ASTHMA — A NEW LOOK AT AN OLD DISEASE

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Historical outline

Asthma has attracted a great deal of attention over the centuries probably because its clinical manifestations of breathlessness and wheezing present themselves in such a dramatic manner. The word asthma is derived directly from the Greek asthma — meaning a hard drawn breath or panting. The first clinical description is attributed to Aretaeus the Cappadocian who, emphasizing the plight of the asthmatic patient, wrote: 'they eagerly go into the open air, since no house sufficeth for their respiration'.

In the early 17th century, van Helmont, himself an asthmatic, provided us with what is thought to be the first reference of allergy being involved in the aetiology of asthma. He has given us a vivid description of a monk who had attacks, 'as oft as any place is swept, or the Wind doth otherwise stir up the Dust'. This poor monk must have had quite a rough time, especially on Fridays, for van Helmont also describes him as having attacks when "he eateth Fishes fried with Oyl'. To van Helmont should be given the credit for being the first to point out that asthma resulted from "a drawing together of the smallest terminal bronchi" an observation which has given rise to endless controversy ever since. We owe the modern concept of asthma to T. Willis, perhaps better remembered for his famous circle. Willis,

says of asthma, 'there is scarce anything more sharp or terrible than the fits thereof'. He describes two forms of asthma; pneumonic and convulsive; he associated the former with "obstruction of the bronchi by thick humors, swelling of their walls and obstruction from without" and believed convulsive asthma to be due "to cramps of the moving fibres of the bronchi'. In 1698, Sir John Floyer, who like van Helmont was an asthmatic, published his classical book on asthma. He adopted Willis's classification, calling convulsive asthma: periodic, and pneumonic asthma: continued, and assigned as a cause for the paroxysms "a contracture of the muscular fibres of the bronchi".

For a long time asthma was considered to be a disease of moderate morbidity and negligible mortality. Indeed, Oliver Wendell Holmes is quoted in Osler's book as calling asthma "the slight ailment that promotes longevity" and the French physician Armand Trousseau called it "le brevet de longue vie". Until Huber & Koessler's paper in 1922, it had been claimed that death did not occur in the asthmatic paroxysm. Although the dangers of asthma are now fully appreciated, it is disturbing to come across statements in the literature such as "Bronchial asthma alone rarely causes death. When it does prove fatal it is due either to the concurrent bronchitis and bronchiolitis or to heart failure". (Spencer, 1968).

Between 1959 and 1966 a steady rise in mortality from asthma was observed in England and Wales, the increase being more pronounced between ages 5 — 34 years. Speizer and his co-workers (1968) showed that the rise was real and not due to a change in diagnostic methods or registration of cause of death. They subsequently examined the possible reasons and concluded that the increase in mortality was most likely to be due to changes in treatment. Sympathomimetic aerosols and corticosteroids were the only drugs to have been used by a large proportion of the patients who died. The use of corticosteroids, which had been introduced in 1951, did not seem to be related to the cause of death, and sympathomimetic aerosols, introduced in 1961, were incriminated. Following the publicity given to the possible dangers of excessive inhalation, there was a drop in sales which has been paralleled by a downward trend in the reported number of deaths due to asthma (Fraser *et al*, 1971).

Several mechanisms whereby sympathomimetic aerosols might be responsible for the increase in the asthma death rate have been suggested. The induction of fatal cardiac arrythmias by sympathomimetic drugs, especially in the hypoxic state, is one of the explanations given by a number of workers, amongst whom Lockett (1965); Greenberg & Pines (1967) and Collins *et al*, (1969). Bass, in 1970 blamed the fluorocarbons, used as propellent agents in the aerosols, for producing arrythmias. More recently, Conolly and his co-workers (1971), have claimed that prolonged administration of these bronchodilators might result in resistance being developed not only to the sympathomimetic drugs themselves but also to endogenous sympathetic stimulation. They suggest that this could have led to the deterioration, and finally to death, in asthmatic patients using sympathomimetic aerosols.

Aetiology and Pathogenesis

Asthma, which may best be regarded as a complex functional state which can be triggered off by a wide variety of agents, still presents a great number of difficult problems and there are far more questions to be asked than answers to be given. Although there have been several attempts at defining this condition — Ciba Guest Symposium 1959; American Thoracic Society, 1962; Scadding, 1969 — there is still no agreement between clinicians, respiratory physiologists, immunologists and pharmacologists on a final definition, as evidenced by a report of the Working Group on the Definition of Asthma, published in 1971.

The aetiology and precise pathogenesis of bronchial asthma are still uncertain although a great deal of evidence is now forthcoming about the various factors that are capable of triggering off an attack. The relative importance of a genetic predisposition, enviromental allergens, im-

munological mechanisms, infection and emotional factors, in determining the different patterns of the disease is far from clear.

(i) Hereditary factors.

As early as 1916 Cooke and Van der Veer stressed the hereditary nature of allergic diseases. Williams and Williams in 1949 found that about 50% of the asthmatic patients gave a history of allergy in close relatives. Leigh and Marley in 1967 found that about 40% of first degree relatives of patients with asthma developed the disease by the age of 65 years. Rajka (1960) pointed out that what may be inherited is not the allergic manifestation but the allergic disposition. Although it has been suggested that atopy is determined by a single, autosomal, dominant gene with reduced penetrance, the exact genetic factor and the mode of inheritance are still far from certain, and although the clinical evidence of inheritance of atopic diseases is often very suggestive, the evidence is not as conclusive as it is sometimes made out to be.

(ii) Immunological aspects.

Bronchial asthma is often very broadly classified into two major sub-divisions, 'extrinsic' and 'intrinsic'. In extrinsic asthma, an external allergen can be demonstrated, the age of onset is usually early and a Type I (Gell and Coombs, 1968) immediate allergic reaction is generally the cause. The term intrinsic asthma was applied by Rackemann in 1947 to describe a group of patients in whom no external allergen could be shown (prick tests being negative to a wide range of antigens) and whose symptoms begin in adult life.

The type of hypersensitivity most commonly encountered in extrinsic asthma is that due to a Type I immediate reaction. In Type I allergy the antibody responsible for mediating the release of pharmacological factors responsible for this kind of asthma was originally termed "reagin" by Coca and Grove in 1925. Reagin has recently been shown to belong to a separate class of immunogolobulin (Ishizaka *et al*, 1966; Johansson, 1967) and is now termed IgE, (WHO, 1968). IgE is present in very small quantities in normal individuals, but levels of over 700 ng/ml, representing a 6 fold increase, were found in 63% of a series of patients with extrinsic allergic asthma by Johansson, in 1967. There are innumerable allergens that have been implicated in IgE mediated asthma. They include such commonly encountered substances in the environment as pollens, animal dander and fur, and the house dust mite, described by Voorhorst *et al* in 1964.

Besides the well established evidence for the role of immediate Type I allergy in asthma, it now seems probable that the disease may also be initiated by hypersensitivity mechanisms which do not involve reagin. Pepys in 1972 subdivided extrinsic asthma into atopic and non-atopic types. He has shown that precipitating, heat stable antibodies, which are complement dependent and known to be important in Type III reactions, may play a part in asthma developing slowly over several hours, becoming maximal about 7 to 8 hours after allergen exposure. In this type of extrinsic, non-atopic asthma it is the particular environmental exposure which is of primary importance, whereas in the Type I group it is the subject's constitution which is so. Late asthma of this tpe has been associated with *Aspergillus fumigatus* infection and has also been shown in bird fanciers using avian protein extracts and in workers exposed to enzymes extracted *from Bacillus subtilis*. In certain circumstances, e.g. bronchopulmonary aspergillosis there may be a combination of Type I and Type III reaction. The patients when challenged with extracts of *Aspergillus fumigatus* develop immediate airway obstruction which rapidly resolves, only to recur after 4-5 hours, when it is more severe and persistent.

Intrinsic asthma remains a very obscure form of the disease. There is no evidence in this form of asthma of any history of extrinsic allergy or a Type I allergic reaction to skin or inhalation tests. IgE levels in this group have been reported to be either normal or low. Blood eosinophilia tends to be higher than in extrinsic type.

Another type of asthma that cannot

strictly be included in the above classification is Exercise induced asthma. In patients suffering from this form of the disease, an attack of dyspnoea and wheezing come on some time after the patient has performed some kind of strenuous exercise. No satisfactory explanation is as yet available for this form of asthma.

(iii) Pharmacological mediators.

In man, definite evidence is now available that histamine, slow reacting substance of anaphylaxis (SRS-A) and a third factor, eosinophil chemotactic-factor (ECF-A) described recently, (Kay and Austen, 1971) are pharmacological mediators associated with asthma. Up to now, no reports on the release of kallikrein, bradykinin or 5-hydroxytryptamine from antigen-stimulated sensitized human tissue have been published; this is also true of the prostaglandins, E_1, E_2 and $F_2\alpha$.

Histamine was shown to be released by an antigen-antibody reaction from human isolated lung by Schild *et al.* in 1951. There is still a great deal of controversy regarding blood histamine levels in asthma. Porter & Mitchell (1970) have recently reported blood histamine levels, in asthmatic children which were significantly higher than in a control group. These levels fell to near normal in the asymptomatic period and during long-term steroid treatment. The significance of histidine decarboxylase, the enzyme involved in the formation of histamine is still not sufficiently appreciated. It is known however that its activity can be very quickly increased as a result of stress and it is conceivable that this might well be one of the mechanisms involved in the triggering off of asthma during periods of particular stress.

There is a great deal of indirect evidence indicating that SRS-A has a role to play in asthma, (Brocklehurst, 1960) although the importance of such a role has not as yet been definitely evaluated. It is known that the contraction due to SRS-A is very long lasting, much more than that produced by histamine. All the evidence at present available seems to indicate that SRS-A is formed by enzymic processes activated by the union of antigen with reaginic antibody, whereas histamine is released from a pre-formed store. (Brocklehurst, 1970)

(iv) Non-Immunological mechanisms.

In addition to the immunological aspects of asthma it has been suggested that this condition may also be due to a functional imbalance of the autonomic nervous system, a hypothesis first put forward by Eppinger and Hess in 1917. An important advance in the study of the autonomic nervous system was made by Ahlquist in 1948 who first suggested that the different pharmacological effects of adrenergic drugs on smooth muscle could be accounted for if one accepted the existence of two sets of receptors, which he designated alhpa and beta, in or near the target organs affected by these substances. Beta adrenergic action, as produced for example by isoprenaline, is associated with bronchial smooth muscle relaxation, myocardial stimulation and peripheral vasodilation. Stimulation of alpha receptors is claimed to cause bronchoconstriction. The beta receptors were further subdivided into the B_1 receptors which are concerned with the effects on the heart and the B_2 receptors which are mainly associated with bronchial smooth muscle relaxation, by a group of workers led by Lands, in 1967. It is now generally believed that the B receptor is an enzyme, adenyl cyclase. In 1968 Szentivanyi proposed the theory that the major cause of bronchial hypersensitivity in asthma was a partial beta-adrenergic blockade. This theory is supported by the results of McNeill (1964) who reported that propranolol, a B adrenergic receptor blocking drug, reduced the vital capacity in asthmatics and that this was not reversed by isoprenaline. Similar effects have been reported by Besterman and Friedlander (1965).

McDonald and his co-workers (1967) showed that the effect of propranolol on asthmatics could be largely prevented by atropine and hence the bronchoconstriction could be explained on the basis of unopposed vagal activity. Fleish *et al* in 1970 put forward the idea that the effect of beta

blockers could be ascribed to their unmasking alpha adrenergic receptor activity in bronchial smooth muscle.

(v) Respiratory infection.

Acute respiratory infections are often known to trigger off attacks in asthmatics. The cause of this altered reactivity is unknown. There is some evidence suggesting a role for microbial products in the development of bronchial hyperreactivity. Cooke (1947) reported attacks of asthma developing in asthmatic patients following injections of autogenous bacterial vaccine. Ouellette and Reed in 1965 noted that asthmatics were more sensitive to metacholine following an injection of killed influenza virus vaccine; normal subjects did not show this increase in sensitivity. Various microbial products are known to be able to release some of the pharmacological mediators of bronchoconstriction. The nature of such microbial activity is not known but it is presumed to be a non-immunological direct effect on such cells as the mast cells (Szentivanyi, 1971).

(vi) Psychological factors.

It has been a long standing clinical observation that emotional factors and stress frequently precipitate attacks of wheezing in some asthmatic patients. Dekker and Green in 1956 showed that attacks of asthma could be regularly produced in some of their asthmatic patients through inducing anxiety by discussing with them emotionally charged situations derived from their case histories. In 1970, Zealley *et al*, investigating psychopathology in asthmatics concluded that traits of sensitivity, anxiety, obsession, dependency and low self confidence were commoner in these patients than in normal controls. They pointed out however, that psychopathology need not be implicated as the cause of the asthmatic diathesis; it is as likely that concomitant psychopathology only determines the clinical presentation. It thus appears likely that these various factors contribute to a different degree and in a different manner in various patients and act upon some final common path resulting in the clinical picture that is so well known.

Pathology

Most of the knowledge at present available about the pathology of asthma has been obtained from lungs of patients dying in status asthmaticus. Little is known about the pathology of the less severe forms of asthma. However, important information has also been yielded from bronchial biopsy material and sputum studies. One need hardly describe the gross aspects but at post mortem there are two striking features. The lungs often appear over-distended and fail to collapse and Gough (1955) likened them to the lungs in a case of fresh water drowning. The other outstanding finding in any section of an asthmatic lung is the presence of a dense exudation in the bronchial lumen. A detailed description of the changes present in the bronchial mucosa of patients dying in status asthmaticus has been given by Dunnill (1960). Salvato (1959, 1968) biopsied the bronchial wall of asthmatic patients before and during an asthmatic attack and found significantly lower mast cell counts in biopsy material removed from patients during an episode of asthma than in biopsy material obtained from the same patients during the asymptomatic phase of the disease. His findings were corroborated by the work of Connell (1971). It is suggested that the paucity of the mast cells is almost certainly due to the fact that they are degranulated, and degranulated mast cells cannot be identified in tissue sections. It is well known that degranulation of mast cells occurs following anaphylaxis with the liberation of such biologically active substances as histamine, heparin and most probably SRS-A. It seems likely that mast cell degranulation in asthma has the same functional significance.

Connell (1971) also observed an inverse relationship between the eosinophilic infiltrate present in asthma and the mast cell content of the bronchial wall; the greater the number of eosinophils, the fewer the number of mast cells. It is tempting to infer that in asthma the tissue eosinophilia is secondary to massive

degranulation of mast cells; it is known for instance that eosinophils appear in mastocytomas only when there is disruption of mast cells (West, 1959). Although it has been demonstrated that eosinophils are capable of phagocytosing antigen-antibody complexes, little is actually known of their action in asthma, (Hansinger *et al,* 1972) or of the inter-relationships between eosinophils and mast cells in this condition.

One other striking feature in the pathology of asthma is the presence of marked hypertrophy of the bronchial muscle which was first described by Huber & Koessler in 1922. Dunnill *et al,* in 1969 found that 12% of the segmental bronchial wall was occupied by smooth muscle in cases of status asthmaticus compared with 4.6% in normals. The relative importance of bronchial muscle hypertrophy and muscle contraction, mucosal oedema and congestion, increased mucus secretion and the obstruction of small bronchioles by tenacious mucus plugs in the pathogenesis of bronchial asthma is still a matter of some controversy (Ellul-Micallef, 1973). But although "bronchospasm" has long been regarded as an important if not the main, component of bronchial obstruction in asthma, there has been little direct proof of this. Frankland (1968) rightly makes a plea for the word "bronchospasm" not to be used in reference to asthma as its use would seem to indicate a precise knowledge of the pathogenesis of asthma which at present we do not have. The dominant role of smooth muscle contraction in the pathogenesis of asthma is now being questioned by various workers, as the importance of mucosal oedema, increased mucus secretion and blocking of peripheral airways by tenacious mucus plugs is becoming increasingly more recognised. Dunnill (1960, 1969) speculated that the smooth muscle hyperthrophy found in asthmatic lungs, where ciliary action is often defective, was a response to increased clearance of exudate, possibly by a milking action; as suggested in the cineradiographic study of Holden & Aradran (1957).

It seems probable that in the earlier stages of an attack active broncho constriction is the major factor, since dramatic relief is often obtained with sympathomimetic drugs, but when an acute attack becomes protracted or the condition becomes more chronic, the situation is complicated by mucosal oedema and by retention of very viscid mucus.

Since it was established that corticosteroid therapy is frequently of benefit in asthma, it has been tempting to postulate that failure of the adrenal cortex may be an underlying defect in some patients. Recently there have been reports of asthma occurring in patients with Addison's disease and in one of these asthma appeared to be the presenting symptom of adrenal insufficiency (Green and Lim, 1971, Harris and Collins, 1971). The infrequency of asthma in Addison's disease, variously reported as 0.5% (Maranon *et al,* 1956) and 4% (Carryer, 1960), however make the proposition most unlikely. Several papers on adrenal function in asthma have been published, some reporting inadequate basal function or inadequate response to stress and others finding no evidence at all of such dysfunction. Reviewing the evidence at present available in the literature, it seems fair to state that it appears that dysfunction of the hypothalamic-pituitary-adrenal axis is not a necessary predisposing factor for the development of asthma. But one cannot exlude the possibility that it may well be a conditioning factor in some patients, although the relative infrequent occurrence of atopic diseases in patients with Addison's disease lends little support to this conjecture.

Altered pulmonary function in asthma

Increased airway resistance (Raw) may be said to be the physiological hallmark of bronchial asthma. This increase in resistance to the flow of air is well reflected in the physiological indices used as tests in its detection and monitoring. In general the forced expiratory volume in one second (FEV_1) and the maximum mid-expiratory flow rate (MMFR) and peak expiratory flow rate (PEFR) are found to be consistently decreased from the predicted and are usually well related to the severity of symptoms. The ratio of the

FEV_1/FVC is also found to be reduced. However, it is now recognised that subjective improvement is not always necessarily reflected in a similar change in the tests mentioned above. Raw as measured by body plethysmography provides a direct measurement of the resistance to the flow of air. Various studies using plethysmography have been carried out in asthmatic patients both during the symptomatic phase as well as following therapy. The Raw is always increased, frequently very considerably and the specific conductance (SGaw), that is, the conductance divided by the thoracic gas volume at which Raw is measured, correspondingly decreased during the acute phase, both indices returning towards normal values as the patient's condition improves (Pelzer and Thomson, 1969, Ellul-Micallef *et al*, 1972). An increased airway resistance has been found to be present even during the asymptomatic phase in some asthmatics. (Bernstein & Kreindler, 1963).

A number of reports have appeared in which measurements of total lung capacity (T.L.C.), functional residual capacity (F.R.C.) and residual volume (R.V.) in asthmatics were found to be elevated, thus reflecting the presence of a certain degree of hyperinflation. In general, the more severe the degree of airway obstruction the greater the amount of hyperinflation present, as shown by an elevated R.V. and F.R.C. and both indices tend to decrease following treatment. In some of the patients reported on by Woolcock & Read (1965) the F.R.C. during acute asthma was greater than the T.L.C. after recovery. In these patients tidal breathing during severe obstruction was taking place at a higher level than the point of maximal inspiration after recovery. Mead, Milic-Emili & Turner (1963) hold the view that inhibiting reflexes normally limit the degree of voluntary lung inflation; it this is true, then one must presume that such reflexes are modified in asthma. The vital capacity is generally decreased in asthma and is usually more severely diminished the greater the degree of airway obstruction. Such a decrease in vital capacity not infrequently persists in the asymptomatic phase. Hyperinflation is not only present in the acute phase of the disease. Lung volumes have also been reported to be elevated in chronic asthma, returning towards predicted normal values following corticosteroid therapy (Ellul-Micallef *et al*, 1971).

The increase in F.R.C. may be compensatory to the decreased bronchial calibre found in asthma, and to a certain extent this may have a guy-rope effect in maintaining the patency of the airways. This, however, is not obtained without considerable cost to the patient, for as the lung volume increases, compliance diminishes progressively so that the further inspiration of a given volume of air will require the production of a higher transpulmonary pressure difference because the subject is breathing on a flatter part of the pressure-volume curve.

Various workers amongst whom are Gold *et al* (1967), Woolcock & Read (1968) and Finucane and Colebatch (1969) have reported a reduction in the lung elastic recoil pressure in asthmatics both during exacerbations as well as in asymptomatic phases. The cause of the loss of elastic recoil of the lungs in asthma is unknown. The lung elastic recoil pressure is dependent on two factors: the tension exerted by surfactant and the elastic properties of pulmonary tissue. In emphysema the fibre network making up the pulmonary tissue is disrupted and elastic retraction of the lung would be expected to be, and is, in fact, reduced. In asthma however, this network is intact and hence other factors must be responsible for the loss of elastic recoil. It has been suggested that prolonged distension of the connective tissue of the lungs causing temporary structural deformation is a possible explanation. Another alternative that has been put forward is that the change could be related to the forces exerted by surfactant. There is however very little evidence to support either possibility.

One other parameter that is causing a lot of controversy in asthma is the pulmonary diffusing capacity. (Tco) Over the past five years a number of papers have appeared in which this has been found to

be decreased (Palmer and Diament, 1969, 1970; Levine *et al*, 1970). Results by equally reliable workers have shown the Tco to be remarkably normal (McFadden & Lyons, 1968; Daly, 1971). The difficulty in sorting out the apparent discrepancy of the diffusion capacity values in asthma obtained by various workers can be ascribed to three main factors: patient selection, variation in degree of airway obstruction and differences in technique. Thus there is not infrequently difficulty when selecting patients, in differentiating between those suffering from asthma and those with chronic bronchitis with a degree of emphysema. However, the interpretation of reports of Tco in asthma is perhaps most seriously hampered by the variety of methods used in its determination. It is obvious that each method measures something different and probably none measures the true diffusing capacity of the 'pulmonary membrane'. The transfer of gas in asthma thus appears to be more impeded by failure to deliver inspired gas to the alveolar surface than by interference with diffusion through the 'pulmonary membrane' as happens in pulmonary fibrosis or emphysema.

Very little attention was paid to changes that occur in blood gases during asthma until comparatively recently. Bates and Christie in 1964 stated that "the patient with moderately severe bronchospasm but not in status asthamaticus only rarely shows any significant abnormality of arterial oxygen saturation of CO_2 tension". It had been generally assumed that the $PaCO_2$ is usually normal or low, due to hyper ventilation, until the terminal stages of status asthmaticus, when the $PaCO_2$ rises rapidly and respiratory failure supervenes. Tai and Read in 1967 were the first to report CO_2 retention with $PaCO_2$ values ranging up to 200 mmHg and marked respiratory acidosis with a blood pH as low as 6.81, in twelve patients in status asthmaticus admitted to their care. Their data showed that in other patients with only moderate clinical severity considerable hypoxaemia could also be present. Similar results have now been reported by a number of different workers. They found a general correlation between the degree of reduction of the FEV_1 and the extent of disturbance of blood gas tensions in patients with moderately severe asthma. They pointed out that FEV_1 levels of less than 1 litre were especially associated with a significant reduction of arterial PO_2; at the same time they emphasized that the correlation was not good enough to make FEV_1 levels greater than a litre a reliable index of a fairly normal PaO_2. The same conclusion was reached by Rees *et al* in 1968, who stated that since increases in FEV_1 were not always accompanied by a rise in PaO_2, such changes could not be relied upon to indicate improved oxygenation. Rees, Millar & Donald in 1968, followed the clinical course and arterial blood gas tensions of 24 patients in status asthmaticus and found that hypoxaemia was invariably present, was frequently quite marked and persisted despite intensive therapy sometimes for weeks. Most patients were normocapnic or even hypocapnic. When severe hypercapnia was present the patients generally died. They found that the pulse rate correlated well with PaO_2 and in the severely hypoxaemic patients the frequency exceeded 130 beats/min. It is now generally accepted that hypoxaemia, often of a dangerous degree, may be present in asthmatic patients, and that severe hypercapnia is not usually present except terminally. When the $PaCO_2$ is high this is usually of grave prognostic significance. The accompanying disturbance in acid-base balance as reflected in the arterial blood, shows that hypercapnia in most of these patients probably develops acutely. Chronic elevation of $PaCO_2$ is relatively uncommon in asthma — the converse of what occurs in chronic bronchitis.

The increased renal reabsorption of bicarbonate which is an important defence against respiratory acidosis both in adults and in children thus appears to be too slow a mechanism to be of great importance in acute asthma, in which dangerous hypercapnia may develop very acutely. Mithoefer *et al* (1968) have found that correction of the respiratory acidosis by infusion of sodium bicarbonate was valuable in treat-

ing intractable asthma, but others seem to have had less success with this approach (Flenley, 1971). The mechanism of hypoxaemia with or without CO_2 retention implies a maldistribution of ventilation and perfusion in the lungs which is shown by an elevated alveolar to arterial oxygen tension difference, (A-a)DO_2, and higher than normal dead space-tidal volume ratios (VD/VT). Elevated values for (A-a)DO_2 and VD/VT have now been shown to be present both during the acute attack (Field, 1967), in chronic asthma (Ellul-Micallef, 1972) as well as during the asymptomatic phase (Levine *et al*, 1970).

Conclusion

Although no agreement has yet been reached on a final definition of asthma, (Working Group on the Definition of Asthma, 1971) none would contest that the main pathophysiological hallmark of this disease is an increase in airway resistance to the flow of air due to widespread narrowing of the airways. The actual site of such narrowing is still a matter of some controversy (Ellul-Micallef, 1972b, Bainbridge *et al*, 1973). Hyperinflation frequently occurs and it has now become widely recognized that this may be present when the more common spirometric indices used for detecting airway narrowing are normal, indicating an attempt on the part of the asthmatic patient to overcome the obstruction present by breathing at a higher lung volume. Further research is necessary to elucidate the precise nature of the changes in lung elastic recoil and transfer factor that have been reported in asthma. Blood gas changes in this disease, often of a severe nature, are now an established fact and appear to be mainly due to V^A/Q abnormalities. The aetiology and pathogenesis of this condition as has been shown is still far from clear and a lot of wor kstill remains to be done to try and unravel this problem. Bearing all this in mind it is perhaps not surprising that treatment for asthma is anything but satisfactory, even in centres which have been specifically set up to deal with it.

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