Introduction

In 1975 Sandra Anderson, Michael Silverman, Peter König and Simon Godfrey, working at the (then) Institute of Diseases of the Chest at the (then) Brompton Hospital in London published a review of exercise-induced asthma (EIA) in the (then) British Journal of Diseases of the Chest. Eighteen years have now passed and the original team has scattered to the four corners of the earth. Much has changed, including the names of our beloved Brompton Hospital, the Institute and this journal, but interest in EIA remains as keen as ever. From Israel where the present authors now work, approximately midway between the U.K., U.S.A. and Australia where the others work, we thought of taking out the old review and looking again at the issues we raised in the light of what has been learned since. One simple index of the continuing interest in the subject is the fact that our own, very personal collection of highly selected, directly relevant references from the literature increases by 20 or 30 articles per year. While we acknowledge the immense contribution of all those investigators whose work we quoted in the 1975 review (1), we shall only refer directly to the most relevant earlier papers in this update.

History

Even with the limitation given above it is never the less interesting to look again at the earlier historical review and see to what extent some of the older theories have shown to be true in the light of more recent studies. It now seems likely, but not certain, that Sir John Floyer (2) was not correct when he wrote in the 17th century that different forms of exercise caused different amounts of EIA, at least as far as equally intense forms of exercise are concerned, performed under identical conditions. However, he did suggest that the mechanism of EIA was related to ‘putting the Spirits to a great expansion’ or making the ‘blood boil’. At this very moment there is a heated argument as to the mechanism of EIA and the school headed by Dr Regis McFadden (3) would most certainly agree with these statements of Sir John’s that vascular phenomena in the lung are of great importance in the pathogenesis of EIA. In our original review (1) we noted but rather dismissed the work of Herxheimer (4) who, in 1946, was probably the first to make objective studies of EIA and suggested that it was the hyperventilation of exercise which caused the attack. Since then we have learned that he was almost certainly correct in assigning a central role to hyperventilation although it does not explain all the features associated with EIA.

Many of the other historical observations and more modern studies, including our own, which appeared in the review have now either been shown to be incorrect or have been considerably modified. The present review will therefore concentrate on the important changes which have occurred since then in our knowledge of this subject.

Pattern of Lung Function Changes in EIA and HIA

The changes in lung function which occur in response to approximately 6 min of reasonably hard exercise are quite characteristic and are illustrated in Fig. 1. During most of the actual period of exercise lung function changes little or may even improve somewhat. Towards the end of the exercise period lung function may begin to deteriorate and in some patients this fall can be quite marked, even during the exercise. The major fall in lung function normally occurs 5–10 min after stopping the exercise after which lung function normally returns spontaneously to baseline over 30–45 min. Of interest are the recent findings which showed a dichotomous response of the airways to exercise (5–7) where the upper airways dilate concomitantly with central and peripheral
bronchoconstriction. However, the net result in the asthmatic is an increase in airway resistance.

Given the similarity between EIA and the early phase of allergen induced asthma it was always puzzling that late phase responses were not seen after EIA. There have now been a number of very carefully controlled studies which have shown an incidence of late phase reactions after EIA of between 10 and 38% (8–10). In the study of Speelberg et al. (9), of the 86 patients challenged 27 developed an early response only, seven a late response only, and 26 had a dual early and late phase response. Other investigators have not, however, obtained such definite results or even denied the existence of a late phase reaction (11–13). On the whole, the bulk of evidence seems to support the existence of a late phase reaction in a small proportion of asthmatics, possibly those with greater responsiveness (14,15).

Although this review is concerned chiefly with EIA, the importance of the hyperventilation during exercise in the pathogenesis of EIA and the many similarities (and differences) between EIA and hyperventilation induced asthma (HIA) means that HIA must also receive some attention. The overall pattern and time course of HIA generally resembles EIA. The early bronchodilatation which is often seen during the exercise period also occurs during hyperventilation (16–19), but the existence of a late phase reaction after HIA is even less certain (13).

**Incidence of EIA in Normal Subjects and Asthmatics**

At the time of our previous review we found that the upper limit of the post-exercise fall in lung function expressed as a percentage of the baseline pre-exercise value was 9–10%, this being the mean $+2\sigma$ of the change in the peak expiratory flow rate (PEFR). At that time there were no good data using other indices of lung function nor studies which took account of the influence of climate and other factors on the severity of EIA. In a recent study (20) we found the mean $+2\sigma$ of the fall in FEV$_1$ in 19 normal children under controlled laboratory conditions to be 8.2%. As far as the incidence of EIA in asthmatics is concerned, it is clear that this is influenced by the severity of the asthma in the population being studied (21) and by factors such as seasonal allergy which influence bronchial responsiveness (22). With random testing of asthmatics of average severity attending an asthma clinic it appears that about 70–80% will develop a fall in FEV$_1$ which is outside the normal range (20,21,23). However, random testing of asthmatics in the community (see below) will yield fewer positive results because there will be many more very mild asthmatics amongst them.

The sensitivity and specificity of exercise testing in asthma has been addressed in a number of studies but it must be pointed out that the results are influenced by the choice of the population studied and the choice of the cut-off point for accepting the test as positive.
When attempting to answer the question as to the value of exercise testing for asthma in epidemiological studies it is essential to study a randomly selected population and to use a meaningful cut-off – ideally in our view a fall in lung function of greater than say the 95th percentile or 2 SD above the mean fall of a totally normal (non-asthmatic) population. Such studies have been undertaken in children by Burr and his colleagues (24,25) in large numbers of children using peak flow measurements and by Backer (26) albeit using FEV₁ with a rather lower cut-off. The results were quite similar giving an average sensitivity (asthmatics with positive test/all asthmatics in population) of 56% and a specificity (non-asthmatics with a negative test/all non-asthmatics) of 93%. However, the positive predictive value of an exercise test (the likelihood of a subject with a positive test having asthma) was only about 40% since some non-asthmatics respond to exercise and in a whole population there are far more non-asthmatics than asthmatics. Interestingly, the results from equivalent studies using inhaled methacholine or histamine as the challenge (27,28) yield almost identical figures for average sensitivity (55%), specificity (94%) and positive predictive value (53%). Many other studies have compared selected groups of asthmatics with various control groups or with atopic subjects and these are of limited value epidemiologically. In another approach we compared asthmatic children with children who had other types of chronic lung disease and used a normal control group to define the range of normality (20). In this study the sensitivity of exercise testing (79%) was a little lower than that for methacholine (94%) but its specificity was far greater (100% vs. 18%). This suggests that while exercise testing is of relatively little value in population studies aimed at finding the incidence of asthma, it is very useful in differentiating asthma from other types of chronic lung disease including those with bronchial hyperreactivity to methacholine.

**Factors Affecting the Severity of EIA**

Eighteen years ago we believed that the severity and duration of exercise influenced the severity of the post exertional EIA and, like Sir John Floyer (2), we believed that different types of exercise also affected the severity of EIA. More specifically, we knew that EIA was minimal with swimming under normal conditions even if the severity and duration of exercise was similar to that with running (29). All this was a great puzzle, especially to exercise physiologists which we considered ourselves to be. As so often happens, this enigma was to lead to some very important advances in our understanding of both EIA and the physiology of respiration in general.

**The Effect of the Climate of the Air Breathed**

In a number of important studies it has been noted that the severity of EIA is greatly influenced by the climate of the air breathed (30–32). Breathing warm, humid air virtually abolishes EIA while breathing cold, dry air increases its intensity. Breathing dry air leads to drying and cooling of the airway mucosa as the water evaporates from the surface and this cooling is accentuated if the dry air is also cold. The cooling was first demonstrated by recording temperature change in the esophagus (33) and later by direct recording within the airways (34,35). For a given level of ventilation similar losses of heat and water occur whether the challenge is exercise or isocapnic hyperventilation provided they are carried out under identical climatic conditions.

Cooling, or more probably drying, of the airways could explain the differences between swimming, in which the subject breathes relatively humid air and running, in which under normal laboratory conditions, the air is relatively dry. Realizing the fundamental importance of this phenomenon in the pathogenesis of EIA, Dr Sandra Anderson and her colleagues began to investigate the possibility that it was the changes in osmolarity of the fluid lining the airways which was the triggering event in EIA (36). They showed that asthma closely resembling EIA could be provoked by inhaling hypotonic or hypertonic salt solutions (37). When delivered through an ultrasonic nebulizer, quite small quantities of such solutions provoke attacks of asthma in a dose–response fashion. Moreover, with osmotically induced asthma (OIA) as with both EIA and HIA, there is a refractory period after the challenge during which the subject is less responsive to another challenge and there is protection from all three types of challenge by the prior administration of sodium cromoglycate (38,39). Careful inspection of the earlier data relating the severity of induced asthma to the temperature of the air breathed showed that there could be very wide fluctuations of temperature with relatively little difference in the severity of the asthma provided the water loss was similar (40). There has been some argument as to where the evaporation takes place within the airway and whether or not the volume of fluid available could prevent any significant change in osmolarity (36,40,41). However, Dr Anderson and her colleagues (40) have produced compelling evidence to suggest that drying of the mucosa would take place over the most relevant generations of airways as shown in Fig. 2.
Recent animal experiments involving the perfusion and ventilation of isolated lung lobes with gases and blood of different temperatures lend some support to the concept that the climatic effect operates primarily through water exchange (42). In these studies, cooling of the lobe by ventilation increased resistance but not cooling by perfusion with cool blood. If both were cooled then resistance did not increase because there was no loss of water from the (cool) blood to the (cool) gas. In this latter situation the lung was, of course, cold and the resistance should have increased had cooling been the important stimulus.

However, the osmolarity hypothesis cannot entirely account for the triggering of EIA and HIA. Were it the only factor involved, then neither exercise nor hyperventilation should be able to provoke an attack of asthma under conditions in which cooling and drying of the airway is prevented. Normally when patients breathe warm, humid air at body temperature and humidity they develop little if any EIA. However, there is the occasional patient who does develop EIA under these conditions (43). In the study of Anderson and her colleagues (44) 14/24 patients developed a greater than 10% fall (mean 20%) in FEV₁ after exercising breathing air conditioned to body temperature and humidity. If heat and water loss from the airways are held constant, then the severity of EIA should be constant whatever the severity of the exercise. To study this idea we exercised a group of children at two levels of exercise while the amount of heat and water loss from the airways was kept constant by varying the conditions of the inspired air (45). Thus during the lesser work load they breathed cooler, dry air while at the harder work load they breathed warmer, more humid air. As can be seen from Fig. 3 there was almost twice as much asthma after the harder exercise challenge as compared with the less strenuous challenge even though the heat and water losses were virtually identical.

These apparent paradoxes could be explained by the observations that the inhalation of not only hypertonic solutions but also hypotonic solutions also provoke asthma (37). Aitken et al. (46) undertook isocapnic hyperventilation studies with subjects breathing air of different temperatures and humidities and showed that HIA was least (16-6% fall) when air at body conditions was breathed but increased under conditions in which water (and heat) was either removed or added to the airway. During hyperventilation or exercise under normal climatic conditions some water and heat is lost from the airway, and preventing this by breathing warm humid air could result in a hypotonic stimulus. Keeping the heat and water loss constant but varying the exercise or hyperventilation load could well mean that the drying affected different generations of airway as the flow profiles of ventilation changed. Thus both EIA breathing air at body conditions and different quantities of EIA for the same heat and water loss but different exercise levels are both compatible with the trigger being a change in osmolarity in the airways.

There is, however, still the possibility that the nature of the exercise itself has an independent effect. When we arranged for children to swim breathing dry air they developed more EIA than when swimming breathing humid air from the pool surface as expected but they still developed significantly less EIA than they did after running breathing dry air (47).

### The Allergic Environment and Air Pollution

Another important factor which has been shown to influence the severity of EIA is the overall level of bronchial reactivity of the subject. It is well established that non-specific bronchial reactivity to histamine can be markedly increased for several days or weeks following a specific bronchial provocation challenge with allergen (48). Equally, removal of an individual from an environment in which he is exposed to allergens to which he is sensitive reduces non-specific reactivity to histamine (49). To see if this also applied to exercise we undertook exercise challenges in asthmatic children on the day before and during the week after specific allergen bronchial provocation tests (22). There was a clear cut increase in the response to the same level of exercise with the fall in FEV₁, almost doubling. This was true whether or not there was both an early and late reaction to the allergen but, as has been documented before, histamine responsiveness in our study only increased in those children with
both early and late reactions. From these observations it is to be expected that the severity of EIA will vary from time, even for the same severity of stimulus and climatic conditions, depending upon the recent exposure of the patient to relevant allergens. Air pollution, simulated in the laboratory by adding small amounts of sulphur dioxide to the air, has also been shown to considerably enhance EIA (50) further complicating the prediction of the severity of EIA under conditions of natural exposure.

Pathophysiology of EIA

In our earlier review (1) we discussed what was then known about the mechanism of EIA but reached the conclusion that 'As yet we have no real evidence of the triggering mechanism. Any future hypothesis must take account of the differing degrees of airway narrowing resulting from different types of isometabolic exercise'. One of the problems in previous attempts to unravel the pathophysiology of EIA has been the failure to clearly distinguish between the three phases of any physiological reaction, namely the trigger, the intermediary pathway and the effector mechanism.

The Trigger Mechanism for EIA

It is almost certain that a change in the osmolarity of the lining fluid of the larger central airways brought about as a result of the heating and humidification of inspired air is the major triggering event (40). It is still not certain that exercise and hyperventilation provide identical triggers nor is it certain to what extent the nature of the exercise itself and the pattern of breathing contribute to the stimulus. While we are much more knowledgeable than we were 18 years ago about the trigger for EIA, the way in which this trigger becomes translated into an attack of asthma remains hotly disputed.

The Intermediary Pathway

Whatever the exact nature of the trigger, the pathway leading from this receptor site to the smaller airways which narrow could be humoral, neural or a combination of these mechanisms. In addition it has been suggested that the whole phenomenon of EIA and HIA is really vascular and that the cooling and rewarming of the airways causes reactive hyperaemia which directly affects bronchial calibre (41,51). For reasons which are discussed later, this latter suggestion seems highly unlikely. A direct neural reflex originating in the airway and terminating in the bronchial smooth muscle also seems an unlikely mechanism given the relatively slow onset of EIA and the even slower return to baseline.

The possibility that chemical mediators are involved in the intermediary pathway seems much more likely, although much of the evidence in favour is highly circumstantial. Thus sodium cromoglycate (SCG), which certainly prevents mediator release in vitro, prevents EIA if given before exercise but not if given
immediately afterwards (52). Neutrophil chemotactic factor, a mast cell derived mediator, has been found to rise in the blood during exercise in patients developing EIA and its rise can be prevented by pretreatment with SCG (53). Recently, a potent H₄ histamine antagonist, terfenadine, has been shown to markedly reduce the severity of EIA, HIA and osmotic (fog) induced asthma (54,55). EIA has also been shown to be reduced by treatment with an inhibitor of leukotriene D₄ (56–58) and HIA by an inhibitor of 5-lipoxigenase (59). In animals, HIA is reduced by pretreatment with capsaicin which reduces the availability of eicosanoids (60). The fact that Broide et al. (61) failed to detect significant elevations of mast cell derived histamine or tryptase in bronchoalveolar lavage washings from subjects with EIA could easily be explained by the increased blood flow of exercise simply washing the mediators out of the lungs. The eosinophil is now widely believed to be important in the inflammatory process which accompanies asthma and hence the observations of Venge et al. (62) are very interesting. They showed that levels of serum eosinophil cationic protein (ECP) were higher in those asthmatics who developed EIA and the level fell after exercise. Both the level of ECP and the severity of EIA could be reduced by pretreatment with sodium cromoglycate or by 4 weeks of treatment with the inhaled corticosteroid, budesonide. This could mean that ECP is involved in the process whereby exercise causes an attack of asthma. Alternatively, ECP could merely reflect the level of overall bronchial hyperreactivity.

Originally, the refractory period which was seen after EIA and sometimes after HIA and OIA was thought to be due to the depletion of stored mediators which required time to be resynthesized. The half-life of recovery of responsiveness to EIA was found to be about 60 min (63) which would fit with a metabolic function. Stearns and colleagues (64) suggested that refractoriness was due to the secretion of endogenous catecholamines but this seems unlikely given the small and transient changes in catecholamine levels in this kind of exercise (65) and the lack of any catecholamine release in either HIA or OIA. In any case, Dosani et al. (65) found no difference in catecholamine levels between asthmatics who became refractory to EIA and those who did not. Moreover, any such catecholamine secretion should inhibit the initial attack of EIA and not just that following a second challenge some 30–40 min later. Refractoriness does not seem to reside in end-organ hyporesponsiveness because subjects remain responsive to histamine while refractory to exercise (66–68). However, bronchial reactivity is not entirely without influence on refractoriness because O'Hickey et al. (69) showed that the more reactive the subject to methacholine the less was the refractoriness to hypertonic saline. The fact that there is also some degree of cross-refractoriness between EIA and HIA (70) and between EIA and OIA (71) supports the concept that similar mediator mechanisms are involved in all three types of asthma.

Some years ago (72), we were surprised to find refractoriness to EIA in subjects exercising and breathing cold, dry air following a previous exercise challenge breathing warm, humid air which itself did not provoke asthma (Fig. 4). In fact, such an observation can be deduced from an earlier study by Henriksen (73) and was recently repeated with exactly the same results by Wilson et al. (74). These observations suggest that neither bronchospasm nor the presumed mediator release are necessary for the development of refractoriness to EIA and direct measurements of at least one mediator (NCA) have not shown any reduction in release by exercise when the subject is refractory (75). We were unable to
Fig. 5 Change in lung function in a 9-year-old asthmatic girl during and after a 6-min exercise challenge. At 2 min of exercise there was a small increase in peak expiratory flow rate but thereafter there was a progressive fall during exercise and for 5 min after stopping. The value at the 6th min of exercise represented a fall of 28% from the baseline value immediately before exercise.

demonstrate the same phenomenon with hyperventilation (76) and with this challenge refractoriness was only seen if the initial challenge caused HIA. A totally new light on the refractoriness issue was shed by several studies which showed that the prostaglandin inhibitor, indomethacin, could prevent the appearance of refractoriness to EIA and OIA but not to HIA (77–79). This suggests that refractoriness, at least to exercise and hyperosmolar challenges, is due to the release of an inhibitory prostaglandin whose effect persists for 30–60 min or so after the initial challenge and whose release does not require that the initial challenge cause actual bronchospasm.

On balance, it now seems almost certain that mediators are released in the lungs by all forms of challenge which cause changes in the osmolarity of the fluid lining the airways. Moreover, it seems that the intermediary pathway involves the release of rapidly acting bronchoconstricting mediators and slowly reacting bronchodilating prostaglandins.

THE EFFECTOR MECHANISM

The most straightforward concept of the effector mechanism of EIA or HIA is that the airways obstruction is simply due to bronchospasm because it is rapid in onset and recovery, and is rapidly reversed by $\beta_2$ agonists. In these respects EIA closely resembles the early phase type of allergic bronchial reaction rather than the late phase allergic inflammatory response. An alternative hypothesis for the mechanism of the airways obstruction of EIA and HIA has been proposed by McFadden and his colleagues (41,80) which attributes the obstruction to reactive hyperaemia of the bronchial mucosa. They believe that the airways cool during exercise or hyperventilation and rewarms once the exercise or hyperventilation stops. The rewarming of these cooled airways causes reactive hyperaemia and obstructs the airflow. In support of their idea they reported greater airways obstruction when the rewarming was increased by breathing warm, humid air at the end of the challenge. It must be pointed out that other investigators have not confirmed that the rate of rewarming affects the degree of obstruction (81,82). If cooling and subsequent vaso-dilatation on rewarming were the stimulus it is difficult to understand why the severity of post-exertional asthma should be directly related to the duration of exercise for durations at least up to 6 min (83) when airway cooling reaches its lowest plateau level in about 2–3 min (41,84). In any case, this hypothesis seems to
A tentative model of EIA has been developed based on the facts discussed above and this is illustrated in Fig. 6. It must be emphasized that this is a model in which it is possible to make substitutions as our knowledge improves. One such substitution in relation to earlier models has already taken place as far as the refractory period is concerned.

In this model, exercise (a) results in hyperventilation, (b) may have a direct (intrinsic) trigger effect, (c) increases sympathetic drive or reduces bronchial tone, and (d) probably releases an inhibitory prostaglandin. The hyperventilation of exercise, or voluntary isocapnic hyperventilation per se, results in cooling and drying of the airways which is dependent upon the climatic conditions of the inspired air. As a result of the osmotic changes, there is release of mediator(s) from mast cells or other cells which acts on the bronchial smooth muscle causing bronchospasm. During exercise the subject is relatively (though not always completely) protected either by an increased sympathetic drive or alternatively by a reduction in bronchial tone which has also been found with isocapnic hyperventilation (16–19) and could be due to a differential effect of deep breathing on the hysteresis of lung parenchyma and airways (19). The model shows an increase in sympathetic drive for simplicity but this meant to cover either possibility. This short term protection stops as soon as the exercise ends allowing the bronchospasm to become manifest. Another type of protection is built up more slowly by the release of an inhibitory prostaglandin and this may account for the refractory period after EIA and possibly for that following HIA. Finally, the effect of the released mediator depends upon the basic level of bronchial reactivity which, in turn, depends upon such factors...
Fig. 7 Response of children with asthma (∆, n = 52), other chronic lung diseases (□, n = 22) and children without organic lung disease (▲, n = 19) to bronchial provocation by the inhalation of methacholine. The results are expressed in terms of the concentration of methacholine causing a 20% fall in FEV₁ (PC₂₀). The horizontal dashed line represents the lower limit of normal as determined by 2 SD below the log mean PC₂₀ of the normal group. Redrawn from Godfrey et al. (20).

Relationship Between Bronchial Reactivity and EIA

In our original review (1) we pointed out that increased bronchial reactivity could be demonstrated by exercise challenges in subjects other than those with active asthma. This had been noted in close relatives of asthmatic children, formerly wheezy infants and their close relatives and in children with cystic fibrosis. However, we also noted that it was only the subjects with active asthma who developed the characteristic post exercise fall in lung function and that the other labile groups demonstrated their increased lability by bronchodilatation during the exercise.

More recent work also suggested that as asthmatic children grow out of their clinically active disease so their responsiveness to exercise decreases while their responsiveness to inhaled pharmacological agents may persist. Thus we found (86) that while EIA persisted even after the children had begun to improve, once they had become totally free of symptoms for at least 6 months their exercise induced bronchial reactivity returned to normal. An interesting study by Martin et al. (87) showed a dissociation between reactivity to exercise and to non-specific pharmacological agents. In their study the children who had grown out of their asthma or were in complete remission often retained their responsiveness to histamine but no longer reacted to exercise. This may mean that pharmacological agents merely test end-organ responsiveness while exercise (and probably hyperventilation) test the whole physiological pathway.

We have recently compared the non-specific bronchial reactivity to exercise and methacholine of children with asthma and with other types of chronic airways obstruction or infection (20) (Figs. 7 and 8). As can be seen, some 79% of asthmatic children responded abnormally to exercise while almost none of the others responded. Both groups of children showed a high incidence of responsiveness to as the level of allergenic stimulation, recent viral infections and air pollution.

This model emphasizes the following important points about EIA:

(a) EIA is inherently variable because of the many factors which interact to produce the bronchoconstriction.

(b) The severity of the response to exercise on any one occasion is largely unpredictable since not all the variables can be quantified.

(c) When using exercise as a challenge in the same subject on different occasions or in different subjects, it is vital to standardize the exercise, environmental and allergenic factors as far as possible.
Fig. 8  Response of children with asthma (□, n = 52), other chronic lung diseases (▽, n = 22) and children without organic lung disease (△, n = 19) to bronchial provocation by exercise. The results are expressed in terms of the post exercise fall in FEV₁ as a percentage of the baseline value (Δ FEV₁). The horizontal dashed line represents the upper limit of normal as determined by 2 SD above the mean Δ FEV₁ of the normal group. Redrawn from Godfrey et al. (20).

methacholine. These studies in children, and comparable data from studies in adults, suggest that asthma is not only characterized by end-organ hyperresponsiveness, which it shares with a number of other chronic lung diseases, but is also characterized by a specific intermediary pathway which can be activated by an osmotic challenge in the airways and does not exist in other types of chronic lung disease.

Pharmacological Modification of EIA

Almost everything of importance concerning the action of drugs in preventing or reversing EIA was known well before our original review was written. Since then we have seen advances in terms of finding a number of drugs which may reduce EIA through the blocking of the effect of various mediators as has already been discussed. In point of fact, none of these are as effective as the simple administration of a selective β₂ agonist before exercise if the prevention of EIA is desired. Although not yet widely available, a new generation of long-acting inhaled β₂ agonists has been developed and these drugs inhibit EIA for substantially longer than β₂ agonists currently in use (88).

While sympathomimetic agents are very potent inhibitors of EIA, there is some doubt as to the relative efficacy of oral versus inhaled preparations, even though bronchodilatation occurs after administration by either route. Anderson et al. (89) found oral salbutamol to be ineffective compared with the inhaled drug, but Francis et al. (90) found both forms to be equally effective. Of the antihistaminic compounds the most commonly tested, ketotifen, totally failed to inhibit EIA (91,92) but a more specific anti-histamine drug, terfenadine, has now been shown to block the appearance of EIA (54,56) and OIA (55,93) but not of HIA (54). We noted the theoretical importance of sodium cromoglycate in reducing EIA even though it is not a bronchodilator and it is interesting, but hardly surprising, that its more recent analogue, nedocromil, has similar properties (94,95). Perhaps more exciting has been the finding that the diuretic frusemide can also block both EIA and osmotically-induced asthma when given by inhalation (96,97). In truth, the mechanism of action of frusemide in preventing EIA is still uncertain but it is tempting to link it to osmotic changes in the airway lining fluid.

There persists the argument as to whether or not corticosteroids reduce EIA. At the time of writing our previous review it was generally believed that steroids did not affect EIA and that in this respect EIA closely resembled the early response to the inhalation of allergen. It now appears that inhaled corticosteroids can reduce the response to both exercise and pharmacological agents (98,99). It may be that the efficacy
of inhaled steroids is drug specific, dose and time-dependent. Those studies showing an effect have utilized budesonide rather than beclomethasone. A single (1000 µg) dose of budesonide was unable to inhibit EIA in the study of Venge et al. (100) while 4 weeks of the same daily dose produced a significant reduction. The dose of inhaled corticosteroid, at least in the recent study of Vathenen et al. (99) was also quite high (1600 pg day⁻¹) and given for 6 weeks. In controlled conditions in parallel groups of asthmatics, it is interesting that there appears to have been a greater effect on reactivity to histamine (approximately a six-fold reduction) as compared with isocapnic hyperventilation (approximately a two-fold reduction). It may be that inhaled steroids are more effective in altering end-organ responsiveness to histamine than responsiveness to the mediator(s) which appear to be liberated by exercise.

Most drug studies that have been performed have shown similar effects on EIA and HIA but two are important because they appear to differentiate between the two types of challenge. Thus terfenadine can reduce EIA by almost half while having no effect on HIA (54). A refractory period has been demonstrated after both EIA and HIA during which it is more difficult to elicit a response to a repeat challenge. It has now been shown that this refractory period following EIA can be eliminated by treatment with indomethacin while the drug has no effect on the refractory period following HIA (78).

Conclusion

After 18 years of exciting research by many investigators in various parts of the world, we believe that our original conclusion still stands with the addition of one word – 'complete'. We quote 'It is concluded that there is as yet no 'complete' explanation for the mechanism of exercise-induced asthma, but it is a tool of potentially great value for research into the physiology and treatment of clinical asthma'. We also believe that this potential is being realized given the material reviewed in this article.

References


