The basic purpose of risk-benefit analysis is not to detect practices with an unfavorable risk-benefit balance, but to do something about these practices once detected. Bronchial asthma is a case in point.

During the past decade there has been a progressive and impressive increase in asthma mortality in the United States. The increased mortality is most striking in the older age groups, but younger age groups have not been spared.

It is usually considered that the past 20 years have been characterized by major improvements in the management of the disease. The grim reality of decreased survival provides a striking contrast to the general perception that major progress has been made in the understanding and management of bronchial asthma.

Bronchial asthma is a splendid topic to be discussed in books and a favorite topic to be covered during medical postgraduate courses and meetings. Medical textbooks provide learned discourses and squads of asthma experts roam the country dispensing information to physicians. Asthma can often be detected in an early phase by suitable lung function tests and thus treated at an early stage. Many laboratories provide bronchial challenge tests so that physicians can treat the disease more rationally and effectively. Hyper-responsive airways in asthmatic patients have been discussed extensively. Exercise asthma has been studied and classified extensively. The coughing asthmatic has been added to the list of sufferers. The pulmonary vascular component of asthma is better understood.

The pharmaceutical houses have provided selective adrenergic bronchodilator drugs. Long-acting methylxanthines have become available. The widespread availability and use of aminophylline plasma levels have become incorporated into the management of bronchial asthma as a result of the experts' opinion. These and other advances have provided a sense of satisfaction with current management practices, but such satisfaction is entirely unwarranted if the bottom line is, as it seems to be: management is highly successful but more patients die of bronchial asthma than in former, less enlightened, times.

This article will review the data establishing increased mortality, consider some possible causes of increased mortality, quantitate the absolute increase in the number of deaths per year, provide some historic perspective, and suggest some approaches for dealing with the issues raised by the rising mortality rate.

**The Data**

Figure 1 summarizes the data on death rates from bronchial asthma between 1968-1984 in the US. Figure 2 summarizes age-specific data. Death rates reached a nadir in 1977 and, since that time, there has been a progressive increase in the total death rate (deaths per 100,000 population) from asthma which approximately doubled from 0.6 in 1977 to 1.1 in 1984. The increase in death rate is most dramatic in the oldest age group, almost tripling in patients 85 years or older, but, aside from patients less than 14 years of age, no age group is spared. In the youngest age groups, although dramatic increases are not demonstrated, neither are significant decreases. The issue persists: why no improvement despite substantial advances in the management of bronchial asthma?

As a generalization, the increased mortality is not confined to the United States, but may be found in Canada, the United Kingdom, Denmark, Sweden, Australia and New Zealand.

These results should be a warning that something may be drastically wrong with current approaches to management and that something needs to be done.

**Possible Explanations for the Increased Mortality**

Any theory to explain the increased death rates since 1977 should meet three criteria: 1) the theory should explain the rise since 1977; 2) the theory should explain...
the preferential increase in the older age groups; and 3) the theory should explain the fact that the death rate does not appear to be plateauing.

For example, the theory that the increased death rates result from massive undertreatment is not attractive because of lack of evidence that the frequency of massive undertreatment increased since 1977, that massive undertreatment is found largely in the older age groups, and that the frequency of massive undertreatment continues to increase. If massive undertreatment remained constant, then a new steady state should develop in which the number of excess deaths plateaued.

One (comforting) theory is that the upward shift is merely an artifact related to a change in classification of asthma in 1979, so that some deaths previously attributed to chronic bronchitis and emphysema are now attributed to asthma.\(^5\) This seems unlikely. The increase in asthma death rate was already underway before the classification was changed and was well established before the change in classification would have affected the statistics to a major extent. Another possibility is that the overall prevalence of asthma is increasing from some unknown cause. In the absence of highly accurate data, it is therefore possible that there is no real change in the (case fatality)/(prevalence rate) ratio. Given the lack of any supporting data, neither of these theories is attractive. A closely allied possibility is that our ability to diagnose bronchial asthma is improving, so that previously unrecognized cases are now included in the statistics. This does not seem likely.

It is theoretically possible that there has been a shift in the age distribution of incidence to increasing

---

**Figure 1.** Death rates from bronchial asthma in the US, 1968-1984.

**Figure 2.** Age-specific death rates from bronchial asthma in the US, 1968-1984. For comparison, note the overall nonage-specific death rate.
representation from older age groups. This would explain the dramatic increases in the older age group, but there is a trend to increased mortality in even the younger age groups, so that this explanation is not attractive.

Another possibility is that bronchial asthma is mysteriously becoming a more virulent disease. Again, there is no supporting evidence.

One possibility is that there has been a marked increase in “over the counter deaths” from asthma. At some point in the 1970s, over-the-counter sale of beta adrenergic agonists was legitimized. Commercial firms have hyped this practice, which led to increased self-treatment with these agents. Given an individual treating his own asthma, increasing refractoriness of the disease could provoke increased and unsupervised use of inhalers to the point where cardiotoxicity caused death.

The most useful theory (see below) is that the increased mortality rate is related to changes in management of bronchial asthma since 1977. This theory holds that the increased death rate is iatrogenic in origin and that the entire phenomenon is an iatropidemic. Such changes would have an unfavorable but unrecognized risk-benefit balance and thus increase mortality in most age groups, but selectively increase the death rate in the older age groups.

What are some of the possible candidates for augmented lethality? One is the widespread therapeutic use of methylxanthines. This would be consistent with the selective increase in death rate in the older age group, which might be expected to show an enhanced susceptibility to methylxanthine toxicity.

At least three important changes have occurred during the 1970s with respect to the use of the methylxanthines. One change is the view that one can achieve therapeutic effects and minimize toxic effects by maintaining aminophylline blood levels in the range of 10-20 mg/L. Efforts to achieve this goal are usually directed by measurements of aminophylline plasma levels. The data base on which this concept is based is suspect. Blood levels do not necessarily reflect tissue levels, and there must be wide individual patient variation in the toxic/therapeutic ratio. A priori, those who are old, those with oxygen depletion, and those with preexisting heart disease would be expected to show an increased toxic/therapeutic ratio.

A second change is increasing dependence on formulae for calculating loading dose of aminophylline. The problems cited above likewise apply to these calculations.

Since 1975 there has been increased usage of the combination of methylxanthines with beta agonists. These classes of asthma medication operate synergistically to produce fatal arrhythmias in laboratory animals, particularly older ones. There is accumulating anecdotal information which suggests that the combination can produce intractable arrhythmias in humans.

There is increasing dependence on polypharmacy in the treatment of bronchial asthma. Individual patients are provided with a host of medications, some of which are used primarily to treat the disease; others are used to counteract the side-effects of the primary agent. It is not much of an exaggeration to comment that some asthmatic patients live their lives to treat their asthma rather than having their asthma treated to live their lives. Of course, the risks of polypharmacy are at least additive and perhaps synergistic.

There probably has been a marked increase in the use of ICUs to treat patients with severe or at least difficult-to-manage asthma. Treatment in the ICU subjects these patients to a series of diagnostic and therapeutic hazards whose risk-benefit balance is not at all clear. Of concern is whether current indications for intubation and ventilatory support are accurate in terms of patient outcome. For example, the risk-benefit ratio of the use of the Swan-Ganz catheter has recently become a point of major concern.

Beginning in the 1970s, there has been increasing use of nonsteroidal antiinflammatory agents for a wide variety of ailments. It is clear that, rarely, these agents, like aspirin, can produce sudden death. What is not known is whether in asthmatic patients, in the absence of nasal polyps, these agents represent a more potent threat to the patient than does aspirin. The fact that some asthmatic patients may have improvement in manifestations of asthma by the use of these drugs does not ensure that life-threatening asthma in other patients may not be caused by these agents.

Since the 1970s, anticholinergic agents have been used increasingly in patients with bronchial asthma. To my knowledge, there is no adequate controlled clinical trial which provides an estimate of the safety of these agents, either alone or in combination with beta-adrenergic agonists and/or methylxanthines. Perhaps these agents as used are entirely safe, but the data are lacking. The widespread use of anticholinergic agents is a recent phenomenon and thus would not explain the early rise in death rates after 1977.

Corticosteroid therapy has been used for over 30 years in the treatment of bronchial asthma. Expert opinion seems to be divided. Some feel that the agent is used too frequently or in too high a dose, whereas others feel that it is not used frequently enough or in too low a dose. The long-term complications of its use are well known and do not require reiteration.

Cromolyn sodium is believed to be effective as a prophylactic agent in the treatment of bronchial asthma. Its only reported toxic effect is the precipitation of acute bronchospasm. I am not aware of any reports of severe toxicity or, indeed, any studies which
address the possibility of chronic toxicity following long-term use. Moreover, this agent is probably used only rarely in the aged asthmatic, so that it is unlikely to be involved in the increased mortality.

The most accurate evaluation is that the precise cause of increased mortality is not known. The possibility that the apparent increase is artifactual is at least a formal alternative. It is also possible that the causes are multifactorial and that no single cause is involved.

However, focusing on iatrogenesis as the key factor is prudent. Not only are iatrogenic causes theoretically under physician control, but expansion of knowledge concerning the safety and efficacy of the various medications would benefit all patients with asthma independent of life and death issues.

The Magnitude of the Problem

How large an absolute problem is fatal asthma? Precise data on mortality are not available. Statistical analyses are usually based on secondary and somewhat unreliable sources such as death certificates. One approach is to use the concept of excess deaths, deaths that would not have occurred had a given intervention or set of interventions not been used. A modification of this concept may be used to approximate the magnitude of the problem.

The nadir of recent asthma mortality was achieved in 1977. Let us assume that the interaction between the disease and its treatment was optimal at that time. In 1977 there were a total of approximately 2,400 deaths from asthma in the population as a whole. Using that value as a baseline, then excess deaths during the next nine years can be calculated as follows:

<table>
<thead>
<tr>
<th>Year</th>
<th>Total Deaths</th>
<th>Excess Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>1977</td>
<td>2,400</td>
<td>NA</td>
</tr>
<tr>
<td>1978</td>
<td>2,400</td>
<td>0</td>
</tr>
<tr>
<td>1979</td>
<td>3,600</td>
<td>1,200</td>
</tr>
<tr>
<td>1980</td>
<td>3,900</td>
<td>1,500</td>
</tr>
<tr>
<td>1981</td>
<td>3,900</td>
<td>1,500</td>
</tr>
<tr>
<td>1982</td>
<td>4,200</td>
<td>1,800</td>
</tr>
<tr>
<td>1983</td>
<td>4,500</td>
<td>2,100</td>
</tr>
<tr>
<td>1984</td>
<td>4,500</td>
<td>2,100</td>
</tr>
<tr>
<td>1985</td>
<td>4,800</td>
<td>2,400</td>
</tr>
</tbody>
</table>

Total deaths from bronchial asthma: 34,200
Excess deaths: 12,600
Percentage of excess deaths to total deaths: 37%.

Obviously, the data are not sufficiently precise to calculate confidence limits. Bronchial asthma is not a major cause of death in the US, as compared to acute myocardial infarction or carcinoma of the breast. However, if the excess deaths are preventable deaths, then the public health problem is not inconsiderable. The impact of these deaths as tragedies of individual patients is incalculable.

Historic Perspective

In the 1960s, there was a gradual increase in mortality from asthma in England and Wales. The increase affected all age groups, but mainly involved the young. There were a variety of theories to explain the phenomenon. One theory implicated systematic undertreatment of asthma. Another implicated systematic overtreatment of the disease. The most specific theory stemmed from the fact that widely used canisters of isoprenaline delivered 400 μg for each inhalation rather than 80 μg (the usual dose). Although absolute proof is not available, the epidemic subsided roughly concurrent with the time employment of high-dose canisters was abandoned. There is no absolute certainty as to the cause of that epidemic of excess death because some of the facts are inconsistent with a simple one-medication overdose theory. Independent of the question of cause, investigation of the phenomenon benefited all asthmatics by reducing the potential dose to many patients, and focusing on the potential risks of therapy with isoprenaline.

What Might Be Done?

The credit for detecting and describing the recent increased death rate from bronchial asthma in the US belongs to Sly and to Paulozzi, Coleman and Buist. They are to be congratulated. Their observations may turn out to provide a major contribution to increased safety for asthmatic patients. However, as is traditional in matters of this kind, both articles take a somewhat indolent view of what might be done and both recommend further investigation and observation.

If there is a remediable approach to limit excess deaths, then patients will die needlessly while such observations and investigations are carried out.

There are a number of steps which could be taken while investigation and observation are going on:

1. Physicians generally should be warned about the upward drift of the death rate, particularly in older patients. This might lead to more conservatism in the use of current agents.

2. The general public should be alerted to the potential dangers of current therapy. In particular, the use of massive polypharmacy should be discouraged. Dispensing this information would help patients select physicians more rationally. Alerting the public might decrease death from use of over-the-counter drugs.

3. The use of single-patient controlled randomized trials by individual physicians in developing appropriate drug regimens should be encouraged. The single-patient clinical trial can be used to weed out drugs which are not effective in individual patients.

4. The summed data from such trials might be collected and published. This might provide a general base for eliminating excess deaths.
5. A meeting dealing with the increased mortality from asthma should be convened rapidly. This meeting, ideally, would not be an academic exercise, but should have as its goal the formulation of actions to deal with the problem.

6. Key areas for research should be identified, such as:
   a) how safe are current regimens for the use of methylxanthines?
   b) how safe are current loading doses for the use of the methylxanthines?
   c) how safe is the combination of beta agonists and methylxanthines?
   d) can a clinical trial be organized to spell out appropriate use of corticosteroids?
   e) what are the hazards (if any) of therapy with anticholinergic agents, alone and in combination, in the treatment of asthma?
   f) what is the safety, efficacy and indications for ICU management of bronchial asthma?
   g) is there augmented risk to patients with bronchial asthma from use of nonsteroidal antiinflammatory agents as compared to aspirin?

7. Physicians should caution asthmatic patients about the possible consequences of nonsteroidal antiinflammatory agents and proprietary anti-asthma inhaler drugs.

8. The organization of an asthma registry to record, investigate and analyze individual deaths from bronchial asthma would be helpful in providing accurate data and identifying approaches to reduce mortality.

**SUMMARY**

There is now incontrovertible evidence that there is a progressive and strikingly increased mortality from bronchial asthma in the US. The increase is more dramatic in the older age groups, but younger age groups are not spared.

The exact cause or causes of this increased mortality are not known, and it is even possible (although not likely) that the increase is artificial. This increased death rate is in sharp contrast to the general medical perception that major advances in the management of bronchial asthma have occurred. Perhaps they have, but if so, more patients are dying during this period of advances than were dying before. The most prudent course would be to assume that the excess deaths are iatrogenic in origin and to act accordingly. Even if this assumption is flawed, acting on it would improve the management of patients with bronchial asthma. If it is true that the major purpose of risk-benefit analysis is to improve patient outcome rather than merely analyze risk-benefit balance, then a series of proposals can be generated to grapple with this problem in bronchial asthma.

**ACKNOWLEDGMENT:** I gratefully acknowledge the provision of data by Dr. John W. Kusek, Division of Lung Diseases, National Heart, Lung and Blood Institute (National Institutes of Health, Bethesda, MD).

**REFERENCES**

2. Paulozzi LJ, Coleman JJ, Buist AS. A recent increase in asthma mortality in the northwestern United States. Ann Allergy 1986; 56:392-95
3. Mortality Statistics Branch, National Center for Health Statistics. Obtained through the courtesy of John W. Kusek.