ASTHMA

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Asthma is commonly defined in clinical terms. Thus Derbes and Engelhardt state: 'The term asthma means... a symptom complex characterized by a wheezing or whistling type of recurrent dyspnoea, having a prolongation of the expiratory phase of the respiratory cycle... The attack may last for a few hours to weeks or longer. Thereafter the subject may be entirely free of subjective symptoms until the appropriate stimulus initiates the above sequence.' Feinberg draws attention to the secretion of tenacious mucus during attacks; this is usually expectorated in the recovery phase. As the disease progresses wheezing may persist between attacks and the latter may become less evident as disability increases. This change is usually seen in the age group 40 to 60 when infection has supervened, but lung function studies show that prolonged expiration due to bronchial obstruction often persists between attacks even in young patients.

Asthma defined in this way must clearly be regarded as a syndrome rather than a disease entity. On aetiological grounds a further subdivision can be made into primary asthma and a variety of wheezy states in which the asthma is secondary to some other disease. These include cardiac asthma, asthma secondary to bronchitis and rarely to foreign bodies and neoplasms which sometimes give rise to widespread spasm, possibly of reflex origin; localized wheezing, which is more commonly encountered with foreign body or neoplasm, does not, of course, constitute asthma. Pathological criteria exist which may help in doubtful cases to make this distinction clearer. Thus in the active phase of primary asthma the bronchi show thickening of the basement membrane, hypertrophy of the muscle coat of the bronchioles, oedema of the submucosa, enlargement of the goblet cells and eosinophilic infiltration. These appearances are not usually seen except at post-mortem, but some of them, including eosinophilic infiltration, are clearly visible in biopsy specimens taken at bronchoscopy. They are, of course, modified by prior treatment with corticoid preparations. Low-grade inflammation with infiltration of the submucosa with lymphocytes is sometimes also present: the relationship between infection and asthma is discussed more fully later on. The presence of eosinophils in sputum and a raised blood eosinophilia are also points suggestive, though not necessarily diagnostic, of primary asthma. For the remainder of this paper the word 'asthma' will be taken to mean primary or 'bronchial' asthma unless otherwise qualified.

The most important predisposing cause of asthma is undoubtedly the hereditary or constitutional, and most authors find that approximately 40 per cent. of asthmatics have a family history of asthma. Schwarz in a careful survey shows that 6.6 per cent. of near relatives of asthmatics suffer from the condition compared with 1 per cent. of relatives of controls. There is, moreover, a familial tendency to develop 'allergic' disorders, such as hay-fever, perennial rhinorrhea, flexural eczema and angio-neurotic oedema in the asthmatic group. Several of these conditions are commonly found in one individual.

While many precipitating factors are recognized, the pathogenesis of asthma remains unknown. Allergy, infection and emotional stresses are the most important and treatment is largely directed to dealing with these individually or in combination, as they are recognized, together with the administration of bronchodilator drugs. In the confirmed asthmatic the bronchi become so sensitive that almost any non-specific irritant, such as cigarette smoke, fog, or cold air, will also induce an attack. Whereas it was at one time the custom to classify asthmatics as infective, allergic or nervous in origin, it is now increasingly recognized that all these factors are frequently operative in the same patient either concurrently or consecutively.

Allergy

Historically, the first recognition of specific sensitizing agents as a factor in asthma may be attributed to Jerome Cardan, Professor of Medicine at Padua, who in the 16th century advised John Hamilton, Archbishop of St. Andrew's, to give up the use of a feather bed for the cure of his asthma. Hyde Salter observed that pollen, animal hairs and substances such as ipecacuanha were capable of...
provoking asthmatic attacks and he merits the honour of being considered the father of allergy, even though his offspring was not christened till a number of years after his death.

The immunological mechanism upon which allergic responses depend is now well recognized. Reagins to antigenic materials can be demonstrated in the plasma of sensitive individuals in vivo by the Prausnitz-Kustner technique. This test is based on the observations of the two authors that if the serum of one of them who was sensitive to fish was injected into the skin of the other a triple response developed at this site on the recipient's skin if he ate fish 24 hours later. An urticarial wheal could also be reproduced by injecting fish extract into the sensitized area, but not elsewhere. It is of great theoretical importance, but is rarely used in practice because of the risk of transferring the virus of infective hepatitis: it demonstrates clearly, however, that specific antibodies are present in the patient's serum and become attached to cells in the recipient's skin with consequent liberation of histamine and perhaps other substances when reagin is brought into contact with them. This property of allergic antibodies to become attached to the cells in the nasal and bronchial mucosa, and in the skin, where they combine with specific reagins to liberate preformed histamine is characteristic and supplies the theoretical basis of the skin test. The immunological aspects of allergy were reviewed by Kallos in 1953.

Unfortunately, the clinical sensitivity of the bronchial mucus membrane to the allergen inhaled in its natural form is not necessarily identical with that of an extract injected or pricked into the skin. Positive skin tests to allergic substances are therefore not infrequently found in normal people who have never had clinical allergy, or in asthmatics who are not affected by the test material when encountered under natural conditions. That subclinical sensitivity may be present in unsuspected organs is sometimes accidentally demonstrated in the desensitization treatment of hay-fever, when too big a dose of pollen has been injected: the patient, who may never previously have had symptoms of asthma or urticaria, develops not only hay-fever, but a widespread urticaria and acute dyspnoea, which may have serious consequences unless rapidly controlled with adrenaline or antihistamine drugs. In practice a diagnosis of clinical sensitivity is based on a history of sensitization to a food or inhalant confirmed by a positive skin test, whereas a history of sensitivity unsupported by a skin test or a positive skin test without clinical confirmation should be accepted only with caution.

On evidence of this kind in a recent survey of 625 patients 54.7 per cent. of asthmatics were found to have allergic sensitization. This was thought to be of predominant importance in about half of these. Many of them had other allergic disorders, such as flexural eczema or rhinorrhea, in addition to their asthma and if the association of such conditions with asthma is accepted as evidence of allergy then 74 per cent. of all cases could be regarded as having an allergic element in their condition.

In practice the recognition of allergic sensitivity depends mainly on the history. This is perhaps most evident in those cases whose asthma is limited to or deteriorates during the early summer as a result of pollen sensitivity. Recent studies have shown that there is close correspondence between the severity of symptoms and the concentration of grass pollen in the air in such cases. This group accounted for 18 per cent. in the survey referred to, including 6 per cent. in whom pollen was the only recognized allergen. In another smaller group asthma was associated with occupation, since attacks were experienced only at work and not at weekends or on holidays: they accounted for 3 per cent. of cases and included carpenters (sensitivity to ebony, red cedar, African hardwood), market gardeners (plant pollen), laboratory workers (guinea-pigs, rabbits), dispenser (senna), printer (gum acacia) and farmers (chicken feed, grain dust). Multiple sensitivities are the rule, however, among many asthmatics also recognize from experience the importance of house dust, animal hairs and feathers as a cause of symptoms. Reproduction of attacks can readily be demonstrated by inhalation of the suspected substances themselves, or their extracts, and compared with the failure of control preparations to cause asthmatic symptoms. This method is, however, inconvenient as a means of testing for multiple sensitivities and not without risk. It is, therefore, in most clinics only used in difficult cases and is usually replaced by skin tests as a routine method of investigation.

**Infection**

The importance of infection in the precipitation of asthma cannot be doubted. Thus 195 patients out of 393 who were able to indicate a reason for their first attacks of asthma attributed this to some form of bronchial tract infection, including bronchitis, influenza, pneumonia, measles or whooping cough. A high proportion of asthmatics state that head colds, chest colds or bronchitis are regularly associated with attacks of asthma. Sometimes these infective episodes are the only known precipitating factor and such patients are worse in the winter months. Apart from such a history, the presence of degenerated polymorphs in the sputum can usually be regarded as evidence of infection, particularly if associated with pathogenic bacteria.
Infection of sinuses or throat sometimes appears to be responsible for causing attacks.

The mechanism by which infection leads to asthma is not known and speculation, though rife, is supported by little evidence. Bacterial allergy is regarded by many as responsible mainly because of the similarity between attacks of asthma induced by infection and those caused by extrinsic allergens and because microscopical pathology of the lungs is often identical in cases with confirmed extrinsic allergy and those with evidence of infection only. The difficulty in accepting this view is that it is based solely on analogy and that sensitivity to a particular organism or group of organisms can rarely be demonstrated: the infective agent often seems to vary from one attack to another and in many instances pathogenic organisms, such as Haemophilus influenzae or Staph. aureus, cannot be isolated. It is possible that non-pathogens, such as Strep. viridans, may act as antigens, but there is no proof that they do so and their presence in the throats of patients between attacks is strong evidence against their complicity. Other suggested explanations are:

1. Infection causes increased sensitivity to extrinsic allergens, possibly by localizing antibodies at the site of infection (Vallery Radot).
2. Infection sets up a process of auto-allergy (Bergguist and Gear).
3. Infection causes reflex bronchial spasm.

Baird has recently reviewed the whole subject of bacterial allergy.

Many intelligent asthmatics will state clearly that they recognize two distinct forms of asthma, namely, that associated with exposure to known allergens which normally responds readily to treatment with bronchodilator drugs and is of relatively brief duration, and that associated with nose colds, bronchitis, etc., which is of longer duration (days and weeks) and responds poorly to bronchodilators.

A history of recurrent attacks of bronchitis (with cough, pyrexia), in many cases confirmed by the finding of pus (degenerated polymorphs) in the sputum, was obtained in 51.7 per cent. of asthmatics; another 12 per cent. developed asthma which appeared to be secondary to bronchitis, which had often preceded the onset of wheezing dyspnoea at rest for many years. Linford Rees found infection in 68 per cent. of his series of cases. Of all those cases with an allergic factor, 57 per cent. also had evidence of infection; if the pollen-sensitive cases (111) are taken as an isolated subgroup of allergic patients, evidence of bronchitis leading to attacks of asthma was present in 47.7 per cent. The incidence of recurrent attacks of bronchitis in this group of asthmatic patients is far above that of a control series of out-patients attending with diseases other than that of the chest (20 per cent.) and there is little doubt that asthma is a predisposing cause of bronchitis. Analysis by age shows that the frequency of infection arises after 30 years to reach approximately 85 per cent.* in those over 50 years. In many of these it is the only factor recognized. It is of least importance between 10 and 30 years of age, when it is found in 52 per cent.*; at this age infection is seldom the predominating factor.

**Psychological**

Sir John Floyer, in 1717, stated that 'the passion of anger' and 'fear, solicitude and much study' produced attacks of asthma. Most asthmatics consider that worry or excitement are responsible for precipitating attacks. Of 326 adult asthmatics who were asked about this, 68 per cent. thought they were affected by minor emotional stresses. Many of these patients also gave evidence of other neurotic traits. Leigh and Marley have attempted to determine whether asthmatics are more neurotic than healthy controls by comparing the incidence of neurotic traits based on a comprehensive questionnaire (Cornell Medical Index), by statistical methods in asthmatics, neurotics and healthy controls. The resulting analysis showed that the asthmatics fell midway between the neurotic and the control groups. These findings suggested that the incidence of certain personality traits, particularly inadequacy and tension, and to a less extent depression and anxiety, is greater in asthmatics than in normal subjects. Linford Rees, in a study of 441 asthmatics, also found that in comparison with a control group they were more timid, sensitive, anxious, obsessional and unstable. The asthmatic group found greater difficulty in adapting themselves to environmental changes. Both authors agree that abnormal personality traits are found most commonly in female asthmatics over the age of 30. There is evidence that these traits often precede the onset of asthma.

The effect of environmental factors leading to emotional disturbances has been the subject of considerably study. Some authors, particularly Miller and Baruch, stress the importance of rejection by one or other parent as a cause of asthma. It seems unlikely that there is such specificity in the emotional background as they suggest, but any situation which threaten security certainly seems to have special significance for the asthmatic: these include parental aversion, the arrival of a new sibling without adequate preparation of the patient, parental quarrelling, separation of the parents, quarrelling between the patient and marriage part-

* These figures include those with asthma secondary to bronchitis.
ner, and the death of near relatives or friends. The excessive anxious care shown by some parents for their asthmatic offspring may also nourish a feeling of insecurity. Sometimes the relationship between the emotional incident and the attack of asthma is dramatic, as in the case of a young woman whose first attack occurred half an hour after seeing a man run over by a car, but often it is less obvious; for example, attacks may increase in number and severity during a period of marital unhappiness. Rees found definite evidence of emotional factors in 70 per cent. of his cases and considered that they played a dominant part in 37 per cent.

Groen considers that conditioned reflexes may play an important part in some cases: he has shown that in pollen-sensitive patients attacks can be precipitated by inhalation of pollen, but not at first by a saline aerosol. After a series of positive tests with pollen, attacks may occur after inhaling saline aerosol, and eventually even breathing through the disconnected mouthpiece of the apparatus may induce attacks.

One source of anxiety to which all severe asthmatics are subjected is that secondary to the attacks themselves. This is readily understandable and can best be relieved by active therapeutic measures to overcome the spasm.

Most physicians accept the fact that emotional stress, however induced, can cause a serious deterioration in the asthmatic condition, though the mechanism is still obscure. There is less agreement as to how often emotional factors are the sole or even the predominant factor, or how far successful treatment can be undertaken by psychotherapeutic measures.

Prognosis

There are few figures to indicate how often recovery of asthma can be expected. Grant found a history of asthma in 3.3 per cent. of 4,571 Cardiff University students; in 1.4 per cent. the attacks had ceased at the time of the interview, a recovery rate of over 40 per cent. Rackemann, who followed up 688 asthmatics first seen before the age of 20, found after 20 years that 46 per cent. had lost their asthma completely, 35 per cent., though still asthmatic, were rarely troubled by it and 17 per cent. remained seriously affected; 2 per cent. had died (1.5 per cent. of asthma). Flensborg recorded freedom from symptoms in over 40 per cent. of children with asthma by the time they were 18. Once more there was a mortality of 1.5 per cent. from status asthmaticus. There is general agreement that the prognosis is considerably better in those who start their asthma in childhood than those commencing in adult life, and the female whose asthma commences after 35 is thought to have a particularly poor prognosis. Long periods of freedom commonly occur in the natural history of the disease. Thus in the author’s series 47 patients (7.5 per cent.) gave a history of periods of freedom from one to 50 years or more before the asthma recurred: in 17 the period of freedom was more than 10 years. Such remissions were associated with a variety of conditions, including changing house (2), service in the armed forces (4), and were sometimes attributed to desensitization, spa therapy or psychotherapy. Most commonly no obvious reason for improvement was recognized. They often relapsed after infective or emotional incidents.

That asthma is not always the benign disease Hyde Salter considered it to be (‘Asthma Never Kills,’ p. 135) has been pointed out by Williams, who drew attention to the fact that approximately 3,000 deaths from asthma are recorded annually in this country. Leigh recorded a mortality of 22 per cent. in a follow-up of 32 cases whose asthma commenced after 35 years.

In our cases (625) 25 deaths (14 male, 11 female) occurred within seven years of their first attendance, an overall figure of 4 per cent. Nineteen died in status asthmaticus, two from anaphylaxis (one in the course of pollen desensitization and one from the administration of intravenous ACTH when in mild status), one committed suicide, one died of oedema of the glottis and one of broncho-pneumonia after surgical removal of an emphysematous cyst. Fourteen died between the ages of 40 to 60 and none under the age of 20. Of those who died in status, three succumbed in their first attack, but the remainder had had previous attacks, sometimes on 10 or more occasions. Status was recorded in 100 patients, excluding the three who died in their first attack, so that the mortality for this group was 19 per cent., 16 in status. Three of those dying in status were also found to have patchy broncho-pneumonia and one a spontaneous pneumothorax at post mortem. There can therefore be no doubt that a previous history of status, particularly if this occurs repeatedly, materially reduces the patient’s expectation of life and it is in these cases that long-term treatment with corticoid substances is justifiable. Another feature noticed in those cases who died was the high incidence of infection (85 per cent.).

Summary

An attempt has been made to survey the present position of asthma and to distinguish as far as possible the known facts from conjecture.

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prophylaxis. This involves minimal exposure to infections, air pollution and adverse climatic factors. Medicinal measures designed to reduce excessive mucus are very disappointing. Inhalations of friars balsam, menthol and eucalyptus sometimes ease expectoration; aerosol trypsin, although expensive, reduces viscosity and often gives temporary relief. The effectiveness of the so-called expectorant mixtures must not be underestimated in long-term management.

**Bronchospasm**

This complication is very difficult to eradicate once it has become established. The greatest benefit is likely to be derived from prophylaxis. Ephedrine is a remarkably good drug for short periods, particularly if it is taken intermittently. Aminophylline is another favourite, but has the disadvantage that it is most likely to afford relief when given parenterally or by suppository. Steroids are uncertain in their effect and their action in individual patients can only be determined by trial and error. Often a dose of 5 to 10 mg. of prednisone a day for a few weeks will tide a patient over a bad spell, but larger doses should be avoided if possible and long courses are undesirable.

**Emphysema**

In clinical terms, this is a disease of reduced effective alveolar surface and obstructed air flow. The best that treatment can offer is to counteract these mechanical disadvantages. For this purpose special breathing exercises have been devised which aim to reduce muscular rigidity, increase skeletal suppleness and to promote controlled respiration. Untreated emphysematous patients usually rely to a large extent upon the muscles of their neck and the upper intercostal muscles for respiration. The exercises encourage lateral expansion of the lower ribs and diaphragmatic breathing, thus allowing patients to maintain their tidal air with much less effort. Most of these patients are benefited by these exercises, and some to a remarkable degree.

**Conclusion**

In conclusion, chronic bronchitis offers a formidable medical problem. It is responsible for roughly 7 per cent. of all deaths in Britain and 7 per cent. of sickness absence from all causes. Undoubtedly infection and air pollution contribute to its development. If these could be reduced, less attention would need to be paid to the rather ineffective curative measures at present available.