli. They described the process in terms of clinical parameters (such as wheezing and dyspnea), physiologic aberrations (such as altered forced vital capacity, forced expiratory velocity, airway resistance, intrapulmonary gas mixing, and arterial blood gases), and pathology (the classic combination of bronchial mucus plugging with an increase in size and number of goblet cells, inflammatory cellular infiltration of the mucosa, smooth muscle hypertrophy, and thickening and irregularity of the basement membrane).

TRIGGER FACTORS IN ASTHMA

Table I. Triggers of asthma

Allergic
Weather
Pollution
Infection
Drug
Exercise

Table 1.

A key feature of the definition of asthma is the notion that the airway reactivity is the consequence of some stimulus. A variety of such stimuli have been identified over the years. Dr. Tim Sullivan reviewed allergic allergy very nicely in his 1984 edition of Medical Grand Rounds[13]. Consequently, I will devote little attention to the specifics of that triggering factor. Dr. Sullivan's review cites a 50-80 % prevalence for allergy as a trigger among asthmatics. Textbooks of Internal Medicine have traditionally cited a much lower figure for allergic, or extrinsic, asthma, typically around 10%[16,17]. The disparity probably arises from several sources. The background prevalence of atopy is high making the distinction of asthma in an atopic patient from atopy-induced asthma more difficult. Additionally, patients whose asthma may be triggered by atopy are often triggered by other factors as well. Consequently, perception of allergens as a significant component may depend on the season and location of assay. Indeed, epidemic E.R. utilization as a consequence of atopy-induced asthma has been well documented in northern California. Reid and coworkers from Travis Air Force Base have identified ryegrass pollen as a significant contributor to E.R. visits for asthma during the month of May for the years 1981-1984 and 1986[18,19]. Also, the age-distribution of the patients who are studied will affect

estimates of the involvement of atopy in asthma. The younger asthmatic is more likely to have an atopy history[20]. It is clear that the incidence of atopy in patients with asthma is much higher than in the non-asthmatic members of the same population[20]. Thus, it seems most likely that Dr. Sullivan's estimates are much more reasonable in the context of current knowledge of asthma.

Specific allergens are well detailed in Dr. Sullivan's Grand Rounds and include mold spores, Dermatophagoides mites, animal dander, pollen, food, and occupational exposures (e.g. metal salts, cotton dust, grain, tidoluene isocyanate, and pharmaceuticals)[15].

Weather and, more specifically cool air, has been implicated as a trigger factor for asthma. Greenburg, et. al. correlated epidemic periods of E.R. utilization for asthma with temperature drops in New York City[21,22] (Figure 4.). He specifically looked at those days when the ambient temperature dropped to the level that the New York City Health Code would require landlords to turn on the heating in their dwellings (55°F). These "epidemics" of asthma could not be correlated with detectable pollutants or allergens. Similar autumn peaks for asthma-related E.R. visits were noted in the early reports of the New Orleans "epidemics"[23] (Figure 5.). However, more recent analysis of seasonal variation in E.R. visits for asthma in New Orleans have failed to confirm a significant monthly difference while again finding the autumnal rise in New York[24]. It must be noted, however, that the New Orleans epidemics have declined in recent years and this may confound the more recent analysis[25]. Another obvious difference is the amount of temperature change which one experiences in New York compared to New Orleans during autumn. Certainly, airway cooling has been implicated as a contributor to exercise-induced asthma[6]. Asthma-related visits to an E.R. in Bermuda were correlated inversely with temperature and humidity[26]. This would make sense in that airway cooling is more brisk when the inspired air is dry[6]. Nevertheless, it is reasonably likely that the seasonal variations described in the New York and New Orleans epidemics are grounded in allergen exposure even though clear-cut allergens were not identified. The patients involved in the New Orleans outbreaks were generally atopic patients[27]. Also, a consequence of cold weather is to drive asthmatics indoors and, once inside, to fire their furnaces. This would tend to enhance exposure to household allergens, such as Dermatophagoides mites or other antigens derived from animals commonly found indoors. Indeed, Goldstein has shown that E.R. utilization for asthma in New York City is greatest on weekends and holidays, a pattern not observed with non-asthma utilization of the E.R.[28]. This pattern did not hold in New Orleans. Again, this would support an indoor exposure as etiologic for triggering of asthma in these areas. Thus, although it is likely that if the weather contributes as a triggering factor, it may be that it does so more as a consequence of the effects of weather on sporulation of unmeasured antigens or by placing people in contact with the triggering allergens by driving them indoors.

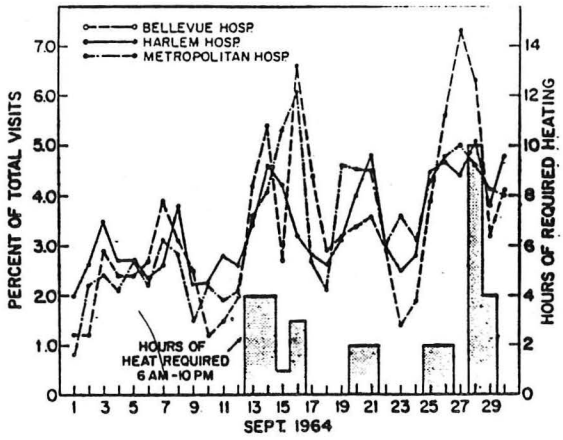

Figure 4. Asthma E.R. Visits As Compared to Days Requiring Heat Use, (Greenberg, et al, 1966[21])

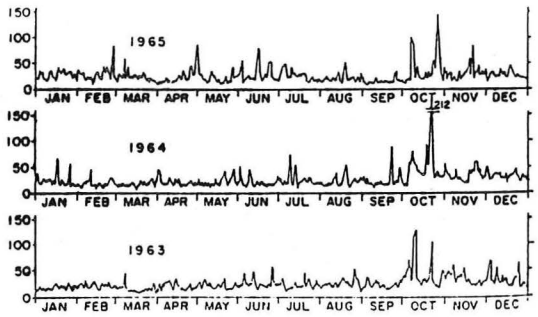

Figure 5. Epidemic Asthma in New Orleans, (Carroll, 1968[23])

Another postulated environmental trigger is air pollution. There is a tendency for patients with baseline chronic lung disease to be more severely affected when pollution is most intense, usually the consequence of "inversion" conditions in industrialized areas[6]. A variation of air pollution as a trigger is an increase in E.R. utilization in children with asthma whose parents smoke[29]. Decreases in FEV_1 and FVC with concomitant increases in methacholine sensitivity have been shown after periods of exposure to cigarette smoke in two studies[30,31], but not in a third[32]. All of the studies noted above involved few patients and controlling periods of exposure or non-exposure is obviously impossible.

Infection of the upper and lower respiratory tract is often implicated in the acute asthmatic exacerbation. The incidence of infection in patients presenting with asthma has traditionally been put at approximately the 10% level[33,34]. Clarke found that symptoms suggestive of an upper respiratory tract infection were present much more frequently, however. About 1/2 of his patients had discolored sputum or sore throat. The majority of patients with infection as a precipitating factor in asthma have viral infections. Bacterial infection is an uncommon trigger for asthma[6].

Seggev, et. al. recently looked at the prevalence of Mycoplasma pneumoniae antibodies in the sera of hospitalized asthmatics[35]. Twenty of ninety-five (21%) asthmatics so studied had high levels of IgM to Mycoplasma, suggesting recent infection with this agent. Serum levels of IgG and IgM were elevated in this group of Mycoplasma exposed asthmatics as compared to 20 of the asthmatics who were seronegative. Additionally, five of the twenty had rheumatoid factor present whereas none of the aforementioned 20 nonexposed asthmatics had rheumatoid factor. Controls from the non-asthmatic population were not presented, but the possibility

that Mycoplasma pneumoniae may be a contributor to hospitalization for an acute asthmatic exacerbation is suggested.

Kava reports a cohort of 92 asthmatics followed serially with peak expiratory flow rates (PEFR) and correlating changes in these with symptoms of respiratory infections.36 He found that 68 subjects experienced 141 episodes of symptomatic respiratory infection. Sixty-three of two hundred-fifty-three (25%) of asthma exacerbations were associated with symptomatic respiratory infection. Those exacerbations associated with symptomatic respiratory infection took longer to clear (11.4 days vs. 8.1 days).

Several other factors have been associated with exacerbations which I will only mention in passing. Exercise-induced asthma is well described and has already been referred to. Aspirin can clearly precipitate asthma in a subset of patients. The topic of aspirin associated asthma is a broad one and will not be delved into any deeper here. The relevance of aspirin induced asthma to the physician managing an acute asthmatic exacerbation is the need to remember the large number of over-the-counter medications which contain aspirin. Beta-blocking agents and sulfating agents are other chemicals which may trigger asthmatic exacerbations. Lastly, emotional and psychologic factors are oft mentioned precipitants for asthmatic exacerbations. It is felt that this is mediated by vagal efferent activity[6].

ASTHMA MORTALITY

Asthma mortality has increased in recent years, first in the United Kingdom and now in the United States. This seems paradoxical in light of the much wider variety of agents available for therapy and the enhanced understanding of the pathophysiology of the disease. Mortality in a disease that is generally defined in terms of its reversibility is particularly frustrating. This rise in mortality has prompted considerable literature on the subject with much speculation as to the etiology of the "fatal asthma epidemic." That body of literature is worthy of review at this juncture.

Although death from asthma was reported in the late 17'th century by Floyer[37], asthma was regarded as a disease which rarely caused death in its sufferers until the 20'th century. Laennec, Osler, and other physicians of historical importance are often quoted as saying that asthma was not a fatal process[38]. Indeed, Dr. Hart's Grand Rounds quotes Osler as suggesting that the disease was associated with longevity[1]. The great physician stated in his 4'th edition of <u>The Principles and Practice of Medicine</u> published in 1901, "the asthmatic pants into old age." Osler himself quoted Oliver Wendell Holmes as saying that asthma is "the slightest ailment that promotes longevity"[39]. However, the pathologic

findings of asthma were described in 21 cases by Huber and Koessler in 1922[40]. Eight of their series had died principally of asthma, the remaining 13 of other causes with asthma present at the time of death.

Pathology of asthma

Mucus plugs
Smooth muscle hypertrophy
Mucus gland hyperplasia
Leukocytic mucosal infiltration
Mucosal edema
Basement membrane thickening

Table II.

Earle was one of three authors reporting a series of asthma fatalities in 1953[39,41,42]. Earle's series, as well as the other two, called attention to the fact that patients did die of asthma, although they usually did so at home since that was where they commonly were treated for their malady. Earle reported 15 patients dying as a consequence of asthma. Eleven were between the ages of 35 and 60 and three were under five years of age. In the older age groups, eight had had asthma for more than ten years, only one of the remaining four patients dying at ages greater than five had had asthma fewer than five years. This pattern was similar to the other two series reported in 1953. Earle's own series found a wide variation in the duration of the attack prior to death, ranging from under 12 hours to weeks. Three of his cases were associated with the use of morphine (one of whom received 30 mg.!). Earle cites work from the late 1940's suggesting that adrenaline inhalers were dangerous, leading to damage of the respiratory tract epithelium and allowing access of bacteria[43], suggesting that this may have contributed to death in his own series. He also cites French literature published just prior to the inhaler paper suggesting that repeated use of adrenaline would lead to a resistant state. Indeed, he suggests that two of the deaths in his own series were related to adrenergic resistance. It is also clear from his series that some of the patients just did not respond to therapy and simply asphyxiated, a seemingly predictable occurrence in the pre-positive pressure ventilator days. These findings and speculations are obviously anecdotal, but do represent one of the earlier series on fatal asthma. They also call attention to the fact that while death as a consequence of asthma was infrequent, it did occur. Additionally, whether intentional or not, his suggestion in the early part of the work that most died at home because that was where most were treated calls one's attention to underassessment of the severity of the process as a potential correctable aspect of mortality.

Speizer, et. al. reported a rise of asthma mortality in the United Kingdom which had its onset in the mid-1960's[44]. This epidemic affected mostly younger asthmatics. The authors raised the point that this epidemic occurred at a time when metered dose inhalers were becoming widely available (indeed, they were not even prescription medications in England at the time). A follow-up article published adjacent to the above-mentioned article attempted to correlate inhaler use with fatalities[45]. The authors obtained death certificates of persons dying of asthma aged 5 to 34 years from England and Wales over the time period October 1, 1966 to March 1, 1967. Questionnaires were then sent to physicians caring for the decedent or the coroner who certified the death regarding drug use during and before the terminal event. Also queried was whether or not the death was anticipated or not. Like Earle, this survey found that the majority of fatalities had long-standing asthma, the mean duration being 13.1 years. One hundred-thirteen post mortem reports were available, 110 of which revealed hyperinflated lungs and 106 had mucus plugging. Adrenal atrophy is noted in six patients, all of whom had received steroids in the past. Not surprisingly, inhaled bronchodilators were frequently used (150 of 168 patients for whom information was available). There were no statistical differences between use as compared to estimates of severity of asthma or whether or not the death was expected. The physician queried volunteered in 29 of the deaths that inhaler use was excessive. Sedatives had been used in 39% of cases (in spite of two decades of experience that this was potentially lethal). The authors state that "the severity of the illness was often underestimated". The authors go on to suggest several mechanisms by which inhaled bronchodilators could contribute to death in these cases. These included cardiac irritability as a consequence of systemic absorption, paradoxical desaturation, and delay in seeking a physician's help as a consequence of partial relief of symptoms without correcting the underlying pathology. However, the concluding words of the article concede that "further evidence is required before their [inhaled bronchodilators] effect can be assessed adequately".

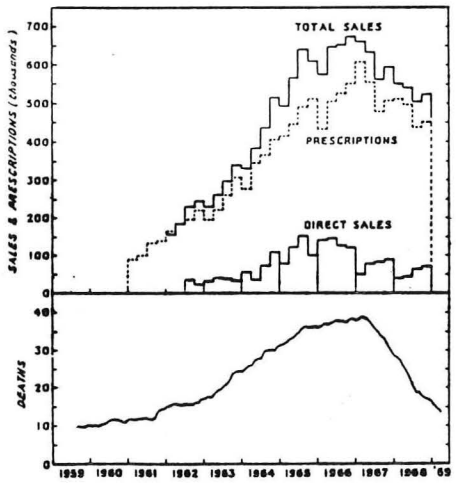

Figure 6. Asthma Deaths and Inhaler Sales in England (Imnan and Adelstein, 1969[9])

In spite of obvious weaknesses, the Speizer work formed the basis for an argument that overtreatment was a key feature of the increase in asthma mortality. A number of rebuttal arguments were quickly exchanged, the content of which will be reserved until after consideration of the potential negative side effects of inhaled adrenergic agents.

The Case for Overtreatment

Although the temptation to link potent B-adrenergics to cardiac arrhythmias is strong, there is little data to support such a contention. A tendency to develop arrhythmias has not been clearly demonstrated for asthmatics treated with inhaled B-agonists alone.

Recent data examining the response of plasma potassium in healthy volunteers to varying dosages of inhaled fenoterol, a resorcinol B-2 adrenergic, have demonstrated a potentially deleterious effect[46]. A dose related decline over the study interval was documented (Figure 7.), with the highest dose group (12 puffs in 3 sessions thirty minutes apart) showing a mean decline of 0.9 mmol/l 15 minutes after the third inhalation. The group using a more normal dosage, two puffs at thirty minute intervals, had less of a decline at 15 and 75 minutes, levels dropping 0.1 and 0.4 mmol/l respectively. The declines were statistically significant at 90 minutes for all regimens. Plasma potassium levels as low as 2.9 mmol/l were encountered. This will certainly enhance arrhythmogenicity. However, similar studies with inhaled albuterol, a saligenin B-2 adrenergic have not shown a similar response[47].

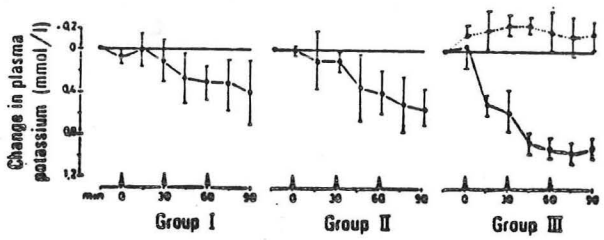

Figure 7. Beta-Agonist Induced Changes in Plasma Potassium (Haalboom, et al, 1985[46]).

Adjunctive methylxanthine therapy has been suggested to exaggerate this hypokalemic response. Data from anesthetized dogs shows induction of ventricular fibrillation when 5 ug/kg of epinephrine was given to animals pretreated with theophylline[48]. Similar findings have been demonstrated in an isolated rat heart preparation.49 Josephson compared the development of supraventricular and ventricular arrhythmias in asthmatics under 50 years of age who were treated in a blinded fashion with either subcutaneous epinephrine or subcutaneous epinephrine combined with aminophylline[50]. He found more frequent dysrhythmias in the combination group (all three patients with complex ventricular ectopy and six of seven with more than one APC/30min.). No severe dysrhythmias were observed in the 44 subjects and potassium levels are unavailable. Josephson did note that the patients with the complex ectopy tended to be older than those without and suggested that occult cardiac disease may have contributed to his observations.

Wilson, et. al. examined drug use in 25 cases of fatal or near fatal asthma in an effort to explain the continued rise in asthma mortality in New Zealand and found that patients dying "suddenly" of asthma were almost uniformly on the combination of a B-2 agonist and theophylline[51]. Autopsy results were available in eight patients, all showing mucus plugging, bronchial smooth muscle hypertrophy, basement membrane thickening, and hypertrophy and hyperplasia of mucus glands. No cardiac changes were identified. Unfortunately, it is not stated how many of the eight autopsies were performed on patients dying "suddenly and unexpectedly". Although the authors suggest that the drug combination may have played a role in the sudden deaths, they admit that many of the patients were not receiving medications which might have been beneficial to them at the time of death. Additionally, although the sudden and unexpected deaths were said to have occurred in patients who were "walking or talking" until just before their demise, all were noted to be dyspneic.

One can argue that such arrhythmogenic effects are no more likely to occur in the outpatient than the hospitalized patient. Indeed, in as much as inhaler usage is so inefficient in most

asthmatics[52] (especially those acutely dyspneic), one might predict higher systemic levels in hospitalized patients receiving updraft nebulization delivered B-agonists. In spite of this fact, deaths are more frequent outside the hospital in a number of studies[39,53-58]. Additionally, in-hospital deaths are most often the consequence of asphyxiation because of refractoriness to conventional therapy[39]. Although either the substrate for or the arrhythmia itself is suggested in a few studies, clinical significance of these findings has not yet been demonstrated.

A second deleterious effect associated with inhaled bronchodilators has been the development of hypoxemia after their administration. Tai and Read demonstrated this effect with both isoproterenol and aminophylline in patients with stable reversible obstructive airways disease[59]. The drops were typically small, although occasionally were more severe. The authors suggested that the bronchodilators were having a pulmonary vasodilator effect in excess of the bronchodilation with resultant worsened ventilation-perfusion mismatch. These results have been shown by others and with other agents including subcutaneous epinephrine and atropine methonitrate[60-62]. Hedges, et. al. demonstrated a fall in SaO2 by oximetry in a series of patients treated with inhaled metaproterenol for acute exacerbations of reversible obstructive airways disease. Mean saturation fell from 94.6% to 91.4% in that series[63]. One can imagine that even small changes in P_aO_2 in a patient already poised on the steep portion of the oxygen saturation curve can be clinically quite important. However, the above-mentioned argument regarding the outpatient nature of most deaths is hard to integrate into this hypothesis.

Development of tolerance, tachyphylaxis, or resistance to B-agonist use is a well-known phenomenon. Such tolerance has been invoked by numerous authors on the topic of fatal asthma over the years. Indeed, an entire literature has grown out of the invocation of B-agonist tolerance as a mediator for the epidemic of asthma mortality in the mid-1960's. Conolly's group followed Speizer's paper closely with an evaluation of the development of resistance. They found a resistance to the tachycardia developing in response to protracted administration of isoproterenol in 1968[64]. This work regarding cardiac tolerance to intravenous isoproterenol was reconfirmed in man, dog, and guinea pig in 1971[65]. The human subjects were not said to be asthmatic or atopic. The dog model demonstrated that the tolerance induced by one B-agonist would extend to other B-agonists. The guinea pig model studied B-agonist protection from histamine-induced bronchospasm and again demonstrated that tolerance could be induced.

Parker and colleagues investigated the phenomenon at the cellular level in a series of articles aimed at understanding atopy[66,67]. The initial work revealed that baseline leukocyte cAMP levels were lower in atopic or asthmatic patients than in healthy subjects. They also demonstrated that adrenergic stimulation of

the cells with either isoproterenol or norepinephrine resulted in a lesser rise in cAMP in the atopic/asthmatic patients (Figure 8.). This group also noted that asthmatics on corticosteroids had better cAMP responses than the asthmatics not on steroids. The follow-up study demonstrated that addition of corticosteroids improved the B-agonist response[67] (Figure 9.).

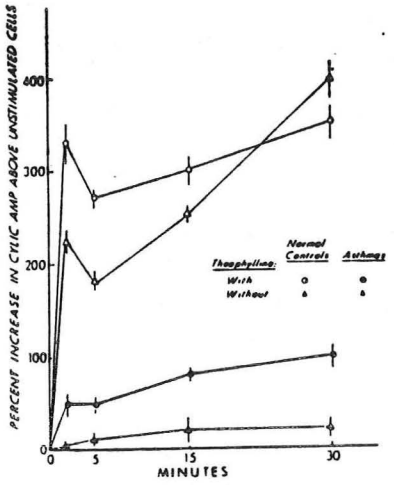

Figure 8. Cyclic AMP Responses of Leukocytes to Isoproterenol on Asthmatics and Non-asthmatics, (Parker, et. al., 1973[66])

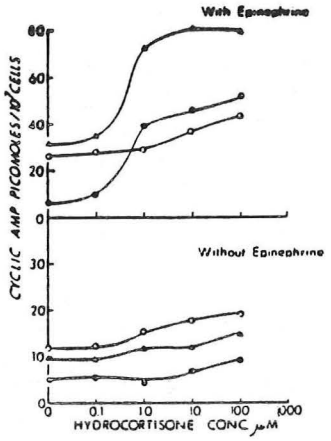

Figure 9. Effect of Cortisone Incubation of Asthmatics Lymphocytes on cAMP Production, (Parker, et. al., 1973[67])

A myriad of studies have followed, studying both intact patients and cellular models. Most studies have demonstrated that tolerance as measured by airways conductance, tachycardic response, and tremor is easily induced in normal subjects[68-71]. Demonstration of the development of tolerance to bronchodilation in asthmatics has proven much more difficult[70-75]. Those studies which have shown tolerance to develop have generally not shown dramatic changes in airways response although tolerance to the tremor and tachycardia are usual and probably permit the widespread continued use of some of these agents[76-78] (Figure 10).

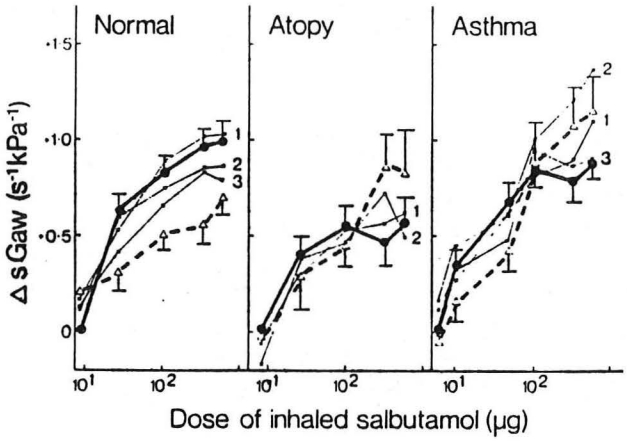

Figure 10. Attempted Induction of B-agonist Tolerance in Normals, Atopic, and Asthmatic patients. Solid-line Week 1, Broken Line, week 4. (Harvey and Tattersfield, 1982[71]).

The studies must be interpreted critically in that cellular studies suggest that atopic asthmatics may be characterized, at least at the cellular level, by poor B-agonist responsiveness[66]. That is to say that these patients' disease process may simply represent a state of chronic B-agonist tolerance which very well may be maximal at baseline. Selection criteria may bias the studies considerably from the outset as only mild to moderate asthmatics can be taken off of their B-agonists for any period of time which might allow adequate wash-out of the agents to be tested. They then require additional agents such as methylxanthines and steroids to control the residual symptoms[79]. Integration of cellular information into the framework of physiologic processes has long-debated limitations. Certainly, the cellular data concerning B-agonist tolerance are difficult to interpret in many respects[80]. Even making sense of the cellular data is difficult in the context of other cellular studies. One example is the discovery that in spite of decreased cAMP production at baseline, receptor number on the lymphocytes of asthmatics are comparable to those of normal patients. Likewise, the receptor numbers decline after incubation with B-agonists in both, but cAMP levels decline much more in the normal patients[70]. Lastly, if tolerance does occur, at least for cardiac sensitivity, to B-agonists, this would actually serve to protect the asthmatic from the first-mentioned mechanism of increased mortality[81].

Therefore, it seems that the current investigative tools do not allow us to make statements regarding the development of B-agonist tolerance in asthmatics with any certainty. The fact that it would seem that any such effect would likely be a small one argues that tolerance is probably not a major contributor to asthma mortality. However, caution must still be exercised as, even in the face of an asthma mortality "epidemic", deaths from asthma have remained low (about one to three per thousand asthmatics)[38]. Since

we are talking about a select group, even difficult to demonstrate effects may be contributory if they occur in an already marginal group.

The final suggested mechanism for B-agonists to contribute to the epidemic of asthma mortality is that of patients delaying seeking care because of their trust that the inhaler would control the attack[82]. It is certainly obvious that in a severe attack, B-agonists alone are suboptimal therapy as they do not address the inflammatory aspects of the disease or the mucus plugs. The fact that most of the patients died as outpatients would be consistent with this mechanism. The work of MacDonald, et. al. demonstrated that almost one half (41 of 90) of the outpatient deaths in Cardiff, England from 1963 through 1974 (63% of all asthma deaths in that area during that time period) either occurred without the doctor being summoned or with the doctor responding promptly only to find either a dead or dying patient[54]. Similar findings were reported in other studies out of the United Kingdom[55,57] and New Zealand.83 It is likely from the data presented in the British studies that adequate time existed between the onset of the attack and death for the patient to seek help. This information is not available in the New Zealand study.

Although these data are certainly consistent with the suggestion that a delay in seeking therapy contributed to mortality, they obviously say nothing about why the delay occurred. The British and New Zealand approaches to health care may have contributed with house calls being a frequent method of therapy as opposed to more frequent treatment in an E.R. setting. The ambulance services seem less well developed and harder to get than those in the U.S.. Whatever the etiology of delays in seeking therapy, and they will obviously be difficult to ferret out, it is certainly important for patients to understand that the inhaler is not the only mode of therapy for their asthmatic exacerbations. Instructions to seek more sophisticated care when either the inhaler is providing suboptimal relief or when the attack is prolonged is an important part of the physician's management of the asthmatic.

The Case Against Overtreatment

The reply to Speizer's suggestion that B-adrenergic inhalers contributed to the asthma mortality epidemic was swift and spirited. Several of the counter arguments have already been mentioned in the preceding paragraphs. Read summed up the logical response to the observation offered by Speizer that some patients "'died clutching aerosol[s]'" when he asked "if you were dying of asphyxia, what would you do with the aerosol?"[84]. Clearly, if asthma is getting worse (and this were manifest by increasing mortality) one would expect the sales of therapeutic medications to increase. Read's article also makes the point that, in spite

of invocations of sudden cardiac death in these patients, all the published autopsy data on the epidemic indicated that the pathologic changes of asthma were present. Additionally, Read's article was followed immediately in the same issue by the work of Gandevia showing that, in spite of a plateau in the death rate from asthma in Australia, the sales of aerosol bronchodilators had continued to climb[8] (Figure 11). Indeed, the more thorough investigations of the asthma death epidemic that followed in the late 1970's and early 1980's tended to disregard the suggestions of Speizer and his colleagues[54,55,57,85] that overuse or overprescribing of inhaled bronchodilators contributed to the asthma death epidemic of the 1960's.

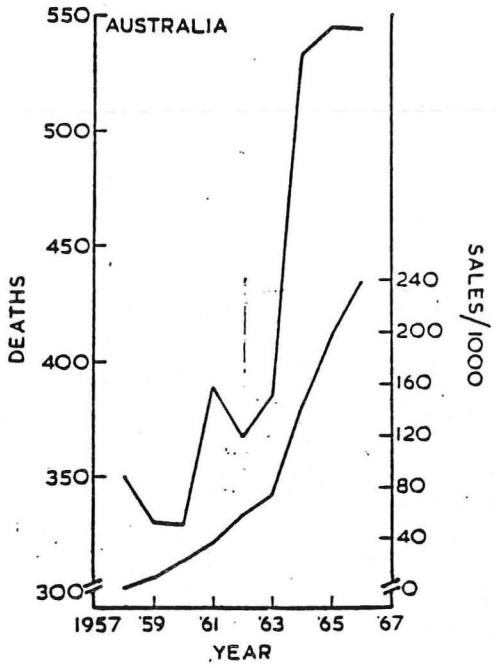

Figure 11. Asthma Deaths in Australia as Compared to Inhale Sales (Gandevia, 1968[8]).

Two more "overtreatment" causes of asthma mortality have been identified. The use of sedation in the therapy of the asthmatic has been appreciated for quite some time as a contributor to mortality and was mentioned in Earle's work as noted above[39]. It was also appreciated that intermittent positive pressure breathing as a method of bronchodilator administration was likely involved in some deaths by contributing to the development of pneumothorax[86]. Little controversy exists as regards these two therapies being contraindicated in the asthmatic.

The Undertreatment Argument

Speizer indicated in his controversial 1968 article that he originally set out to show that corticosteroid use was contributing

to the rise in asthma mortality[44]. Even he was surprised to learn that most of the asthmatics had not received steroids during their fatal episode. The work of others has since confirmed that steroids were underutilized in settings where the inflammatory components and mucus plugging aspects of asthma were likely to be prominent[54,55,57,85,87]. Although the rationale for the use of steroids in hopes of reducing the non-bronchospasm components of the asthmatic exacerbation are clear and a significant body of literature supports their use, it's hard to imagine how their underuse, in and of itself, would contribute to a rise in mortality. As there was no suggestion that usage had been reduced (but instead, only taken less than full advantage of), one would expect either flat mortality rates or a gradual decline in mortality as their use slowly increased.

McFadden demonstrated the presence of significant hypoxemia in most asthmatics presenting for therapy of exacerbations in the late 1960's[88]. Read emphasized in his aforementioned critical review of Speizer's paper that when a patient with a potentially worsening pulmonary process is perched on the knuckle of the steep part of the saturation curve at the point that they come into the care of a physician, it is surprising that mortality is not much higher than that observed in asthma[84]. This would be particularly true if the agent used in therapy were capable of producing a fall in oxygen tension itself (as bronchodilators had been shown to do). The failure to note oxygen therapy in the case records of patients dying in hospital was mentioned in one report[87]. Although this represents a problem for the quality assurance committee, it remains difficult to incorporate this aspect of undertherapy into a scheme explaining the rise in asthma mortality for the same reasons as were cited in the steroid argument. Also, this should not contribute at all to outpatient mortality where oxygen therapy is not a part of management.

Lastly, reluctance to rapidly initiate assisted ventilation was offered as a problem[1,85]. Although this no doubt contributed to excess mortality, again a rise in mortality should not occur when a relatively new therapeutic modality is underutilized.

The Underassessment Argument

Earle had pointed out 15 years before the Speizer paper that most asthmatics died at home where they were most often treated[39]. Read's rebuttal to the Speizer paper also suggested that the physician's estimate of severity of illness was a problem[84]. Indeed, he points out an interesting aspect of the Speizer article to support his argument. He points out the inconsistency of the reported observation that 91% of deaths in patients felt to have severe asthma were sudden and unexpected while only 63% of death in those with asthma felt to be not severe died suddenly and unexpectedly (Table III). Looked at another way, the physicians

caring for those patients with asthma felt to be not severe expected the deaths of 37% of those patients. Certainly most would agree that a process with an anticipated mortality of 37% is a severe process, therefore the physicians reporting these degrees of severity were internally inconsistent.

Clinical Category	No. of Patients			Tota No. of Patients
	Known to have Used Aerosols	Known Not to have Used Aerosols	Aerosol History Not Known	
Severe asthma:				
Death sudden ..	82	11*	2	95
Death not sudden ..	7	2†	0	9
Asthma not severe:				
Death sudden ..	34	4	4	42
Death not sudden ..	20	5	0	25
Category not known ..	3	0	0	3
All categories	146	22	6	174

* Three on inhalant sprays. † One on inhalant spray.

Table III.

Several subsequent papers focused on underassessment as a key precipitant of the asthma death epidemic[54,55,57,85,87]. Perhaps the best analysis of the British epidemic was the 1982 article from the British Thoracic Association[57]. The investigators administered questionnaires concerning the illness and the circumstances leading to death to the physicians and family of patients identified by the word asthma appearing on their death certificate. Physician and hospital records were reviewed. A panel headed by a pathologist agreed on which deaths really were the consequence of asthma. The members also recorded their views on patient cooperation, supervision, management, treatment, and factors contributing to death and then arrived at a consensus opinion.

Asthma was present on the death certificates of 153 patients in Mersey and West Midland during the study year, 1979. The panel judged 90 to have died as a consequence of asthma. Sixty-four of the ninety had either autopsy evidence of asthma or reversible obstruction documented by pulmonary function testing. Twenty-one of the deaths occurred in patients seen by their physician at some time during the fatal attack (fourteen on the last day of life) and treated at home. Seven were seen during the final phases of the attack and still managed at home (one did refuse to go to the hospital). Thirty-four summoned ambulances and all but two either died in route or soon after arrival at the hospital. In the final analysis, the panel felt that the physician delayed hospitalization in 23 of 36 fatalities where the opportunity existed. However, in 67 cases, the panel felt the patient failed to appreciate the severity of the illness.

General practitioner called (41 patients)		
Patient alive: managed at home	7	15
Patient alive: admitted to hospital	8	
Patient dead or moribund	21	
999 emergency call because general practitioner delayed	4	
Patient taken to hospital because general practitioner delayed	1	
General practitioner not called (49 patients)		
999 emergency call	30	
Taken direct to casualty	2	
Already in general hospital for reasons other than acute asthma	3	
In prison	1	
Found dead	13	

Table IV.

The British Thoracic Association study is often cited in support of the feeling that underassessment was a major contributor to asthma mortality. However, the weaknesses of this assessment are also quite obvious. The conclusion that the asthma was mismanaged is more likely to be rendered when the outcome was, by definition, death. The families' recollections of the terminal episode will be framed in that context. Recording of data will be inconsistent in such a retrospective analysis and the failure to document evaluations and therapy is not the same as not having done those things. Lastly, why should physicians suddenly in the 1960's begin to underestimate a disease as common as asthma?

What then accounts for the asthma death epidemic of the 1960's? The question is not a matter of idle interest. The epidemic persisted unchecked in New Zealand through current times[82]. Sly indicated in 1984 that the epidemic had finally arrived in the United States.12 Unlike the other epidemics, both young and older asthmatics are affected in U.S.studies. The analysis of mortality is complex as a consequence of two recent revisions in the coding of asthma by the ICD-9. The Ninth Revision went into effect in 1979 allowing more deaths previously coded as emphysema and bronchitis to be coded as asthma. Indeed, the increase in deaths from 1978 to 1979 was within the range expected for changes solely the consequence of coding differences. However, the deaths increased an additional 11% in 1980 and deaths in children increased by 43%. These changes are unlikely to be the consequence of coding alone. These data were subsequently extended to show that death rates continued to rise through 1984[3]. Therefore, the question of why is as timely as ever. The answer, however, remains as obscure as ever.

It would seem most likely that several factors are operating. It is likely that the inhaler has placed a tool in the hands of the patient that delays his reporting for further treatment. It also seems likely that physicians are not appreciating the severity of the illness in many of the patients who die. The physician may begin to rely too much on the burgeoning armamentarium of agents

to treat asthma and fail to appreciate the degree of illness of the patient. It may be that the natural history of asthma is simply becoming more aggressive. The New Zealanders believe this to be true in their country[89] although there is no way to assess the validity of that belief. One might invoke air pollution as a mediator of such a change in natural history. However, U.S. studies show that death rates have increased all across the country and large increases have been noted in more rural states as well. There are two papers which suggest a rise in prevalence of asthma which would also result in a rise in deaths[4,5].

Certainly the more important question is what to do to try to lower the death rate. A group in Scotland has reported on 15 years of experience with a service that permits asthmatics with prior episodes of life-threatening asthma to admit themselves to the hospital whenever they feel that their asthma is sufficiently severe[90]. Mortality in this otherwise high-risk group has been quite low, 4.6% (9 of 195). Two-thirds of the deaths occurred outside the hospital (one of which was ascribed to a myocardial infarction and one which occurred when the patient was out of town). Two of the three in-hospital deaths were not resuscitated because their poor baseline pulmonary status had made them invalids and the third died of a tension pneumothorax soon after the service was started. The authors found minimal abuse of the system. It must be noted that such services are more justifiable in the United Kingdom where E.R. use is much less common and the ambulance service less efficient. It is clear from their paper that some patients were treated and released much as we routinely do with asthmatics in the emergency room. Additionally, it is impossible to make broad recommendations in the absence of even historical controls for the highly selected group.

Some work aimed at identifying risk factors for fatal asthma has been done. Westerman, et.al. studied the characteristics of 39 patients requiring assisted ventilation for asthma-induced respiratory failure[91]. As would be expected, this group was likely to have subsequent life-threatening episodes of asthma. Nine of the thirty-two discharged alive for whom there is follow-up died during the follow-up period (nine months to seven years), eight of asthma. Subsequent publications have confirmed this risk factor[92,93]. Westerman's group also found that those patients with markedly labile PFT's were at high risk of death from asthma. Likewise, those showing a steady decline in pulmonary function were a poor risk group.

Rea, et. al. did a case control study to assess relative risks for asthma death[93]. The cases represented all asthma deaths over a two year period in Auckland, New Zealand. Two control groups were selected. They were matched for sex, age, and race. One group had been hospitalized for asthma at about the same time as their matched decedent, but survived to discharge. The second control group was taken from the ambulatory practices of local

physicians after visits at about the same time as the case's death. The fatality group had significantly more frequent psychosocial problems than either control group. When compared to the community group, the cases were more likely to be on three or more medications, less likely to have PFT's measured within the last year by their physician, and were more likely to be non-compliant.

Table V. Risk factors for life-threatening asthma

Previous life-threatening episode
Non-compliance
Labile PFTs: "morning dippers"
Psychosocial problems

Therefore, measures which might be helpful in stemming the rise in asthma deaths would include those mentioned by Dr. Hart- close follow-up of PFT's (especially in patients with previous severe asthma), careful assessment during exacerbations (realizing that physician and patient tend to understate the severity of the disease), and aggressive use of steroids in patients with severe asthma at presentation[1]. It should be added that educating the patient that when the inhaler seems to be less effective or when an attack persists for several days without breaking, evaluation by a physician is needed. This group of patients certainly merits consideration for hospitalization, but at the least should be given steroids in an effort to counter the inflammatory changes contributing to the exacerbation.

PHYSIOLOGIC ASPECTS OF ASTHMA

Respiratory Mechanics

The pulmonary function abnormalities occurring during an asthma attack are well characterized and will be mentioned only briefly. Emergency room evaluation of these abnormalities usually consists of measurements of some combination of the forced expiratory volume in one second (FEV_1), the forced vital capacity (FVC), the maximal mid-expiratory flow rate (MMEF or FEF_{25-75}), and the peak expiratory flow rate (PEFR). Although the tendency in the Parkland E.R. is to follow the FEV_1, the FEF_{25-75} is more sensitive and less effort-dependent. However, it is also more variable than the FEV_1 which makes estimating predicted values more difficult[17]. It is certainly the case in Parkland's emergency room, and should be in all emergency rooms, that all asthmatics receiving therapy therein are followed using these objective parameters as well as clinical clues. Failure to utilize these very helpful measures was frequently implicated in the aforementioned studies of asthma mortality. Residual volume, functional residual capacity, and total lung capacity will be increased during an asthmatic exacerbation, but the methods for measurement of these values is

not feasible in the E.R. setting. McFadden demonstrated that the patient obtains symptomatic relief well before the pulmonary function parameters return to normal[94]. Also, the abnormalities may persist for days after the attack resolves symptomatically[17].

Interest has developed in respiratory muscle fatigue as an important contributor to death in patients with pulmonary disease over the past ten years. Although much of the work has been done with patients suffering from chronic obstructive pulmonary disease, the principles are still applicable to the acute asthmatic. Indeed, one experimental model is to take healthy patients and have them breathe through a resistance circuit. This is the closest model to asthma that one can approximate using a healthy subject. Roussos and Macklem reviewed the topic in 1982[95]. They point out first that, patients breathing at normal resistances can increase their minute ventilation several-fold without major increases in respiratory muscle oxygen consumption (Vo2,resp.). However, even at fairly normal minute ventilations, the patient with high resistance requires substantial increases in blood flow to those muscles (Figure 12). It is clear that if these high blood flow and oxygen demands can not be met, the driving forces of gas exchange will fail.

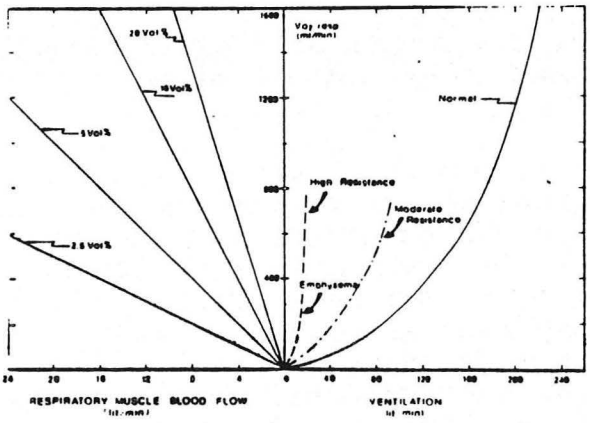

Figure 12. Blood Flow Requirements of Respiratory Muscles as a Function of Obstruction (Roussos and Macklem, 1982[95]).

The second adverse effect on the respiratory muscles is that of hyperinflation. The hyperinflation lowers the diaphragm and causes its force-length relationship to worsen. Hence, the hyperinflated chest diminishes the efficiency of the most principle muscle of respiration. The accessory muscles of respiration are similarly affected. This increased work of breathing is indeed found in asthmatics or normal subjects breathing through a resistive circuit. Additionally, the intercostal muscles are tonically contracted throughout the respiratory cycle during such conditions, increasing their Vo2, resp. and, perhaps, hindering blood flow. The shallow respiratory pattern of the acute asthmatic is also inefficient.

As the diaphragm is displaced downward, its geometry makes it less able to expand the rib cage with contraction. Indeed, if it is displaced far enough downward, its contraction results in expiratory movement of the rib cage (Hoover's sign). Similar problems can occur with the intercostal muscles, hyperinflation thus making them expiratory muscles. Therefore, the patient with high airways resistance is confronted with a very high Vo2, resp, increased work of breathing, markedly diminished muscular efficiency, and, perhaps, diminished blood flow. It is clear that the patient can easily respiratory failure in such a situation.

The same group has also shown that hypercarbia induced by an increased carbon dioxide content of the inspired gas also hastens respiratory muscle fatigue[96]. The diaphragm was stimulated to do isometric work at varying F_ICO_2 and intrathoracic pressure changes were measured with an esophageal manometer. Declines in force generated were on the order of 10-30% compared to subjects breathing room air, indicating muscle fatigue was worse in the high CO2 group. Hence, the patient in the later stages of respiratory muscle fatigue will have an additional problem to cope with.

Lastly, there appears to be a reflex arc which decreases the neural input into fatiguing respiratory muscles. This reflex presumably protects the organism from developing rigor mortis of the respiratory muscles by way of driving them to the point of total ATP consumption.

A clinical clue advanced as a sign of respiratory muscle fatigue is paradoxical motion of the abdomen during respiration[97]. Normally, in the upright position, the descent of the contracting diaphragm displaces the abdominal wall outward. However, if the diaphragm fatigues, the accessory muscles expand the thoracic cage and the flaccid diaphragm is pulled passively upward. The result is the inward motion of the abdominal wall. The examiner must assess the status of the abdominal wall muscles with palpation as contraction of the abdominal muscles with inspiration will result in the same motion. This sign will also be present when the diaphragm is displaced far downward as mentioned above.

The second clinical sign is respiratory alternans. This consists of utilizing alternately the accessory muscles and then the diaphragm for the work of breathing. A cyclic alteration in abdominal pressure should be present with this condition. In animals driven to respiratory muscle fatigue, there is a period of bradypnea just prior to full respiratory arrest. This has been interpreted as clinical evidence of the previously mentioned reflex arc.

Gas Exchange

McFadden's classic work in 1968 defined the alterations in gas exchange experienced by the asthmatic with an acute exacerbation[88]. He showed that PaO2 fell in correlation with FEV_1 (Figure 13). Likewise, at very low values of FEV_1, the P_aCO_2 rose sharply (Figure 14). The FEV_1 which corresponded with that rise in P_aCO_2 was less than 25% predicted. Nowak reproduced these findings using a PEFR of 25% as well as FEV_1 criteria[98,99]. In general, McFadden found that the asthmatic presented with hypoxemia and hypocarbia. Their work also confirmed the mechanism of ventilation-perfusion mismatch as the major mechanism operative for the hypoxemia. About 10% of the patients studied (all with severe obstruction) also demonstrated shunting as a mechanism of hypoxemia. No abnormalities of diffusion were detectable in those patients studied.

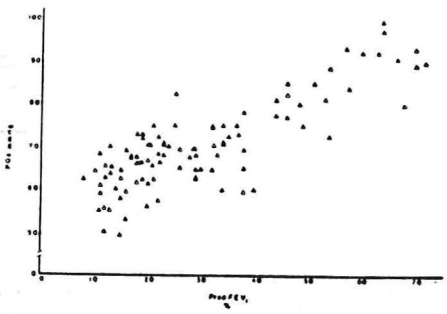

Figure 13. $_pO_2$ Vs. FEV_1 in Acute Asthma (McFadden, 1968[88]).

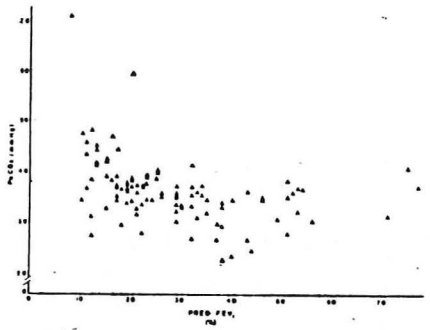

Figure 14. $_pCo_2$ Vs. FEV_1 in Acute Asthma (McFadden, 1968[88]).

EMERGENCY ROOM ASSESSMENT OF THE ASTHMATIC

A considerable amount of effort has gone into trying to define the ideal assessment plan for the asthmatic. This is not unexpected in that underassessment has often been designated as a major cause of asthma mortality. The majority of the effort has focused on rapid triage of the patient in the E.R. into a group of patients who will require hospitalization for optimal management and a second group who will respond to therapy in the E.R. and do well as outpatients. Criteria examined have included clinical data, laboratory data, and multifactorial indices.

Clinical Criteria

The first historical criteria that might be examined is the patient's estimate of severity. McFadden's 1973 study demonstrated that significant airway obstruction could be present in the absence of significant symptoms[94]. Subsequent studies have shown that although the patient is a better judge of his airways obstruction than physicians are[100] (Figures 15 and 16), the patient does indeed

tend to underestimate his own obstruction[101,102]. The asthmatic does tend to be a good judge as to whether he is improving or worsening as measured by PFT's[100,101]. This tendency of the asthmatic to sense airways obstruction poorly might contribute to delays in seeking care as well as give the physician false reassurance that a patient is ready for discharge at a point where airway obstruction is still severe.

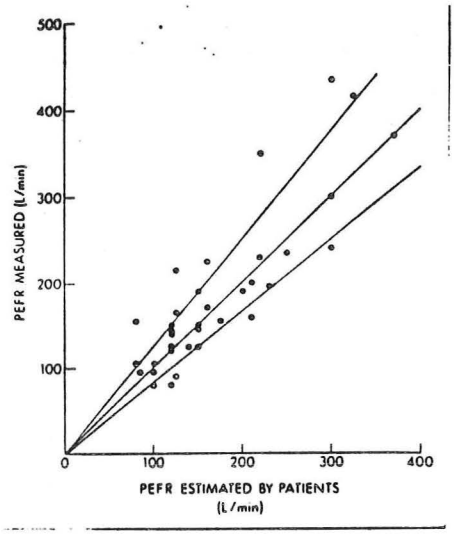

Figure 15. PEFR Estimates of Patients (Shim and Williams, 1980[100]).

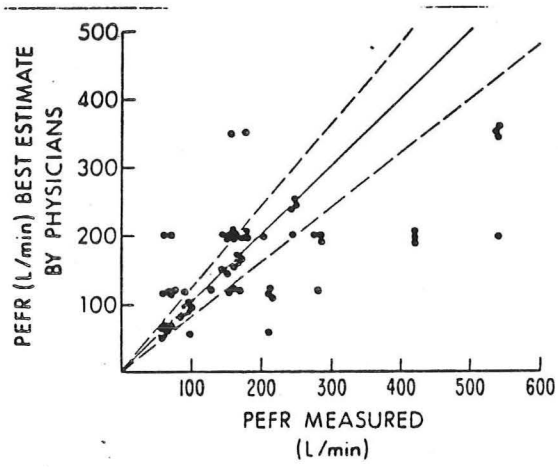

Figure 16. PEFR Estimates of Physicians (Shim and Williams, 1980[100]).

A second clinical criteria might be that of the duration of the attack. It is logical that longer established attacks should have more of the accompanying inflammatory changes and mucus plugging than for attacks of shorter duration. This is a view espoused by some, but not clearly demonstrated[103]. Banner, et. al. did correlate response of spirometry to epinephrine therapy to duration of the attack[104]. Zwicke, et.al. also found a higher incidence of symptoms of greater than 24 hours duration in patients who went on to be admitted in a small series of E.R. patients[105]. Arnold, et. al. found no significant difference in the presenting PEFR data or severity scores (based on best level of activity with the attack) which could be correlated with the duration of the current attack[106]. The study is severely limited as neither disposition nor follow-up is compared to the duration of the attack. Bellamy and Collins reported similar findings in a group of patients hospitalized for asthma. They were able to give follow-up on 11 (25%) of their patients and could see no difference in time to recovery when compared to speed of onset[107]. An important effect of rapidity of onset may have been missed in that only hospitalized patients were studied. McFadden could find no association between duration of an asthmatic attack, arterial blood gases, or spirometry in his classic work[88].

The prior history of life-threatening episodes as a risk factor for mortality has already been noted and should certainly be inquired about[92,93].

The first physical examination criteria for consideration will be the position of the patient at the time of arrival[108]. Patients in a 1983 study were instructed by a nurse on their arrival to an emergency room to lie back on a gurney which had the head inclined at 20° (Table VI). They were recorded as being "upright" if they did not lay back. Diaphoresis was scored as well and the results of these were compared to a patient assessment of the severity of symptoms, PEFR, pulsus paradoxus, and sternocleidomastoid retractions. The patients presenting "upright" were more tachycardic, more tachypneic, and had a higher paradox than those recumbent. The mean PEFR for the "upright group" was one-half that of the recumbent group (113 vs. 225 l/min). The "upright" group had a lower pH and PaO2. All nine of the diaphoretic patients were in the "upright" position. Their mean PEFR was 73 l/min vs 201 l/min for the non-sweating group. Thus, the patient who won't lie back is indeed a sicker patient.

Factor	Value		p Value
	Recumbent	Upright	
Patients (n)	29	20	
Pulse rate (beats per minute)	108.1 ± 2.6	122.5 ± 2.8	<0.01
Respiratory rate	28.2 ± 0.5	33.4 ± 1.1	<0.001
Pulsus paradoxus (mm Hg)	10.5 ± 0.6	25.1 ± 6.1	<0.01
Peak expiratory flow rate (liters per minute)	225.3 ± 7.5	113.2 ± 13.5	<0.001
Arterial pH	7.47 ± 0.01	7.41 ± 0.02	<0.001
Partial pressure of arterial oxygen (mm Hg)	75.9 ± 1.2	66.4 ± 1.1	<0.001
Partial pressure of arterial carbon dioxide (mm Hg)	30.8 ± 0.5	39.7 ± 1.6	<0.001

Table VI.

Routine vital signs are usually the next phase of the evaluation. Cooke, et. al. demonstrated that those patients admitted for asthma who had courses complicated by pneumothorax, lobar collapse, assisted ventilation, cardiac arrest, death, or acidosis/hypercarbia usually had a presenting pulse of greater than 130[109]. Likewise, the incidence of complications increased as did the heart rate. They went so far as to advocate admission of all patients presenting with a heart rate of greater than 130. Carden, et.al., in a group of E.R. patients, compared pulse rate to a raw FEV_1 and found, of patients with a heart rate of 130 or more, only 33% (3 of 9) had a FEV_1 of 600 ml or less at presentation[110]. Only 13% (3 of 24) with an FEV_1 of 600 ml or less had a heart rate of 130 or more.

Fischl's multivariate study (which was aimed at identifying those patients who were discharged only to return within ten days) used a heart rate of 120 or above as one of the seven variables[111]. Fifty-eight percent (23 of 40) of the relapse group had a heart rate of 120 or more. Fourteen percent (17 of 120) of the successfully treated group had heart rates in this range. Looked at another way, 58% of the patients with a heart rate of 120 or more at presentation relapsed. Rose, using a design similar to Fischl's, found that 14% of his patients that relapsed had a heart rate of 120 or more[7]. Eighty-four percent (16 of 19) of the patients who presented with a heart rate of 120 or more did not relapse. When a cut-off of 130 is used, 63% (5 of 8) of the patients in Fischl's study with a heart rate of 130 or more were successfully discharged. Only 8% of the relapse group had a presenting heart rate of 130 or more. Rose's group subjected to the same criteria reveal similar results- 60% of patients with a heart rate of 130 or more were successfully discharged and only 9% of the relapse group had such heart rates. Eliakim, et. al. performed an analysis similar to Fischl's in Israel and found no significant difference between the successfully discharged and relapse groups with regard to mean heart rate at presentation[112]. Thus, the heart rate alone does not seem to be a discriminating tool in the disposition decision.

The other vital sign typically abnormal in the asthmatic exacerbation is the respiratory rate. Looking again at the Carden paper[110], 28% of patients presenting with a respiratory rate of 30 or more had a FEV_1 of 600 ml or less. The rate of 30 was 42% sensitive for an FEV_1 of 600 ml or less. Applying a rate of 30 as the discriminant to the Fischl work[111] reveals that 53% of the patients with that rate or higher were in the successfully discharged group. Forty-eight percent of the relapse group had a respiratory rate of 30 or more. Looking at the Rose work[7] in the same manner, 79% of the patients with a respiratory rate of 30 or more were in the successfully treated group. Only 32% of the relapse group had rates that high. Eliakim[112] again found no significant difference between the relapse group and the successfully discharged group with regard to presenting respiratory rate. We again find that this variable by itself does not assist us tremendously in the disposition decision or assessment.

Pulsus paradoxus has been associated with asthma since at least 1952[113]. Rebuck found a lower FEV_1 and a higher pulse in the 34 (of 76) admitted patients presenting with pulsus paradoxus[114] (Figure 17). Only those patients with a FEV_1 of less than 40% of their best recorded value had pulsus paradoxus. However, only a third of all patients with an FEV_1 of less than 40 % had a pulsus paradoxus. All patients with a FEV_1 of 20% predicted or less had at least a ten mmHg paradox. The paradox resolved within hours of therapy. Knowles and Clark showed that, in their small series of admitted patients, a paradox was only found when the FEV_1 was less

than 40% predicted[115]. Again, with therapy, resolution of this finding was brisk. Kelsen's study found a poor, but statistically significant correlation between pulsus paradoxus and absolute values of presenting FEV_1[116]. He studied patients treated in the E.R. and either released or admitted. Thirty-eight percent (5 of 13) patients with a FEV_1 of less than 600 ml did not have a paradox. Only 28% of patients with a paradox of 10 mmHg or more had a FEV_1 of less than 600 ml. Carden, et.al., using a similar patient population, provided a more recent look at the pulsus paradoxus and found that 84% (26 of 31) of patients presenting with a FEV_1 had pulsus paradoxus of ten or more[110]. However, the sign was frequently present when the FEV_1 was higher. Indeed, one patient with an FEV_1 of 2000 ml had a paradox of 20 mmHg. Thus, although the negative predictive value of a paradox less than ten mmHg is a reasonable indicator that the FEV_1 is greater than 600 ml or 20% predicted, the presence of a paradox is only indicative of moderate asthma or worse.

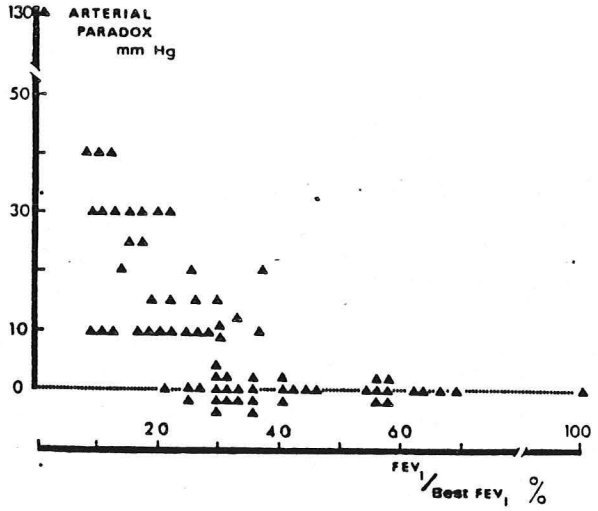

Figure 17. Pulses Paradoxus as a Function of Airways Obstruction, (Rebuck and Read, 1971[114]).

Fischl used a paradox of 18 or greater as one of the variables in her multivariate index to predict the likelihood of relapse in patients treated and released from the E.R.[111]. Seventy percent (28 of 40) of the relapse group had a paradox of greater than ten at presentation whereas 50% (61 of 120) met those criteria in the group who were successfully treated. Of patients with a paradox of 10 or more, 63% (60 of 95) were successfully discharged. When the cut-off of 18 mmHg was used, only 40% of the relapse group had a positive paradox. Thirty percent of patients with a paradox of 18 or more were successfully discharged. Rose, using Fischl's index in a different group of patients later reported 41% (9 of 22) positivity at a level of ten mmHg for his relapse group and 36% (25 of 70) for his successfully treated group[7]. Seventy-five percent

of the patients with a paradox of 10 or more were successfully discharged. When the cut-off was raised to 18 mmHg, 14% of the relapse group was positive and 77% of the patients with a paradox of 18 or more were successfully discharged. These studies are not directly comparable in that different treatment methods were used, but in either case, pulsus paradoxus as an isolated variable to identify patients needing hospitalization is a weak tool.

Several authors have identified the use of accessory muscles, especially the sternocleidomastoid, as indicative of severe asthma. McFadden found that when sternocleidomastoid retraction was present, the FEV_1 was usually less than one liter[94]. Like pulsus paradoxus, this was found to resolve quickly with therapy. Kelsen also found the presence of accessory muscle use indicative of severe obstruction. Sternocleidomastoid retraction was present in 48% of patients with a FEV_1 of less than 1000 ml at presentation[116]. Fischl's study revealed that accessory muscle use was moderate to severe in 65% of the relapse group while 90% of patients sent home who presented with moderate-severe sternocleidomastoid retraction relapsed[111]. Eliakim's study again showed no difference in retractions between relapse and successful discharge groups[112]. Sternocleidomastoid retractions, then, seem to behave like pulsus paradoxus. When they are present, we may infer that severe obstruction is present and that the patient is at higher risk to relapse than the patient without these findings. However, many patients with these findings do well with E.R. therapy and discharge, and some patients with disease that will not reverse in the E.R. are without these findings.

The findings of respiratory muscle fatigue have already been reviewed. Data on the significance of these findings are not available. One would guess that most patients with these findings are identifiably quite ill by other criteria and that these findings, although of grave significance, add little to management.

Laboratory criteria

A number of studies have examined the utility of the chest X-ray in the acute asthmatic attack. It is usually normal or shows only hyperinflation. The general recommendation is that, in the absence of fever or other clinical evidence of pneumonia or pneumothorax, chest X-ray can be safely reserved for only those asthmatics requiring hospitalization[117,118]. Rarely, unsuspected pneumothorax or pneumomediastinum will be found, but most of these patients come to admission without the chest X-ray[114].

Arterial blood gas findings in asthmatics were briefly reviewed in the physiology section of this Grand Rounds. When any significant obstruction is present, hypoxemia will occur. As McFadden demonstrated, the P_aCO_2 rises only when the obstruction has become quite severe.88 As hypoxia is often quite profound, even

when pulmonary function tests are not markedly abnormal, it is generally recommended that supplemental oxygen be given with other therapy for the asthmatic in the E.R.. This is particularly important in that the aforementioned desaturation can occur with bronchodilator therapy[59-63]. However, the arterial blood gas usually does not assist in the disposition decision[98]. With the widespread availability of ear oximetry, continuous monitoring of arterial oxygen saturation (S_aO_2) is now painless and feasible. However, a recent study was unable to demonstrate an advantage to adding this data to the E.R. assessment of the acute asthmatic[119].

Perhaps the best tool for the emergency room physician in the evaluation of asthma has been spirometry. Banner offered the first report of the use of PEFR measurements in making dispositions[104]. He found that all of his admissions and return visitors either started with a PEFR of less than 16% predicted or failed to show a 15% improvement in PEFR with the initial dose of subcutaneous epinephrine. Unfortunately, his follow-up data were dependent on the patient either calling the physician or returning to the E.R. where he was treated. The study is also suspect in that PEFR data were used in making the admission decision.

Kelsen's series examined the FEV_1 as well as other variables in outcome[116]. The physicians obtaining the measurements were the physicians caring for the patients. Kelsen states that admission criteria consisted of 1) failure to have dyspnea relieved, 2) continued labored breathing, or 3) failure to either markedly reduce or eliminate wheezes on auscultation after six hours of therapy. Patients were called at ten days if they were discharged to determine if they had needed further care after discharge. The FEV_1 initially was the same for the relapse group and the successful discharge group (about 1150 ml). However, the relapse group showed a considerably smaller response to therapy than the successful discharge group (413 ml vs. 730 ml). Two-thirds of patients with less than a 400 ml response relapsed. Another variable which was noted was that the relapse patients were treated a shorter period of time (in spite of aiming for the same clinical endpoints, but having such different spirometric responses).

Nowak, et. al. performed a similar study soon after the Kelsen study[120]. The spirometry was performed by a person not involved in the patients care and the attending physicians were blinded to the results of the spirometry. Discharged patients were administered a questionnaire 24-48 hours after discharge which was aimed at assessing the severity of their post-discharge symptoms and need for additional care. The initial FEV_1 stratified these three groups with the admitted group having the lowest FEV_1's, the relapse group having an intermediate FEV_1, and the successful discharge group having the highest FEV_1 (Figure 18). The differences were still present after treatment, all groups doubling their mean initial FEV_1. Eighty-eight percent of the patients requiring admission had an initial FEV of 600 ml or less. Eighty

percent of those patients with an initial FEV_1 of 600 ml or less required admission or required additional therapy. Ninety percent of the patients with an initial FEV_1 of 600 ml or less and a post-treatment value of 1600 ml or less required admission or relapsed. Although these figures are impressive, the positive predictive value of these tests is not above 50% unless one considers the relapse group as equivalent to the admitted group. In fact, this is usually not the case. For instance, in Kelsen's study, only 25% of patients requiring additional care after discharge required admission at follow-up. Unfortunately, Nowak does not give us information on the outcome of his relapse group. Additionally, Nowak's relapse group was defined at 48 hours instead of the usual 10 days. Thus, these spirometric criteria warn us that the patient who fails them needs more care, but still do not define who clearly needs admission. Nowak repeated this work using both PEFR and FEV_1 data and demonstrated similar results. The highest risk group was an initial PEFR of less than 100 l/min which failed to rise above 300 l/min[121].

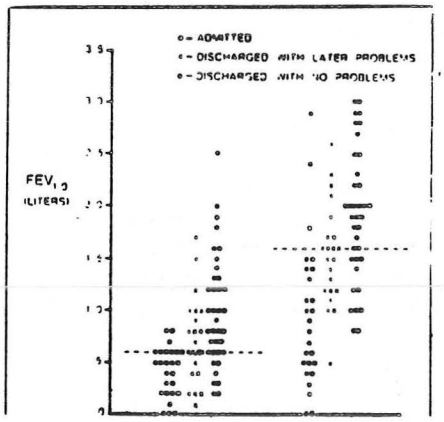

Figure 18. Spirometry in Admitted, Relapsed, and Successfully Discharged Asthmatics, (Nowak, et. al., 1979[121]).

Brandstetter, et.al. published similar work demonstrating a high-risk group as one with an initial PEFR of 100 l/min or less and a failure to respond to B-adrenergic agents[122]. This study gave an initial PEFR of 100 l/min or less a positive predictive value of 35%. The negative predictive value for an initial PEFR of greater than 100 l/min was 93% however. Again, a positive test has screening value, but does not allow us to define the group narrowly enough.

Fischl's data[111] used a cut-off of 120 l/min for the PEFR. Only 20% of the relapse group had an initial PEFR greater than 120 l/min. However, 56% of the patients presenting with a PEFR of 120 or less were discharged successfully. The negative predictive value was again quite high, 93%.

Rose found that only 5% of his relapse group had an initial PEFR of 120 or less and that 94% of patients with an initial PEFR of 120 or less were successfully discharged[7]. Eliakim's work[112] only gives mean values for group-wide initial PEFR's, but actually finds the relapse group lowest of all. The admitted group was lower than the successfully discharged group.

From all of this then we might conclude that, generally speaking, spirometric data are very helpful when they are negative (i.e. above the designated cut-off). When positive however, they are generally little better than a coin toss in assigning the patient to hospital therapy correctly.

It was in an effort to circumvent the above-mentioned weaknesses that Fischl published her multivariate index[111]. The index was developed on the basis of data acquired on E.R. patients at Jackson Memorial Hospital in Miami. Seven criteria were given a score of either 0 or 1 based on the absence or presence of the criteria involved (Table VII). The authors proposed that a score of 4 or more was predictive of either the need for admission or relapse within ten days. The index was 95% sensitive with a 95% positive predictive value for the population it was derived from. However, when the index was prospectively applied to other populations using more aggressive E.R. therapy regimens, it failed miserably[7,123]. Rose's study showed a sensitivity and positive predictive value of about 40%. Centor's study[123] found a sensitivity of only 18% for predicting relapse and 50% for predicting hospitalization. Both authors attribute the differences in their results as compared to Fischl's to more aggressive and longer E.R. therapy for asthmatics. They also acknowledged that there may have been population differences not covered by the index. An Israeli study[112] subsequently demonstrated successful application of the Fischl index to a group of 39 patients treated in an E.R. over one year's time. They found a sensitivity of 70% with a positive predictive value of 74%. The reason for this discrepancy is unclear, as the Eliakim study did employ a regimen of similar aggressiveness to the Rose and Centor studies. The Israeli study, like Fischl's work, did mandate shorter E.R. stays than the Rose and Centor studies.

Factor	Value for Score of 0	Value for Score of 1
Pulse rate (beats/min)	<120	≥120
Respiratory rate (breaths/min)	<30	≥30
Pulsus paradoxus (mm Hg)	<18	≥18
PEFR (liters/min)	>120	≤120
Dyspnea	Absent–mild	Moderate–severe
Accessory-muscle use	Absent–mild	Moderate–severe
Wheezing	Absent–mild	Moderate–severe

*Score 0 or 1 for each factor as listed and add to give a total index of 0 to 7. The factor values used are those noted at presentation. PEFR denotes peak expiratory flow rate.

Table VII.

One can thus readily see that no scheme is highly accurate at predicting who needs hospitalization. When the criteria mentioned above are negative, the otherwise uncompromised asthmatic may be discharged comfortably when the symptoms are relieved. Capturing the remaining patients will either require admitting two to three times as many asthmatics as are sick enough to justify admission or clinical acumen that has yet to be published in a usable form. An important, but unanswered, question revolves around the clinical significance of the relapse group. This group ranges in size from 18-26%[14,112,116,120]. The characteristics of this group need further investigation, specifically, how many need hospitalization at revisit, how much did non-compliance contribute to relapse, and could other therapies or longer E.R. therapy reduce the size and morbidity of this group?

An alternative approach to the assessment problem is to simply defer the question with "observation units." It was previously noted that patients treated for longer periods in the emergency room tended to have better outcomes[116]. A study out of Chapel Hill demonstrated that asthmatics were the group of patients most frequently utilizing their observation unit and suggested that such utilization was safe and not used for "procrastination in decision making"[105]. The study was a retrospective chart review of all patients discharged with a diagnosis of asthma over a four month period. Follow-up data was based on review of the same charts for a ten day period after the attack and is therefore likely to underestimate relapse as defined in the aforementioned studies.

Fifty percent of the 46 patients reviewed were placed in the observation unit, 37% were discharged home, and 13% were admitted. Thirty-nine percent of the patients admitted to the observation unit were admitted to the hospital. Only 4% of the patients treated and released from the observation unit relapsed whereas the

discharged group relapsed at a rate of 41%. It is of note that only one of the discharged group required admission on revisit however. One patient did arrest while in the observation unit and was adequately resuscitated. Generally speaking, the conclusion that the unit was not abused is reasonable. It is obvious that the safety record would be more impressive if there had not been the patient who arrested. Certainly, it is better that that event occurred in the observation unit than at home, and, depending on the set-up of the four bed unit, may have even been better than it happening on the ward. However, more information obtained in a prospective and organized fashion would be helpful in assessing this modality of therapy. It is also noteworthy that four months of asthma visits counted for only 46 patients. A busier service, such as a large county hospital, would have a difficult time placing 50% of its asthma exacerbations in a 24 hour observation unit.

DRUG THERAPY OF ASTHMA

Adrenergic agents

The neural inputs to asthma have been well studied and the place of adrenergic, especially B-adrenergic, agents in the therapy of asthma is well established[1,6,16,17,124,125]. The adrenergic agents used fall into one of three broad categories-catecholamines, resorcinols, and saligenins[124] (Figure 19). The catechols are those whose structure is based on epinephrine and include isoproterenol, and isoetharine. The catechols are rapidly metabolized by catechol-o-methyl transferase (COMT) and are therefore short-acting. When inhaled, they reach peak effect within five minutes and persist for one to two hours. Isoproterenol and isoetharine are both B-selective, although both have substantial effects on both B_1 and B_2 receptors (isoetharine slightly less active on the B_1 receptor). By substituting the catechol nucleus with a 3-5 hydroxybenzene ring, the resorcinol class of agents is formed. These include metaproterenol, terbutaline, and fenoterol. These agents are not metabolized by COMT and are thus longer acting. Their peak effect occurs at about 15 minutes when inhaled and effects persist for 4 to 6 hours. They are also somewhat more B2 selective than the catechols. Substitution of the catechol nucleus at the 3 hydroxyl site results in the saligenins, of which only albuterol is in use in this country. The behavior of these agents is similar to that of the resorcinols.

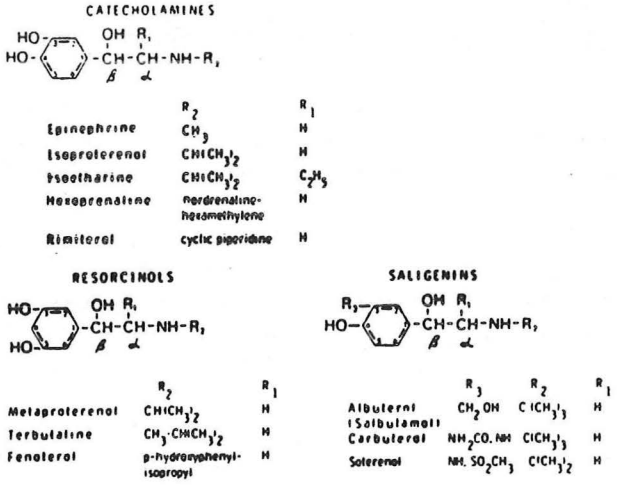

Figure 19. Examples of the Beta-Adrenergics, ($Popa_{173}$).

Reports of the use of parenteral epinephrine can be found in the early 1900's[126,127]. A number of adrenergic agents have been developed and released in recent years, most attempting to maximize selectivity to the B_2-adrenergic receptor. The principle parenteral adrenergic agents in the United States are epinephrine and terbutaline. The parenteral route offers slightly more rapid delivery, decreased requirement for patient cooperation (especially important in children), and, possibly, better delivery to the small airways. However, it usually entails more cardiac side effects for any given degree of bronchodilation. Comparisons of the two agents parenterally have shown no particular advantages of one over the other[128,129]. Bronchodilation as measured by FEV_1 and PEFR were similar as was heart rate. Hence, it is difficult to give an edge to either parenteral medication. A number of agents have been used intravenously overseas, but such use of intravenous adrenergic agents has been reserved for extreme circumstances in the U.S.. A recent study has challenged the notion that subcutaneous epinephrine is forbidden in patients over the age of 40[130]. Patients with a history of angina or myocardial infarction within the past three months were excluded. Atrial arrhythmias were more common in the older patients, but ventricular ectopy was not. This study must be approached cautiously as only 106 patients were enrolled from a large Chicago hospital over two years and some selection bias may skew the data. Also, with inhaled agents available, such therapy is usually not necessary in these patients. An exception is the patient who is being transported by emergency medical personnel who usually do not have access to inhalation therapy, but the concerns over exclusion of heart disease in that setting should encourage caution.

The more common usage of these agents is as an inhaled aerosol. This tends to maximize bronchodilation for any given degree of cardiac side effects. Although Dr. Hart's review suggested that

a slight edge might go to the parenteral over the inhaled agents in opening small airways when sensitive measures are used, this does not seem to be a clinically significant effect. Multiple studies find equivalence of inhaled agents and subcutaneous epinephrine[131-134] and McFadden's review advocates this route of therapy in the acute setting[124]. Additionally, the differences in efficacy are trivial if existent[124]. Terbutaline and albuterol are probably slightly more B_2 selective than the others. Isoproterenol clearly has the most cardiac activity. Thus, choice will more likely depend on the desired duration of effects and the amount of B_1 agonist activity tolerable.

	Mechanism			Potency	Duration in Hours
Agent	Alpha	Beta-1	Beta-2		
Epinephrine	+++	++++	+++	+++	1-2
Isoproterenol	·	++++	++++	++++	2
Isoetharine	—	++	+++	++·	2-3
Metaproterenol	—	++	+++·	+++·	4
Albuterol	—	+	++++	++++	4-6
Terbutaline	—	+	++++	++++	4-6
Fenoterol	—	+	++++	++++	4-6

Table VIII.

One other consideration in the use of inhaled B-agonists is the route of delivery. Common E.R. therapy presently involves nebulization with updraft devices. These are driven by compressed air and require considerable time from a respiratory therapist. Several reservoir devices to assist in the delivery of aerosols generated by metered dose inhalers are currently available. Studies of hospitalized patients have generally been favorable for these devices[135,136]. A recently published study from San Francisco General Hospital examined the utility of these devices in E.R. management of asthma[137]. The two devices were equivalent in the group of asthmatics as a whole (Figure 20). In a sub-group of severely obstructed asthmatics, there was a trend favoring the updraft nebulizers. Further work needs to be done with larger numbers of patients, especially those with severe obstruction. If similar results are obtained, these devices might save considerable money, free respiratory therapists for other tasks, and even hasten therapy since a compressed air source and respiratory therapist are not necessary to start therapy.

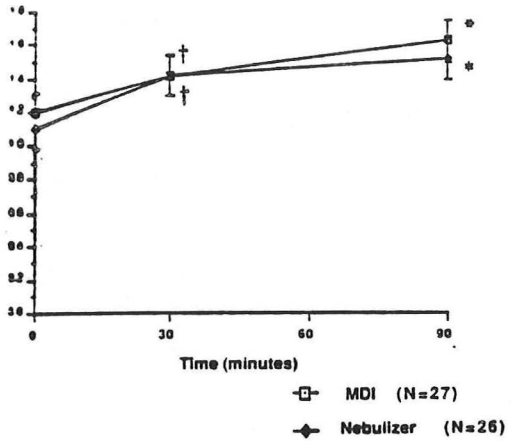

Figure 20. FEV_1 as a Function of Time, Nebulizer Vs. Inspir-Ease, (Turner, et al., 1988[137]).

Oral forms of terbutaline, meteproterenol, and albuterol are available and effective in the therapy of chronic asthma. At least one author has advocated the use of purely oral therapy in the E.R. management of asthmatics, but the paper is more anecdotal than anything[138]. This route of administration can not be advocated in the E.R. setting.

The debate on B-agonist tolerance has already been covered, but leads to the question of responsiveness of the asthmatic who has been using an inhaler at home without success. This has been addressed by McFadden's group[139]. Subjects were randomized to either inhaled isoproterenol or subcutaneous epinephrine and a history of outpatient B-agonist use was sought at the outset of therapy. Although the B-agonist users had a slightly lower mean FEV_1 at outset, this was not statistically significant. More importantly, the slopes of the response to B-agonists over the first hour were identical in the two groups. Outpatient corticosteroid and theophylline use was identical in the two groups (although theophylline levels were not given). Thus, failure to respond to inhaled B-agonists as an outpatient does not seem to identify a group of non-responders in the E.R. setting.

Theophylline

Theophylline is another agent which has been used for years in the therapy of asthma. A methylxanthine derivative, its mode of action had long been held to relate to phosphodiesterase inhibition which would increase intracellular concentrations of cAMP. This belief has fallen from grace now and the mechanism of action of this agent is less certain. Concentrations which induce phosphodiesterase inhibition are in excess of the therapeutic range. Currently suggested mechanisms of action hinge on adenosine

antagonism. This does occur at concentrations within the therapeutic range and adenosine inhibits the tracheorelaxant properties of theophylline[140].

The drug is administered either intravenously (in an ethylene diamine form as it is insoluble in water) or orally. The therapeutic window is narrow, and target levels are in the 10-20 mg/l (55-110 umol/l) range. Mitenko and Ogilvie demonstrated the response of FEV_1 in hospitalized patients at varying levels of theophylline which were maintained by constant intravenous infusion[141]. They demonstrated that the FEV_1 response rose rapidly as the level approached 10 mg/l and then began to plateau. They provided the 5.6 mg/kg recommendation for intravenous loading with maintenance at 0.9 mg/kg/hr. Their studies suggested that patients without levels at presentation would achieve a level of 10+5 mg/l with this dosing. Klein, et.al. showed similar results studying nine stable outpatients comparing FEV_1 and theophylline level[142] (Figure 21). They could not demonstrate a significant change in spirometry as the level increased from 12.8 to 19.2 mg/l in this group of patients. Good data on optimal levels in the setting of acute exacerbations of asthma are not available. The work of Vozeh is occasionally quoted as supportive of levels more near 20 mg/l in acute exacerbations, but that study is flawed in that 15 of the 20 patients had COPD and not asthma[143]. As toxicity increases substantially as the level approaches 20 mg/l, it would seem wise to target a level of 15 mg/l when using this agent.

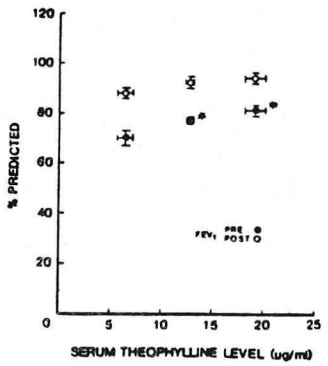

Figure 21. FEV_1 as a Function of Theophylline Level, (Klein, et al, 1983[142]).

Empiric dosing in the E.R. has generally proven difficult in patients already on theophylline. Prediction of the level at presentation is very difficult. Predictors of pretherapy levels were examined by Stine, et. al.[144]. Only when the history was of no use of long-acting theophyllines for more than 15 hours or short-acting theophyllines for more than 8 hours were the levels consistently less than 10 mg/l. When a clinic-drawn level was available, it was within 5 mg/l of the acute level in 62.5% of

cases. Similar results have been published from other centers[145-148]. Many combination medications, some available over the counter (e.g. Tedral), contain theophylline and may not be reported by the patient queried as to theophylline use[145]. Thus, it is advisable to base dosing on levels when these are available. When a subtherapeutic level is present, administration of 2.8 mg/kg as a loading dose is usual.

Theophylline metabolism occurs primarily by way of the mixed function oxidases (MFO). Consequently, a number of drugs and conditions will alter its handling. Patients with congestive heart failure or liver disease clear the drug more slowly than healthy subjects. Smoking markedly enhances clearance, presumably by way of induction of the MFO system by the tars. A number of drug interactions are known. Cimetidine increases levels, usually within 24 hours of the first dose. This effect is generally not seen with ranitidine. Erythromycin probably increases levels after several days of use. Oral contraceptives have also been reported to increase levels. Dilantin enhances theophylline metabolism and lowers levels[140].

Rossing, et. al. published data in 1980 on the efficacy of aminophylline as a bronchodilator in the E.R. treatment of asthma in comparison to subcutaneous epinephrine and inhaled isoproterenol[149] (Figure 22). Standard dosages were used at the usual intervals. They found that the B-agonists were superior to the theophylline. They found the two B-agonists equivalent in their effects on FEV_1. Appel and Shim performed a comparison of subcutaneous epinephrine and aminophylline and the combination[150]. They found that the epinephrine gave about three times the improvement the aminophylline did and that the combination offered nothing at one or two hours of therapy that was not obtained with the epinephrine alone. Several other investigators have shown that, at least in the E.R., the combination of B-agonists and aminophylline offers nothing over the B-agonist alone when either FEV_1 or PEFR is followed[151-154]. The Rossing study154 did show a slightly better response when aminophylline was added to subcutaneous epinephrine (Figure 23). The Fanta study151 compared intravenous with oral aminophylline (as elixir) and found that, when combined with isoproterenol inhalation, the two were equal (Figure 24). Again, however, the combination added nothing to the isoproterenol alone. The Siegel study[152] used metaproterenol as a B-agonist with results similar to the other studies- no additive or synergistic effect. They did find more palpitations, tremor, anxiety, and nausea with the combination.

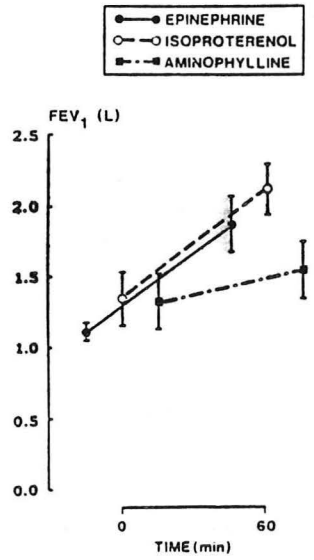

Figure 22. FEV1 Response to Three Different Bronchodilators Used Singly, (Rossing, et. al., 1980[149]),

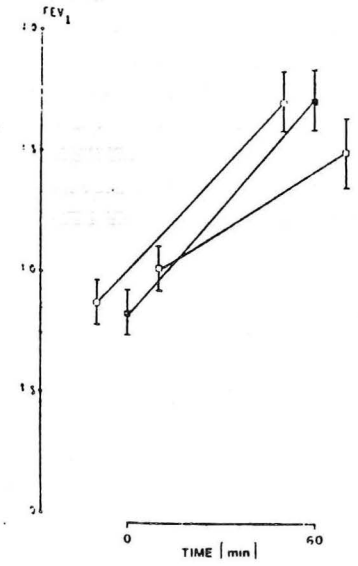

Figure 23. Beta-Agonist/ Aminophylline Combinations Vs. Epinehrine alone. (Fanta, et al.,1981[154]).

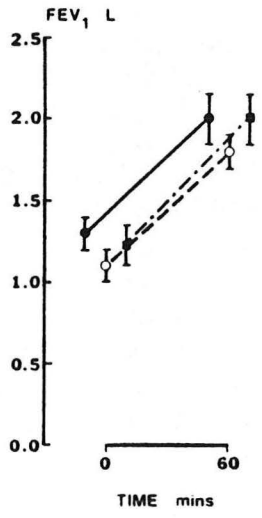

Figure 24. Vs.Isoproterenol Vs.Isoproterenol and Aminophylline (Rossing, et. al.,1983[162]).

All of these studies involved short periods of time. Unfortunately, none of the studies provide follow-up data. As the combination of theophylline and B-agonists is accepted as beneficial in outpatient therapy, one might ask whether or not the combination reduces relapses. Certainly, this is the rationale for E.R. use of corticosteroids in asthma. Also, the patients studied do not appear to have been severely ill (although it is not

commented on as to whether or not patients required assisted ventilation). Aminophylline has been shown to ameliorate and slow the development of respiratory muscle fatigue[155-157]. It is possible that this sub-group of severely ill asthmatics might benefit more from this agent. However, it does seem that E.R. administration of this agent should be aimed at something other than discharge or short-term improvement in spirometry if this agent is to be employed.

Corticosteroid therapy

The last Grand Rounds on the topic of E.R. management of asthma dismissed corticosteroids as therapy more appropriate for inpatients[1]. Several studies have since been published to challenge that notion. Corticosteroids exert much of their activity by binding sites in the cell nucleus and promoting DNA transcription[158]. Consequently, most activities of steroids are delayed by at least six hours from their administration. An example is the steroid-induced production of the protein lipocortin which inhibits phospholipase A2, thereby reducing arachidonic acid liberation. However, some activities are detected sooner. For instance, the effects on B-receptors are too quick to be mediated by DNA transcription[67,159] (Figure2 25). It is certainly likely that steroids have several effects which are beneficial to the asthmatic. Included among these would be the reactivation of B-receptors, inhibition of IgE-mediated histamine release, decreased arachidonic acid metabolism, diminished release of lysosomal enzymes from neutrophils, decreases adherence of neutrophils to inflamed endothelium, decreased chemoattraction, and decreased mucus secretion[158].

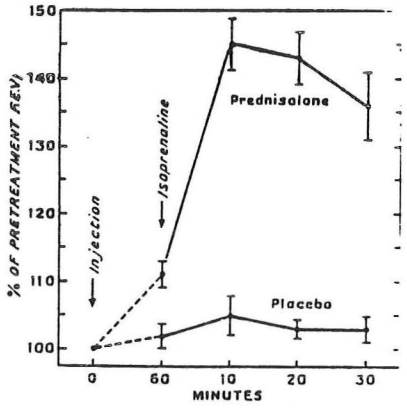

Figure 25. Steroid Effect on Isoproterenol Response One Hour After Administration, (Ellul-Micallef and Fenech, 1975[159]).

Corticosteroid use in asthma was first critically examined in 1956[160]. Patients did not receive steroids until they had been in the hospital for 24 hours. A tapering schedule beginning with 350 mg of cortisone acetate was added to "standard" therapy with

B-agonists, theophylline, oxygen, and antibiotics (as appropriate) in a placebo-controlled, randomized, double-blinded fashion (Figure 26). The patients were followed on clinical grounds. The steroid group did improve more rapidly than the placebo group although this was not appreciated until the second day of corticosteroid therapy.

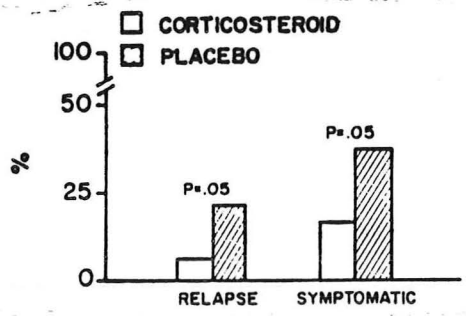

Figure 26. Outcome Effects of Steroid Bolus at E.R. Discharge, (Fiel et. al., 1983[163]).

McFadden, et. al. examined a single large dose of hydrocortisone (placebo, 250 mg, 500 mg, or 1000 mg) in patients seen in the E.R. for exacerbations of extrinsic asthma[161]. He followed plethysmographically determined parameters as well as spirometry and found no differences in response over six hours of therapy with the study drug and isoproterenol inhalations. No follow-up data were offered.

McFadden's group looked at patients hospitalized after failing to respond to the usual B-agonist and theophylline therapy[162]. After eight hours of such unsuccessful therapy, either 2 mg/kg of hydrocortisone hemisuccinate or placebo was added to continued standard therapy. Six hours after the administration of the study drug, the steroid group began to improve whereas the placebo group did not.

The definitive study regarding steroids and E.R. management followed soon thereafter. Fiel, et. al. published a study in which patients treated in an emergency room and released after adequate clinical improvement were given either a methylprednisolone bolus intravenously or placebo and an oral taper of either the steroid or placebo[163]. The patients also received a long-acting theophylline- 300 mg twice daily. All other asthma medications were discontinued. The patients were contacted at ten days to assess the status of their pulmonary symptoms. The two groups were similar with respect to admission and discharge PEFR. The steroid group relapsed at a rate of 5.9% while the placebo group relapsed at a rate of 21%. Respiratory symptoms were present at follow-up in 15.6% of the steroid group and 36.4% of the placebo group. Eleven of the seventy-six (four placebo and seven steroid) patients

reported side effects attributed to the medication (mostly gastrointestinal upset).

Littenberg and Gluck treated patients on presentation to the E.R. for asthmatic exacerbations with either 125 mg of intravenous methylprednisolone or placebo in double-blind fashion[164] (Table IX). The patients were evaluated with spirometry and symptoms (none, mild, moderate, or severe) on presentation and at the time of disposition. Other therapy was at the discretion of the treating physician and included some combination of subcutaneous epinephrine or terbutaline, inhaled metaproterenol, and intravenous aminophylline. Patients were treated in the E.R. for one to 12.5 hours (four hours, mean). Attempts were made to contact the subjects within seven days of discharge. Thirty-eight of sixty-five were reached. The patient log in the E.R. was also monitored for return visits. Significantly fewer of the steroid treated patients were admitted. The steroid group scored significantly better on the subjective index, but spirometry was not significantly different. Relapses were the same in the part of the population recontacted.

	Control Group	Methylprednisolone Group	P Value†
Hospital admission rate (%)	46.9	18.8	0.00287†
FVC (mean % of predicted)	65.98	73.00	0.076
FEV_1 (mean % of predicted)	57.56	64.98	0.068
Subjective index‡	1.02	0.68	0.026†

Table IX.

Thus, we now have two studies which suggest that there is benefit to giving steroid therapy in the E.R. for acute asthmatic exacerbations. It remains to be shown what the optimum dosage of steroids will be, if a sub-group of patients with maximum benefit can be clearly identified, what routes of administration are most effective, and what duration of follow-up oral steroids will be necessary. A recent study in hospitalized patients suggests that an oral regimen alone might be sufficient for even severe asthma[165].

Anticholinergic agents

Anticholinergic agents are probably the group of drugs with which asthma has been treated the longest. Use of atropine-like drugs dates back at least 200 years[166]. A 1986 study is one of the few however, to examine atropine in comparison to metaproterenol in the emergency room management of asthma[166]. These investigators were unable to demonstrate a significant benefit of atropine in acute exacerbations of asthma.

Ipratropium bromide is quaternary derivative of atropine which is poorly absorbed into the systemic circulation when inhaled as an aerosol. A number of recent studies have looked at this agent in comparison or combination with B-agonists in patients hospitalized for asthmatic exacerbations[167-170]. These studies find a small benefit of the agent which is additive to a variety of B-agonists. Only one emergency room study is available. Rebuck, et.al. followed spirometry in patients treated with fenoterol, ipratropium, or a combination of the two[171]. Fenoterol resulted in a greater improvement in FEV_1 than the ipratropium, although both caused a significant improvement. The combination was significantly better than fenoterol alone. The effects would appear to be additive at 45 and 90 minutes after therapy. Side effects were mild and consisted of tremor, dry mouth, and a bad taste.

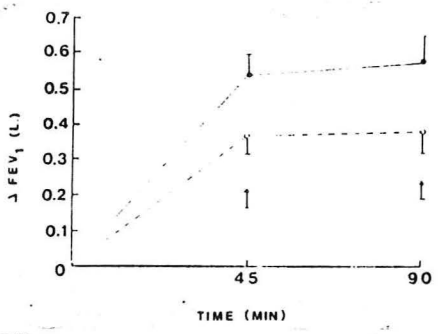

Figure 27. Fenoterol, Iprtropium Bromide, and the Combination in E.R. Management of Asthma, (Rebuck, et. al., 1987[171]).

Therefore, this appears to be another agent available to us in the E.R. management of asthma. Its relatively small effect in comparison to B-agonists alone make it a poor choice for single agent therapy, but combination therapy for patients with severe or poorly responsive asthma might prove helpful. Indeed, Rebuck's study looked at the sub-group with the most severe obstruction and suggested that combination therapy was particularly efficacious in that group. These agents might also be considered in those patients with contraindications to or poor tolerance of B-agonists. Studies which use disposition and outcome as an endpoint will be beneficial in the assessment of the exact role of this agent in the therapy of acute asthma.

CONCLUSIONS

The past twenty years have rendered a vast amount of knowledge about the management of the asthmatic with acute symptoms. This explosion of asthma knowledge has occurred in the context of apparent large rises in asthma mortality. It is certainly the case that the asthma death epidemic which had its beginnings in Europe and Australia during the 1960's has had a causal role in the

acquisition of this knowledge. In spite of these efforts to better understand and control the disease, the death rate has remained slightly high in the United Kingdom and at epidemic levels in New Zealand. It now appears that the epidemic is coming to the United States. The precise etiology of the epidemic remains unclear although failure of patient and physician to appreciate the severity of the fatal attack is a common theme. The rise in mortality in conjunction with newer and more aggressive therapeutic approaches caused early investigators to implicate the therapy itself as causal.

One possible synthesis of these ideas would be that patients and physicians, armed with new and powerful weapons for the treatment of asthma, began to underestimate the strength of the foe. Our comfort with the disease may have lowered our anxiety threshold. This could be catastrophic when the difficulty in appreciating hypoxia on clinical grounds is considered. It is clear that evaluation of the asthmatic with a host of clinical and laboratory tools is still far from a perfect science. Likewise, although reviews of mortality series have generally found that 80-90% of asthma deaths were preventable, these conclusions were always reached knowing the outcome. When one tries to find those criteria that identify the asthmatic at risk for death, several patients who won't die of asthma will be swept up as well. Nevertheless, the data acquired as a consequence of our analysis of these deaths has taught us that objective data need to be incorporated into our assessment of the severe asthmatic. Also, we have realized that sedative agents and IPPB can be hazardous therapies in these patients. There is still much work to do. Continued evaluation of those factors that predict poor outcome is necessary. Further evaluation of the observation unit as a measure to keep care affordable but maximize therapeutic benefit may be worthwhile. Lastly, if an optimistic note is to be sounded on mortality in asthma, it is that death from asthma is still infrequent, even in the face of an epidemic.

This Grand Rounds has tried to emphasize that the players in the treatment of asthma aren't new. We may have new agents in particular, but drug therapy for the greater part of the century has included adrenergic agents, methylxanthines, steroids, and anticholinergics. The past ten years has seen considerable advances in demonstrating which of these therapies are effective and which aren't. Considerable work remains to be done with the agents currently in use, much less new classes of agents. Amongst the B-agonists, optimal delivery systems need definition. There is a real need to define the role of methylxanthines in the therapy of asthma in light of their toxicity. A new methylxanthine has begun to be studied in Europe that seems to lack the potential for neurologic toxicity[172]. Important information on the dosage, route of administration, and confirmation of beneficial effects needs to be done with steroids. We have barely scratched the surface in our understanding of the use of the anticholinergic agents, those

agents which have been in use the longest. The roles of patient education have not been touched on in this review, but innovative approaches to this area will be necessary if we are to effectively involve the patient in the monitoring and self-management of asthma. It would seem that this will be necessary if we are to minimize morbidity and mortality in this disease.

How then should we approach the asthmatic presenting to the emergency room in 1989? The following is the approach which seems logical based on the presented data.

1) Assess with rapid acquisition of the clinical clues (prior history of life-threatening episode, accompanying symptoms suggestive of complications such as pneumothorax and pneumonia, the patient's own assessment of severity, presence of agitation, pulsus paradoxus, or respiratory paradox) and objective data (spirometry, arterial blood gases if patient is in extremis).

2) Begin therapy with inhaled B-agonists, if possible, otherwise, subcutaneous epinephrine (unless contraindicated). Each dose should be followed by spirometry.

3) If the initial spirometry reveals a value of less than 25% predicted, strong consideration to the use of intravenous methylprednisolone- 125 mg should be given. If admission is likely for any reason, methylprednisolone should be administered. Likewise, if the patient is on chronic steroids, methylprednisolone is indicated on presentation to the E.R. for asthma.

4) Intravenous aminophylline should be considered if admission is likely, the attack is quite severe (FEV_1 less than 25% predicted), or a poor response to B-agonist therapy is encountered. Dosing should be based on levels when the patient is chronically on theophylline.

5) Admission should be arranged if, within four to six hours, the patient demonstrates a poor spirometric response to therapy (to less than 50% predicted), is not symptomatically improved, or any time he is discovered to have a complicating pneumonia or pneumothorax.

6) If the patient responds nicely, discharge should occur on an intensified regimen. When intravenous steroids are used, a tapering schedule should be given. Follow-up in seven to fourteen days should be arranged to allow for medication adjustment and reassessment.

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