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Editorial

Exercise-induced asthma

Interest in exercise-induced asthma (EIA) has grown enormously during the past decade. Several factors are responsible for this, not the least of which is the fact that no simple uniform answers have yet emerged. EIA is in some ways an easy condition to study since many patients suffer from it, and the equipment needed can be found in most respiratory or cardiac laboratories. Exercise is a relatively physiological, though not necessarily normal, activity for the subjects concerned, and this form of challenge usually produces a moderate increase in airways obstruction that resolves spontaneously within 30–60 minutes. The accessibility of EIA to study has resulted in publications from many centres and produced a predictable variety of opinions on possible underlying mechanisms. The early reports have been well reviewed by Anderson *et al* (1975). Developments within the past four years have produced a measure of agreement between different investigators that has not previously existed, and have also shown that, in terms of unresolved problems, some of the giants that were tilted at five to ten years ago have proved to be windmills.

Exercise-induced asthma is not a disease but a symptom of non-specific bronchial hyperreactivity where the form of challenge is exercise, and as such it is an almost universal finding in asthmatic subjects if sought intensively (Haynes *et al*, 1976; Godfrey, 1977). Research into the mechanisms of EIA has broadly concentrated on two problems: firstly, to find the peculiar property of exercise that is responsible for it, and secondly to discover how this produces bronchoconstriction. Most of the advances that have taken place in the past four years concern the first area of research, which is the initial step in the sequence of events leading to EIA.

In 1946 Herxheimer published the first account of EIA that included objective measurements of vital capacity. He called his paper "Hyperventilation asthma" as he thought it was this aspect of exercise that produced asthma in four of his six subjects, while five of them developed wheezing after voluntary hyperventilation. During the next 30 years other workers variously thought that hyperventilation was important (Rebuck and Read, 1968; Chan-Yeung *et al*, 1971) or unimportant (McNeill *et al*, 1966; Silverman, 1973; McFadden *et al*, 1977b). As was pointed out by Rebuck and Read, carbon dioxide is itself a bronchodilator, so that carbon dioxide-induced hyperventilation cannot be used as a model for comparison with exercise. Silverman (1973) and McFadden *et al* (1977b) used a partial rebreathing technique to maintain isocapnia during voluntary hyperventilation, and could show only small and variable changes in airflow obstruction, usually far less than those seen in the same individuals after exercise. More recently, Zeballos *et al* (1978) used a different technique, that of adding small quantities of 100% carbon dioxide to the inspired air, sufficient only to maintain isocapnia, and showed that voluntary hyperventilation produced the same degree of asthma as exercise. They pointed out that any rebreathing technique will tend to warm and humidify the inspired air, and so lessen asthma, for reasons discussed below. Their conclusions regarding the primary role of hyperventilation are now widely accepted (Deal *et al*, 1979a) and are confirmed again in a comparison of running, walking, and hyperventilation in this issue (Kilham *et al*, 1979). It is rather depressing to realise that it has taken so long to confirm Herxheimer's initial impression.

If hyperventilation is important in exercise, by what means does it induce bronchoconstriction? Herxheimer believed that hypocapnia was important, but later work has not been able to substantiate this conclusively. In view of the story of hyperventilation, perhaps we should be cautious about excluding any role for hypocapnia, but present interest has centred on another effect that hyperventilation certainly does have, and that is cooling of the oropharynx and upper airways.

Air is normally conditioned by the nose, pharynx, and trachea so that by the time it reaches the intrapulmonary airways it is fully saturated with water vapour at body temperature. This requires evaporation of water from the mucosal surfaces, and the cooler and drier the air the more evaporation must occur. Conditioning of inspired air during tidal breathing is helped by the nose, and is complete by the time air reaches the carina.

During the hyperventilation of exercise, when mouth breathing is used, not only does the mucosa in the upper respiratory tract become even cooler, but the level at which full conditioning occurs may move further down the respiratory tract (Chen and Horton, 1977). Humidification or warming of the inspired air reduces EIA (Weinstein *et al*, 1976; Bar-Or *et al*, 1977; Chen and Horton, 1977; Strauss *et al*, 1978; Deal *et al*, 1979b), while cooling it exacerbates the response (Strauss *et al*, 1977; Deal *et al*, 1979b). Nasal breathing also produces a smaller response than mouth breathing in the same individuals (Shturman-Ellstein *et al*, 1978). Elegant expressions to calculate the asthmatic response from the "thermal load" on the airways have been derived by Deal *et al* (1979b). Yet again it has taken a long time; as long ago as 1952, in the discussion that followed Pearson's paper on "The effect of exercise in asthma" presented to the British Association of Allergists, Dr C Britton asked "whether air had been breathed through the nose or the mouth, and whether therefore the temperature of the inspired was not an important factor."

These studies perhaps help to explain some of the variation of EIA with time, and between different centres where atmospheric conditions may differ considerably. They probably explain too the differences reported between various forms of exercise in their ability to induce EIA. Swimming, in particular, has always been less effective than other exercises, but has been studied in heated indoor pools, where the high water content of the inspired air would blunt any response (Fitch and Morton, 1971; Anderson, 1972). The differences between other forms of exercise, about which so much has been written, are probably due to the different degrees or patterns of hyperventilation. It would appear that if hyperventilation is sufficient and comparable, there is nothing to choose between different forms of exercise carried out in the same environment in their ability to induce EIA.

While there appears to be international agreement, so far, on the initial events leading to EIA, there is not yet agreement as to how hyperventilation and airway cooling lead to bronchoconstriction. There are essentially two schools of thought, one supporting a central role for the vagus nerve (Zeballos *et al*, 1978) and the other putting forward a similar role for mediator substances released from mast cells in the airways (Deal *et al*, 1978, 1979a).

The vagus nerve certainly would seem to be well suited in such a role, since it is easy to envisage a physical effect, such as mucosal cooling, triggering vagal irritant receptors in the oropharynx and large airways. Direct stimulation of these receptors is known to result in bronchoconstriction experimentally (this subject has recently been reviewed by Widdicombe, 1975) and EIA has been inhibited by oropharyngeal anaesthesia using 2% lignocaine (McNally *et al*, 1978). The degree of protection afforded by local anaesthetic in this study was variable, although significant overall, and it is of course not possible to compare an adequate placebo in such an experiment. Most investigators have concentrated on trying to block vagal efferent activity with anticholinergic drugs rather than to abolish afferent activity with local anaesthetic, which, apart from its potential hazards, is also extraordinarily unpleasant. There seems to be no doubt that a proportion of all patients studied are protected by anticholinergic premedication, provided that this is given in more than just bronchodilator doses, and this proportion may be as high as 50–70%. Protection is greatest in those with predominantly large airway responses to exercise as assessed by helium-oxygen expiratory flow-volume curves, and this is perhaps to be expected in view of the known sites of vagal airway innervation (McFadden *et al*, 1977a; Thomson *et al*, 1978). The doses of drug required are about 4–6 mg of inhaled atropine or 1–2 mg of ipratropium bromide (Deal *et al*, 1978; Thompson *et al*, 1978). Care must be taken in the interpretation of results to allow for the bronchodilator effects of anticholinergic blockade, but the concept of these large doses of drug is compatible with the enormous doses that may be needed to block reflex vagal effects in experimental animals (Gold, 1975). Large doses of atropine were found not to prevent the cold air-induced increase in EIA by Deal *et al* (1978), which argues against a central vagal role. No study has yet shown uniform protection from EIA by vagal blockade, and while there is no doubt that many individuals may have a predominant vagal component to their EIA, it is still not known if this is due to the direct effect of cooling on irritant receptors. An alternative theory is that cooling induces mediator release from mast cells, rather as in cold urticaria, which in turn might activate vagal receptors in some individuals, or which might act directly on bronchial smooth muscle in others (Deal *et al*, 1978).

It is difficult to see how present techniques of blockade can improve our knowledge about the vagus and EIA further, since even larger doses of anticholinergic drugs will become very unpleasant, and local anaesthetic drugs may themselves produce effects on mast cells even if the

problems of safety and tolerability can be overcome (Weiss *et al*, 1978). It is probably to mast cells and mediators that we must look for further information, since technical advances have by no means reached their full potential in this field.

It is important to realise that there is no direct evidence that mediators are involved in EIA. The most often quoted evidence is that sodium cromoglycate, a drug that is thought to act by stabilising mast cells, can block EIA in many people (Davies, 1968; Silverman, 1973). No-one has yet shown this mode of action in man, and many drugs are better in-vitro "mast cell stabilisers" than cromoglycate without being effective in asthma, let alone EIA. Another indirect piece of evidence that mediators are important is that there is a refractory period after one attack of EIA when it is much less easy to induce another attack (Edmunds *et al*, 1978). Full recovery of sensitivity to exercise may take 90–120 minutes, and this has been taken to indicate that stores of mediator substances need replenishing (McNeill *et al*, 1966; Edmunds *et al*, 1978). More direct evidence for mediator release has only recently been sought, and studies are still at an early stage. Several centres have looked for histamine in peripheral arterial plasma during EIA and have found no increase (McFadden and Soter, 1977), a large increase but without control subject data (Ferris *et al*, 1978), or a moderate increase, not significantly different from that in normal controls (Charles *et al*, 1979). The difficulty of this approach is that basophilia is a normal response to exercise, and some histamine from these basophils may leak into the plasma, without necessarily implying intrapulmonary mast cell degranulation. At the same time histamine is removed rapidly from the circulation, and relatively large quantities must be released to influence plasma concentrations. A search for other mediators may be more rewarding, provided the technical problems of assaying them in minute quantities can be overcome.

Another approach which will certainly be more widely applied and which perhaps offers the best immediate chance of providing evidence for the involvement of mediators, is the use of specific mediator antagonists such as antihistamines (H_1 and H_2) and anti-SRS-A compounds. The pharmaceutical industry is now producing several such substances, and it is important that they receive properly controlled trials in EIA.

EIA is generally agreed to be a heterogenous condition, and workers who support vagal or mast cell theories would probably not claim that one mechanism is totally exclusive of the other. It is even possible that different mechanisms may operate in the same individual at different times, depending on the underlying state of his asthma. During the past few years, definite progress has been made in understanding EIA, but the roundabout way in which this progress has been made should deter anyone from being too dogmatic or predicting future advances too confidently.

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