before—that is, hypersensitive. The mechanism of this is not understood, but it seems that cortisone suppresses it and, at the same time, allows hyposensitization to proceed undisturbed and on a larger scale than would otherwise be possible.

This action of cortisone is very different from that of sympathomimetics and antihistamines. These substances are capable of protecting against or suppressing minor and even major attacks caused by overdoses of antigen; but as soon as their effect has faded the violent reaction to the overdose becomes apparent and requires a new dose of sympathomimetic; it seems that hypersensitization as a secondary effect cannot be avoided, although this can be deduced only from general experience. Evidence from experiments is still lacking.

Our experiments have so far been done on patients with mild or moderate asthma who were either in an asthma-free interval or had chronic asthma of moderate intensity kept under control by small amounts of drugs. Whether the same effect can be achieved with severe cases of asthma remains to be seen. We know from clinical experience that the continuous severe asthmatic reaction to the allergen can be suppressed by cortisone, and that it continues to be absent for a short time after the omission of the cortisone. Gradually, however, the asthma returns. One might think that in these cases the hyposensitizing effect which may develop under cortisone is soon replaced by the hypersensitizing mechanism which has been present before.

We shall not be able to understand these observations until the action of the cortisone is more fully understood. It may be concluded, however, that in certain types of asthma hyposensitization is greatly facilitated by cortisone.

One practical conclusion follows. It will be possible to shorten the cumbersome process of hyposensitization by proceeding in bolder steps under cortisone protection. So far the therapeutic success of hyposensitization has been poor, in spite of the sometimes enthusiastic statements in many textbooks of allergy (see also Rackemann, 1932; Unger and Wolf, 1943). Hurst (1943) has expressed strong doubts of the efficacy of hyposensitization, and Herxheimer and Prior (1952) have shown that objective success is rare and can probably be achieved in only 2.5 to 4% of all asthmatics. With the help of cortisone it may be possible to by-pass some of the otherwise unavoidable setbacks, and perhaps to extend the procedure to patients with polyvalent allergy in whom this treatment so far has been less successful.

Summary

In 18 experiments on 11 asthmatic patients the amount of inhaled allergen causing a mild attack was determined. The patients were given cortisone, and when under its full influence were exposed to double or treble the amount of the same allergen. This exposure was repeated when cortisone dosage had been reduced and again after the cortisone influence had ceased.

The doubling or trebling of the amount of inhaled allergen, which normally would have caused a violent and severe attack, caused under cortisone influence either a very mild and transient attack or, in the late reactors, no attack at all. The same overexposure under reduced cortisone dosage had the same result, and this did not change after the omission of cortisone. In the immediate reactors the asthma attack tended to become still milder towards the end of the experiment, until it finally disappeared when the exposure was repeated a second or a third time after omission of the cortisone. In two other patients* cortisone did not influence a mild induced attack, and these patients were therefore not exposed to double or treble the antigen dosage.

It is concluded that, in most moderate and mild cases of asthma, cortisone protects the patients from the violent attacks through overexposure. Moreover, it prevents the otherwise unavoidable hypersensitization and permits hyposensitization to develop in spite of overdosage.

Cortisone can therefore be used to speed up the process of hyposensitization.

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*See note at foot of page 186.

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FATAL BRONCHIAL ASTHMA

A REVIEW OF 18 CASES

BY

C. KELMAN ROBERTSON, M.D., F.R.C.P.Ed. D.P.H.

Assistant Physician, the Royal Infirmary, Edinburgh

AND

KENNETH SINCLAIR, M.B., M.R.C.P.Ed.

Registrar, the Royal Infirmary, Edinburgh

The serious results of repeated attacks of bronchial asthma are well recognized, the usual sequence of events being that emphysema gradually develops, giving rise so often to "pulmonary failure" (Fulton, 1953) and ultimately to death. The asthmatic attack itself, however, although regarded as an annoying interlude in a patient's life, causing domestic and social upset, rarely ends fatally.

The first full pathological review of a case of asthma was given by Leyden in 1886, but during the ensuing 35 years only 15 further case reports, giving both macroscopic and microscopical details, seem to have been published. Huber and Koessler (1922) summarized those 15 cases together with six of their own. Since then at least six outstanding articles (Lamson and Butt, 1937; Thieme and Sheldon, 1938; Craige, 1941; Rackemann, 1944; Unger, 1945; Walton *et al.*, 1951) have appeared, dealing with conjoint clinical and necropsy findings, the most recent of which stresses the low number of recorded cases and gives the opinion that this could be due to lack of recognition of the condition at necropsy.

The distressing consequences of this disease, both immediate and remote, have been recorded by various authors. Lamson and Butt considered that approximately 40% of cases may survive not more than four years of symptoms. In a review for insurance purposes Old (1933) estimated that the ratio of actual to expected deaths in 274 asthmatic subjects was 121% ± 5%. In differentiating between extrinsic and intrinsic asthma,

Cecil and Loeb (1951) believe that extrinsic cases do not die of the disease alone unless in very exceptional circumstances, whereas the death rate for the intrinsic group is 7.6%. The possible causes of death—hypoxaemia, dehydration, peripheral vascular collapse, drug intoxication, etc.—are fully dealt with by Segal (1950). Herxheimer (1952) reminds us that the course of bronchial asthma is always unpredictable and that even the psychologically induced attack may end fatally.

It is impossible to obtain accurate figures of death directly attributable to asthma; nevertheless reference has been made to the Statistical Review of the Registrar-General for England and Wales (1940–8) and to the Annual Reports of the Registrar-General for Scotland (1940–8), bearing in mind possible errors of certification due to diagnostic difficulties. From these reports it would seem that the average annual death rate is 3,268 for England, Wales, and Scotland. It is significant that by far the greatest number of deaths in England and Wales were recorded during 1940 (4,167), a time of particular stress in the life of the nation, which no doubt affected the asthmatic personality as adversely as those prone to perforation of gastric and duodenal ulcers (Illingworth *et al.*, 1944).

The possibility of a serious outcome from any asthmatic attack should always be borne in mind, however mild it may appear to be in the beginning. Because of the small number of reviews dealing with combined clinical and pathological findings, it has been decided to record a series of cases which fulfil all the recognized criteria of asthma.

Investigation

The following consists of a review of 18 cases, all of which were treated as in-patients in the Royal Infirmary and associated hospitals in Edinburgh between the years 1939 and 1952.

Post-mortem examination, including a careful microscopical study of the lungs and bronchi, was carried out in all cases. The clinical features of each patient were consistent with a diagnosis of bronchial asthma. In some, although other factors contributed to death (as noted in Table III), the main immediate cause was always asthma.

TABLE I

Case No.	Sex	Age	Known Duration of Asthma	Date of Death
1	F	54	Many years	24/9/39
2	F	46	4 days	5 10 45
3	M	57	9 months	7/12 47
4	M	42	35 years	16 1 48
5	F	65	Unknown	20 9 49
6	M	14	5 years	26 9 49
7	F	47	42 ,,	17 10 49
8	F	49	9 ,,	18 6 50
9	M	48	3 months	18/7/50
10	F	66	6 years	6 10 50
11	M	45	10 ,,	19 10 50
12	F	50	1 year	26 10 50
13	M	67	21 years	31 10 50
14	F	59	10 ,,	24/2 51
15	F	47	1½ ,,	17 9 51
16	M	46	22 ,,	24 4 52
17	F	41	8 ,,	17 7 52
18	F	47	4 ,,	2/10/52

The sex incidence, 11 females to 7 males, in such a small review, cannot be regarded as significant. The majority died between the ages of 40 and 50 years. The variable duration of the disease (Table I) suggests that this factor cannot be related to a fatal outcome in the present series. The seasonal distribution of deaths—11 out of 18 in the months of September and October—corresponds with previous findings (Williams, 1952), the incidence having been related to respiratory infections.

For the purpose of aetiological classification three groups were recognized: psychological, allergic, and infective. It was realized, however, that more than one of these factors could be operative in the same patient at the same time, as is evident in Table II, in which the predominant factor is placed first. A psychological background was present as either a primary or secondary factor in 12 cases. Two

TABLE II

	P	P and A	P and I	A	A and I	I	I and P
Sex:	F M	F M	F M	F M	F M	F M	F M
No. of cases ..	4 1	3 —	1 1	— 1	1 2	— 2	2 —
	5	3	2	1	3	2	2

modes of death were apparent: sudden and unexpected in 13, and progressive exhaustion and terminal coma in 5. The duration of the fatal attack varied from a few minutes to 12 days.

The pathological criteria accepted were: *Macroscopic:* (1) Voluminous lungs which did not collapse when the thorax was opened. (2) Mucous plugs in the large and small bronchi. *Microscopical:* (1) The presence of mucous plugs in the bronchi associated with excessive mucus production by the bronchial glands. (2) Hyaline thickening of the basement membrane of the medium-sized bronchi. (3) Hypertrophy of the muscle of the medium-sized bronchi. (4) Eosinophilic infiltration, especially in the bronchial walls.

These features were looked for and recorded in each case. All were not constantly found, but no case was included unless the pathologist discovered unequivocal evidence of asthma. Eight cases fulfilled all criteria. All cases showed

TABLE III.—*Summary of Pathological Findings*

Case No.	Voluminous Lungs	Mucous Plugging	Thickened Basement Membrane	Hypertrophy of Muscle	Eosinophilia	Active Mucous Glands	Other Pathological Findings
1	−	+	+	−	+	+	Left ventricular hypertrophy. Polypi in sinuses
2	+	+	+	−	+	+	
3	+	+	−	+	+	+	
4	+	+	−	+	−	+	
5	+	+	+	+	+	+	
6	+	+	−	−	+	+	
7	+	+	+	−	+	+	Small area probably allergic pneumonia. Right lower lobe
8	+	+	+	+	+	+	
9	+	+	−	−	+	+	Bronchitis
10	+	+	−	+	+	+	Scattered areas of local organization. Right ventricular hypertrophy
11	+	+	+	+	+	+	Partial collapse. Left lower lobe. Atheroma, pulmonary arteries. Right atrial and ventricular hypertrophy
12	+	+	+	+	+	+	Early basal bronchopneumonia
13	+	+	+	+	+	+	Right ventricular hypertrophy
14	+	+	+	−	+	+	,, ,,
15	+	+	+	+	+	+	Right ventricular hypertrophy, early bronchopneumonia
16	−	+	+	−	+	+	Bronchitis
17	+	+	+	+	+	+	Right ventricular hypertrophy
18	+	+	+	+	+	+	,, ,,

mucous plugs in the bronchi with active glands. Eosinophilia was present in all but one. The right ventricle was hypertrophied in seven. Records of Cases 3 and 15 are given below.

Case 3

A miner aged 57 was admitted on November 26, 1947. He had felt well until nine months before admission, when he first developed attacks of sneezing in the mornings, soon to be followed by attacks of breathlessness in bed at night. No precipitating cause for this could be found. The attacks at first lasted 30–60 minutes but became more severe and of longer duration, and eventually occurred nearly every night.

He also had occasional milder attacks during the day. Oral ephedrine gave slight relief. A severe attack developed in the early hours of the day of admission and adrenaline subcutaneously gave only temporary relief. He had a cough with slight mucoid sputum. His previous and family history showed nothing relevant.

On examination he was seen to be a hardy well-built man, distressed, dyspnoeic, and slightly cyanosed. His temperature was 98° F. (36.7° C.), pulse 100, and respirations 32. There was no finger-clubbing. Wheezing was audible in both phases of respiration. The chest was emphysematous. Auscultation revealed rhonchi, mainly expiratory, all over the chest. There were no crepitations. Cardiovascular system: the blood pressure was 130/80; pulse 100; no oedema; heart sounds were of poor quality. There was slight tenderness over the right antrum. On November 27 the E.S.R. was 8 mm. in the first hour; W.B.C., 9,000; Hb, 100%; a few organisms were found in the sputum. On November 28 an *x*-ray film of the chest showed slight emphysema, and an *x*-ray film of the sinuses showed some opacity in the right antrum. The E.C.G. was normal on December 2.

The patient responded initially to intensive adrenaline therapy and slept well after taking paraldehyde. He was maintained on oral ephedrine and stramonium mixture, frequently supplemented by adrenaline, "adrenutol," theophylline with ethylenediamine by injection, also phenobarbitone, amylobarbitone sodium, phenobarbitone sodium, and on one occasion pethidine, 50 mg. intravenously. He was very nervous and tense, and "sat waiting for his next injection." On December 6 all drugs except phenobarbitone and adrenaline were stopped, some 40 minims (2.4 ml.) of the latter being given during the day. The bronchospasm subsided and he was much better. He then collapsed and died suddenly and unexpectedly at 1.30 a.m. on December 7.

Necropsy showed only bronchial asthma with marked plugging of the bronchi.

Case 15

A married woman aged 47 had suffered from a winter cough of only mild severity for many years and was not incapacitated. Eighteen months before admission she became breathless and wheezy one morning. She was in bed for 14 days, relieved by isoprenaline and theophylline with ethylenediamine. Since then she had had several relapses. The attacks were usually worse at night and were best relieved by isoprenaline. She was able to go about, apart from occasional spells of a few days in bed. There was some tension regarding her employment, and at the time of admission she was apprehensive and in bronchospasm of moderate severity. She had had an acute anxiety state when her husband died of cerebral tumour in 1933. Since then she had been very nervous and easily upset. She had had an artificial menopause induced in 1939.

On examination she was pale, thin, and anxious, but not cyanosed. Her temperature was 98° F. (36.7° C.), pulse 90, and respiratory rate 22; no finger-clubbing. There was slight emphysema; rhonchi, mainly expiratory, were heard all over both lungs. There were no crepitations. Cardiovascular system: the pulse was 102, regular; blood pressure, 110/70; heart not enlarged—sounds normal and no oedema. Endocrine system: palms were warm and moist, there was slight tremor. There was no thyroid enlargement, and no bruit was heard over the gland. On September 3 the sputum contained the usual respiratory organisms. The Hb (Sahli) was 110% and W.B.C. 7,700. On September 6 an *x*-ray film of the chest showed possible slight emphysema, and an *x*-ray film of the sinuses was negative.

Bronchospasm of moderate degree was present on admission. She responded to sedation with phenobarbitone sodium and oral theophylline with ethylenediamine, plus phenobarbitone. Isoprenaline sulphate was also used on occasion. As it was thought there might be a thyrotoxic state, thiouracil was begun on September 7 with slight effect. The patient was reasonably well at 12 noon on September 17, with slight bronchospasm. She collapsed suddenly at 1.30 p.m. and died in a few minutes.

Necropsy revealed asthma and emphysema, with marked plugging of the bronchi with tenacious mucus.

Discussion

It is generally thought that most cases of asthma react to treatment. A fatal issue can, however, be tragically sudden and unexpected. The possibility of error in an unduly optimistic attitude is emphasized by the fact that 18 such deaths have been available for review (3 in 1949, 6 in 1950, 2 in 1951, 3 in 1952, along with 4 earlier ones) from four general hospitals in this area. Analysis of the aetiology, age, and duration of disease has shown that these factors are unreliable aids to prognosis in any single attack.

The treatment carried out in all cases consisted of the usual measures employed in hospital. The drugs used included bronchodilators, expectorant mixtures, sedatives, antihistamine drugs, and antibiotics. Oxygen and oxygen–helium mixture were often used. Bronchoscopy was performed in some cases. Cortisone was available for the most recent case.

No new pathological feature was observed, but ample confirmation of the importance of plugging of the bronchi with tenacious mucus was apparent.

The immediate cause of death in bronchial asthma has not yet been clearly defined. From the nature of the condition it would seem probable that several factors can be responsible. It is proposed to review a few which have emerged from this investigation.

As previously noted, two modes of death were observed. It is reasonably easy to account for exhaustion and ultimate death from a prolonged severe resistant attack of bronchospasm which has lasted several days without remission. Progressive anoxia and failure of the right heart are responsible. Although it may be significant that a psychological element existed in 12 cases, the reason for the failure of response to therapy cannot be related to any constant clinical or pathological pattern.

The sudden death of an asthmatic patient who was relatively well until within a few minutes of death is more difficult to explain. At the present time we can only offer the following suggestions for consideration.

In a very severe acute attack progressive rise in the intra-alveolar pressure must quickly overcome the pulmonary capillary blood pressure of 10 mm. Hg. This would lead to occlusion, as when the pressure in the cuff of a sphygmomanometer approximates to that in the brachial artery. The much-increased resistance of the pulmonary vascular bed thus cannot be overcome by the right ventricle, which fails, with consequent cyanosis, collapse, and death.

It must be regarded as significant that mucous plugging was invariable in this series. The possibility of mechanical asphyxiation by this means has been previously noted in the literature. This may be explained by tenacity of mucus, bronchial spasm, and oedema, along with the fact that the mucus is sucked deeper and deeper down into the bronchial tree until it becomes impacted. The effect of this is inadequate alveolar gaseous interchange, with sudden death due to suffocation. Such can occur in a relatively well asthmatic subject with much mucus in the large bronchi who inspires deeply because of emotional or physical stress —for example, excitement, or, as happened in one of our cases, straining at stool on a bedpan.

The importance of an adequate initial clinical assessment and subsequent management of the asthmatic patient between attacks is already recognized. In view of the varied therapeutic measures used in the cases under review, it is thought that suggestions outlining a programme of treatment for the acute attack, rationally based on clinical and pathological findings, might be of interest.

The patient in an acute attack who shows signs of increasing cyanosis, dyspnoea, and distress within a few hours, in spite of attempted control, should be transferred to

hospital. This decision would be hastened by a history of previous resistant attacks. On admission attention must first be directed towards relief of bronchial spasm.

Adrenaline when used "in adequate dosage" must still be considered the most effective bronchodilator. It should be stressed that many allegedly resistant cases have been shown to be due to too small a dose. In the absence of obvious cardiovascular contraindications we would recommend the immediate injection of 20 minims (1.2 ml.) of 1:1,000 adrenaline hydrochloride as advised by Herxheimer, and used by one of us (C. K. R.) Where contraindications exist 0.25 g. of theophylline with ethylenediamine may be given intravenously.

For the severe, acute, cyanosed asthmatic sufferer from anoxic anoxaemia the early use of oxygen/carbon-dioxide mixture 95.5% is obviously indicated at a rate of 6 litres a minute. This mixture is used in preference to pure oxygen as the carbon dioxide helps to prevent the onset of apnoea and has an expectorant action (Basch *et al.*, 1941).

While one cannot condemn the use of morphine in status asthmaticus too strongly, because of its central depressant action on a respiration already barely adequate, these patients are as a rule fatigued and apprehensive, and benefit from the safe sedation produced by phenobarbitone sodium, 3 gr. (0.2 g.) intramuscularly.

Mucous plugging has been stressed throughout this paper, as it has apparently often contributed to the death of the patient. Potassium iodide renders sputum less viscid and thus easier to expectorate. It should therefore be given as soon as possible, in the form of Lugol's solution, 10 minims (0.6 ml.) three times a day.

Cortisone and A.C.T.H. are accepted as powerful anti-allergic agents and can be used in attacks resistant to the scheme of treatment outlined above. These drugs encourage fluid retention, however, and this should be borne in mind if there is any sign of cardiac failure.

In the asthmatic patient with an infective sputum penicillin should be given in anticipation of bacteriological results.

Summary

The relevant literature on bronchial asthma is briefly reviewed. Eighteen cases of fatal asthma are recorded, with clinical and pathological findings. Thirteen deaths were sudden and unexpected.

Possible immediate causes of death are discussed.

Treatment is considered.

We wish to thank Dr. Robertson Ogilvie and the staff of the Pathology Department of the University of Edinburgh for valuable co-operation. We are indebted to the physicians of the Royal Infirmary, Edinburgh, and associated hospitals for access to case records.

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CHRONIC BRONCHITIS IN GENERAL PRACTICE

BY

JOHN FRY, M.B., F.R.C.S.
General Practitioner

Diseases which are commonly encountered in hospital practice are not necessarily the most important from the point of view of national health and personal suffering. In considering disease from these aspects we must have regard to (*a*) its total incidence; (*b*) its average duration; (*c*) the types of persons affected and the period of life at which it produces its effects—thus a disease during the working years is of more national economic significance than one affecting the retired age groups; (*d*) the loss of time from work which it causes; (*e*) its mortality; (*f*) its preventability; and, above all, (*g*) the suffering which the victim undergoes. The most important national diseases, with regard to these factors, are the infections of the upper and lower respiratory tracts, the nervous and mental disorders, acute and chronic rheumatic manifestations, tuberculosis, and disorders of the digestive and cardiovascular systems.

As a distinct clinical entity, chronic bronchitis is one of the most important of diseases in this group—both numerically and socially. It is only in general practice that it is seen in all its stages and in all the effects it produces on the individual and the family group. In hospitals the condition is encountered only when the patient is referred there by the general practitioner, and this is usually only for diagnostic purposes—*x*-ray examination and sputum analysis—during an acute exacerbation and during the late stages with cor pulmonale.

Chronic bronchitis is in some degree responsible for over 30,000 deaths annually in Great Britain. It has been estimated to account for the loss of some 16½ million working days a year (Report of Ministry of National Insurance, 1950), and this does not include the condition as it affects the housewives, who, although an important and essential working group, do not receive insurance benefits. In general practice it accounts for a large volume of work. In my own practice in S.E. London it was in 1952 responsible for some 8% of all attendances, while Pemberton (1949), in Sheffield, estimated that it accounted for some 11% of all attendances. Proportions are probably higher still in some north-west areas of England.

The condition produces serious disablement—the Disabled Persons Register (*Ministry of Labour Gazette*, May, 1950) lists 7.9% of its total as being disabled on account of "non-tuberculous disease" of the lungs, of which chronic bronchitis constituted the largest proportion. The Treasury Deputy Medical Adviser's Report for the G.P.O. for 1951 shows that chronic bronchitis was responsible for 15% of all retirements on health grounds.

Other factors which make the disease one of such major national importance are its long duration, often causing trouble for 25 to 30 years, and the fact that each winter it causes a considerable loss of worktime. In addition, it affects principally middle-aged men in their most active and able years, which makes the absence from work of even greater significance. The fact that it is probably largely a preventable condition adds to its