REVIEW ARTICLE

Mortality from asthma

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AT the turn of this century it was commonly believed in England that nobody ever died of asthma. Statements to this effect were made by Sir William Osler, and by other eminent physicians. As recently as 1948, a standard British textbook on respiratory diseases stated that death from asthma was very rare (Coope 1948), and medical students were taught this at this time. In spite of this, the official death rate from asthma was eight per 100,000 living population in England Wales in 1900 and seven in 1948—*considerably higher than it is now.*

This complacency continued to be widespread until in 1952, D. A. Williams drew the attention of the Thoracic Society to the fact that death in status asthmaticus was common and that the mortality figures from 1939–1949 showed an average death rate of seven per 100,000. He reviewed 140 cases of death from status asthmaticus in whom post-mortem examinations had been made and concluded that the patients most highly at risk were those over the age of 30 years and who had had previous attacks of status asthmaticus. At present there is widespread concern in this country over the upward trend of mortality in asthma, particularly in children. It must not be forgotten, however, that the majority of deaths still occur over the age of 30 years—and in these patients the death rate is ten times that of the younger age groups. The alarming fact in children is that the proportional increase in mortality (as opposed to the actual number of deaths) has been more than in adults, and the child mortality is now higher than ever before.

Considerable difficulty arises in making long-term comparison of mortality statistics. Revisions in classification are made every ten years and inaccuracy of death certification has been estimated as high as 39 per cent (an editorial, *British Medical Journal*, 1967). In 1900, standards of diagnosis were very different from those of today. At this date, causes of sudden death certified by coroners were as follows: "Convulsions", 2,453; "Atrophy and debility", 532; "Syncope", 149; "Dentition", 171, and so on; "Bronchitis" accounted for 792 deaths and asthma was not mentioned. This kind of thing makes nonsense of comparisons back to 1900, but by 1930 standards were becoming more comparable to nowadays and it is interesting to see how constant were the death rates for asthma and bronchitis from then until 1955. Figure 1; this graph shows the death rate from asthma in England and Wales from 1930–1966. Two major changes in classification occurred during this period—one in 1940 which artificially increased the rate and one in 1957 which artificially lowered it. It will be seen that the mortality figures for asthma and bronchitis are remarkably parallel until 1952. The bronchitic rates then continue in a similar pattern but the asthma deaths drop rapidly and consistently until 1960. This was the period during which corticosteroid treatment became widely used and it has been considered by some to be the cause of the decline (Pearson 1961). After 1960 the deaths have risen sharply, but overall are not yet much more than one half of the pre-1950 average.

When different age groups are examined separately, a different pattern emerges (figure 2). In subjects over 35 years of age the number of deaths is ten times that in the younger age groups and overshadows them. There is a marked rise in both older and

younger age groups from 1960, but the rise is proportionally much greater in the younger (figures 3 and 4). These graphs show the actual number of deaths from asthma and from bronchitis in children and young adults from 1930–1965. We see that the deaths from bronchitis were very high until 1940, but then fell sharply to 1950, and remain at a low level thereafter—this may have been due to the introduction of effective antibiotic

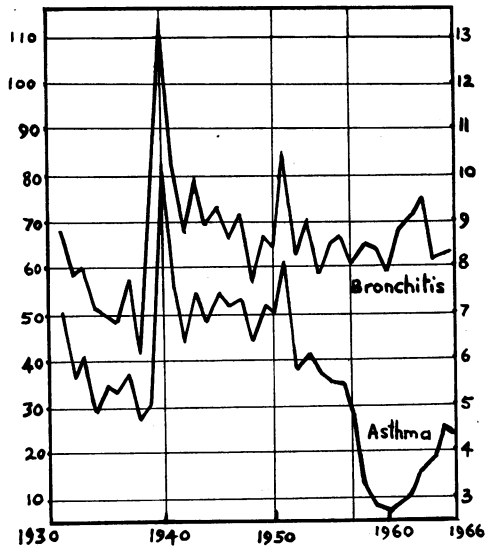

Figure 1.
Death rates per 100,000 population.

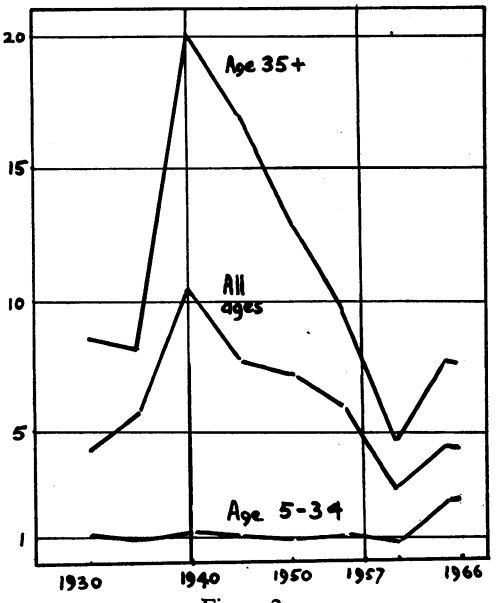

Figure 2.
Death rates—asthma, 1930–1966.

treatment. Asthma, on the other hand, shows a gradual and slight fall in the young adults from 1940–1960, but in the children the deaths remain steady. From 1960

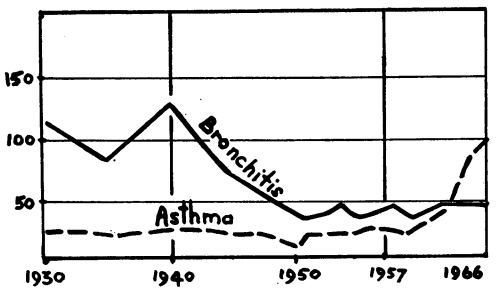

Figure 3.
Actual numbers deaths—1930–1966—age 5–14.

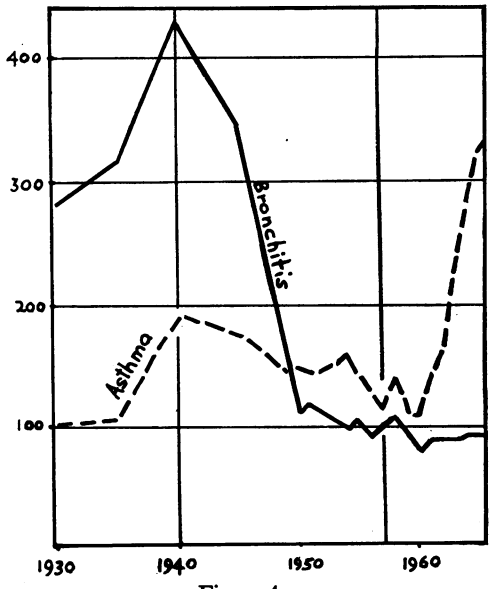

Figure 4.
Actual numbers deaths—1930–1966—Age 15–34

onwards there is a very marked rise in both children and young adults and this reaches a higher level than has ever been seen before. The fact that the figures for bronchitis mortality do not drop between 1960 and 1965 indicates that the increase in asthma deaths is not due to the better differentiation between asthma and bronchitis and more accurate certification.

Figure 5 is on a log scale to show the proportional changes in the death rate from asthma in three age groups; the middle aged, the young adults and the children. Here the differences are even more marked in the youngest group. The greatest rise has taken place between the ages of 10 and 14 years. The fall in the overall mortality which we

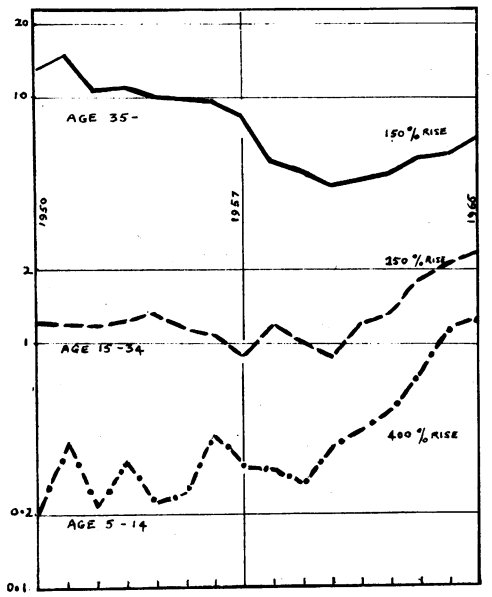

Figure 5.
Log graph—death rate—asthma 1950–1965

TABLE I

Adrenergic drug effects	
χ receptors	*β receptors*
Vasoconstriction	Vasodilatation
Tachycardia	Tachycardia
	Increased force of heart beat
Contraction of smooth muscle of: Uterus Spleen	Relaxation of smooth muscle of: Bronchi Uterus
Relaxation of smooth muscle of: Gut	

saw in the first graph is not seen in the children and is very much less marked in the young adults than in those over 35 years.

This alarming state of affairs was pointed out by Morrison Smith in early 1966 and was followed by an extensive correspondence in the journals about its possible association with bronchodilator aerosols. Much of this information was spurious and anecdotal, but the Committee on Safety of Drugs issued a warning about the possible dangers of aerosol bronchodilators in June 1967.

The reasons for the rising death rate and its particular accent on children are not at all clear. Perhaps we should consider such reasons under four headings:

1. Possible increase in morbidity
2. Non recognition of status asthmaticus and anoxia
3. Overuse of bronchodilators
4. Underuse of steroids.

It is likely that all of these possible factors may have played at least some part in the rise.

1. *Possible increase in morbidity*

We do not know if there has been a rise in asthma morbidity. Morbidity figures in surveys of general practice from 1961 to 1966 (Speizer *et al.* 1968a) have been estimated.

These figures are based on the number of *episodes* of asthma leading to consultations and do not give any idea of the *actual number* of patients involved. The number of episodes of consultation have not increased and this could be interpreted in more than one way.

It is possible that more patients with mild asthma were managing at home with treatment which was available without prescription, such as ephedrine and bronchodilator aerosols, and have not consulted their doctors because of this. If this is so, it could well mask an increased case incidence of asthma. It could also be possible that patients who have severe asthma are trying to 'save trouble' and are not consulting their doctors unless their attacks are excessively severe. This would reduce the number of 'patient episodes' and mask an increase in morbidity and severity.

2. *Failure to recognize status asthmaticus and anoxia*

Status asthmaticus may be defined as a failure to respond adequately to bronchodilator therapy. During the past few years the consumption of pressurized aerosols has increased enormously and the sales of these preparations are higher in England and Wales, per head, than anywhere in the world (Speizer 1968b).

Patients have received these aerosols free under N.H.S. prescriptions and could sit at home using them until they were literally at their last gasp. They "do not like to bother the doctor". How often this happens we do not know—but one hears of it happening frequently and it must be very common.

A survey of asthma deaths in the first half of 1967 showed that death was 'sudden or unexpected' in 80 per cent of cases and this was confirmed by the number of cases referred to the coroner. The terminal illness was estimated as lasting less than one hour in 30 per cent of the deaths and the great majority of these patients died at home or on the way to hospital (Speizer *et al.* 1968b).

It could be inferred from this that delayed recognition of the severity of the asthma contributed to many of these deaths. *Status asthmaticus does not come on in minutes and kill within the hour.* If the patients themselves would call their doctors earlier and if the doctors were aware that a rising pulse rate associated with an inadequate response to bronchodilators was a warning of impending disaster, oxygen therapy and adequate steroid treatment might save many lives.

We cannot exclude the doctors from blame. I have known of several instances when a patient with known severe asthma died at home while waiting for the doctor to come. It must be recognized that status asthmaticus is a medical emergency and probably just as urgent a situation as a patient who has developed a coronary occlusion. This is certainly not what we were taught as students and perhaps we should alter our priorities.

Anoxia in severe asthma is a subject on which many articles have appeared in the last few months. In all, some 200 patients in severe or moderately severe asthmatic states have been found to have arterial oxygens well below normal. The patients in severe status were reported as having P_aO_2 values of as low as 39 mm Hg. Ambulant patients have been found to have values as low as 60 (normal is 90–95). It has been pointed out by several of these authors that hypoxia may be present without any physical signs and that many such patients may be walking about with very low P_aO_2 values. It has also been shown that hypercapnia is not present in asthma until a terminal stage has been reached.

These reports indicate that a serious state of asthma may be present without the patient, his relatives, or his general practitioner being aware of the severity of his condition. It would not seem unreasonable to infer that these patients who are clearly very

much at risk may be finally reduced to a state of hypoxia which could produce sudden death.

The authors uniformly report that the arterial oxygen tensions were frequently further lowered following isoprenaline inhalation and that injection of adrenaline or aminophylline may also produce the same effect. (Tai and Read 1967, Waddell *et al.* 1967, Chapman and Hughes 1967, Palmer and Diament 1967a and 1967b, Rees *et al.* 1967a and 1967b, Palmer and Diament 1968).

The reason for the increase in hypoxia in these patients following isoprenaline inhalation has been shown to be due to an increase in imbalance of the perfusion–ventilation ratio which is present in the lungs in asthma. This is due to direct pulmonary vasodilatation effects of isoprenaline. There may be at the same time a slight improvement in airways resistance and the patient feels a little relief. A further dose of bronchodilator may then be taken with perhaps disastrous result.

3. *Pressurized aerosols and overuse of bronchodilators*

The sales of pressurized isoprenaline aerosols have increased greatly since they were introduced in 1958. During the past 5–6 years there has been a 400-fold increase in the sales of these inhalers. It has been estimated that over 85 per cent of patients who died in 1966–67 were using pressurized aerosols (Speizer *et al.* 1968), but to incriminate these aerosols on this basis alone is not justifiable; almost all severe asthmatics use aerosol bronchodilators.

Much of the evidence for assuming that isoprenaline is dangerous has been accumulated from reports of patients who have died clutching an inhaler after using excessive amounts of the drug. But this does not mean that other factors are not involved.

Gandevia (1967) states that in Australia there is no correlation between pressurized aerosal sales and asthma mortality in different states. He found a much closer correlation between low prescription rates for corticosteroids and high asthma mortality. Nevertheless, there is considerable pharmacological evidence for cardiovascular toxicity of both isoprenaline and orciprenaline in animals.

Adrenaline and its derivatives are all powerful sympathomimetic drugs and have certain properties in common (figure 6). Adrenaline has a variable action on both the alpha and beta adrenergic receptors throughout the body. Under physiological conditions its effects are mainly on the alpha receptors but in larger amounts the beta receptors are also affected. Isoprenaline acts almost entirely on the beta receptors. Orciprenaline also acts on beta receptors. Both isoprenaline and orciprenaline have a marked bronchodilator effect when inhaled and are rapidly absorbed into the blood stream. Owing to their beta receptor affinity they produce vasodilatation and there may be a drop in blood pressure. Pulmonary vasodilatation occurs.

Adrenaline, isoprenaline and orciprenaline are all known to produce ventricular arrhythmia in the animal heart when given in high dosage, and cardiac arrest finally occurs in ventricular fibrillation with lethal doses. It has been suggested that the combination of adrenaline by injection with isoprenaline by inhalation is particularly liable to cause ventricular arrhythmia in the human subject (*Lancet* 1965), but there does not appear to be any direct evidence of this in any textbook of pharmacology. It has also been suggested that the toxic effects of isoprenaline on the heart may be greatly increased when it is under strain. Lockett in 1965, published a report on the lethal effects of isoprenaline and orciprenaline on the cat heart-lung preparation under strain. Their effect was more than 15 times greater than in the unembarrassed heart, but one cannot conclude that effects of drugs on isolated heart-lung preparations of cats, subjected to artificial loading due to electrical stimulation or increased volume of venous return can have a direct bearing on the human subject in a severe asthmatic state when hypoxia

is present. There does not appear to be any pharmacological or physiological information on the effects of sympathomimetic drugs on the cardiac performance in anoxic animals or in man in hypoxia.

There have been two reports recently on cardiac arrest in status asthmaticus when the patient has been monitored (Grant *et al.* 1968); Miller and Semple (1967) reported a patient who had two episodes of cardiac arrest in asystole (not fibrillation) following excessive use of bronchodilator drugs for status asthmaticus. Resuscitation included intravenous adrenaline which was successful in reducing the asthmatic spasm and returning the cardiac state to normal.

Grant *et al.* (1968) reported three patients in status asthmaticus where ventricular asystole occurred following a period of progressive bradycardia. Open cardiac massage restored rhythm and recovery in two of the three cases.

It seems unlikely that in these four patients with cardiac arrest in status asthmaticus blame could be put upon bronchodilator drug effects on the heart as ventricular fibrillation did not occur.

On the other hand, two patients of mine have used up to one whole container of isoprenaline (Medihaler Forte) per day (one patient had done this for six consecutive days) and having been admitted to hospital for observation were found to have no evidence of cardiac arrhythmia. In both these patients the arterial oxygen tension was over 80 mm Hg. They were not in true status asthmaticus.

The only evidence to incriminate bronchodilator aerosols seems to be their effect (which indeed is a very serious one) on increasing hypoxia in patients in status asthmaticus, due to their direct vasodilatory effect on the pulmonary circulation.

4. *Inadequate steroid therapy*

In the survey of deaths from asthma in the first half of 1967 (Speizer *et al.* 1968), it was interesting to note that the majority of patients dying of asthma had not had adequate steroid therapy. More than 45 per cent of these patients had had no steroids at all in the terminal episode and a further 25 per cent had had inadequate dosage (i.e., less than 30 mg per day).

Withdrawal of steroids may also be a factor when other less effective treatment is substituted. Patients undergoing reduction of steroid treatment under hypnosis have tended to increase their consumption of isoprenaline very greatly. Houghton (1967) has had six deaths occurring suddenly in such patients who had reduced their steroid dosage to below 15 mg per day and had increased their bronchodilator inhalations to 30–100 times per day.

Conclusions

The recent increase in asthma deaths certainly cannot be attributed to excessive use of steroids—in fact, it may not be unreasonable to conclude that failure to use adequate dosage of these drugs may be the most important factor. There is also certainly not enough evidence to conclude that the rising asthma death rate is due to bronchodilator aerosols alone and any attempt to withhold these valuable drugs from the average mild asthmatic patient would be unjustified.

It must be emphasized that status asthmaticus comes on insidiously. The patients will admit to having been in an asthmatic state for several days before a really severe situation has arisen needing the doctor to be called to their home. Then we have an emergency which needs treatment with 100 per cent oxygen and steroids or ACTH in adequate dosage. Assisted respiration in a special unit may be required.

Children, particularly, do not complain of shortness of breath until the situation has become very acute and are frequently using far too much isoprenaline to be safe

when they are in an hypoxic state. They also tend to be resentful of their asthma and try to hide it.

Patients must be educated to call for medical help before it is too late. The doctors must be prepared to go to them quickly with oxygen and casualty departments of hospitals must be prepared to admit them for resuscitation if necessary. They must not be allowed to stay at home clutching a useless little can until they are literally at their last gasp.

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Self-certification for brief spells of sickness absence. P. J. TAYLOR, B.Sc., M.D., M.R.C.P., D.I.H. *Brit. med. J.* 1969. **1**, 144

For three years manual workers at an oil refinery have been allowed to certify their own short periods of sickness absence, instead of obtaining certificates from a doctor. There was no evidence of serious abuse with this system, and the increase in short periods of absence has been more than compensated for by a saving in the total time off work.

"The decision that a patient is unfit for work is very seldom strictly medical particularly when the condition is not severe, and in the great majority of cases the decision is really taken by the patient."

The company operates a full-time occupational medical service so that employees are aware that their statements are liable to scrutiny by a doctor. This may act as a disincentive to unjustified declarations of sickness.