

Exercise-Induced Bronchoconstriction

Celebrating 50 Years

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• Airway cooling • Refractory period • Athletes

The study of exercise-induced bronchospasm (EIB), alternatively called exercise-induced asthma (EIA), by many investigators over 50 years provides an outstanding example of how the techniques of classical physiology were applied in an attempt to determine the mechanisms underlying a troublesome clinical problem. Following the trail of this research in a more or less historical order enables the acknowledgment of the contributions of these investigators and follows the manner in which physiologic research was logically applied.

Perhaps the earliest description relating asthma to exercise was by Arataeus the Cappadocian around end of first century AD, as related by Brewis¹:

If from running, gymnastic exercises, or any other work, the breathing become difficult, it is called Asthma (ασθμα)

The initial classical description of EIB was published in 1717 in a book by Sir John Floyer,² himself an asthmatic, who wrote:

All violent exercise makes the asthmatic to breathe short—and if the exercise be continued it occasions a fit.

IS EIB A PROBLEM THAT NEEDS ATTENTION?

The practical implications of EIB were that 50 to 60 years ago, many asthmatics avoided exercise either from past personal experience of EIB or because parents restricted their children's involvement in sports and exercise. Such avoidance of

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physical activity was unfortunate because the lower a person's aerobic fitness, the higher the percentage of their maximum oxygen consumption ($\text{VO}_{2\text{ max}}$) that is required to perform an exercise task.³ Because the onset and severity of EIB is related to exercise intensity,⁴ improved aerobic fitness allows asthmatics to undertake the same exercise at a lower percentage of their $\text{VO}_{2\text{ max}}$ and thus reduce the resultant EIB.⁵ Conversely, in the very unfit, EIB is likely to appear even at low levels of exercise. However, although unaware of these principles of exercise physiology, there was a minority who had an alternative view that somehow exercise would benefit asthmatics and demonstrated this admirably. Theodore Roosevelt, who was President of the United States from 1901 to 1908, was a sickly child because of severe asthma. During adolescence, on advice from his physician, he undertook a program of vigorous exercise to grow into a fine athlete when he entered Harvard, only mildly inconvenienced by asthma.⁶ Others would emulate Roosevelt and achieve great sporting success. One notable person was Dawn Fraser, from Australia, who commenced swimming "to lick asthma" and won the 100-m freestyle at 3 consecutive Olympic Games in 1956, 1960, and 1964, despite being troubled with asthma before her 1964 race.⁷ Subsequently, the better understanding of the physiology of EIB and the benefit of a range of effective preventer medications has allowed those prone to EIB to achieve a level of fitness and enjoy a physical lifestyle comparable to their counterparts without EIB.⁸

1946–1970: EARLY MODERN ERA—ESTABLISHING BASIC FEATURES OF EIB

In 1946 Herxheimer⁹ described 6 asthmatics with hyperventilation asthma, but in fact he meant hyperventilation induced by exercise. He made a most important observation, namely that the asthma (EIB) usually occurred after stopping exercise and not during the exercise.

A series of definitive studies of EIB were undertaken by a Liverpool, UK pediatrician, R.S. Jones,^{10,11} and his colleagues from 1962 onwards,¹² which outlined almost all the important physiologic features. Brief exercise (running) of 1 to 2 minutes produced a rise in forced expiratory volume in 1 second (FEV_1) within 1 minute after stopping exercise, whereas prolonged exercise of 8 to 12 minutes produced a decrease in FEV_1 , reaching its lowest level 1 to 5 minutes after exercise, which then rapidly returned to the resting level. **Fig. 1** shows an exercise challenge in a child with marked EIB in which there was a decrease of 55% in FEV_1 after exercise. They noted that the

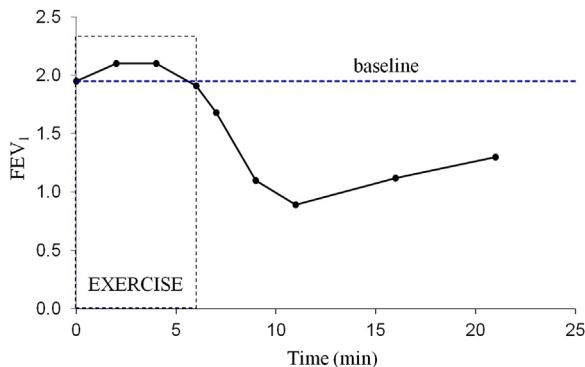


Fig. 1. Exercise-induced bronchoconstriction in a child who ran for 6 minutes on a treadmill. During the exercise there was a small rise in FEV_1 . After stopping exercise, FEV_1 decreased to its lowest level 12 minutes after the end of exercise and then began to return to baseline.

intensity of exercise determined the severity of the response and that the EIB was minimized or abolished by the inhalation of a β -agonist, isoprenaline (isoproterenol). Subsequently Jones and colleagues¹³ reported that the level of exercise had to be sufficient to produce moderate breathlessness. Even more importantly, they noted that in some subjects with a greater tendency to bronchoconstriction, the FEV₁ could decrease below the resting level even during the exercise. Thus EIB could occur during exercise—something that is discussed again later in this article. They also made an attempt to relate the exercise-induced changes in lung function and the clinical severity of asthma¹⁴ and noted exercise performance could be limited because of bronchoconstriction during exercise.

About this time, McNeill and colleagues¹⁵ showed that adults also developed EIB and found that with repeated exercise challenges on 6 occasions within 5 hours, the decrease in FEV₁ after exercise was less—the first recorded example of the development of refractoriness. Later, colleagues in North America also became interested in the diagnosis and treatment of EIB.^{16,17}

1971–1976: STUDIES TO BETTER DEFINE THE STIMULUS OF EIB

Jones and colleagues¹³ reported that they used free-range running as their stimulus for EIB because cycling was less effective, and a formal controlled study was undertaken by Anderson and colleagues¹⁸ to compare treadmill running, free-range running, and cycling. They also found free-range running caused the most EIB but could not explain why this occurred. At the same time, Fitch and Morton¹⁹ compared running, cycling, and swimming and found less EIA with swimming than running or cycling, whereas again running caused most EIB. The confusing situation in which exercise of different types but similar intensity caused different amounts of EIB resulted in Anderson and colleagues²⁰ writing a letter to the editor of the *British Medical Journal* stating, “Finally, we would like to repeat our earlier suggestion that the mechanism of exercise-induced asthma and the difference between the severe constriction due to running compared with the virtual absence during swimming may reflect neuromuscular differences in the types of exercise.” How wrong we were! Various possibilities were considered related to hyperventilation versus exercise and changes in blood gases, which led to a vigorous exchange of letters in the *Lancet* by the major pioneers Herxheimer, Jones, and Anderson^{9,21–27} but there was no convincing evidence to account for triggering EIB.

Although it had already been established that β -agonists could prevent EIB, presumably by a direct effect on bronchial smooth muscle, a new drug, sodium cromoglycate (cromolyn sodium), thought to block the release of mediators from mast cells, was shown by Davies²⁸ and Poppius and colleagues²⁹ to be effective in reducing the severity of EIB if inhaled before exercise but not if given once the attack had begun.³⁰ Oral glucocorticosteroids, which by then were known to be highly effective in treating troublesome asthma, and the newly developed beclomethasone dipropionate taken by inhalation, were demonstrated to have little or no effect in preventing EIB in most asthmatics.³¹ This latter outcome was so disappointing that it was more than a decade before a study of a newer inhaled corticosteroid, budesonide, was shown to be moderately effective in inhibiting EIB in children.³² In more recent times the efficacy of regular use of inhaled corticosteroids in preventing EIB in both children and adults became well established.^{33–35}

Silverman and Anderson³⁶ reported the results of carefully controlled studies to define the stimulus needed to obtain the maximal EIB response in children who ran or walked on a treadmill. EIB reached a maximum when the duration of exercise

was 6 to 8 minutes and when the gradient of the treadmill was 10% to 15%, representing exercise at about 70% of maximum exercise performance. Exercise for longer periods or at steeper gradients produced no significant increase in bronchoconstriction. When tests were repeated at 2-hour intervals throughout the day, no significant diminution in EIB was found so that there was no refractoriness if the interval between challenges was 2 hours. In 1975 Anderson and colleagues³⁷ summarized what was known about EIB up to that time but were forced to admit that the mechanisms involved in the production of EIB remained largely unknown. Even something as apparently obvious as the site of action of a β -agonist in preventing EIB received a jolt when Anderson and colleagues³⁸ found that while an oral β -agonist, terbutaline, and an inhaled β -agonist, fenoterol, were equally effective as bronchodilators before and during exercise, only the inhaled drug prevented a post-exercise fall in lung function. There was still a decrease after the oral drug, albeit from a higher pre-exercise FEV₁ level. They suggested that perhaps the inhaled β -agonists had a second site of action "in or on the surface of the bronchial mucosa (perhaps the mast cell)."

The problems facing asthmatic athletes were reviewed by Fitch and Godfrey³⁹ in relation to the 1976 Olympic Games. They noted the ability of asthmatics to succeed especially in swimming and the effectiveness of β_2 -agonists and sodium cromoglycate in preventing EIB. Although asthmatics could clearly now take part in sports with appropriate management, Fitch and colleagues⁴⁰ also showed that swim training for 5 months in children could improve physical fitness but, unfortunately, did not affect severity of EIB in response to running.

EXERCISE BRONCHIAL CHALLENGE IN NONASTHMATICS

In a foretaste of what would become of significant clinical interest much later, Day and Mearns⁴¹ studied the response to exercise in 52 children with cystic fibrosis and found that most had increased bronchial lability or airway hyperresponsiveness (AHR), which was often manifest as bronchodilation rather than bronchoconstriction. This showed that AHR was not limited to asthmatics, although the pattern of response was different in that the response in asthmatics was mainly the decrease in lung function after exercise.

1976–1980: CLUES ABOUT THE MECHANISMS INVOLVED IN EIB START TO APPEAR

In 1976 Weinstein and colleagues⁴² presented a paper at a meeting of the American Academy of Allergy in which he reported that 14 asthmatics exercising on a treadmill developed a mean decrease of FEV₁ of 29.5% breathing normal room air but only 13.5% breathing ultrasonically nebulized normal saline. He commented, "These results are similar to the results of others comparing the degree of bronchoconstriction occurring during treadmill running versus swimming. Bronchial drying may be an important mechanism in the development of EIA." A year later Bar-Or and colleagues⁴³ studied asthmatic children who exercised in a climate chamber. There was no effect of climate on resting lung function but breathing warm humid air virtually prevented EIB. Chen and Horton⁴⁴ obtained an identical result with asthmatic adults and suggested, "The results indicate that the primary stimulus for exercise-induced asthma may be heat loss and/or water loss from the airways during exercise." Strauss and colleagues⁴⁵ reported that subfreezing cold air had a negligible effect on lung function in asthmatics at rest but substantially increased the amount of EIB.

In several studies Deal and colleagues^{46–48} measured respiratory heat exchange using inspired gas of differing temperature and humidity and showed a correlation between severity of EIB and respiratory heat loss. The emphasis in this study was on

thermal load rather than drying of the airways and they concluded, “that the magnitude of exercise-induced asthma is directly proportional to the thermal load placed on the airways and that this reaction is quantifiable in terms of respiratory heat exchange.” Subsequently they demonstrated that breathing cold dry air actually lowered esophageal temperature during exercise. They also showed that asthmatics could get bronchoconstriction with isocapnic hyperventilation (hyperventilation induced bronchoconstriction, HIB) similar to that seen with exercise and that it responded similarly to ambient conditions and severity of hyperventilation.

At this time there began a long controversy as to the relative importance of cooling and drying of the airways in the triggering of EIB. That both the thermal effects on the vasculature and the osmotic effects on mediator release could occur separately or together to enhance one another was discussed in depth much later by Anderson and Daviskas.⁴⁹

The next clue was the refractory period. Although a study in 1966 had noted reduced EIB with repeated exercise,¹⁵ it was 12 years later that Edmonds and colleagues⁵⁰ undertook a formal study and showed that an episode of EIB was followed by a refractory period and that the response in the second of a pair of challenges decreased as the interval between them decreased. When exercise challenge tests at varying metabolic loads were followed after 30 minutes by tests at a constant load, the severity of EIB in the constant load challenge decreased in proportion to the load in the first challenge of each pair. They commented that, “These results were compatible with the suggestion that the development of EIB requires the release of a stored mediator or enzyme precursor.” Another clue was provided by Schnall and Landau,⁵¹ who showed that short warm-up sprints could prevent EIB in a subsequent 6-minute run. Not everyone agreed with this suggestion and Deal and colleagues⁵² measured arterial histamine and neutrophil chemotactic activity during hyperventilation, which they considered was the same thing as exercise and found no changes in either activity. They concluded that mediators derived from mast cells were not involved in EIB. They chose to dismiss refractory period data because there could have been persistent sympatho-adrenal activity between closely spaced challenges. In other words, the secretion of adrenaline during the first exercise challenge could have persisted and reduced the response in the second. Even so, a lot of similarities were found between EIB and HIB, including refractoriness and cross-refractoriness between the 2 types of challenge,^{53,54} making the sympatho-adrenal theory of refractoriness very unlikely. The similarities led investigators to develop a protocol for using voluntary hyperpnea with dry air containing 4.9% CO₂ as a surrogate for exercise to identify EIB in defense force recruits. This protocol is still widely used for identifying EIB in athletes.⁵⁵

Both knowledge of the ameliorating effect of humidity and the development of refractoriness to repeated exercise were put into practice as nonpharmacologic methods of ameliorating EIB. Warm-up exercises, whether continuous or intermittent, were shown to result in modest reductions of EIB.^{56,57} The use of face masks to humidify and heat the inspired air in an attempt to attenuate EIB was investigated in 1980 and did produce modest protection.^{58,59}

1981–1985 AND THEN OSMOLARITY AS A STIMULUS FOR EIB AND SOME OTHER OBSERVATIONS

Exploring a different type of challenge, Schoeffel and colleagues⁶⁰ in Anderson’s laboratory found that an attack of asthma could be provoked in asthmatics but not in normal subjects by having them breathe an ultrasonically nebulized aerosol, which

was either hypertonic or hypotonic, but not by breathing an isotonic aerosol. Later when Anderson and colleagues⁶¹ measured respiratory heat and water loss in young asthmatics exercising under various ambient conditions, they showed that EIB became worse as the water content of the inspired air was reduced, although some subjects experienced EIB, albeit to a lesser degree, when breathing warm humid air. The authors postulated that water loss from the airways during exercise may induce a change in osmolarity similar to that observed with the inhalation of hypertonic saline. Moreover, at the high levels of ventilation during exercise with “hot wet” air, there could be a net gain in water in the airways in some patients leading to a reduction in osmolarity of the respiratory tract fluid. Anderson and colleagues⁶¹ postulated “A unifying hypothesis for the bronchoconstricting effect from water gain and water loss from the airways may be a change in the tonicity of the fluid lining the respiratory tract.” This hypothesis emphasized for the first time, the very small volume of fluid in the generations of airways involved in conditioning the inspired air, and the capacity for the osmolarity of this small volume to change rapidly.⁶²

In 1982 Bar-Yishay and colleagues⁶³ finally tackled the problem of swimming versus running as the challenge for EIB by having children run and swim while breathing either dry or humid air. Although the EIB was less under both conditions with swimming, nevertheless the children had substantial EIB swimming while breathing dry air and so the difference between running and swimming in earlier studies must have been climatic.

Despite an earlier study that failed to detect any mediator release during HIB,⁵² neutrophil chemotactic factor (NCF) was shown by Lee and colleagues⁶⁴ to be released during exercise in asthmatics but not in normal subjects. The level peaked 10 minutes after exercise and returned to baseline by 1 hour and paralleled the decrease in lung function. Later they demonstrated that NCF was liberated in asthmatics breathing cold dry air but not warm humid air⁶⁵ and that NCF was also liberated in hyperventilation-induced asthma.⁶⁶ The present authors and many others were all very excited by these observations but, as it is now known, NCF is almost certainly interleukin-8 and not a mast cell-liberated mediator at all!

By placing a probe in a segment of the right lower lobe in normal subjects who hyperventilated, McFadden and colleagues⁶⁷ showed that the airways can get very cold when breathing cold air. In a further study in 1985⁶⁸ using multiple probes, they showed that the intrathoracic and intrapulmonary airways can undergo profound thermal changes that extend into the periphery of the lung.

1986–1990: A NEW HYPOTHESIS—REWARMING AND REACTIVE HYPEREMIA IS THE TRIGGER FOR EIB

In 1986 McFadden and colleagues⁶⁹ reported that the temperature of the air breathed on rewarming after the airways were cooled during exercise affected the severity of EIB such that the quicker the rewarming, the worse the EIB, which led them to postulate that perhaps the trigger for EIB was a type of reactive hyperemia of the airway vasculature. “This in turn could result in luminal narrowing from vascular engorgement and edema in the mucosa and submucosa.”⁶⁹ By contrast, however, Hahn and colleagues⁷⁰ found that the airway response to exercise was not significantly different when inspired air temperature varied considerably provided the amount of water required to saturate the inspired air remained the same. They concluded that it was the osmotic and not the cooling effects induced by the vaporization of water that was the more important factor determining EIB. Moreover, Smith and colleagues⁷¹ also undertook a rapid rewarming study and were unable to show any difference in

the severity of EIB in relation to the rate of rewarming. Continuing the “battle” over the trigger for EIB, Gilbert and colleagues⁷² presented calculations showing that the fluid loss from the airways in relation to the amount available during exercise would not be enough to cause a change in osmolarity. These conflicting hypotheses, drying-osmolarity versus cooling-hyperemia, were summarized in detail by Anderson in 1989⁷³ and Anderson and colleagues in 1992,⁷⁴ who presented strong arguments against the hyperemia hypothesis and in favor of the osmolar hypothesis. Suffice to say that it was and remains very difficult for the hyperemia hypothesis to explain the appearance of EIB in many subjects during exercise while the airways were still cold and when no rewarming had occurred, nor why the duration of exercise affects the severity of EIB. It also does not explain why severe EIB can occur when hot dry air is inspired during exercise and the airways do not cool abnormally.⁷⁵

ANOTHER POSSIBLE PATHWAY TO EXPLAIN REFRACTORINESS

Although the release of a chemical mediator in response to a trigger was attractive to many as the intermediary pathway to explain why EIB exhibits refractoriness, there were several problematic observations. Some years ago Ben Dov and colleagues⁷⁶ were surprised to find refractoriness to EIB in subjects exercising and breathing cold, dry air following a previous exercise challenge breathing warm, humid air, which itself did not provoke EIB. In fact, such an observation can be deduced from an earlier study by Henriksen and colleagues⁷⁷ and was repeated in 1990 with exactly the same results by Wilson and colleagues.⁷⁸ Interestingly NCF did not show any reduction in release by exercise when the subject was refractory⁷⁹ but it is now known that it is not a mediator. A totally new light on the refractoriness issue was shed by O’Byrne and colleagues⁸⁰ in 1986 and later by others who showed that the prostaglandin inhibitor, indomethacin, could prevent the appearance of refractoriness to EIB and osmotically induced bronchospasm but not to HIB,^{81,82} which suggests that refractoriness, at least to exercise and hyposmolar challenges, is due to the release of an inhibitory prostaglandin, the effect of which persists for 30 to 60 minutes or so after the initial challenge and whose release does not require that the initial challenge causes actual bronchoconstriction. However, not everyone agreed with the observation of refractoriness after a challenge that did not provoke asthma. Studies by Hahn and colleagues⁸³ using exercise and by Bar-Yishay and colleagues⁵³ using hyperventilation failed to demonstrate refractoriness after such challenges. The 3 major mediators considered important in EIB were histamine, prostaglandins, and leukotrienes. Histamine and prostaglandins were implicated in EIB, however, by the finding that alone or in combination an antihistamine terfenadine and a prostaglandin synthetase inhibitor, flurbiprofen, gave significant protection from EIB.⁸⁴ One of the first studies to investigate concentrations of all 3 mediators used 5 minutes of dry air hyperpnea at 22°C as the stimulus and measured changes in bronchoalveolar lavage fluid. They showed significant increases in levels of leukotriene B4 and SRS-A (a mixture of other leukotrienes).⁸⁵ As with the earlier studies, some, but not all, subjects had increases in prostaglandin D2 and histamine levels. It is still a mystery as to what causes refractoriness to EIB and a challenge for a new generation of investigators.

1991–1995: EXERCISE CHALLENGE HAS A DIFFERENTIAL DIAGNOSTIC ROLE

In 1991 Godfrey and colleagues⁸⁶ began to explore the use of bronchial challenges as an aid in the differential diagnosis of pediatric lung diseases. Bronchial provocation challenges with exercise and methacholine were performed on the same day or within a short interval in 52 children with asthma, 22 with other types of chronic lung disease

(including cystic fibrosis), and 19 control subjects with no evidence of chronic lung disease. In the methacholine challenges 94% of patients with asthma and 82% of patients with chronic lung disease responded abnormally. However, in the exercise challenges 79% of asthmatic patients but none of those with chronic lung disease responded abnormally. Thus the response to the 2 types of challenge was able to distinguish asthma from other types of chronic lung disease in children. The same investigators⁸⁷ compared the responses of asthmatic children, children with chronic obstructive pulmonary disease (COPD), and normal controls, to challenges by exercise, by the inhalation of methacholine (thought to act directly on bronchial smooth muscle), and by the inhalation of adenosine 5'-monophosphate (AMP), thought to act indirectly by liberating mediators. They found the direct challenge by methacholine distinguished both asthma and pediatric COPD from controls with a sensitivity of 82% to 92%, but did not distinguish between asthma and pediatric COPD. In contrast, both exercise and AMP distinguished asthma from controls with a sensitivity and specificity of 84% to 98% but they also distinguished asthma from pediatric COPD with a sensitivity and specificity of 85% to 90%. The similarity of the exercise and AMP results also suggested that exercise acted through a mediator-related intermediary pathway like that activated by AMP.

AN UPDATED REVIEW OF EIB

In 1993 Godfrey and Bar-Yishay⁸⁸ updated the review of EIB published in 1975.³⁷ They concluded that after 18 years of exciting research their original conclusion still stood with the addition of one word—complete. “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.”

A possible further piece of the jigsaw puzzle came to light when Manning and colleagues⁸⁹ undertook crossover challenges with exercise and the leukotriene D₄ (LTD₄) with and without flurbiprofen (a prostaglandin synthetase inhibitor). They found refractoriness occurred with all types of paired challenges and was reduced by flurbiprofen in all cases. They proposed that EIB was partly due to release of LTD₄ and this in turn released an inhibitory prostaglandin. Subsequently, Reiss and colleagues⁹⁰ showed that montelukast, a potent cysteinyl leukotriene receptor antagonist, attenuated EIB, providing further evidence of the role of leukotrienes in the pathogenesis of EIB.

1999: WHEN IS EIB REALLY ABNORMAL EIB?

Throughout most of the time that EIB has been studied, different investigators have chosen different criteria to define a decrease in lung function, which was considered a positive asthmatic response. In almost all cases there was no serious attempt to use statistical techniques to define the cutoff between a normal and an asthmatic response. The same applied to bronchial challenges by other means, such as an inhalation challenge by methacholine. In 1999 Godfrey and colleagues⁹¹ addressed this problem by extracting much data from published reports of the response of young normal subjects and asthmatics to challenges with exercise or methacholine. Using receiver operating characteristic curves, they found that the optimal cutoff point to distinguish asthmatics from normal subjects was a decrease in FEV₁ after exercise of 13%, with a sensitivity of 63% and a specificity of 94%. For inhalation challenges, the optimal cutoff point for the dose of methacholine (or histamine) causing a 20% decrease in FEV₁ was 6.6 μ m, with a sensitivity of 92% and a specificity of 89%. Unfortunately, despite the availability of this evidence, many studies continue to be reported using arbitrary criteria to define a positive response and even the Guidelines

for Methacholine and Exercise Challenges published by the American Thoracic Society⁹² state that “A decrease below 90% of the baseline FEV₁ (ie, a 10% decrease) is a generally accepted abnormal response. Some authors suggest a value of 15% is more diagnostic of EIB, particularly if exercise has been performed in the field.”

SO WHAT MORE HAS BEEN LEARNED ABOUT EIB SINCE THEN, IN THE PAST FEW YEARS?

To be honest, despite the impressive amount of information accumulated by many talented investigators, there still remains much for future generations to sort out.

- Although there is a general consensus that both drying and cooling are involved in the triggering of EIB, how this occurs is still uncertain and other articles in this series discuss this important issue.
- It is still not known for sure whether mediators are liberated by the trigger and, if so, what mediators are involved.
- It is still not known for sure what makes an asthmatic refractory to EIB shortly after a previous attack.

Work on these and other aspects of EIB has continued and an interesting new aspect of the subject has opened up with competitive athletes giving us much more to think about.

1993–2012: WINTER AND SUMMER ATHLETES AND ASTHMA/AHR

The finding of a high prevalence of bronchial hyperresponsiveness in athletes was reported in 1986 and many studies followed. Weiler and colleagues⁹³ documented a positive response to methacholine challenge in 76 of 151 young adult footballers, although only 12% admitted to a history of asthma. In 1993 Larsson and colleagues⁹⁴ noted a high prevalence of asthma in cross-country skiers and undertook methacholine challenges in 42 skiers and 29 controls. No less than 33 skiers had either asthma symptoms or AHR compared with just one in the control group, raising the question of the relationship between exercise and asthma, although inspiring cold air was considered to be a major factor. However, a later study by Helenius and colleagues⁹⁵ identified a higher prevalence of physician-diagnosed asthma in elite long-distance Finnish runners compared with their counterparts who participated in speed and power events. This discrepancy seemed to incriminate years of endurance exercise training as a factor, actually provoking AHR and thus being prone to EIB. In time, this would be considered to be due to an inability to condition large volumes of inspired air during years of endurance training causing airway injury.⁹⁶ A high prevalence of EIB was found by Mannix and colleagues⁹⁷ among competitive ice skaters. Other indoor athletes, such as ice hockey players, were also reported to be at risk and initially considered to be at risk because of the lower air temperatures in ice rinks,⁹⁸ but later inhaling particulate matter from diesel-powered ice resurfacers was found as the incriminating factor.⁹⁹

When the International Olympic Committee demanded in 2001 that athletes who wished to use an inhaled β -2 agonist (IBA) at the Olympic Games must confirm asthma/AHR by either a positive bronchodilator or a positive bronchial provocation test,¹⁰⁰ this resulted in the accumulation of considerable data over the next 5 Olympic Games.^{101,102} Not only did it confirm that athletes engaging in endurance training had a higher prevalence of asthma/AHR and were approved to use IBA but also that many did not have any history of childhood asthma with their onset of asthma/AHR being after the age of 16 years. One additional and perhaps surprising finding was that

athletes who had been approved to use IBA at Olympic Games actually outperformed their rivals. The reason was unclear because IBAs do not enhance performance. It is postulated that these athletes train harder and longer and thus became superior athletes, but in doing so, sustain more airway injury because they are unable to condition the increased volumes of inspired air. However, what occurs to the airways of these endurance trained athletes when they cease training? There is some anecdotal evidence that they may lose their AHR and proneness to EIB and this has been reported to occur in Finnish swimmers 5 years into their retirement¹⁰³; however, more research is necessary to confirm this outcome.

In 2010 Sue-Chu and colleagues¹⁰⁴ studied bronchial responsiveness in 58 elite cross-country skiers to several challenges including eucapnic hyperventilation, exercise, methacholine, AMP, and mannitol. They found that although 25 (43%) skiers had hyperresponsiveness, in the large majority the hyperresponsiveness was to methacholine, which according to the work discussed earlier is relatively nonspecific.⁸⁷ Only 5 and 3 subjects, respectively, were hyperresponsive to AMP and mannitol, which are much more specific for asthma. Even more surprising, methacholine hyperresponsiveness was more prevalent in subjects without asthmalike symptoms. They concluded that the low prevalence of hyperresponsiveness to indirect stimuli (exercise, hyperventilation, AMP, and mannitol) may suggest differences in the pathogenesis of methacholine hyperresponsiveness between elite skiers and nonathletes. In a review of asthma and airway hyperresponsiveness in Olympic athletes, Fitch suggested that the increased incidence of abnormal responses was likely to have been a consequence of their training.¹⁰⁵ Some might suggest that the symptoms in most athletes are due to a type of airway trauma and not to genetically based atopic allergic asthma, which is the common pattern seen in children and young adults.

SUMMARY

Therefore, for over 50 years, from the first modern studies in 1946, a large number of investigators have gradually pieced together most, but not all, of the pathophysiologic pathways involved in EIB. The story of EIB surely provides a case for the need to understand and apply classical physiology in this era of molecular genetics. As a consequence of this research, the burden of EIB has largely been removed from asthmatics of all ages, who can now lead much more normal lives.

REFERENCES

1. Brewis RA. Classic papers in asthma. London: Science Press Limited; 1990.
2. Floyer SJ. A treatise of the asthma. London: R. Wilkin & W. Innis; 1698.
3. Astrand PO, Rodahl K. Textbook of work physiology. New York: McGraw Hill; 1970.
4. Carlsson E, Engh G, Mork M. Exercise-induced bronchoconstriction depends on exercise load. *Respir Med* 2000;94:750–5.
5. Henriksen JM, Nielsen TT. Effect of physical training on exercise-induced bronchoconstriction. *Acta Paediatr Scand* 1983;72:31–6.
6. Szanton VL. Theodore Roosevelt, the asthmatic. *Ann Allergy* 1969;27:485–9.
7. Frazer D. Gold medal girl. Melbourne (Australia): Landsdowne; 1965.
8. Fitch KD. Pharmacotherapy for exercise-induced asthma: allowing normal levels of activity and sport. *Expert Rev Clin Pharmacol* 2010;3:139–52.
9. Herxheimer H. Hyperventilation asthma. *Lancet* 1946;1:83–7.
10. Jones RS, Buston MH, Wharton MJ. The effect of exercise on ventilatory function in the child with asthma. *Br J Dis Chest* 1962;56:78–86.

11. Jones RH, Jones RS. Ventilatory capacity in young adults with a history of asthma in childhood. *Br Med J* 1966;2:976–8.
12. Blackhall M. Ventilatory function in subjects with childhood asthma who have become symptom free. *Arch Dis Child* 1970;45:363–6.
13. Jones RS, Wharton MJ, Buston MH. The place of physical exercise and bronchodilator drugs in the assessment of the asthmatic child. *Arch Dis Child* 1963;38:539–45.
14. Jones RS. Assessment of respiratory function in the asthmatic child. *Br Med J* 1966;2:972–5.
15. McNeill RS, Nairn JR, Millar JS, et al. Exercise induced asthma. *Q J Med* 1966; 35:55–67.
16. Sly RM, Heimlich EM, Busser RJ, et al. Exercise induced bronchospasm: effect of adrenergic or cholinergic blockade. *J Allergy* 1967;40:93–9.
17. Pierson WE, Bierman CW, Stamm SJ. Cycloergometer induced bronchospasm. *J Allergy* 1969;43:136–44.
18. Anderson SD, Connolly NM, Godfrey S. Comparison of bronchoconstriction induced by cycling and running. *Thorax* 1971;26:396–401.
19. Fitch KD, Morton AR. Specificity of exercise-induced asthma. *Br Med J* 1971;4: 577–81.
20. Anderson SD, Silverman M, Tai E, et al. Specificity of exercise in exercise-induced asthma. *Br Med J* 1971;4:814–5.
21. Herxheimer H. Exercise asthma. *Lancet* 1972;1:436–7.
22. Beaudry PH, Wise MB, Seely JE. Respiratory gas exchange at rest and during exercise in normal and asthmatic children. *Am Rev Respir Dis* 1967;95: 248–54.
23. Seaton A, Davies G, Gaziano D, et al. Exercise induced asthma. *Br Med J* 1969; 3:556–8.
24. Katz RM, Whipp BJ, Heimlich EM, et al. Exercise induced bronchospasm, ventilation and blood gases in asthmatic children. *J Allergy* 1971;47:148–58.
25. Anderson SD, Silverman M, Walker SR. Metabolic and ventilatory changes in asthmatic patients during and after exercise. *Thorax* 1972;27:718–25.
26. Jones RS, Godfrey S, Silverman M, et al. Exercise asthma. *Lancet* 1972;1:533.
27. Silverman M, Anderson SD, Walker SR. Metabolic changes preceding exercise-induced bronchoconstriction. *Br Med J* 1972;1:207–9.
28. Davies SE. The effect of disodium cromoglycate on exercise-induced asthma. *Br Med J* 1968;3:593–4.
29. Poppius H, Muijtari A, Kreis KE, et al. Exercise induced asthma and disodium cromoglycate. *Br Med J* 1970;4:337–9.
30. Silverman M, Andrea T. Time course of effect of disodium cromoglycate on exercise-induced asthma. *Arch Dis Child* 1972;47:419–22.
31. Konig P, Jaffe P, Godfrey S. Effect of corticosteroids on exercise-induced asthma. *J Allergy Clin Immunol* 1974;54:14–9.
32. Henriksen JM, Dahl R. Effects of inhaled budesonide alone and in combination with low dose terbutaline in children with exercise-induced asthma. *Am Rev Respir Dis* 1983;128:993–7.
33. Hofstra WB, Sterk PJ, Neijens HJ, et al. Prolonged recovery from exercise-induced asthma with increasing age in childhood. *Pediatr Pulmonol* 1995;20: 177–83.
34. Jonasson G, Carlsen KH, Hultquist C. Low-dose budesonide improves exercise-induced bronchospasm in schoolchildren. *Pediatr Allergy Immunol* 2000;11: 120–5.

35. Subbarao P, Duong M, Adelroth E, et al. Effect of ciclesonide dose and duration of therapy on exercise-induced bronchoconstriction in patients with asthma. *J Allergy Clin Immunol* 2006;117:1008–13.
36. Silverman M, Anderson SD. Standardization of exercise tests in asthmatic children. *Arch Dis Child* 1972;47:882–9.
37. Anderson SD, Silverman M, Konig P, et al. Exercise-induced asthma. *Br J Dis Chest* 1975;69:1–39.
38. Anderson SD, Rozea PJ, Dolton R, et al. Inhaled and oral bronchodilator therapy in exercise induced asthma. *Aust N Z J Med* 1975;5:544–50.
39. Fitch KD, Godfrey S. Asthma and athletic performance. *JAMA* 1976;236:152–7.
40. Fitch KD, Morton AR, Blanksby BA. Effects of swimming training on children with asthma. *Arch Dis Child* 1976;51:190–4.
41. Day G, Mearns MB. Bronchial lability in cystic fibrosis. *Arch Dis Child* 1973;48:355–9.
42. Weinstein RE, Anderson JA, Kvale P, et al. Effects of humidification on exercise-induced asthma (EIA). *J Allergy Clin Immunol* 1976;57:250–1.
43. Bar-Or O, Neuman I, Dotan R. Effects of dry and humid climates on exercise-induced asthma in children and adolescents. *J Allergy Clin Immunol* 1977;60:163–8.
44. Chen WY, Horton DJ. Heat and water loss from the airways and exercise-induced asthma. *Respiration* 1977;34:305–13.
45. Strauss RH, McFadden ER, Ingram RH, et al. Enhancement of exercise-induced asthma by cold air. *N Engl J Med* 1977;297:743–7.
46. Deal EC, McFadden ER, Ingram RH, et al. Role of respiratory heat exchange in production of exercise-induced asthma. *J Appl Physiol* 1979;46:467–75.
47. Deal EC, McFadden ER, Ingram RH, et al. Esophageal temperature during exercise in asthmatic and non-asthmatic subjects. *J Appl Physiol* 1979;46:484–90.
48. Deal EC, McFadden ER, Ingram RH, et al. Hyperpnea and heat flux: initial reaction sequence in exercise-induced asthma. *J Appl Physiol* 1979;46:476–83.
49. Anderson SD, Daviskas E. The mechanism of exercise-induced asthma is.... *J Allergy Clin Immunol* 2000;106:453–9.
50. Edmunds AT, Tooley M, Godfrey S. The refractory period after exercise-induced asthma: its duration and relation to the severity of exercise. *Am Rev Respir Dis* 1978;117:247–54.
51. Schnall RP, Landau LI. The protective effects of short sprints in exercise induced asthma. *Thorax* 1980;35:828–32.
52. Deal EC, Wasserman SI, Soter NA, et al. Evaluation of role played by mediators of immediate hypersensitivity in exercise-induced asthma. *J Clin Invest* 1980;65:659–65.
53. Bar-Yishay E, Ben Dov I, Godfrey S. Refractory period after hyperventilation-induced asthma. *Am Rev Respir Dis* 1983;127:572–4.
54. Ben Dov I, Gur I, Bar-Yishay E, et al. Refractory period following induced asthma: contributions of exercise and isocapnic hyperventilation. *Thorax* 1983;38:849–53.
55. Phillips YY, Jaeger JJ, Laube BL, et al. Eucapnic voluntary hyperventilation of compressed gas mixture. A simple system for bronchial challenge by respiratory heat loss. *Am Rev Respir Dis* 1985;131:31–5.
56. Reiff DB, Choudry NB, Pride NB, et al. The effect of prolonged submaximal warm-up exercise on exercise-induced asthma. *Am Rev Respir Dis* 1989;139:479–84.

57. McKenzie DC, McLuckie SL, Stirling DR. The protective effects of continuous and interval exercise in athletes with exercise-induced asthma. *Med Sci Sports Exerc* 1994;26:951-6.
58. Brenner AM, Weiser PC, Krogh LA, et al. Effectiveness of a portable face mask in attenuating exercise-induced asthma. *JAMA* 1980;244:2196-8.
59. Schachter EN, Lee M, Gerhard H, et al. A non-pharmacologic approach to the treatment of exercise-induced bronchospasm. *Yale J Biol Med* 1980;53:485-96.
60. Schoeffel RE, Anderson SD, Altounyan RE. Bronchial hyperreactivity in response to inhalation of ultrasonically nebulised solutions of distilled water and saline. *Br Med J* 1981;282:1285-7.
61. Anderson SD, Schoeffel RE, Follet R, et al. Sensitivity to heat and water loss at rest and during exercise in asthmatic patients. *Eur J Respir Dis* 1982;63:459-571.
62. Anderson SD. Is there a unifying hypothesis for exercise-induced asthma. *J Allergy Clin Immunol* 1984;73:660-5.
63. Bar-Yishay E, Gur I, Inbar O, et al. Differences between swimming and running as stimuli for exercise-induced asthma. *Eur J Appl Physiol* 1982;48:387-97.
64. Lee TH, Nagy L, Nakagura T, et al. Identification and partial characterization of an exercise-induced neutrophil chemotactic factor in bronchial asthma. *J Clin Invest* 1982;69:889-99.
65. Lee TH, Assoufi BK, Kay AB. The link between exercise, respiratory heat exchange, and the mast cell in bronchial asthma. *Lancet* 1983;1:520-2.
66. Nagakura T, Lee TH, Assoufi BK, et al. Neutrophil chemotactic factor in exercise- and hyperventilation-induced asthma. *Am Rev Respir Dis* 1983;126:294-6.
67. McFadden ER, Denison DM, Waller JF, et al. Direct recordings of the temperatures in the tracheobronchial tree in normal man. *J Clin Invest* 1982;69:700-5.
68. McFadden ER, Pichurko BM, Bowman HF, et al. Thermal mapping of the airways in humans. *J Appl Physiol* 1985;58:564-70.
69. McFadden ER, Lenner KA, Strohl KP. Postexertional airway rewarming and thermally induced asthma. New insights into pathophysiology and possible pathogenesis. *J Clin Invest* 1986;78:18-25.
70. Hahn A, Anderson SD, Morton AR, et al. A reinterpretation of the effect of temperature and water content of the inspired air in exercise-induced asthma. *Am Rev Respir Dis* 1984;130:575-9.
71. Smith CM, Anderson SD, Walsh S, et al. An investigation of the effects of heat and water exchange in the recovery period after exercise in children with asthma. *Am Rev Respir Dis* 1989;140:598-605.
72. Gilbert IA, Fouke JM, McFadden ER. Heat and water flux in the intrathoracic airways and exercise-induced asthma. *J Appl Physiol* 1987;63:1681-91.
73. Anderson SD, Daviskas E, Smith CM. Exercise-induced asthma: a difference in opinion regarding the stimulus. *Allergy Proc* 1989;10:215-26.
74. Anderson SD, Daviskas E. The airway microvasculature and exercise induced asthma. *Thorax* 1992;47:748-52.
75. Anderson SD, Schoeffel RE, Black JL, et al. Airway cooling as the stimulus to exercise-induced asthma - a re-evaluation. *Eur J Respir Dis* 1985;67:20-30.
76. Ben Dov I, Bar-Yishay E, Godfrey S. Refractory period after exercise-induced asthma unexplained by respiratory heat loss. *Am Rev Respir Dis* 1982;125:530-4.
77. Henriksen JM, Dahl R, Lundquist GR. Influence of relative humidity and repeated exercise on exercise-induced bronchoconstriction. *Allergy* 1981;36:463-70.

78. Wilson BA, Bar-Or O, Seed LG. Effects of humid air breathing during arm or treadmill exercise on exercise-induced bronchoconstriction and refractoriness. *Am Rev Respir Dis* 1990;142:349–52.
79. Belcher NG, Murdoch RD, Dalton N, et al. A comparison of mediator and catecholamine release between exercise- and hypertonic saline-induced asthma. *Am Rev Respir Dis* 1988;137:1026–32.
80. O'Byrne PM, Jones GM. The effect of indomethacin on exercise-induced bronchoconstriction and refractoriness after exercise. *Am Rev Respir Dis* 1986;134:69–72.
81. Margolskee DJ, Bigby BG, Boushey HA. Indomethacin blocks airway tolerance to repetitive exercise but not to eucapnic hyperpnea in asthmatic subjects. *Am Rev Respir Dis* 1988;137:842–6.
82. Mattoli S, Foresi A, Corbo GM, et al. The effect of indomethacin on the refractory period occurring after the inhalation of ultrasonically nebulised distilled water. *J Allergy Clin Immunol* 1987;79:678–83.
83. Hahn AG, Nogrady SG, Burton GR, et al. Absence of refractoriness in asthmatic subjects after exercise with warm, humid inspirate. *Thorax* 1985;40:418–21.
84. Finnerty JP, Holgate ST. Evidence for the roles of histamine and prostaglandins as mediators in exercise-induced asthma: the inhibitory effect of terfenadine and flurbiprofen alone and in combination. *Eur Respir J* 1990;3:540–7.
85. Pliss LB, Ingenito EP, Ingram RH Jr, et al. Assessment of bronchoalveolar cell and mediator response to isocapnic hyperpnea in asthma. *Am J Respir Crit Care Med* 1990;142:73–8.
86. Godfrey S, Springer C, Noviski N, et al. Exercise but not methacholine differentiates asthma from chronic lung disease in children. *Thorax* 1991;46:488–92.
87. Avital A, Springer C, Bar-Yishay E, et al. Adenosine, methacholine, and exercise challenges in children with asthma or paediatric chronic obstructive pulmonary disease. *Thorax* 1995;50:511–6.
88. Godfrey S, Bar-Yishay E. Exercised-induced asthma revisited. *Respir Med* 1993;87:331–44.
89. Manning PJ, Watson RM, O'Byrne PM. Exercise-induced refractoriness in asthmatic subjects involves leukotriene and prostaglandin interdependent mechanisms. *Am Rev Respir Dis* 1993;148:950–4.
90. Reiss TF, Hill JB, Harman E, et al. Increased urinary excretion of LTE₄ after exercise and attenuation of exercise-induced bronchospasm by montelukast, a cysteinyl leukotriene receptor antagonist. *Thorax* 1997;52:1030–5.
91. Godfrey S, Springer C, Bar-Yishay E, et al. Cut-off points defining normal and asthmatic bronchial reactivity to exercise and inhalation challenges in children and young adults. *Eur Respir J* 1999;14:659–68.
92. Crapo RO, Casaburi R, Coates AL, et al. Guidelines for methacholine and exercise challenge testing-1999. *Am J Respir Crit Care Med* 2000;161:309–29.
93. Weiler JM, Metzger WJ, Donnelly AL, et al. Prevalence of bronchial hyperresponsiveness in highly trained athletes. *Chest* 1986;90:23–8.
94. Larsson K, Ohlson P, Larsson L, et al. High prevalence of asthma in cross country skiers. *Br Med J* 1993;307:1326–9.
95. Helenius IJ, Tikkanen HO, Haahtela T. Association between type of training and risk of asthma in elite athletes. *Thorax* 1997;52:157–60.
96. Anderson SD, Kippelen P. Airway injury as a mechanism for exercise-induced bronchoconstriction in elite athletes. *J Allergy Clin Immunol* 2008;122:225–35.
97. Mannix ET, Farber MO, Palange P, et al. Exercise-induced asthma in figure skaters. *Chest* 1996;109:312–5.

98. Leuppi JD, Kuhn M, Comminot C, et al. High prevalence of bronchial hyperresponsiveness and asthma in ice hockey players. *Eur Respir J* 1998;12:13–6.
99. Rundell KW. Pulmonary function decay in women ice hockey players: is there a relationship to ice rink air quality? *Inhal Toxicol* 2004;16:117–23.
100. Anderson SD, Fitch K, Perry CP, et al. Responses to bronchial challenge submitted for approval to use inhaled beta2-agonists before an event at the 2002 Winter Olympics. *J Allergy Clin Immunol* 2003;111:45–50.
101. Anderson SD, Sue-Chu M, Perry CP, et al. Bronchial challenges in athletes applying to inhale a beta2-agonist at the 2004 Summer Olympics. *J Allergy Clin Immunol* 2006;117:767–73.
102. Fitch KD, Sue-Chu M, Anderson SD, et al. Asthma and the elite athlete: summary of the International Olympic Committee's consensus conference, Lausanne, Switzerland, January 22–24, 2008. *J Allergy Clin Immunol* 2008;122:254–60, 260.e1–7.
103. Helenius I, Ryttilä P, Sarna S, et al. Effect of continuing or finishing high-level sports on airway inflammation, bronchial hyperresponsiveness, and asthma: a 5-year prospective follow-up study of 42 highly trained swimmers. *J Allergy Clin Immunol* 2002;109:962–8.
104. Sue-Chu M, Brannan JD, Anderson SD, et al. Airway hyperresponsiveness to methacholine, adenosine 5-monophosphate, mannitol, eucapnic voluntary hyperpnoea and field exercise challenge in elite cross-country skiers. *Br J Sports Med* 2010;44:827–32.
105. Fitch KD. An overview of asthma and airway hyper-responsiveness in Olympic athletes. *Br J Sports Med* 2012;46:413–6.